FOOD SAFETY HANDBOOK

FOOD SAFETY HANDBOOK

RONALD H. SCHMIDT
and
GARY E. RODRICK

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PREFACE

Food safety legislation and regulations have long been impacted by a variety of factors, including socioeconomic, consumer, political, and legal issues. With regard to food safety issues and concerns, certain parallels can be drawn between the beginning and close of the 20th century. At the start of the 20th century, several food safety issues were brought to the public's attention. Atrocious sanitation problems in the meat industry, highlighted in Upton Sinclair's novel *The Jungle*, had a major influence on the passage of the landmark legislation, the *Federal Meat Inspection Act* (1906). Likewise, fairly wide-spread food adulteration with the addition of inappropriate chemical substances, and the marketing of a variety of fraudulent and potentially dangerous elixirs, concoctions, and other formulations, led to passage of the *Pure Food and Drug Act* (1906).

We are now in the 21st century and, food safety issues have as high a priority and significance as they did over 100 years ago." Public concerns have arisen regarding high-profile food-borne illness outbreaks due to contamination of food with certain pathogens (e.g., *Salmonella, Escherichia coli* O157:H7, *Listeria monocytogenes*, and others) which have serious acute impact and potential chronic long-term complications in the ever-increasing high-risk population segment (e.g., elderly, children, immuno-compromised). In addition, food-borne illness outbreaks are occurring in foods previously not considered high risk (e.g., fruit juices, fresh produce, deli meats). In response to these food-borne pathogen issues, a presidential budgetary initiative was instituted in 1997 to put a multi-agency food safety strategy in place. This National Food Safety Initiative includes a nationwide early warning system for food-borne illness, expanded food safety research, risk assessment, training and education pro-

grams, and enhanced food establishment inspection systems. Pathogen issues have also resulted in endorsement and implementation of comprehensive prevention and intervention strategies, such as the Hazard Analysis Critical Control Point (HACCP) system, by the regulatory and industrial communities.

Another parallel can be drawn to earlier times. Society today, like that of the early 1900s, is strongly interested in attaining certain therapeutic and health benefits through special foods (e.g., nutraceuticals and functional foods), and, once again, the line between foods and pharmaceuticals has become blurred. The trend to market these products has created certain labeling concerns with regard to health claims, as well as safety and efficacy concerns.

As the world has gotten smaller through increased communication, travel, immigration, and trade, there are current concerns regarding the safety of food products throughout the world. Global consumer concerns regarding genetically modified foods and ingredients, as well as potential chemical residues in foods, have had a major impact on current and future legislation, as well as world trade.

The intent of this book is to define and categorize the real and perceived safety issues surrounding food, to provide scientifically non-biased perspectives on these issues, and to provide assistance to the reader in understanding these issues. While the primary professional audience for the book includes food technologists and scientists in the industry and regulatory sector, the book should provide useful information for many other audiences.

Part I focuses on general descriptions of potential food safety hazards and provides in-depth background into risk assessment and epidemiology. Potential food hazards are characterized in Part II, where biological hazards are discussed, and in Part III, which addresses chemical and physical hazards.

Control systems and intervention strategies for reducing risk or preventing food hazards are presented in Part IV, V and VI. The emphasis of Part IV is on regulatory surveillance and industry programs including Hazard Analysis Critical Control Point (HACCP) systems. Food safety intervention in food processing, handling and distribution are addressed in Part V, while the focus of Part VI is on the retail foods sector. Diet, health and safety issues are characterized in Part VII, with emphasis on food fortification, dietary supplements, and functional foods.

Finally, Part VIII addresses world-wide food safety issues through discussion of *Codex Alimentarius Commission (CAC)*, the European Union perspectives on genetic modification, and other globally accepted food standards.

The topics within each chapter are divided into sections called units. To provide continuity across the book, these units have been generally organized according to the following structure: *Introduction and Definition of Issues, Background and Historical Significance, Scientific Basis and Implications, Regulatory, Industrial, and International Implications*, and *Current and Future Implications*.

This project was a highly ambitious project and the co-editors would like to acknowledge the many people who provided valuable input and assistance and

to express our sincere appreciation for their efforts. This appreciation is especially extended to G. William Chase, LeeAnne Jackson, Austin R. Long, Joan Rose, Mary K. Schmidl, Keith R. Schneider, Barry G. Swanson, and Sara E. Valdes Martinez, for their enthusiasm and diligence in serving as Part Editors and to all of the numerous authors of the Chapters. We would also like to extend a sincere thank you to Virginia Chanda, Michael Penn, and all the staff at John Wiley and Sons, Inc. who provided invaluable assistance to the project.

RONALD H. SCHMIDT and GARY E. RODRICK

PART I

CHARACTERIZATION OF FOOD SAFETY AND RISKS

Edited by JOAN ROSE

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CHAPTER 1

DEFINITION OF FOOD SAFETY

ROBERT (SKIP) A. SEWARD II

INTRODUCTION AND DEFINITION OF ISSUES

The term "safe food" represents different ideals to different audiences. Consumers, special interest groups, regulators, industry, and academia will have their unique descriptions based on their perspectives. Much of the information the general public receives about food safety comes through the media. For this reason, media perspectives on the safety of the food supply can influence those of the general public.

Consumers are the end users and thus are at the last link of the food supply chain from production, through processing and distribution, to retail and food service businesses. Consumers are multidimensional and multifaceted. Populations differ in age, life experiences, health, knowledge, culture, sex, political views, nutritional needs, purchasing power, media inputs, family status, occupation, and education. The effect of the interrelationships of these factors on an individual's description of "safe food" has not been established.

When educated consumers were asked by the author to define safe food, their descriptions included some key elements. Safe food means food that has been handled properly, including thorough washing of fish and poultry that will be cooked and anything to be eaten raw. Safe food means food prepared on clean and sanitized surfaces with utensils and dishes that also are cleaned and sanitized. These consumers mention the importance of hand washing by those involved in food preparation and the importance of not reusing cloths or sponges that become soiled. Common sense is a guiding principle for the educated, informed consumer.

Other consumers want safe food that retains vitamins and minerals but does not have harmful pesticides. They describe safe food as food that is within its shelf life and has been stored and distributed under proper temperature control. Some consumers know the word "contamination" and will define safe food as food that is not contaminated.

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For other consumers, the descriptions of safe food are more practical, like food that does not make a person ill. For these consumers, safe food means purchasing fresh chicken and not having the package leak or drip juice, making them wonder about the integrity of the initial seal. Consumers use their senses in their descriptions of safe food, and they feel that food that looks or smells bad should not be eaten. Surprisingly, not many consumers refer to labeling as a key component of safe food. Consumers believe they know what to do with food after it is purchased, and they assume that the safety of the food is primarily determined before it reaches their hands. Published data suggest otherwise.

McDowell (1998) reported the results of on-site inspections of 106 households in 81 U.S. cities by professional auditors. A college degree was held by 73% of the participants. Inspection of meal preparation, cleanup, temperatures, sanitation, the environment, and personal hygiene resulted in at least one critical violation being cited in 96% of households. The most common critical violations were cross-contamination (76% of households with this violation), neglected hand washing (57%), improper leftover cooling (29%), improper chemical storage (28%), insufficient cooking (24%), and refrigeration above 45°F (23%).

Similarly, Jay et al. (1999) used video recording to study food handling practices in 40 home kitchens in Melbourne, Australia. Households of various types were video monitored for up to two weeks during 1997 and 1998. There was a significant variance between what people said they would do and what they actually practiced with respect to food safety in the home. The most common unhygienic practices included infrequent and inadequate hand washing, inadequate cleaning of food contact surfaces, presence of pets in the kitchen, and cross-contamination between dirty and clean surfaces and food.

A national telephone survey was done by Altekruse et al. (1995) to estimate U.S. consumer knowledge about food safety. The 1,620 participants were at least 18 years old and had kitchens in their homes. One-third of those surveyed admitted to using unsafe food hygiene practices, such as not washing hands or preventing cross-contamination. There was a disparity between the level of knowledge and corresponding safe hygiene practices. This suggested that decisions to practice safe food handling likely are based on various factors including knowledge, risk tolerance, and experience.

Jay et al. (1999) conducted a telephone survey of 1,203 Australian households and found significant gaps in food safety knowledge. The most important were incorrect thawing of frozen food, poor cooling of cooked food, undercooking of hazardous food, lack of knowledge about safe refrigeration temperatures and cross-contamination, and lack of knowledge about frequency and techniques of hand washing. The authors found the participants receptive to educational information regarding the preparation of safe food. Knowledge and compliance regarding the preparation of safe food increased with the age of the participants.

Special interest groups represent a focused view on safe food. These groups study the issues that they believe are most relevant to food safety and then express their concerns to consumers, regulatory authorities, industry, and academia. They typically define safe food by more specific limits for hazards than those used in the food supply chain. The special interest groups define safe foods through more stringent control limits for microbial pathogens and chemical hazards. They seek a higher level of food safety through requirements for more interventions to control hazards and elimination of chemicals used in food production, over fears of adverse health effects.

Special interest groups often question the approvals by governmental agencies of practices designed to increase the productivity and efficiency associated with agriculture and animal husbandry, for example, the use of antibiotics and hormones. Furthermore, the definition of safe food by selected special interest groups would exclude foods made through enhanced technology, such as genetic engineering. Again, they would view with suspicion, the science that established the safety of these new foods for the regulatory authorities responsible for their approval.

Special interest groups such as the U.S.-based Center for Science in the Public Interest (CSPI) do provide guidance for consumers and recommendations for government. CSPI and the Safe Food Coalition have outlined their recipe for safe food by calling for funding for the U.S. National Food Safety Initiative proposed in 1997, more authority for the U.S. Department of Agriculture (USDA) to enforce food safety laws, more power for the U.S. Food and Drug Administration (FDA) to keep contaminated products off the market, and a single agency responsible for food safety.

The CSPI has noted that consumers need to understand the broader range of products involved as vehicles of foodborne illnesses. The CSPI has stated that, although the effort is underfunded and not well-coordinated, government has improved the safety of the nation's food supply through legislation and regulation.

BACKGROUND AND HISTORICAL SIGNIFICANCE

Over his distinguished career, E.M. Foster has provided a unique perspective on the history of safe food (Foster, 1997). He has described how, for many, food production and consumption were tied to daily life on a farm. Through experience, time control became the means by which safe food was ensured, because for many people refrigeration was not available. According to Foster, examples of botulism, salmonellosis, and *Clostridium perfringens* food poisoning from new food vehicles have shown how our perceptions and understanding of safe food change with new knowledge about the capacities of microbial pathogens to adapt and proliferate in selected environments.

SCIENTIFIC BASIS AND IMPLICATIONS

Because academicians are some of the most educated consumers, they generally have the greatest understanding regarding the safety of foods, balancing the science with the practical application of the science in the food supply chain. Academicians can be the most knowledgeable about the science-based research used in defining safe food. However, the specifics of research, and the innumerable questions that are generated through research, lead to inevitably variable viewpoints on the science. The academic questions surrounding safe food are often multidimensional, involving scientific disciplines including biochemistry, microbiology, genetics, medicine, plant and animal physiology, and food science, to name only a few. Because academicians generally are narrowly focused in particular research disciplines, their definitions include details surrounded by boundaries and assumptions.

One of the common scientific measures used to define safe food is the number of illnesses associated with food. In the U.S., data sources for this measure include the Foodborne Diseases Active Surveillance Network (FoodNet), the National Notifiable Disease Surveillance System, the Public Health Laboratory Information System, the Foodborne Disease Outbreak Surveillance System, and the Gulf Coast States *Vibrio* Surveillance System. Similar surveillance systems are in use in other countries to gather foodborne disease statistics. Mead et al. (1999) used these data sources, and others, to estimate that foodborne diseases cause ~76 million illnesses and 5,000 deaths in the U.S. annually. Viruses, predominantly Norwalk-like viruses, accounted for nearly 80% of the estimated total cases caused by known foodborne pathogens.

REGULATORY, INDUSTRIAL, AND INTERNATIONAL IMPLICATIONS

Regulatory authorities are also consumers and thus carry many of the biases and perceptions held by consumers in general. However, regulatory authorities typically have a higher level of training in food safety. They differ in the scope of their responsibilities and influence, working at local, state, federal, or global levels. They also differ in their experiences with food along the food chain, from farming and animal production through manufacturing, distribution, and testing, to retail and food service. These experiences will affect their definitions of safe food.

Regulatory authorities that oversee food production are more aware of the impact of agricultural chemicals, animal hormones, feed contaminants, and antibiotics and would include details of these factors in their description of safe food. In processing environments, regulators would be more apt to describe safe food in terms of the microbiological, chemical, and physical hazards associated with manufacturing. Regulatory authorities overseeing retail and food

service would include the human factors such as cross-contamination by food handlers and personal hygiene behaviors.

Regulatory authorities also describe safe food according to regulations established by authorities such as the World Health Organization (WHO), the European Commission, and the U.S. FDA. The standards and laws set for international trade become part of the regulatory definitions of safe food. For example, the food safety standards adopted by the Joint Food Agricultural Organization/WHO Codex Alimentarius Commission (CAC) have become the international reference used to resolve international trade issues. Some regulatory authorities are using quantitative risk assessment to help define food safety, as well as to determine optimal intervention strategies. Scientific risk assessments have reportedly become the foundation for food safety worldwide with the issuance of the Sanitary and Phytosanitary Agreement by the World Trade Organization (WTO) (Smith et al., 1999).

Government officials often speak of safe food in terms designed to appeal to public emotions about food safety. For example, on July 2, 1998, the U.S. Vice President challenged the U.S. Congress to fund a Food Safety Initiative and "give Americans peace of mind when they reach for a piece of food." The Vice President stated the need for "new authority to seize meat that may be contaminated, to protect America's families." However, experts know that more recall authority does not improve food safety. The U.S. Food Safety Initiative is broad in its vision and scope. A key component of the Initiative is educating consumers on the responsibilities for food safety of everyone involved in the food supply chain.

The industry sector is broad in its constituency. Farmers and ranchers are the basis on which most of the food supply chain exists. At this level, food safety is defined by the practices of the farmers and ranchers, whether in regard to chemical treatment of the soil or use of hormones in animal production. These plant and animal producers define safe food based on the practical application of production principles, balancing economic pressures of production with demands for control of hazards. Safe food at this level means doing what is practical to ensure safety and focusing on optimal use of government-approved chemicals to maximize production. Thus far, there has not been a significant focus on controlling microbiological hazards at this level of the food chain; however, there is increasing recognition of the role of farmers and ranchers in defining safe food through their practices.

The food industry defines safe food by its specifications for raw materials and finished products. These specifications define the acceptable limits for chemical hazards such as pesticides and hormones, physical hazards such as bone and metal fragments, and microbiological hazards such as *Listeria monocytogenes* and *Salmonella*. The industry defines safe food in terms of pathogen reduction associated with processing technologies, whether well-established like pasteurization or new like pulsed, high-energy light.

The industrial sector also includes distribution, retail, and restaurant busi-

nesses, as well as related industries supporting the growth of plants and animals and the use of by-products for nonfood applications, such as for health care and clothing. Distributors, retailers, and restaurants define safe food by the expectations of their customers and the regulatory authorities.

CURRENT AND FUTURE IMPLICATIONS

Safe food is a composite of all of the views and descriptions held by consumers, special interest groups, academicians, regulatory authorities, and industry. Almost any single definition of safe food will be overly simplistic, because safe food is a complex, multifaceted concept. The scientific experts attending the 1998 American Academy of Microbiology Colloquium on Food Safety (AAM, 1999) described safe food as follows: Safe food, if properly handled at all steps of production through consumption, is reliably unlikely (i.e., the probability is low and the variability is small) to cause illness or injury.

Everyone wants a safe food supply. The criteria by which food is defined as safe will become more detailed and comprehensive as new steps are taken to improve safety. As capabilities rise, so will the expectations. The difficult decisions are those relating to perceived risks that drive the unnecessary use of public and private resources. If a food is perceived or reported to be unsafe, the story can be amplified in the press and then validated in the public mind by the involvement of politicians and regulators. All this can happen in the absence of scientific data that truly defines the risk (Smith et al., 1999).

Consumers have a role to play in ensuring that food is safe. They need to make informed choices about their food and how it is handled and prepared. According to Lopez (1999), consumer education about food safety must take place. Without a widely accepted definition of safe food, the public will have unrealistic misconceptions about the degree of safety that is attainable. Lopez pointed out that food safety standards have economic as well as scientific dimensions and that consumers are not likely to pay the high costs of absolutely safe food. To this end, industry and government have responsibility for improving safety as well as for educating consumers on the practical aspects of safe food. Research is needed to determine what impacts consumers' food safety practices (AAM, 1999).

The application of *Salmonella* and *Escherichia coli* performance standards for the U.S. food supply exemplifies a trend by regulators toward using microbial counts and prevalence data to define safe food. Yet there is general agreement among experts in food safety that food sampling and testing is not the sole means of ensuring safe food. The statistics of routine sampling indicate the limits of testing to define safe food. For example, *E. coli* O157:H7 in ground beef and *Listeria monocytogenes* in cooked foods are present at low levels, typically below 0.1%. Even when testing 60 samples per lot, there is a greater than 90% chance of not detecting the pathogen. Companies normally test fewer samples (3–5 per lot) to confirm that their Hazard Analysis and Critical Con-

trol Point (HACCP) system is functioning; thus the likelihood that testing will establish the safety of the food is greatly limited. Furthermore, pathogens will not be homogeneously distributed in many contaminated foods, which may also reduce the value of sampling and testing to determine safety.

Global differences in judgments on safe food are likely to continue, such as the current disagreements over the safety of beef hormone treatments and genetically modified foods between the U.S. and the European Union. These differences exist despite mechanisms such as the dispute resolution system of the WTO. In general, the European view of safe food is fundamentally different from that in the U.S., with culture and history as important as science in some decision-making processes.

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CHAPTER 2

CHARACTERIZATION OF FOOD HAZARDS

ROBERT (SKIP) A. SEWARD II

INTRODUCTION AND DEFINITION OF ISSUES

Hazard characterization with respect to foods began as a means to help prioritize risks and categorize hazards. Over time, hazard characterization has broadened in scope, as the criteria used to evaluate hazards have increased in number and breadth. Today, characterization of hazards is more important than ever in developing food safety control programs. The use of categorization is of lesser importance as susceptibility of the population to the hazards becomes greater. The WHO (1995) described hazard characterization as the qualitative and quantitative evaluation of the nature of the adverse effects associated with biological, chemical, and physical agents that may be present in foods.

Van Schothorst (1998) suggested that hazard characterization might be better termed "impact characterization." The impact can vary from mild (simple acute diarrhea) to severe (chronic illness or death), depending largely on the susceptibility of the person exposed. To accommodate the many assumptions associated with impact characterizations, a worst-case scenario often is used to estimate the risk presented by a particular pathogen in a specific food. Van Schothorst points out that assumptions and uncertainties of hazard characterization ultimately can lead to an unreliable risk assessment, as well as credibility and liability problems.

The National Advisory Committee on Microbiological Criteria for Foods (NACMCF) (1997) defined a hazard as a "biological, chemical, or physical agent that is reasonably likely to cause illness or injury in the absence of its control." Microbial pathogens are the most common biological hazards, and they can cause infections (growth of the disease-causing microorganism) and intoxications (illness caused by preformed toxin produced by a micro-

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organism). Scott (1999) has detailed the characteristics of numerous common microbial hazards and described the factors that affect the risk of illness from the hazards.

Chemical hazards include agricultural compounds such as pesticides, antibiotics, and growth hormones; industrial chemicals such as cleaners and sanitizers; and equipment-related compounds such as oils, gasoline, and lubricants. Other chemical hazards include naturally occurring toxicants such as mycotoxins, environmental contaminants such as lead and mercury, and chemical preservatives and allergens.

Physical hazards include glass, wood, plastic, stones, metal, and bones. The introduction of physical hazards has been characterized as inadvertent contamination from growing, harvesting, processing, and handling; intentional sabotage or tampering; and chance contamination during distribution and storage (Corlett, 1998).

BACKGROUND AND HISTORICAL SIGNIFICANCE

The language surrounding the term "hazard characterization" has referred to the food products themselves, as well as to the hazards that might be present in the food. Hazard characterization has been used in the development of Hazard Analysis and Critical Control Point (HACCP) plans and regulatory policies, as well as for risk assessments. In 1969, the National Academy of Sciences issued a report evaluating the *Salmonella* problem (NAS, 1969). This report described three hazard characteristics associated with food and *Salmonella*:

1. Products containing ingredients identified as significant potential factors in salmonellosis,
2. Manufacturing processes that do not include a control step that would destroy *Salmonellae*, and
3. Substantial likelihood of microbiological growth if mishandled or abused in distribution or consumer usage.

With the various combinations of these three hazard characteristics, five categories were created that reflected the potential risk to the consumer. Category I included food products intended for use by infants, the aged, and the infirm, that is, the restricted population of high risk. Category II included processed foods that were subject to all three hazard characteristics (ABC) listed above. Category III included those products subject to two of the three general hazard characteristics. These would include such products as custard-filled bakery goods (AC), cake mixes and chocolate candy (AB), and sauce mixes that do not contain a sensitive ingredient (BC). Category IV included products of relatively minor microbiological health hazard level, subject to only one of the hazard characteristics. Examples include retail baked cakes (A) and some frosting mixes (B). Category V includes foods that are subject to none of the

microbiological hazard characteristics and therefore of minimal hazard potential, for example, canned foods sterilized after packaging in the final container.

The Pillsbury Company is recognized as the first company to have developed HACCP plans. The Pillsbury approach to HACCP systems also used three hazard characteristics to categorize food products. In this instance, the hazard characteristics were generalized to include all potential microbial, physical, and chemical hazards, not only *Salmonella* (Sperber, 1991). As in the NAS report, the permutations of the hazard characteristics resulted in five product hazard classes.

The use of the three hazard characteristics to assess risks was standard in the 1970s (Bauman, 1974). In 1989, the NACMCF presented a HACCP document that used six hazard characteristics to rank microbial hazards for risk assessments (NACMCF, 1989). Chemical and physical hazards were included subsequently (Corlett and Stier, 1991). Hazard characterization at this time was made on the basis of criteria such as:

The consumers' risks associated with factors such as age and health,
The risk associated with the ingredients used to make the food product,
The production process and its impact on the hazard,
The likelihood of recontamination after processing,
The potential for abuse during distribution and consumer handling, and
The ability of the consumer to detect, remove, or destroy the hazard during the final preparatory steps.

The hazard classification scheme (Hazard Categories A–F) described in the 1989 NACMCF document was updated in 1992 (NACMCF, 1992) and again in 1997 (NACMCF, 1998a). These revisions aligned U.S. HACCP concepts with those published by the internationally recognized Codex Alimentarius Commission (CAC) (1997). The most recent HACCP documents characterize hazards as part of the hazard analysis. The hazard characterization, or evaluation, is done after the hazards have been identified. The criteria for characterizing the hazard include:

The severity of the hazard, to include the seriousness of the consequences of exposure, or the magnitude and duration of the illness or injury,
The likelihood that the hazard will occur, based on published information and epidemiological data,
The potential for both short-term and long-term effects from exposure, and
Available risk assessment data,

as well as many of the criteria stated in earlier documents.

Ultimately, according to William H. Sperber (personal communication), "the hazard characteristics were discarded in favor of an open-ended hazard analysis in which an unlimited number of relevant questions could be asked

about the product and the process by which it is produced. The product hazard categories fell into disfavor as we recognized that a relatively large percentage of consumers are immunocompromised. All foods must be safe for all consumers. The emergence of new foodborne pathogens in relatively narrow niches, e.g., *Listeria monocytogenes* in some perishable ready-to-eat foods, further rendered the concept of product hazards categories moot."

SCIENTIFIC BASIS AND IMPLICATIONS

In addition to its role in the development of HACCP plans, hazard characterization has been identified as the second step of the risk assessment process (Smith et al., 1999). The characterization includes determination of risk factors, defining the site and mechanism of action, and measuring the dose-response relationship (proportion responding or severity of response). Despite large uncertainties, dose-response models are commonly used to predict human health effects and even to establish regulatory policies.

According to the WHO (1995), a dose-response assessment should be performed for chemical hazards. For biological or physical agents, a dose-response assessment should be performed if the data are obtainable. Although potentially hazardous chemicals may be present in foods at low levels, for example, parts per million or less, animal toxicological studies typically are done at higher levels to obtain a measurable effect. The significance of the adverse effects associated with high-dose animal studies for low-dose human exposure is a major topic of debate with regard to the hazard characterization of chemicals.

The extrapolation of animal exposure data to human exposure levels is uncertain both qualitatively and quantitatively. The nature of the hazard may change with dose. Not only is the equivalent dose estimate in animals and humans problematic in comparative pharmacokinetics, the metabolism of the chemical may change as the dose changes. Whereas high doses can overwhelm detoxification pathways, the effects may be unrelated to those seen at low doses (WHO, 1995).

A primary contributor to the uncertainty of the hazard characterization is the intraspecies variance in the dose response at different dosage levels. Large exposures often are used to increase the power of a study yet may be inaccurate for low-dose exposure. Variance also results from many other differences among individual animals and humans.

Toxicologists often use thresholds to quantify adverse effects from chemical exposures, except in the case of carcinogenic effects, where initiating events can occur as persistent somatic mutations that later develop into cancer. Some carcinogens may be regulated with a threshold approach, such as the "No Observed Effect Level (NOEL)-safety factor" approach. A safe level of a chemical often is derived from an experimental NOEL or No Observed Adverse Effect Level (NOAEL) by using safety factors. A safety factor of 100 has been applied when using data from long-term animal studies, but it may be adjusted

if data are insufficient or if the effect is more severe or irreversible. It has been suggested that conservative models and large safety factors should be used for food systems potentially contaminated with biological hazards because of the unpredictability of these systems (Smith et al., 1999). Obviously, the safety factor approach is full of uncertainty and cannot guarantee absolute safety for everyone.

For carcinogens that cause genetic alterations in target cells, the NOEL safety factor approach is usually not used because of the assumption that risk exists at all doses, even the lowest. Risk management options are to ban the chemical or establish a negligible, insignificant, or socially acceptable level of risk with quantitative risk assessment. An alternative approach has been to use a lower effective dose, or a benchmark dose, which depends more on data near the observed dose-response range. This may allow more accurate predictions of low-dose risks.

Characterization of biological hazards is done to provide a qualitative or quantitative estimate of the severity and duration of adverse effects due to the presence of a pathogen in a food. Dose-response data are useful but scarce for microbial pathogens. Furthermore, inaccuracies in the data may occur for the following reasons: host susceptibility to pathogenic bacteria is variable; attack rates from specific pathogens vary; virulence of a pathogen is variable; pathogenicity is subject to genetic mutation; antagonism from other microbes may affect pathogenicity; and foods will modulate microbial-host interactions.

REGULATORY, INDUSTRIAL, AND INTERNATIONAL IMPLICATIONS

As pointed out by Kaferstein et al. (1997), the globalization of trade requires coordination among international regulatory and health protection authorities. Food safety standards, recognized by the WTO, place greater dependence and emphasis on scientific risk assessments. Hazard characterization will remain a key component of the risk assessment (NACMCF, 1998b).

The International Commission on Microbiological Specifications for Foods (ICMSF) has proposed the use of the Food Safety Objective (FSO) as a management tool to control the risk of foodborne illness. The FSO reflects the frequency or maximum concentration of a microbiological hazard in a food that is considered acceptable for consumer protection. FSOs are broader in scope than microbiological criteria. FSOs link risk assessment and risk management processes and establish control measures (ICMSF, 1998). The hazard characterization process will contribute information toward establishing the FSO.

CURRENT AND FUTURE IMPLICATIONS

The Institute of Food Technologists (IFT), a scientific society for food science and technology with over 28,000 members, has stated that food safety policies must be based on risk assessment. IFT agreed with the WHO (1995) that

improvements in risk assessment require more precise characterization of hazards and measures of exposure. Better data on exposure to pathogens, the behavior of pathogens in foods, and dose-response relationships for population subgroups are essential (IFT, 1997). Scientific experts attending the AAM Colloquium on Food Safety (1999) identified future research needs including a cross-discipline definition of dose-response relations and better characterization of hazards causing chronic disease syndromes such as reactive arthritis and ulcers. As new scientific data are developed, the hazard characterization process will continue to be redefined and improved. The acceptable limits for hazards will change, as will the range of hazards included in a given food safety control program.

Harmonization of the hazard characterization approaches will help global trade by facilitating a common basis for setting product standards and defining safe food. The initial steps have been taken with the SPS Agreement and FAO/WHO CAC standards and guidelines. Hazard characterization, although crucial to the development of food safety control programs, will not define safe food by itself. The definition of safe food will improve as we understand how better to integrate hazard characterization, population preferences, cultural biases, and many other considerations into judgments on safe food.

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INTERNET RESOURCES

www.cspinet.org
Web site for Center for Science in the Public Interest that demonstrates the definition of safe food by special interest groups.

www.fao.org/waicent/faoinfo/economic/esn/codex/default.htm
Web site for Codex, summary reports and Joint FAO/WHO Food Standards Programme.

www.fda.gov
Web site for the U.S. Food and Drug Administration that provides information on the role of government in defining a safe food supply.

www.foodsafety.gov
Web site that is the gateway to U.S. government food safety information, including the National Food Safety Initiative.

www.whitehouse.gov
Web site providing governmental viewpoint on safe food and the initiatives necessary to achieve food safety.

www.who.int/fsf/mbriskassess/applicara/index.htm
Web site for Report of Joint FAO/WHO Expert Consultation on the Application of Risk Analysis to Food Standard Issues.

CHAPTER 3

RISK ANALYSIS FRAMEWORKS FOR CHEMICAL AND MICROBIAL HAZARDS

MARGARET E. COLEMAN and HARRY M. MARKS

INTRODUCTION AND DEFINITION OF ISSUES

Human individuals and societies have been identifying risks and managing them since ancient times (When you build a new house, you shall make a parapet for your roof, so that you shall not put blood in your house if [when] one falls from it. Deut. 22:8) by various procedures, including establishing codes of practice and formal laws. What appears to be a more modern concern is the quantitative nature of risk, that is, the precise calculation of probabilities of risk. Performing these calculations is complex and involves input from many areas of the society. In particular, hazards and the risks associated with them need to be identified, and society must value the knowledge that calculation of the risks provides. It is not surprising that in a well-informed, free society, risk analysis has become a serious and growing field. The complexity of the calculations and the political will to make the calculations have created the need to structure the process of risk analysis so that the calculations are performed in an efficient and understandable manner. This chapter is a short discussion of the managerial frameworks that have been adopted in risk analysis and some of the issues surrounding them.

A natural beginning point in a discussion of risk analysis is the definition of risk. Even among practitioners of risk analysis, developing a standard definition of risk has been problematic. A committee of professionals in the newly formed Society for Risk Analysis (SRA) convened in the early 1980s and was unable to reach a single, consensus definition for risk after 4 years of deliberations (Kaplan, 1997). The recommendation of the SRA at that time was that freedom be permitted for professionals to define risk in a manner best suiting the particular discipline or problem at hand.

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A good operational definition of risk is important because from it one can determine how to structure the activities needed to perform the calculations of risk and to disseminate the meaning of the calculations. A general operational definition provided by Kaplan (1981, 1997) will serve, with some modification, as a starting point for our discussions of risk analysis frameworks. Risk was defined (Kaplan, 1981, 1997) with responses to three basic questions. 1) What can happen? 2) How likely is it? 3) What are the consequences? In the Kaplan papers, which use an engineering perspective, the first component, "What can happen?" seems to describe an event such as a fire. Kaplan terms this first component as a scenario, S, and defines S_0 as the successful scenario of nothing happening or nothing going wrong. For risk analysis of foodborne illness, the causal event is always the ingestion of something that is hazardous. Thus, for risk in food, the only answer to the question "What can happen?" is a single event, ingestion of a hazardous chemical or pathogen. Consequently, for our purposes, we shall adapt the concept of "scenario" to mean an event or a process that can produce the specified potential hazard and consequence for a given population. Thus, for food risk analysis, the scenario represents a *conditional* event or process, for which the associated risk must be evaluated. For example, a scenario might be the production of a certain food for which the presence of a certain hazard cannot be excluded. This hazard could result in fetal complications for pregnant women consuming the food. Three aspects of a scenario must be defined for a risk assessment: 1) the process, 2) a potential consequence, and 3) the target population. The "How likely is it?" question represents the conditional likelihood for the given scenario that the hazardous agent will be ingested, for example, the number of times that a pregnant woman would consume a serving of the food. The "What are the consequences?" question represents the probability of the adverse consequence, given the ingestion of the hazard agent.

Our adaptation of Kaplan's definition emphasizes that the risk analysis must specify conditions (termed scenario) and that the results are dependent on these conditions. If one describes a scenario, then the likelihood of an adverse effect for that scenario is predicted with attendant uncertainty. The elements of the triplet (scenario, likelihood, consequences) do not impose limitations on the methodology used to estimate risk.

Societies can choose to control or manage risk by any number of alternative, mitigating strategies. The above definition of risk allows for hypothetical scenarios to be compared, thus allowing a society to determine the benefits of alternative, mitigating strategies. Societies can choose not to control risks or to leave to the individual the decisions of how to manage risks. An individual might be permitted to engage in or avoid a certain risk voluntarily, such as smoking or driving a car. Management of risks that are involuntarily imposed on members of a society, such as risks of foodborne illness, might cause public outrage if not handled in a consistent, open public process. Risk analysis thus is the field that provides the public with the information needed to make informed decisions about risks and how to manage them.

Risk analysis is simply the analysis of scenarios that result in adverse consequences. The overarching term "risk analysis" has come to include, in addition to the above, the control and communication of risk. The management of a risk analysis has become a large undertaking, and many strategies of managing it have been proposed. A common risk analysis framework encompasses three components: 1) risk assessment, 2) risk management, and 3) risk communication, all of which are briefly described in this introductory section. The remaining sections of this chapter discuss managerial frameworks for the risk assessment and risk management components, along with identification of some of the tensions between these frameworks.

Risk Assessment

Risk assessment is the estimation of the probability of the occurrence of adverse events with attendant uncertainty [National Research Council (NRC), 1983]. Sound science is the underpinning of a good risk assessment, which is viewed as a link between research or science and policy (NRC, 1983). A structured process is essential to risk assessment because risk rarely involves the certainty of direct, measurable observations relevant to human health but does involve inference, prediction, and uncertainty. Thus the probability of adverse consequences is formally estimated with derived models that describe mathematically the processes thought to produce adverse consequences.

The earliest publication that dealt specifically with the structure of risk assessment applicable to foodborne human health effects was the "red book" of the NRC (1983). The basic structure or managerial framework of risk assessment was initially described by four elements: hazard identification, exposure assessment, dose-response assessment, and risk characterization (NRC, 1983). A list of 11 principles for risk assessment for microbiological hazards is provided in Table 3.1 (CCFH, 1998).

Risk Management

In managing risk, the risk manager considers the results of risk assessment and other factors, including economic, political, social, and technological inputs or limitations, to develop policies to manage the risk. The decisions made by risk managers also often reflect the priorities of a society. Neither risk management nor risk assessment is conducted in a vacuum. Establishing regulatory standards is a risk management activity that reflects the level of safety deemed appropriate for a given hazard. Policy strategies to control one foodborne hazard may well create new hazards. For example, air bag performance in U.S. automobiles was initially determined to minimize risks of death in severe accidents. Because of these performance standards, a new risk was created to young children and others when air bags deployed. Risk-risk trade-offs and cost-benefit analyses are essential analytical activities for fully documenting the risk management options and their consequences. A list of eight principles for

TABLE 3.1. General Principles of Microbiological Risk Assessment from "Principles and Guidelines for the Conduct of Microbiological Risk Assessment" Document of the Codex Committee on Food Hygiene (CCFH; 1998; *www.fao.org/WAICENT/FAOINFO/ECONOMIC/ESN/codex/Reports.htm*)

1. Microbiological Risk Assessment must be soundly based upon science.
2. There should be a functional separation between Risk Assessment and Risk Management.
3. Microbiological Risk Assessment should be conducted according to a structured approach that includes Hazard Identification, Hazard Characterization, Exposure Assessment, and Risk Characterization.
4. A Microbiological Risk Assessment should clearly state the purpose of the exercise, including the form of Risk Estimate that will be the output.
5. A Microbiological Risk Assessment should be transparent.
6. Any constraints that impact on the Risk Assessment such as cost, resources or time, should be identified and their possible consequences described.
7. The Risk Estimate should contain a description of uncertainty and where the uncertainty arose during the Risk Assessment process.
8. Data should be such that uncertainty in the Risk Estimate can be determined; data and data collection systems should, as far as possible, be of sufficient quality and precision that uncertainty in the Risk Estimate is minimized.
9. A Microbiological Risk Assessment should explicitly consider the dynamics of microbiological growth, survival, and death in foods and the complexity of the interaction (including sequellae) between human and agent following consumption as well as the potential for further spread.
10. Wherever possible, Risk Estimates should be compared over time with independent human illness data.
11. A Microbiological Risk Assessment may need reevaluation as new relevant information becomes available.

risk management is presented in Table 3.2 from the 1996 FAO/WHO consultation on risk management (*www.fao.org/es/esn/risk/riskcont.htm*).

Risk Communication

Risk communication is the process of engaging stakeholders (all interested parties, including consumers, producers, scientists in academia, industry, and government, and various professional or advocacy organizations) in dialogues about risk, its assessment, and its management. The risk assessor might take responsibility for explaining in nontechnical terms the data, models, and results of the risk assessment. The risk manager is responsible for explaining the rationales for various alternative risk management strategies based on the risk assessment. The stakeholders also have a responsibility both to communicate their concerns and to review and understand the risk assessment and risk management options. Some principles for agencies to apply in risk communications are listed in Table 3.3.

TABLE 3.2. General Principles of Food Safety Risk Management from Joint FAO/WHO Expert Consultation on the Application of Risk Management to Food Safety, Rome, Italy (1996; *www.fao.org/WAICENT/FAOINFO/ECONOMIC/ESN/risk/risktext.htm*)

1. Risk management should follow a structured approach.
2. Protection of human health should be the primary consideration in risk management decisions.
3. Risk management decisions and practices should be transparent.
4. Determination of risk assessment policy should be included as a specific component of risk management.
5. Risk management should ensure the scientific integrity of the risk assessment process by maintaining the functional separation of risk management and risk assessment.
6. Risk management decisions should take into account the uncertainty in the output of the risk assessment.
7. Risk management should include clear, interactive communication with consumers and other interested parties in all aspects of the process.
8. Risk management should be a continuing process that takes into account all newly generated data in the evaluation and review of risk management decisions.

BACKGROUND AND HISTORICAL SIGNIFICANCE

Society and Risk Analysis

Risk analysis is continuously evolving to address the concerns of society. The next three sections present a short discussion of key concerns for risk analysis of interest to society. The structure of managerial frameworks of risk analysis has an effect on society because it influences how effectively risk is managed. Discussion is provided of various managerial structures and their impacts on risk communication processes.

Society and risk assessment Prediction of risk and attendant uncertainty is not a simple process. In constructing risk assessment models, assumptions

TABLE 3.3. FAO/WHO Principles of Risk Communication (Joint FAO/WHO Consultation, February, 1998, Rome, Italy)

1. Know the audience.
2. Involve the scientific experts.
3. Establish expertise in communication.
4. Be a credible source of information.
5. Share responsibility.
6. Differentiate between science and value judgement.
7. Assure transparency.
8. Put the risk in perspective.

about the underlying mechanisms or processes and formal statistical inferences from available data are made. These assumptions and inferences from limited data may be very subjective judgments that can become points of dispute and controversy for other risk analysts and stakeholders.

For the risk assessment to be used effectively to support decision making about risk management strategies, the risk manager and the stakeholders must understand the risk assessment. An understanding of the risk assessment involves familiarity with: 1) the simplifying assumptions used in constructing the models; 2) whether or not the particular models used are based on consensus of the scientific community; 3) the magnitude of the uncertainty associated with the data and the models; and 4) the procedures for estimation of the likelihood of the occurrence of adverse events for given scenarios. If clear, complete explanations of the assumptions and methodology are provided so that the analysis could be repeated, then the risk assessment is called "transparent." However, one could say that transparency is in the eye of the beholder, because risk assessors must tailor different levels of technical detail for transparency to various audiences of stakeholders and risk analysis professionals.

Besides estimating the magnitude of the risk and the uncertainty of the risk estimates in a transparent fashion, another desirable aspect of a risk assessment framework includes generality. The models must describe processes in a manner that permits application to a wide range of scenarios, for example, depicting a variety of current farm-to-fork food production processes. However, a model may also be too general, requiring many unsupported assumptions or unwarranted inferences and leading to inaccurate estimates of risk. In contrast, the data and the underlying scientific theory may permit useful estimates of risks for only a small specific set of scenarios.

The underlying tension between these two poles of generality and specificity should be addressed in the preliminary phase of risk assessment. This tension can also be addressed in the risk assessment by conducting sensitivity analysis. Sensitivity analysis reveals the effect of changes in model parameters on the estimates of risk. If values of a parameter have high impact on the estimate of the risk (high sensitivity), and the actual value of the parameter is not known accurately, then the uncertainty of the risk assessment results will be great. A thorough analysis of the uncertainty of estimates and the effect of alternative models derived from different assumptions would permit evaluation of more general scenarios, while providing protection against unwarranted conclusions.

Each risk assessment can be thought of as unique. Therefore, a unique combination of procedures appropriate for that risk assessment needs to be developed by the risk assessor. For example, some of the methodologies appropriate for engineering applications, such as fault tree analysis, lack the flexibility to account for dynamic growth that is necessary for modeling risk of adverse consequences from many microbial hazards. Because risk assessments are unique, the Codex Committee on Food Hygiene (CCFH) does not specify methodologies in its principles and guidelines document for microbiological hazards (Table 3.1). For example, the NRC framework (1983) discussed later

in this chapter is applicable to microbial hazards, although the methodologies to account for dynamic growth of pathogens in exposure models were probably not anticipated during formulation of the framework for carcinogenic risk assessment.

For a society, the goal of risk assessment is to model realistically the probabilities of consequences, with attendant uncertainties, for given scenarios and not to develop "conservative" estimates of the probabilities of consequences. A model should separate for the risk manager and stakeholders "true" variability (irreducible heterogeneity among hosts, pathogens, or environmental matrix) from uncertainty (ignorance reducible by new research data) imposed by the data and the assumptions of the models. The imposition of conservatism throughout a risk assessment model is not good practice, because bias that may be difficult to quantify is imposed on the risk estimate. Conservatism should be the judgment of the risk management process or of the society, informed by the risk assessment that provides a range of possibilities rather than a worst case.

Society and risk management The concerns and influence of a society on risk management might be inferred from the history of legislation passed by elected and appointed representatives and enforced by governmental regulators. Table 3.4 lists some key legislation that influenced food safety and risk assessment in the United States. Of particular note for this chapter is the

TABLE 3.4. Some Legislative History for Food Safety and Environmental Risk Assessment (ENVIRON, 1988; Cohrssen and Covello, 1989; Code of Federal Regulations, Title 9, volume 2, Chapter III, USDA/FSIS Statutory Requirements)

1. Clean Air Act (1970, amended 1974, 1977, 1990, 1997)
2. Clean Water Act; Safe Drinking Water Act (1972, amended 1974, 1977, 1978; 1997)
3. Comprehensive Environmental Response, Compensation, and Liability Act; Superfund Amendments and Reauthorization Act (1981; 1986)
4. Egg Products Inspection Act (1970; 84 Stat. 1620, 21 U.S.C. 1031 *et seq.*)
5. Federal Crop Insurance Reform and Department of Agriculture Reorganization Act of 1994 (Pub. L. 103–354; 7 U.S.. 2204e)
6. Federal Food, Drug, and Cosmetic Act (1938, 52 Stat. 1040, amended 1958, 1960, 1962, 1968; amended 1996, 1998 as Food Quality Protection Act (21 U.S.C. 301 *et seq*))
7. Federal Insecticide, Fungicide, and Rodenticide Act (1948, amended 1972, 1975, 1978; amended 1996, 1998 as Food Quality Protection Act)
8. Federal Meat Inspection Act (1907, 34 Stat. 1260, amended by Wholesome Meat Act, 81 Stat. 584 (21 U.S.C. 601 *et seq.*))
9. Pathogen Reduction/HACCP Rule (1996, 61 FR 38868)
10. Poultry Products Inspection Act (1957; 71 Stat. 441, as amended by Wholesome Poultry Products Act, 82 Stat. 791 (21 U.S.C. 451 *et seq.*))
11. President's Food Safety Initiative (1997)

Delaney Clause of 1958 (Table 3.4. item 6), which imposed a zero-risk cancer standard designed to prohibit food additives including pesticides with carcinogenic potential from concentrating in processed foods. A zero-risk standard does not require quantitative risk assessment, but rather a simple statistical test at some prescribed level for the presence of a carcinogen hazard in a processed food.

The changing climate of risk analysis over the past 40 years is evidenced by two recent pieces of legislation that imply or explicitly require risk assessments for food safety under certain conditions. The Federal Crop Insurance Reform and Department of Agriculture Reorganization Act of 1994 established the Office of Risk Assessment and Cost-Benefit Analysis to review the risk assessments and cost-benefit analyses that are used in support of major regulations in the U.S. Department of Agriculture (USDA). The Food Quality Protection Act of 1996, with amendment in 1998, modified the Delaney Clause relating to pesticides and changed the language from "zero risk" to "reasonable certainty that no harm will result from aggregate exposure to pesticide residue." Thus, "safe" food, with respect to pesticides, is not implied by a lack of statistically significant demonstration for the presence of a carcinogenic hazard. Rather, "safe" food is implied by estimates of "reasonable" dietary risk and consideration of sensitive subpopulations.

Society and risk communication In the past, risk assessors may not have considered that risk communication was their responsibility at all, except for communicating with the risk manager. Public meetings might have been convened to announce the results of the risk assessment or to explain the policy decisions that were drawn from an assessment. The attitudes projected by more recent work of the NRC (1996) and the President's Commission on Risk Management (1996) point the way to opening risk analysis to more interactive dialogue throughout the process. Thus U.S. federal agencies (EPA, USDA, and FDA) are more commonly convening public meetings to introduce risk assessment teams and to solicit data at the start of major risk assessments rather than at the end of the assessments.

Risk Management Frameworks

The initial framework for risk assessment and risk management proposed by the NRC in 1983, as mentioned above, was the first U.S. publication that systematically related foodborne human health, risk assessment, and risk management. The work of the NRC marked the first major U.S. effort to define nomenclature for, and the key steps of, public health risk assessment (NRC, 1983). The Committee met to consider chemical hazards and carcinogenic consequences or end points. However, the work, referred to as the "Red Book," has been applied beyond its initial scope of risk assessment for carcinogens.

Risk Analysis Managerial Strategies

The NRC (1983) outlined a managerial structure of risk analysis in Figure 1.1 of their report. Certain features of this figure are depicted in *Eq. 3.1*.

$$\text{Research} \Rightarrow_{①} \overset{\text{Risk}}{\text{Assessment}} \Rightarrow_{②} \{\text{Decisions}\} \Leftarrow_{③} \overset{\text{Risk}}{\text{Management}} \qquad (3.1)$$

These relationships are consistent with the concept that risk assessment is a structured process that links science and policy. The first unidirectional arrow on the left indicates that research data and information are inputs to risk assessment. However, an implication of *Eq. 3.1* is that the research goals and objectives are not influenced by the needs of risk assessors. In other words, research projects are not specifically designed to meet the needs of risk assessments. The President's Commission on Risk Management (1996) recognized this problem and stated that risk assessments should motivate research. Uncertainty and sensitivity analyses of risk assessment models can identify crucial research needed for improving estimations of risk.

The second and third unidirectional arrows emphasize the objectivity of the science and the independence of risk assessment from other influences that have bearing on the risk manager's decision making process. Developing preliminary analyses for the scope of the risk assessment requires some initial dialogue between risk assessors and risk managers. As the assessment is conducted, a risk manager should clearly refrain from exerting any influence on the process that might bias the results. Therefore, the phases of risk assessment dealing with scientific data generally exclude risk managers. However, as a risk assessment nears completion, risk assessors and risk managers might jointly develop policy options for mitigation or risk reduction and economic analyses such as cost-benefit analysis for potential mitigation, regulations, or guidance. This view of risk analysis demands some dialogue between risk assessors and risk managers, but as implied by *Eq. 3.1*, only at the end of the process, at the decision point.

The results of the risk assessment become an input to the risk manager's decision making process. One consequence, perhaps unintended, of these unidirectional relationships is the hindrance of open and transparent communication with risk managers and other stakeholders about the scientific data, assumptions, and methodologies used in the risk assessment. The possibility exists in this framework that risk assessment will become a "black box" for the risk manager as well as for the stakeholders.

As a consequence of these concerns, a more general framework is needed. *Equation 3.2* represents a simple extension of the NRC model utilizing bidirectional arrows.

$$\text{Research} \Leftrightarrow \text{Risk Assessment} \Leftrightarrow \text{Risk Management} \qquad (3.2)$$

The left bidirectional arrow implies that research should be motivated and directed by the needs of risk assessors in conducting risk assessments. This reflects a new emphasis on the opportunity for risk assessors to identify key data gaps and to take an active part in influencing the direction of research to improve risk assessment models. The right bidirectional arrow implies that not only is decision making a joint enterprise between risk assessors and risk managers, but also the assumptions and inferences used by the risk assessors must be communicated clearly to the risk managers. The bidirectional arrow on the right is not meant to imply that the influence of risk managers diminishes the independence of the risk assessment, but as a consequence independence could be diminished. *Equation 3.1* still does not explicitly include risk communication structure.

The NRC 1983 framework appears to omit risk communication with the stakeholders. One motivation for change, or expansion of the framework, involves including stakeholders who want to understand risk and to choose how they respond to risk as individuals and societies (NRC, 1996). Many risk analysts and stakeholders recognize that the usefulness of unidirectional processes for risk analysis merits further scrutiny (President's Commission on Risk Management, 1996; Marks, 1998; FDA, 1999).

Many levels of communication are needed among researchers, risk assessors, and managers. For example, dialogue is necessary between the risk assessors and managers for defining the scope of the risk assessment, preparing and testing models for various risk management options, engaging in discussions about the results and interpretations of the results of the risk assessment, and influencing the direction of the research. However, communication between the risk analysis professionals and the stakeholders is more complicated. For example, one of the many sources of difficulty is the depth of technical knowledge required to understand the risk assessment. Many technical assumptions are made that can raise questions about the validity of the results. Another problem is that risk assessments often do not address the problem in its entirety, but rather address a portion of it, omitting other associated hazards that could become concerns to the community (NRC, 1996). For stakeholders to develop a better understanding of the nature of the problem and to evaluate possible solutions to the problem, it is necessary for them to understand in detail the risk assessment process. The next section provides a discussion of the nature and limitations of the risk assessment process.

SCIENTIFIC BASIS AND IMPLICATIONS

Risk Assessment Structure

The first task for risk assessors, given an assignment to conduct a risk assessment from their risk managers, is to compile the evidence and structure it in some reasonable manner according to a logical framework, such as the four-

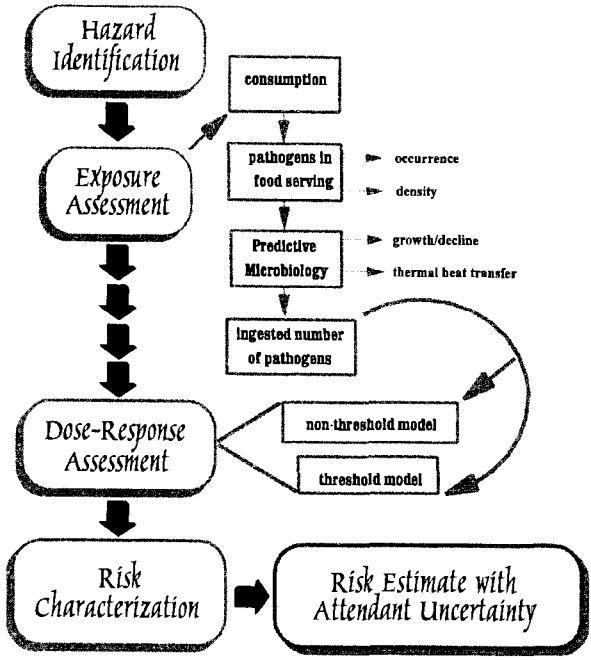

Figure 3.1. Structure of model for microbial risk (Marks et al., 1998; with permission from *Risk Analysis*).

element framework of the NRC (1983). This framework is sufficiently general to be useful for chemical and microbial hazards (Fig. 3.1; Marks, 1998). As discussed above, the output of a risk assessment is the estimation of the probability and severity of adverse outcomes for given scenarios, according to our modification of Kaplan's definition of risk.

Hazard Identification (HI) is the first element of the 1983 NRC framework that describes the nature of the problem and the agents that cause adverse effects in a given scenario. Many types of adverse outcomes or "end points" can be considered. Toxicological or epidemiological studies are used to demonstrate an association of the hazard in food or water with human health risk. However, the identification of a hazard may be controversial, especially for chemical risk assessments that depend on extrapolation from animal studies and may consider only a single chronic "end point."

Exposure Assessment (EA) is the second element that focuses on modeling the occurrence and level of hazards, and the potential ingestion of the hazards in the food, which cause or contribute to adverse outcomes. An EA would typically include an assessment of a hazard in a particular food for given scenarios that describe the production, processing, distribution, and preparation of the food. In addition, the EA must assess the eating habits of the target populations. This assessment is often accomplished by examining consumption surveys or large databases of surveys such as the USDA Continuing Survey of

Food Intake by Individuals. Often, however, there is difficulty in categorizing the foods that are surveyed so that they correspond to the types of foods that contain the hazards.

Chemical risk assessment must take into account the fact that a chemical in food can undergo changes during processing and preparation. Thus, to realistically model exposure, an understanding of food chemistry of the hazardous chemical is necessary. In microbiological risk assessment, the concern is possible continuous growth and decline of pathogens in the food. Methodologies to realistically model chemical changes and microbial growth and decline are still under development by risk assessors.

Stakeholders should know that many technical assumptions for EA are based on very limited data. Because a great deal of information is not known with certainty, simplifying assumptions are often made that could lead to an overstatement of the confidence of the results. For example, the major distinguishing feature for microbial pathogens is modeling to account for the dynamics of microbial growth and decline, termed predictive microbiology. However, at the time of this writing, EA models for microbial pathogens in foods have not explicitly distinguished strain variability, which can be large for some bacterial pathogens. Data are usually available for only a few strains or a cocktail or mixture of several strains, which may differ taxonomically and biologically from the hazard of interest. From the behavior of a few strains, inferences are made for all strains, without regard to population variability. Another example is that predictive microbiology models are designed to be "conservative" rather than unbiased. Reasons for bias include features of the experimental design such as the use of high levels of pure cultures of a cocktail or mixture of pathogen strains grown under optimal conditions in complete nutrient broth in the total absence of the competing microflora of foods. In reality, pathogen growth is influenced by many factors not explicitly accounted for in the models. Another emerging facet of EA, in which simplifying assumptions are made, is modeling the potential for person-to-person transmission in addition to dietary exposure for certain foodborne disease agents (Eisenberg et al., 1996).

Dose-Response Assessment (DRA), the third element of the NRC framework, involves modeling the relationship between the ingested dose of the hazard and the likelihood and severity of the adverse effect. Much of the work of dose-response modelers in chemical risk assessment involves analysis of data from animal studies. For microbial risk assessment animal studies are not often used, but the DRA depends primarily on data from a small set of controlled clinical studies in which human volunteers were administered the hazard, usually at high doses. In chemical risk assessment, mechanistic or genetic considerations could be applied that can contradict the results of animal studies (*www.epa.gov/oppsps1/fqpa*).

When extrapolating beyond the observed range of the data from clinical or animal studies to the low-dose region, the model form can have dramatic effects on the outcome (Coleman, 1998). Another issue with which dose-

response modelers must wrestle, particularly in the microbial area, is the development of surrogate dose-response models in the absence of data for the hazard of interest. Chemical risk assessors make inferences about chemicals for which no dose-response information is known (U.S. EPA and LogiChem, 1997) from chemicals with a similarity of chemical structures for which some information is known. However, in the microbial area, apparently, knowledge or information is not available for making such inferences. Questions about the structural aspects of host-pathogen interactions must be considered to determine plausible surrogates. For microbial risk assessors, selection of surrogate dose-response models will continue to be of interest as long as new pathogenic strains evolve and are recognized. Outputs of the dose-response model are the frequency and severity of human foodborne illness at a given exposure or ingested dose.

The complexity of predicting frequency or probability and severity of illness must be emphasized by risk assessors. Illness is a complex function of variability in all aspects of the epidemiological disease triangle of host, pathogen, and environment (matrix) effects and their interactions. A clear association between age of human hosts and frequency of illness for microbial hazards has emerged from epidemiological surveillance and outbreak investigations (CDC, 1998; Coleman, 1998; Terajima et al., 1999). However, these data are not an ideal proxy for age dependence in dose-response relationships because ingested doses are unknown. Pathogen strains are likely to vary in many aspects of growth, physiology, and both the presence and expression of virulence genes. An example of an environmental effect is that fat in foods appears to provide a protective environment for pathogens, enabling them to survive in inhospitable surroundings. A tremendous amount of controversy is associated with DRA.

Risk Characterization (RC), the fourth element of the NRC framework, begins with linking the output of the EA models with the DRA models to predict the frequency and severity of human illness (the consequence) for given scenarios. RC commonly relies on techniques such as Monte Carlo simulation. Principles of good practice for Monte Carlo simulation have been published to guide risk assessors in developing sound risk assessment models (Burmaster and Anderson, 1994). The major output of RC is a series of distributions of the frequency and severity of illness for the subpopulations of interest.

Often, risk assessors may estimate illness for certain subpopulations under a baseline (as is) scenario and with interventions or possible system failures. Such a process bridges risk assessment and risk management activities and might include developing the concept of comparative risk, the comparison of simulation results for the baseline (as is) and various potential mitigation scenarios most relevant to policy makers. This type of analysis provides information about the relative contribution of different interventions to risk reduction that is necessary to support policy making.

A key analytical aspect of RC is the performance of sensitivity and uncertainty analyses to determine what variables most strongly affect the uncertainty of the risk estimate. Another aspect of RC involves validating the model or

testing the predictive abilities of the model (Bowker, 1993). Standard statistical procedures such as goodness of fit testing and construction of confidence intervals for predictions can be used. However, because risk assessment models are often so complex, other procedures that are nonparametric are used for validation (Bowker, 1993). The most effective way of validating the model is comparing the estimates derived from the model with an independent source of data. The problem is that often there are questions concerning the validity of the independent source of data. For example, active surveillance data from the FoodNet study (USDA, 1998) provide some insight into the possible magnitude of the rates of illness from foodborne pathogens within and between the sentinel sites. However, a variety of difficulties exist in interpretation of these data.

Principles of appropriate analysis used in the RC, and more generally in the risk assessment, are given on pages 100–101 of an informative book, *Understanding Risk: Informing Decisions in a Democratic Society* (NRC, 1996). The principles are for the most part readily understood and include the following concepts: Analysis should be consistent with the state of the art; analysis should be checked for accuracy; assumptions should be clearly pointed out; and superfluous assumptions should be discarded. However, one standard or principle does create some difficulty, the principle that "Calculations are presented in such a form that they can be checked by others interested in verifying the results." There are two real problems associated with this principle. The first is that often the mathematical and statistical procedures used are so complex that, unless the computer programming is independently recreated, the results cannot be verified. In reality, verification of the analysis is just not possible for most interested parties. A second potential problem with this principle is that managers and risk assessors, in an attempt to adhere to this principle, may simplify procedures and adopt less than state-of-the-art methodologies, contradicting the first principle. Our preferred statement of the principle is that methodologies, including mathematical derivations and justification of statistical procedures, should be presented in a clear and *complete* fashion and in accordance with standard practices of the mathematical and statistical professions. Computer programs, in addition to reported results, should be made available to any interested party (USDA, 1998).

Developing Risk Communication

Risk assessment is highly technical and not without controversy. The communication of the results is difficult and decisions made as a result of a risk assessment could be controversial. As noted above, the 1983 NRC depiction did not include a risk communication component. Because of the complexities of a risk assessment, the uncertainty of the results, and the large stakes involved in the decisions, distrust may arise among the various stakeholders and risk analysis professionals.

The National Research Council (1996) addresses these and other problems

in an innovative manner. The concept of risk characterization is expanded to include more than the summary of mathematical models and statistical analyses associated with risk assessment, defined by the NRC "red book" (1983). By 1996, representatives of the NRC conceived of risk characterization as a decision-driven activity "to enhance practical understanding and to illuminate practical choices." Thus stakeholders, either directly or through surrogate representatives, should be involved with the risk assessment from the beginning. The expanded risk characterization process thus can incorporate social, behavioral, economic, and ethical aspects of risk. To make the risk characterization relevant to all parties, the NRC not only includes an analytical component of risk characterization, but adds what is termed a "deliberation" component (NRC, 1996). Thus, risk characterization is an "analytical-deliberative" process.

The new expanded definition (NRC, 1996) is as follows: "RC is a synthesis and summary of information about a potentially hazardous situation that addresses the needs and interests of decision makers and affected parties. RC is a prelude to decision making and depends upon an iterative analytical-deliberative process." Thus, risk characterization is no longer in the domain of risk assessment or is no longer in the hands of the sponsors or managers of the risk assessment. Rather, RC becomes a public or political process. In addition to the term "analytical-deliberative," the NRC also introduces the term "iterative." This term is meant to imply that the risk characterization is a give-and-take process between participants and can include an updating of the risk assessment. The above definition represents an all-inclusive process, and seems to imply an ongoing process.

Of particular interest to us in this chapter is the deliberative process as part of the risk characterization. Deliberation involves the exchange of ideas, opinions, reflections on others' opinions, and so forth. Deliberation is defined formally by the NRC (1996) to be "any formal or informal process for communication and for raising and collectively considering issues." The NRC states that the "deliberation frames the analysis and the analysis informs the deliberation" (NRC, 1996). Two phases of the deliberation are specifically identified. First, for a risk assessment, scenarios must be defined at the beginning of the process, consistent with our definition of risk being conditional on well-defined scenarios. All stakeholders should be involved in constructing the scenarios. The second phase is formulation of decisions from the results of the assessment. A very extensive discussion identifies and describes the principles and difficulties of the deliberative process (NRC, 1996).

Disagreement and controversy are inherent in a deliberative process (NRC, 1996). The NRC encourages organizations not to truncate the analytical-deliberative process but, on the other hand, not to delay needed actions under the guise of needing more analysis. In fact, the latter possibility represents a difficulty that needs to be dealt with from the beginning. The NRC gives examples of ongoing risk assessments, where ongoing monitoring might ensure that the assumptions and theories used in the risk assessment are valid and thus

the initial decisions are still valid. But often risk assessments are well-defined time-limited projects. The decision-driven processes that NRC advocates would imply the need for decision-matrix tables before the analysis begins. The decision-matrix tables, however, would not restrict possible decisions based on the results. In a practical sense, the risk assessment needs to have a clear demarcation point for decision making. To paraphrase Yogi Berra, it's not over until it's over, but once it's over, it's over. Decisions will be made, and the risk assessment may be updated or repeated years later.

This expanded concept of RC changes the managerial frameworks for risk analysis. We have labeled risk characterization with the initial letters "RC," which happen to be the same as those of risk communication. This dual acronym was not our oversight but was intended to make that point that risk communication is the essence of risk characterization.

Managerial Framework Revisited

The motivation for change, as described above, appears to focus on stakeholders who want to understand risk and to participate in the process of risk assessment. The consequence of the expanded concept of RC is to change the structure of risk analysis to include the stakeholders from the beginning.

The figure developed by the U.S. President's Commission on Risk Management (1996; Fig. 3.2) illustrates a framework for risk management that reflects this new concept. In this figure, the stakeholders are in the center and the risk management activities circle around them. This is meant to imply that stake-

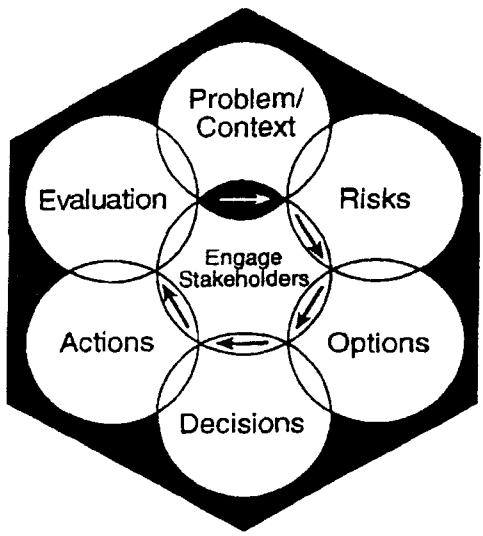

Figure 3.2. Framework for risk management (Presidential/Congressional Commission on Risk Assessment and Risk Management, 1996; *www.riskworld.com/Nreports/*).

holders are involved in each phase of the risk analysis. Such a concept places a tremendous burden on stakeholders to understand the process and the procedures of a risk assessment. The diagram depicts stakeholder input at the first stage, "problem context." In recent years, to implement this objective, U.S. agencies have commonly convened public meetings to introduce risk assessment projects and solicit data at the start of major risk assessments. The diagram also depicts additional processes ("risks," "options," "decisions," "actions," "evaluation"). Integrating stakeholders into these activities, particularly the "risks" and "options" activities, presents a challenge because of the highly technical nature of these areas. Some groups of stakeholders may lack the expertise to fully participate and the financial ability to hire risk analysis experts to provide input to these processes. The burden on U.S. regulators is to promote a fair and balanced process, even for those stakeholders who may be unable to afford to hire expert consultants to represent their interests. A consequence of this strategy is another point of tension or potential conflict and would impose a burden on the regulators to provide a fully independent and transparent risk assessment amenable to input.

Expansion of Risk Analysis

The expansion of the concept of RC to include deliberations, enhancing understanding, and implementing practical solutions, extends to risk analysis itself. The consequence of expanding RC is that risk analysis expands to include non-risk assessment procedures that would lead to an understanding of hazards and to practical solutions of managing them. The requirements for performing a complete risk assessment are sometimes not met, but yet solutions to problems are needed. Constraints of time, funding, expertise, and data available to support risk assessment modeling may not permit a full quantitative risk assessment. The data gaps could be so extensive that the credibility of a full quantitative risk assessment could be questioned.

There are other common approaches to evaluating hazards that, although not full risk assessments, use the tools of risk assessment. These procedures, which we refer to as "quasi-risk assessments," offer mangers practical solutions to problems and thus can fit under the expanded concept of risk analysis. Some of these "quasi-risk assessment" procedures are introduced below.

"Qualitative Risk Assessment"

The term "qualitative risk assessment" describes a process of ranking or categorizing hazards and risks that stops short of estimating risks and attendant uncertainties. This term is inconsistent with the definition of risk described herein. A "qualitative" risk assessment is incomplete because it lacks the calculations of likelihood of adverse consequences. Perhaps a new term such as "qualitative risk accounting" might be more useful to describe a legitimate process of ranking or categorizing risks that stops short of estimating risk

with attendant uncertainty but still has value in problem solving and decision-making. An HI would be performed, and parts of an EA and DRA would be addressed, without providing quantitative results (USDA, 1998). A complete RC as described by the NRC (1996) would not be possible for a "qualitative risk accounting."

The possible benefit of a quantitative risk assessment is that the sensitive variables that most strongly influence the risk could be identified and used for priority setting for a research agenda that might fill essential data gaps. Although a qualitative risk accounting would not include such a sensitivity analysis, a systematic discussion and ranking of hazards and risks can provide useful understanding and reasonable "guesstimates" of variables that might be influential for further study.

"Safety Assessment" and "Worst-Case Scenarios"

Another procedure, which has been termed "safety assessment" (Wilson, 1999), involves calculating "safe levels" of hazards for all in the population. Often the focus is on simplifying default assumptions typified by application of a series of 10-fold "safety factors," such as for inter- and intraspecies extrapolations and high- to low-dose extrapolations, rather than explicitly estimating "risk with attendant uncertainty." The safety factor approach has become a standard practice of government regulators in the U.S. and abroad for managing some chemical hazards. On the basis of these derived "safe levels," tolerances for chemical levels in food are established.

Another approach is based on establishing the "worst-case" level for a hazard for an identified amount of product, using information from surveys or epidemiological studies. Standards are established to ensure that the hazard associated with the worst case would be eliminated from the product with high probability. This approach assumes some knowledge of the "lowest" dose that would result in adverse consequences if ingested. Both of these approaches, although serving an immediate regulatory need, lack the quantification of risk that would be part of a risk assessment.

Other Modifications to the NRC Risk Assessment Framework

Since 1983, the NRC paradigm of risk assessment has been adapted by many risk scientists, including Covello and Merkhofer (1993); National Research Council (1993, 1994, 1996); International Life Sciences Institute (ILSI, 1996); Presidential/Congressional Commission on Risk Management (1996); FAO/WHO Consultation on Risk Management (1996); Kaplan (1997); Marks et al. (1998); Codex Committee on Food Hygiene (1998); FDA (1999); Rand and Zeeman (1998); NACMCF (1998); ICMSF (1998); and McNab (1998). Some suggest that different risk assessment frameworks might be helpful for different types of hazards (chemical, biological, and physical). Some may view the differences between the various proposed frameworks as merely semantic.

The NRC framework (1983) is applicable for quantitative risk assessment. However, as discussed above, the decision not to conduct a quantitative risk assessment, but to rely on a "quasi-risk assessment" may be triggered by the lack of relevant data for either exposure or dose-response assessments. One modification, suggested by the Codex Committee for Food Hygiene (1998), is the replacement of "dose-response assessment" with "hazard characterization," a more general term that emphasizes the value of qualitative approaches when dose-response data for the pathogen and food of interest do not exist for the populations at risk. In a similar vein, Covello and Merkhofer (1993) suggest replacement of "dose-response assessment" with "consequence assessment."

More substantive modifications have been proposed that reflect the need for greater interaction between research and policy areas. Covello and Merkhofer (1993) proposed considering "hazard identification" as a preliminary step before conducting a risk assessment rather than the first step in conducting a risk assessment. To enhance understanding for the stakeholders and to identify scenarios, the hazards must be identified before the calculations of risk. This approach is consistent with our definition of risk and the expanded concept of risk characterization discussed above.

Another deviation from the 1983 NRC four-element risk assessment framework actually predates that framework. An additional phase of modeling exposure termed "Release Assessment" originated in the mid-1970s under the Nuclear Regulatory Commission to simulate unintended releases of radiation by the nuclear power industry (Cohrssen and Covello, 1989). A body of work has accumulated in probabilistic risk assessment describing accidental releases of many other types of hazards. "Release assessment" could be appropriate for chemical spills in animal feeds or bacterial contamination in foods.

Selection of the managerial framework to structure the risk assessment process does not validate or invalidate the process. Of greater importance is that the analysis is based on the best available science and that key principles and guidelines such as those listed in Tables 3.1 and 3.2 are followed. The Codex Committee on Food Hygiene (1998) chose not to provide a methodological recipe for conducting a risk assessment but provided guidance that does not limit methodological approaches, thus encouraging use of the best available science.

REGULATORY, INDUSTRIAL, AND INTERNATIONAL IMPLICATIONS

Risk assessment, as described in the introduction of this chapter, is a structured, systematic process linking sound scientific research and policy. The outputs of a risk assessment, predictions for given scenarios of the risk of an adverse event with attendant uncertainty, would inform the risk manager, who has the responsibility of devising risk management strategies. One possible strategy for government risk managers is imposing regulations that require certain criteria or standards to be met. The justification for establishing stan-

dards is to protect the public health. However, the risk manager would consider other factors such as a cost-benefit analysis, in addition to the results of the risk assessment, that impact the decision about the appropriate level for standards to protect public health. Actually, setting regulatory standards is a risk management activity, which incorporates the stakeholders in structured dialogue through regulatory rulemaking. As such, the expanded concept of risk characterization has many similarities to regulatory activities. As discussed above, there is movement toward requiring standards defined in regulations to be supported by risk assessments. Assessments can be used to support regulations by comparing a "baseline" risk that exists when there are no regulatory requirements to the expected risk when there is compliance with the regulatory requirements.

As alluded to above, often the information and data necessary to conduct a full risk assessment are not available. However, for a variety of social, ethical, and political reasons, there is a compelling need to act. Thus agencies have defined regulatory standards using an assortment of procedures, including the ones described above, qualitative analysis, safety assessment, worst-case scenarios, and other practices, such as grandfathering prior procedures that appeared "safe" on the basis of experience over a long period of time. A possible consequence of applying these somewhat ad hoc procedures is the imposition of standards for exposure that are not directly linked to demonstrated reductions in public health risk. As food safety decisions become more risk based, risk assessments will replace these ad hoc but perhaps workable and useful procedures. A consequence is that the data, assumptions, and methodology supporting a risk assessment will be more carefully scrutinized. Risk assessment methodology will become more crucial as our society moves away from food systems designed simply to reduce exposure to hazards toward more risk-based systems designed specifically to protect public health.

Food Safety Standards

As part of their regulatory activities, agencies set food safety standards. A food safety standard is a description of a specified amount of product relating, in theoretical probabilistic terms, the distribution of levels of hazardous materials that would provide reasonable certainty of no harm to consumers. For example, in the food microbiology area, a food safety standard would specify, in theoretical probabilistic terms, the distribution of the number of pathogens in a finished food product (USDA, 1999) originating from a hypothetical "worst-case" product. In the chemical area, a food safety standard might specify that a process-average level of a hazard must be less than a specified value.

To determine "safety" standards based on science, one would need to know the dose-response relationships or the highest amount of hazardous agent that could be ingested by different human subpopulations in a given food matrix without adverse outcome. Information on the minimum "apparent infective dose" might be inferred from food microbiology data generated in outbreak

investigations of foodborne disease. True "infective dose" is dependent on many factors and is impossible to measure directly in humans and difficult to estimate. One true "infective dose" does not exist for the entire human population. Rather, infective doses depend on humans being in particular situations. In this sense, the infective dose depends on the particular scenario under consideration. For example, the infective doses for healthy adult consumers are expected to differ from the infective doses for the subpopulation of consumers with immune dysfunction or recent antibiotic administration (which reduces the protective effect of the indigenous GI tract microflora). Another example is that dose-response relationships may differ according to food matrix. Because of the enhanced ability of bacteria to survive in fatty matrices, the same doses in fatty foods might result in higher probabilities of illness than those for nonfatty foods. However, in the absence of knowledge about dose-response relationships for given scenarios, the food safety standards are established by some government agencies to reflect conservative estimates of "infective dose" for the hypothetically most susceptible individual based primarily on expert judgment. As more data become available, the standards would be adjusted. For example, the standard with respect to the presence of *E. coli* O157:H7 has become stricter because from recent outbreaks, it is thought that this pathogen may be highly virulent, and apparently, small ingested doses could cause illness and even death in susceptible subpopulations.

Risk Assessment and HACCP

Hazard Analysis and Critical Control Point (HACCP) programs are evolving as a risk management strategy in food production, processing, distribution, and preparation systems worldwide. HACCP programs involve the identification of critical control points (CCPs) of a process. A CCP is defined in the Code of Federal Regulations (Title 9, Chapter III, Part 417.1) as "a point, step, or procedure in the food process at which control can be applied, and as a result, a food safety hazard can be prevented, eliminated, or reduced to acceptable levels." The risk manager determines the acceptable level of safety such that consumption of the product is associated with reasonable certainty of no harm (safe or unadulterated). The USDA is embracing HACCP as a regulatory tool in an effort to properly place responsibilities and to provide flexibility in manufacturing procedures (USDA, 1996, 1999). Thus, under HACCP regulations, establishments are required to identify CCPs and establish process "control limits" for them. These "control limits" are used to evaluate the effectiveness of the processing, that is, whether the process is in control so that the product would be "safe." In this sense, HACCP appears to be an integration of risk management and process control.

Some similarities exist between the inputs for the first elements of risk assessment (hazard identification) and HACCP (hazard analysis). For example, hazard identification and hazard analysis might both consider data from epidemiological investigations that reveal risk factors, food vehicles, associations

with adverse health outcomes, the nature and severity of illness, and effects in sensitive subpopulations.

The result of the hazard analysis is a description of the hazardous agents, their levels, and how they might enter into the product. The goal of processing would be the control of the hazard for the final product, such that the final product would meet a food safety standard defined by governmental regulation. Once this is accomplished, the establishments would identify the CCPs of the process that would control the hazard and result in a product that meets the food safety standard, if the processing at these CCPs were controlled. To determine what "to be in control" means, the establishment needs to determine processing objectives or standards for the CCP and process control procedures for evaluating whether or not the processing objectives are being met.

As discussed above, risk assessment could be used in defining the food safety standard that would be used as an objective for designing an HACCP plan. The standard of "safe" under HACCP, however, may not be risk based. Rather, determining a "safe" product is often a subjective judgment based on historical practices, such as good agricultural or good manufacturing practices. These practices thus may become acceptable for good manufacturing and would be incorporated into the HACCP plan. Alternatively, the judgment of "safe" might be based on use of a "quasi-risk assessment" procedure such as one of those discussed above. A common approach in process design might be that simply *reducing exposure* is sufficient to provide a "safe" product. This approach might lead one to the opinion that occasional samples containing detectable levels of a hazard do not necessarily indicate that the product is unsafe. The consequence of this somewhat flawed logic could be that manufacturing practices may become acceptable that reduce exposure but still would not provide the lowest-risk product that could be obtained.

Under the HACCP regulatory philosophy, once a food safety standard is defined, establishments would be required to determine their own processing procedures to achieve the food safety standard. In reality, establishments may not be able to design processing procedures that guarantee a "safe" product. Thus, in addition to the requirement of a HACCP plan, U.S. agencies are defining acceptable "process performance" goals for selected control steps (USDA, 1999). The regulatory process performance goals assume only minimal procedural constraints. For example, a process performance goal for a thermal treatment control step would require that the process achieve a theoretical $x - \log_{10}$ relative reduction of certain pathogens on raw product that has not been temperature abused or has been handled according to some acceptable handling procedures before the control step. In this example, the government is performing a hazard identification and identifying the control step and processing goals for the control step. The process control procedures and control limits for ensuring that the process is achieving the process performance goal are still the responsibility of the establishment. In addition, the agencies provide compliance guidelines to assist the industry to achieve the process performance goal (USDA, 1999).

Risk assessment can illuminate the possible risks that could occur for particular manufacturing processes. However, risk assessments or other quasi-risk assessment procedures that are performed by government agencies usually estimate possible risk that reflects the product of the industry as a whole. We emphasize here that the calculation of risk in this application depends on the processing scenario that describes the handling or the processing of the product before the product reaches the control step and after the product leaves the control step. From such an assessment, a food safety standard and corresponding process performance goal are established for the control step. The process performance goal is defined such that, for some defined scenario, the product produced at the control step from a process satisfying the process performance goal would satisfy the food safety standard and thus be considered "safe." Thus establishments are required to design their processes for the specified control step, cognizant of handling of the product before and after, to satisfy the process performance goal.

However, it might be possible for an establishment to control its process with the use of certifications for incoming material or other means to produce a product that satisfies the food safety standard, even though their process at the specified control step might not meet the regulatory process performance goal. That is, an establishment might be able to more effectively control the process preceding and subsequent to the control step than the level of control assumed by the government for establishing the process performance goal. In addition, an establishment can develop particular knowledge of its product to design processes such that the final product satisfies the food safety standard, even if the process performance goal is not satisfied. Thus, manufacturers may be able to devise alternative process performance goals such that the final product would satisfy the required food safety standard (USDA, 1999).

A risk assessment that accurately models the processes, including storage, thermal, and cooling processes, would provide information to establishments that would help them define CCPs and processing goals for the CCPs. In general, a good risk assessment model would allow establishments to more effectively design processes based on food safety criteria. In fact, a complete risk assessment would provide estimates of risk and attendant uncertainty corresponding to different scenarios of processing, from which CCPs and control limits could be established (Zwietering and Hasting, 1997). The coevolution of risk assessment and HACCP will be crucial to development of risk-based standards that not only reduces exposure but reduces risk.

International Activities

Much attention has focused in the U.S. and in the international arena on definitions, principles, and guidelines for risk assessment (Codex Committee on Food Hygiene, 1998; ICMSF, 1998; McNab, 1998; NACMCF, 1998). Two leading international organizations in global food safety are the World Health Organization (WHO) and the Food and Agriculture Organization (FAO).

Both organizations participate in deliberations of the Codex Alimentarius Commission (CAC). The 163 member countries of the CAC contribute to the work of various committees, such as the Codex Committee on Food Additives and Contaminants (CCFAC) or the Joint FAO/WHO Expert Committee on Food Additives (JECFA), that develop international consensus documents for assessing and managing risk. The scientists convened by JECFA since 1956 have established Acceptable Daily Intakes (ADIs), Provisional Tolerable Weekly Intakes (PTWIs), and other end points for more than 700 chemical hazards in foods (Kaferstein, 1998). JECFA advises the CCFAC on the appropriate level for numerical standards for these chemical hazards. This advice may lead to approval by the CAC of Maximum Residue Limits (MRLs) or Maximum Limits (MLs) as internationally recognized standards for protection of public health (Kaferstein, 1998). The CAC has also adopted guidelines for radioactive hazards in foods (Kaferstein, 1998). The FAO/WHO are also developing an advisory body similar in function to JECFA that would address scientific issues involved in setting standards for microbiological hazards in foods in for international trade.

The U.S. or any other government may choose to impose standards for foods eaten by its consumers more or less protective than those standards approved by Codex (WHO, 1998). Especially where Codex limits do not exist for certain hazards, disputes may arise between countries that trade in a food commodity but impose different standards or levels of protection for their citizens. The World Trade Organization (WTO) is the body that arbitrates such international disputes (WHO, 1998). Article 5 of the Agreement on the Application of Sanitary and Phytosanitary Measures (SPS) states that sanitary measures to protect public health must be supported by a risk assessment that takes "into account risk assessment techniques developed by the relevant international organizations." Thus, on the international level, development of standardized procedures and risk assessment techniques continues to be important.

The Codex Committee on Food Hygiene (CCFH) is developing key documents relating to this issue of international food safety and microbial hazards. Documents have been prepared to address separate frameworks for risk assessment and risk management. The first document on risk assessment, the "Principles and Guidelines for the Conduct of Microbiological Risk Assessment" (CCFH, 1998), was prepared under an expedited process and was finalized less than 3 years after development of the original discussion paper. The principles from this document (CCFH, 1998) are listed in Table 3.1. A second document dealing with risk management principles was prepared from a FAO/WHO Consultation on Risk Management (1996). The principles from this document (FAO/WHO, 1996) are listed in Table 3.2. At present, a draft document based on the FAO/WHO Consultation on microbiological risk management (1996) is just entering the Codex process (Discussion Paper on Recommendations for the Management of Microbiological Hazards for Foods in International Trade, CX/FH 98/10, *www.fao.org/WAICENT/FAOINFO/ECONOMIC/ESN/codex/Reports*). The structure presented in these three

documents seem to us more consistent with the original NRC paradigm from 1983 in that the RC is defined strictly in the domain of risk assessment. Although these documents acknowledge the need for risk communication as part of risk management activity, they do not address in depth the interactive elements of risk analysis (assessment, management, and communication) described by the NRC (1996) and discussed in this chapter. Undoubtedly, future deliberations of the Codex Committees will address the tensions and interactions involved with risk analysis for both microbiological and chemical hazards.

Another recent development reflected in the Codex discussion paper on risk management is the notion of "Food Safety Objective" (FSO) (ICMSF, 1998) defined in Item 2.2.1.2 as "a statement based on a risk analysis process which expresses the level of hazard in a food that is tolerable in relation to an appropriate level of protection." However, this FSO definition does not represent a consensus position at the time of this writing. Further elaboration of the definition of terms in this definition and corresponding procedures to determine FSOs are needed. As discussed in this chapter, the application of risk analysis for establishing regulations and food safety goals is in its infancy. The openness of the analytical-deliberative process of risk analysis as discussed in this chapter is needed to develop solutions to address global food safety issues.

CURRENT AND FUTURE IMPLICATIONS

Many managerial frameworks are available to support risk analysis processes for chemical, biological, and physical hazards in food and water. The selection of any particular framework may be less important than commitment to the use of sound science in risk assessments and adherence to the principles and guidelines for risk analysis. For example, transparency of both risk assessment and risk management processes is essential for increasing the likelihood of a useful risk management strategy and for gaining public acceptance of the strategy. Complete documentation is critical to identify the points in the risk assessment at which policy decisions, assumptions, and extrapolations beyond the scientific data became inputs or constraints to the risk assessment model.

However, a crucial element needed to ensure effective risk analysis is an interested and active public. Risk analysis is ultimately a political process; the final responsibility for the quality of life in a society depends on a well-informed public. Thus this chapter has come full circle, in that the responsibility for ensuring safe food depends on individual commitment. The opening statement quoting Deuteronomy placed an obligation on every individual to take responsibility to remove hazards. If hazards were ignored, whether or not someone was injured, the individual was guilty of permitting a danger to exist. Each individual in society is obligated to become aware of and to participate in the deliberations about risk and its management. The rest of this book represents a modest beginning for this endeavor.

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INTERNET RESOURCES

www.foodsafety.gov

Gateway from the web to U.S. government food safety information, including links to U.S. Department of Agriculture, Food Safety & Inspection Service and the Office of Risk Assessment and Cost-Benefit Analysis; U.S. Environmental Protection Agency; U.S. Department of Health & Human Services, Food and Drug Administration and Centers for Disease Control and Prevention.

www.fsisusda.gov/OPHS/ophshome.htm

USDA, FSIS, Office of Public Health and Science web page that highlights two risk assessment projects, the first USDA farm-to-fork risk assessment, Salmonella enteritidis in shell eggs and egg products (preliminary pathways and data book; report; and model). The preliminary pathways and data book are also posted on this site from the ongoing project on farm-to-fork risk assessment for E. coli O157:H7 in beef.

www.jifsan.umd.edu

Joint Institute for Food Safety and Applied Nutrition (JIFSAN), established between the U.S. Food and Drug Administration (FDA) and the University of

Maryland (UM) in April 1996; includes information on jointly administered, multidisciplinary research and education programs and research of special interest to risk analysts and the Risk Assessment Consortium.

www.epa.gov/oppsps1/fqpa

Environmental Protection Agency, Office of Pesticide Programs; lists information on the Food Quality Protection Act of 1996, amended in 1998.

www.fao.org/WAICENT/FAOINFO/ECONOMIC/ESN/codex/codex.htm

Website for Joint FAO/WHO Codex Secretariat. The Codex Committee on Food Hygiene news, timetables, agendas and papers, reports, members, standards, information, rules and procedures can be accessed under Reports.

www.fao.org

Website of the Food and Agriculture Organization of the United Nations that includes statistical databases on agricultural products, production, and trade; nutrition; fisheries; forestry; food quality control; and links to other information.

www.sra.org

Website for the Society for Risk Analysis, premier international organization fostering collaborative development of multidisciplinary approaches and methodology for risk analysis. SRA Chapters in the U.S., Europe, and Japan sponsor meetings and workshops. The SRA journal, *Risk Analysis*, is a focal point for new developments in risk analysis for a wide range of disciplines.

www.riskworld.com

Website covering news and views on risk assessment and risk management.

www.foodprotection.org

Website for nonprofit association of food safety professionals. IAFP holds meetings and workshops and publishes the Journal of Food Protection.

www.asmusa.org

Website for the American Society for Microbiology, which holds meetings and workshops and publishes *www.who.int/fsf/index.htm* website for the World Health Organization, Programme of Food Safety and Food Aid. The site includes: aquaculture; health education in food safety; assessment of food technologies; monitoring chemical contaminants in food (GEMS/Food); and epidemiological surveillance of foodborne disease.

www.who.int/fsf/index.htm

Website for World Health Organization Food Safety Programme; lists pdf files for publications and documents and information on microbial risk assessment.

CHAPTER 4

DOSE-RESPONSE MODELING FOR MICROBIAL RISK

CHUCK HAAS

ROLE OF THE DOSE-RESPONSE RELATIONSHIP

In microbial risk assessment, the dose-response relationship is the function that connects the anticipated pattern of exposure to the expected level of adverse effect. In generic terms, the expected proportion of a population that will experience a risk of a particular outcome (p) is written as a function of the average dose (d) administered to that population, that is,

$$p = f(d) \tag{4.1}$$

Hence, the pattern of exposure must be characterized as an input, and the particular outcome or outcomes that are desired to be estimated must be stated. Whereas for some pathogens, dose-response information is available from human trials (i.e., volunteer subjects fed controlled levels of organisms), for other pathogens only animal data are available. Even if human feeding study data exist, the residual level of risk desired for public health protection is far below the lowest dose used, and hence a dose-response model must be relied upon to provide this extrapolation.

Single Exposure vs. Multiple Exposure

All currently known human or animal feeding trials have used single (bolus) exposures and monitored for subsequent adverse outcomes. In actual exposure scenarios, multiple exposures, for example at different meals or from different routes (food, water, contact, etc.). may occur. To apply dose-response models based on bolus doses to these latter scenarios it is necessary to make an assumption about how multiple exposures and doses may combine to produce

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an effect. At present, the default assumption used is one of statistical independence of multiple exposures (Haas, 1996). If $p_1, p_2, \ldots p_n$ represent risks from individual doses (such as individual days), the risk of one or more adverse outcomes from the joint exposure (p_t) is written as:

$$p_t = 1 - (1 - p_1)(1 - p_2)\ldots(1 - p_{n-1})(1 - p_n) \tag{4.2}$$

It is likely, however, that with further developments in the field of microbial dose-response assessment the framework for estimating joint risks from multiple exposures will evolve.

BACKGROUND INFORMATION AND HISTORICAL SIGNIFICANCE

Choice of Outcome vs. Disease Progression

A population exposed to an infectious agent will contain individuals who exhibit a progression of impacts. Infected individuals may be symptomatic or asymptomatic; a portion of the symptomatic (ill) individuals may then exhibit a spectrum of severities, with perhaps a small fraction of the outcomes being fatal. In using a dose-response model, it is important to focus on the outcome(s) of interest or to combine a model for infection as an outcome with additional data on disease progression probabilities as a function of dose. A detailed discussion is given by Haas, Rose et al. (1999).

In much microbial dose-response assessment, infection is used as an end point, because this represents a common point from which other outcomes stem. In addition, it has been argued that public health protection based on infection as an outcome provides some level of conservatism for protection of more sensitive subpopulations (Regli, Rose et al., 1991). Hence the discussion below will focus on dose-response modeling for infection as an end point.

SCIENTIFIC BASIS AND IMPLICATIONS

Processes in Onset of Infection

A dose-response model, if it is to have a mechanistic basis, should take into account several features of the process of infection. First, especially at low *average* doses administered to a population, there is heterogeneity in the actual number of organisms received by individual members. In other words, not all members receive actually identical doses. One or more organisms having been ingested, a birth-death process then occurs, in which organisms may survive to colonize and proliferate or may be extinguished from the host before proliferation. These two processes can be combined to yield dose-response relationships that are biologically founded (Armitage, Meynell et al., 1965; Williams, 1965a; Williams, 1965b; Haas, 1983; Haas, Rose et al., 1999).

Mechanistic Models

The mechanistic features of a dose-response model, as depicted above, can be captured in a straightforward relationship. From this general relationship, a number of specific dose-response models can be derived. Define the following:

1. The probability of ingesting precisely j organisms from an exposure in which the mean dose (perhaps the product of volume and density) is d is written as $P_1(j|d)$,
2. The probability of k organisms of the j ingested surviving to initiate an infectious process (the second step) is written as $P_2(k|j)$.
3. Infection occurs when at least some critical number of organisms survive to initiate infection. If this minimum number is denoted as $k_{\min}$ then the probability of infection (i.e., the fraction of subjects who are exposed to an average dose d who become infected) may be written as:

$$P_1(d) = \sum_{k=k_{\min}}^{\infty} \sum_{j=k}^{\infty} P_1(j|d) P_2(k|j) \tag{4.3}$$

It should be emphasized that the use of $k_{\min}$ in the precise sense of Eq. 4.3 does not correspond to the often-used term "minimal infectious dose" (Duncan and Edberg, 1995; Edberg, 1996). The latter term refers to the average dose administered, and most frequently really relates the average dose required to cause one-half of the subjects to experience a response; the term "median infectious dose" is preferred. If it is understood that $k_{\min}$ may not be a single number, but may in fact be a probability distribution, then Eq. 4.3, or a generalization of Eq. 4.3, is expected to be sufficiently broad to encompass all plausible dose-response models. By specifying functional forms for P_1 and P_2, as well as numerical values of $k_{\min}$, we can derive a number of specific useful dose-response relationships.

Exponential The simplest dose-response model that can be formulated assumes that the distribution of organisms between doses is random, namely, Poisson, that each organism has an independent and identical survival probability r (strictly, this is the probability that the organism survives to initiate an infectious focus), and that $k_{\min}$ equals one. From the Poisson assumption, we have:

Finally, with the assumption of $k_{\min} = 1$, this yields

$$P_1(d) = 1 - \exp(-rd) \tag{4.4}$$

Or this may equivalently be written as:

$$P_1(d) = 1 - \exp\left(-\frac{d}{k}\right)$$

This is the exponential dose-response relationship. It has one parameter, r (or k), that characterizes the process. The median infectious dose (N_{50}) can be given by:

$$N_{50} = \frac{\ln(0.5)}{-r} \tag{4.5}$$

The exponential dose-response relationship has the property of low-dose linearity. If $rd \ll 1$, then $\exp(-rd) \approx 1 - rd$, and Eq. 4.4 can be approximated as:

$$P_I(d) \approx rd, \quad \text{for } rd \ll 1 \tag{4.6}$$

Another property of this and other dose-response curves that we will examine is the slope of the curve at the median point ($P_I = 0.5$). Differentiation of Eq. 4.4 produces:

$$\frac{dP_I}{dd} = r \cdot \exp(-rd) \tag{4.7}$$

Because, at the median point, $\exp(-rd) = 0.5$ (see Eq. 4.4), this can also be written as:

$$\left.\frac{dP_I}{d(rd)}\right|_{P_I=0.5} = 0.5 \tag{4.8}$$

By similar analysis, the slope of a log-log plot at the median point for the exponential dose-response equation can be determined to be:

$$\left.\frac{d\ln(P_I)}{d\ln(d)}\right|_{P_I=0.5} = -\ln(0.5) = 0.69$$

Beta Poisson The exponential model assumes constancy of the pathogen-host survival probability (r). For some agents, and populations of human hosts, there may be variation in this success rate. Such variation may be due to diversity in human responses, diversity of pathogen competence, or both. This variation can be captured by allowing r to be governed by a probability distribution. This phenomenon of host variability was perhaps first invoked by Moran (1954). Armitage and Spicer (1956) appear to have been the first to characterize this variability by a beta distribution; however, computational limitations precluded the use of this model—beta Poisson and other tolerance distributions. Furomoto and Mickey (1967a; 1967b) appear to be the first to have used this model in the context of microbial dose-response relationships.

Under the above assumptions, the dose-response relationship can be expressed as a confluent hypergeometric function as follows:

$$P_I(d) = 1 - {}_1F_1(\alpha, \alpha + \beta, -d) \tag{4.9}$$

Properties of this function are given in standard references [Johnson, 1994 #1139]. Furomoto and Mickey (1967a; 1967b) derived the following approximation to equation (7–18):

$$P_I(d) = 1 - \left(1 + \frac{d}{\beta}\right)^{-\alpha} \tag{4.10}$$

It is convenient to rewrite Eq. 4.10 by redefining the parameters in terms of the median infectious dose. By solving, it can be determined that:

$$N_{50} = \frac{\beta}{2^{1/\alpha} - 1} \tag{4.11}$$

By rearranging Eq. 4.11 to solve for β, and substituting the result in Eq. 4.10, a reparameterized beta-Poisson model can be written in the following form:

$$P_I(d) = 1 - \left[1 + \frac{d}{N_{50}}(2^{1/\alpha} - 1)\right]^{-\alpha} \tag{4.12}$$

By differentiating Eq. 4.12 it is found that the slope at median dose is:

$$\left.\frac{dP_I}{d\left(\frac{d}{N_{50}}\right)}\right|_{P_I=0.5} = \frac{\alpha}{2}(1 - 2^{-1/\alpha}) \tag{4.13}$$

On log-log coordinates, the slope is:

$$\left.\frac{d\ln(P_I)}{d\ln(d)}\right|_{P_I=0.5} = \alpha(1 - 2^{-1/\alpha}) \tag{4.14}$$

Because α is non-negative, Eqs. 4.13 and 4.14 always yield slopes less than the respective exponential, Eqs. 4.8 and 4.9. In other words, the beta-Poisson model is shallower than the exponential model. This is shown in Figure 4.1, in which it is also shown that as α increases, the beta-Poisson model approaches the exponential model. Figure 4.1 (top) also shows that all models at sufficiently low doses yield a slope of 1—indicating linearity, on a log-log plot.

Empirical Models

A dose-response model is fundamentally of the same mathematical form as a cumulative probability distribution function (cdf) defined over the positive real line. Hence, any cdf can be explored as a dose-response function; however such

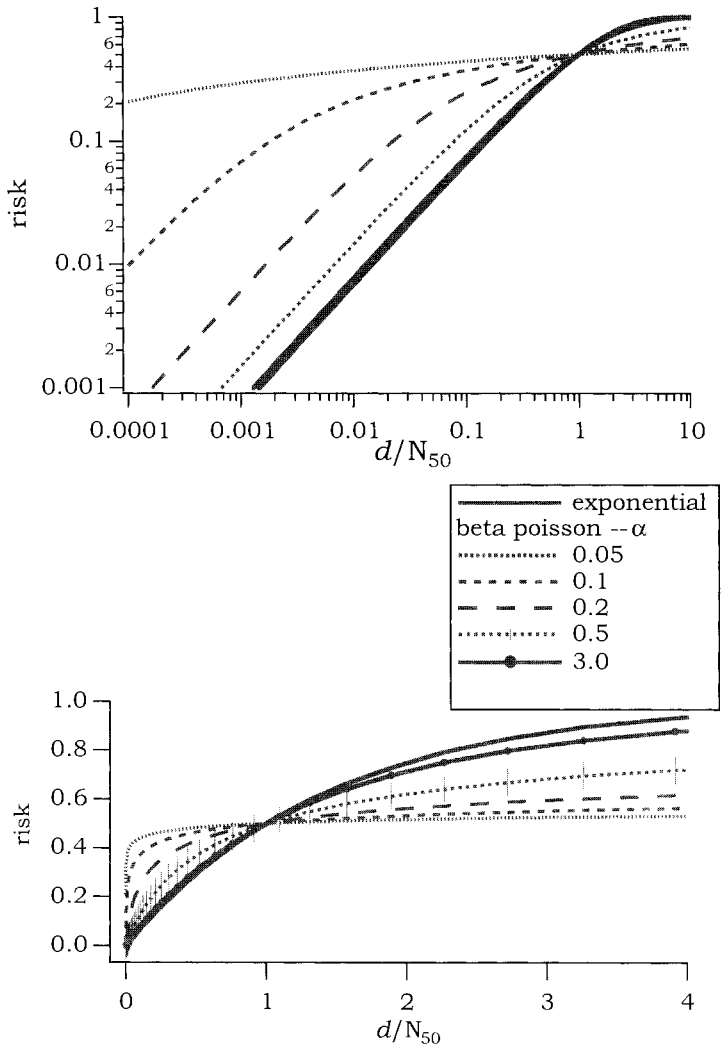

Figure 4.1. Effect of α on dose-response relationship.

empirical models may not have concordance with underlying biological bases of infection. Examples of such empirical dose-response functions are shown in Table 4.1.

Estimating Parameters

For a given data set, and a particular model, the problem of estimating the best fit dose-response parameters is one that can be approached by using maximum

TABLE 4.1. Empirical Dose-Response Functions

Model	Dose-Response Relationship (P_I)
Log-logistic	$\dfrac{1}{1+\exp[q_1 - q_2 \ln(d)]}$
Log-probit	$\Phi\left[\dfrac{1}{q_2}\ln\left(\dfrac{d}{q_1}\right)\right]$ where $\Phi(y) \equiv \dfrac{1}{\sqrt{2\pi}}\displaystyle\int_{-\infty}^{y} \exp\left(-\dfrac{x^2}{2}\right) dx$
Weibull	$1 - \exp(-q_1 d^{q_2})$

likelihood methods (Haas, Rose et al., 1999). This is a standard problem in risk assessment, which has been widely faced in chemical risk assessment (Crump, 1981) as well as microbial risk assessment. The estimation may be made using various computer programs, as well as in a spreadsheet environment (Haas, 1994).

Problem of Low-Dose Extrapolation

Different dose-response models may fit a single data set. For most data sets, particularly when human subjects are used, relatively few subjects per dose are tested, and the average doses used are fairly high (typically to produce an expected proportion of responses in excess of 10%). Under these conditions several different dose-response models may provide acceptable fits and may appear quite similar within the range of observation; however, when these models are used to extrapolate to lower doses they may provide dramatically different estimates of risk.

As an example of this, data for the infectivity of multiple nontyphoid strains of *Salmonella* fit to the beta-Poisson and the three empirical dose-response models in Table 4.1 are shown in Figure 4.2. The original data may be found in the report by Haas, Rose et al., (1999). The adequacy of the fit of the four models is about the same (the beta-Poisson model provided the best fit and is the only mechanistically consistent model tested). There is a large scatter to the experimental data (due to small numbers of subjects at most doses); however, the fit of the data to all of the models is fairly similar within the dose range tested (top panel of Fig. 4.2). However, when the best-fit parameters for the models are used to compute the dose-response relationship at low average dose, there is a dramatic spread between the models. As shown in the lower panel of Figure 4.2, at a mean dose of 10^{-2} organisms, there is a five order of magnitude range to the extrapolated risk between models. In this particular case, the beta-Poisson model estimates the lowest risk (at low dose), whereas the highest risk is estimated by the Weibull model—however, this relative ordering of models will be different for different data sets.

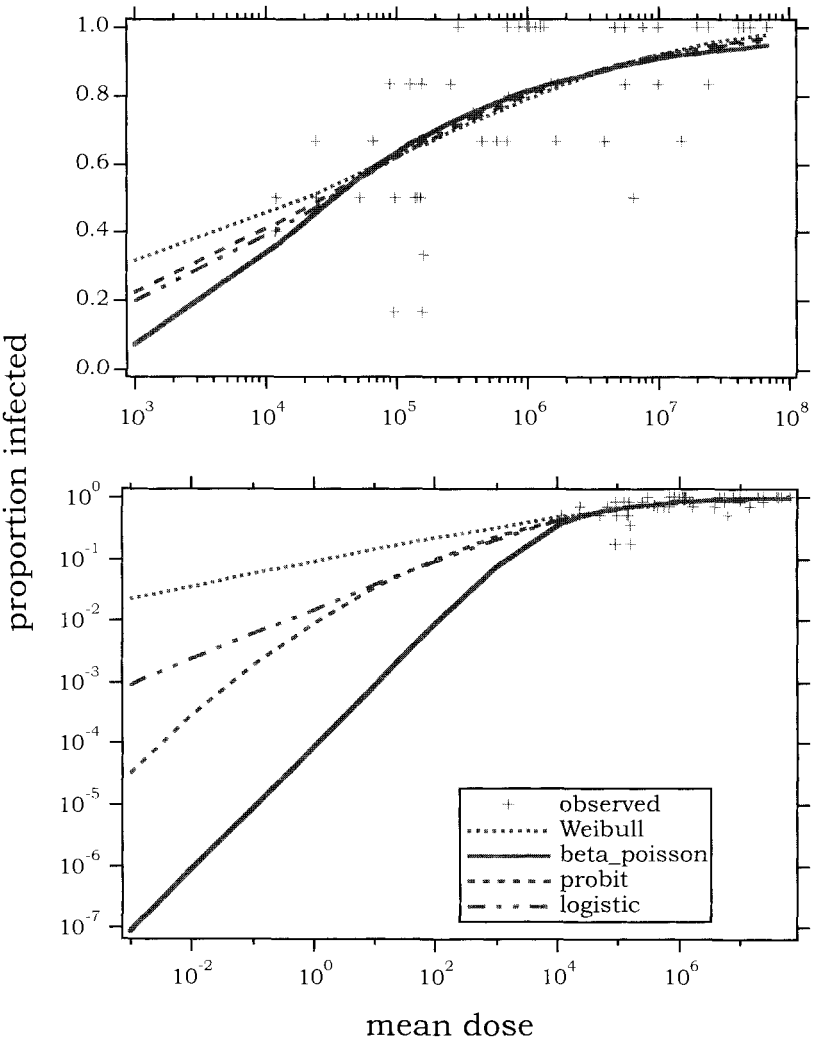

Figure 4.2. Fits of different dose-response models to nontyphoid *Salmonella*.

This problem (of differences between low-dose extrapolated risks) has arisen in the context of chemical risk assessment (for example, see Brown and Koziol, 1983). The use of a biologically plausible dose-response model may add reassurance that the extrapolation is reasonable. In the case of microbial risk assessment, low-dose extrapolation can be supported by validation against attack rates noted during outbreaks (this, in fact, is an avenue that is not realistically available in the case of chemical risk assessment). Hence, the validation of the estimated dose-response relationship forms an important step in confirming the adequacy of the chosen model.

REGULATORY, INDUSTRIAL, AND/OR INTERNATIONAL IMPLICATIONS

Validating Models

The task of validating a dose-response model involves obtaining information on actual human exposure during an outbreak (e.g., average number of organisms ingested) and information on the attack rate. The exposure information is then used to compute an expected attack rate based on the dose-response curve (computed from feeding studies), and the coherence with the measured attack rate is examined.

For example, the best-fit beta Poisson dose-response parameters for nontyphoid *Salmonella* are $\alpha = 0.3126$, $N_{50} = 2.36 \cdot 10^4$ (Fazil, 1996). In 1975, there was an interstate outbreak of human salmonellosis that was attributed to the ingestion of raw or undercooked hamburger. The outbreak occurred in Colorado, Maryland, and Florida (Fontaine et al., 1978). The outbreak in Florida occurred at the U.S. Naval Air Training Station in Orlando; as a result, it is of particular interest because of the presence of a "captive" audience.

For this portion of the outbreak, there were 21 reported cases due to *S. newport* between September 24, 1975 and October 11, 1975. Two of the cases were asymptomatic food handlers. Of the remaining 19 cases, 13 occurred over a four-day span from September 24 through September 28 (Fontaine et al., 1978). By personal communication with base personnel, it was ascertained that the potential exposed population consisted of 7,254 recruits who were fed at the galley.

On the basis of the attack information, the total attack rate was 0.00289 (= 21/7254). Assuming that the exposure occurred over a four-day period, the daily risk is computed (from Eq. 4.2) as $7.2 \cdot 10^{-4}$.

The analysis of the contaminated hamburger detected an MPN of 6–23 organisms per 100 g (Fontaine et al., 1978). The probable inoculum size according to Fontaine, et al. (1978), taking into consideration a 1- to 2-log reduction after freezing, would still place the infecting concentration between 60 and 2,300 organisms per 100 g. Cooking, even undercooking, would further reduce the number of organisms. *Salmonella newport* has a decimal reduction time at 140 F of approximately 1.5 min (Mitscherlich and Marth, 1984). If we assume the meat was undercooked as was described by Fontaine et al. (1978), this would still result in a 1- to 2-log reduction in the number of organisms. The probable inoculum size after cooking would thus be approximately 6–23 organisms per 100 g.

To complete the comparison it is necessary to determine the concentration of the organisms consumed in the hamburger. In 1975, the average hamburger consumption was 30.5 lb per year (American Meat Institute, 1994). The daily consumption can thus be estimated as 37.85 g. Therefore, the daily estimated ingestion of *Salmonella* during the outbreak is estimated as 2.3–8.7 organisms.

Note that this is almost four orders of magnitude below the lowest administered dose in the human feeding trials.

Using this estimate for dose, in conjunction with the best-fit parameters for the dose-response relationship, the expected daily risk is computed to be $2.5 \cdot 10^{-4}$. This is about 1/3 of the observed attack rate. Given the uncertainties in the epidemiological measurement (underreporting of cases, duration of exposure) and exposure assessment (measurement of *Salmonella* and estimation of consumption and losses from freezing and cooking), the expected attack rate and the observed attack rate are in concordance.

Available Dose-Response Parameters

To date, numerous dose-response parameters have been estimated for bacteria, viruses, and protozoa transmitted by the fecal-oral route. A number of these have been summarized by Haas, Rose et al. (1999).

CURRENT AND/OR FUTURE IMPLICATIONS

The field of microbial dose-response modeling remains an active and fertile one for future work. There are a number of areas in which progress is being and will be made.

It is likely that pathogens will emerge for which human dose-response information is unavailable and may not become available. In these cases there may be a necessity to rely upon animal models. In the case of *E. coli* O157:H7 (Haas et al., 2000) and *Listeria monocytogenes* (Haas, 1999), the use of animal data to make inferences with respect to human potency appears realistic. Further studies are needed with other organisms to gain experience with trans-species extrapolation for microbial risk assessment.

As noted above, the assumptions made for treating multiple exposures assume independent behavior. This must be critically examined, probably by using animal models for particular agents. Animal model studies for the assessment of changes in infectivity with host status (immune competency, nutrition, and age) are also needed.

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CHAPTER 5

EXPOSURE ASSESSMENT OF MICROBIAL FOOD HAZARDS

RICHARD C. WHITING

INTRODUCTION AND DEFINITION OF ISSUES

Exposure assessment, one of the four parts of risk assessment, is the determination of the expected consumption of a microbial pathogen or its toxic products. For viruses (*Hepatitis* and *Norwalk*) and protozoa (*Cryptosporidium* and *Cyclospora*), which cannot grow in a food, an exposure assessment is similar to chemical exposure assessments. A quantity of virus particles or protozoans is introduced into the food at some point in the farm-to-table process, and the concentration of the pathogen is reduced, for example, by dilution when combined with other food ingredients, removed by washing, or inactivated by heating. Some bacteria produce toxins that can also be modeled in a manner similar to chemical hazards.

Most microbial foodborne pathogens are infective. To cause illness, these microorganisms must survive the acidity of the stomach, attach to and colonize the intestinal tract, and then invade the cells of the intestinal wall or produce toxins that disrupt these cells. Some then proceed to cause systemic infection. The likelihood of infection or illness is related in a complex manner to the number of organisms ingested. This dose-response relationship depends on the characteristics of the pathogen, host, and food matrix. Evaluation of the effect of the pathogen on the host constitutes the hazard assessment (Coleman and Marks, 1998; Chapter 4).

The differentiating characteristic of microbial exposure assessments comes from the ability of bacteria in particular to grow in or on the foods during storage or to be killed during processing or preparation. The bacterial exposure assessment must typically consider thousandfold increases in population during one or several periods of storage. Thermal or other types of inactivation can result in millionfold reductions in bacterial populations within seconds or a few

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minutes. In foods in which growth is not permitted because of acidity or salt, the bacteria may survive for only a few hours or for extended periods of time (months). These orders of magnitude population changes affect the likelihood of illness when the food is consumed. Because of this potential for repeated increases or decreases in populations, exposure assessment is an extensive part of the bacterial risk assessment.

Currently, microbial hazards are considered to be acute and the result of a single exposure. Increasing attention is being given to the sequelae of various foodborne microorganisms (e.g., Guillain–Barré syndrome from *Campylobacter* or reactive arthritis from *Salmonella*), but insufficient information currently exists to model these conditions. Similarly, frequent exposure to low numbers of *Salmonellae* or *Listeria monocytogenes* may affect their infective dose, but conclusive evidence currently does not exist. The remainder of this chapter discusses methods to estimate changes in microbial numbers that can occur during the processing and storage of foods from raw ingredients to consumption and the uses of these estimates in risk assessments and HACCP plans.

BACKGROUND AND HISTORICAL SIGNIFICANCE

Modeling

Microorganisms are predictable, and their behavior can be described by mathematical relationships. This concept underlies the field of microbial modeling and risk assessment (Baranyi and Roberts, 1994). Although qualitative predictability was previously accepted and the microbiological techniques, models, and statistics were available before the mid-1980s, the advent of personal computers made quantitative treatment of microbiological data feasible. Models allow quantification of the interactions between multiple environmental factors and interpolation of combinations of factors not explicitly tested. A realization of the inability to conduct inoculated pack studies for every food and situation of interest, the need to provide quantitative scientific support for HACCP programs, the farm-to-table concept for food safety, the desire to allow industry more flexibility in designing food processes, and increasing international trade in foods have brought microbial modeling into prominence (McMeekin et al., 1993; Ross and McMeekin, 1994; Whiting, 1995).

Because of the complexity of biological processes and the need to enter easily measurable parameters into the models, microbial models for foods are usually descriptive rather than based on biological principles (mechanistic models). Models usually have environmental factors such as temperature, pH, and salt level as their variables, in contrast to fermentation models, which model growth or metabolite production in response to substrate levels.

The modeling process has three levels. The first (primary) level is an equation that describes the change in microbial numbers with time in a single, con-

stant environment (Whiting and Buchanan, 1993). The linear decline in the logarithm of the population with increasing heating times (the D value) and the exponential growth rate, μ, are examples of parameters from this level. These D or μ values are specific for a temperature, heating menstrum, strain of organism, and other environmental and physiological factors. The second level of modeling (secondary) describes how the parameter values of the first level change with a changing environment. The z value, for example, relates the change in the D value (time for inactivation) to the heating temperature. Because these equations are cumbersome to solve, the third modeling level (tertiary) consists of computer programs that store the equations, accept the desired input values, and calculate and display expected microbial behavior. This level may consist of simple spreadsheets containing an equation, extensive software packages such as the USDA Pathogen Modeling Program or UK Food Micromodel, expert systems, and risk assessment-simulation models (Buchanan, 1993; Whiting, 1995).

Microorganisms in a food can grow, survive, or be inactivated. To model an entire food process, ideally from raw ingredients to a consumer's table, a unit operations approach is taken. Each step is considered separately, and an appropriate growth, survival or inactivation model is applied to that step. Changing conditions may be broken into appropriately short intervals that can be considered as unchanging. Outputs from one step become the inputs for the next.

SCIENTIFIC BASIS AND IMPLICATIONS

Growth Models

Microbial growth consists of lag, exponential growth, and stationary phases. The most widely used primary model to describe growth is the Gompertz equation (Eq. 5.1):

$$N_t = N_0 + C \exp\{-\exp[-B(t - M)]\} \tag{5.1}$$

where N_t is the $\log_{10}$ of the cell population per ml at time t, N_0 is the initial $\log_{10}$ of the population per milliliter, C is the $\log_{10}$ increase in population per milliliter, B is a rate parameter, M is the time of the inflection point, and t is time. This sigmoidal equation was chosen because its asymmetric shape more closely resembles plots of microbial growth than other equations. Once the Gompertz equation has been fitted to the data to estimate the M and B terms, the traditional lag phase duration and exponential growth rate can be calculated as shown in Eqs. 5.2 and 5.3.

$$\text{Lag phase} = M - 1/B \tag{5.2}$$

$$\text{Exponential growth rate} = BC/e \tag{5.3}$$

The linear model (Buchanan et al., 1997) is another model to describe microbial growth (see Eqs. 5.4 and 5.5). It exhibits a lag phase representing the time when the cells are adapting to the new environment. The times for individual cells to adjust is described by a distribution with mean and variation. Once a cell completes the lag phase, it reproduces in an exponential manner.

$$N_t = N_0 \quad \text{If } t < t_l \tag{5.4}$$

$$N_t = N_0 + \mu(t - t_l) \quad \text{If } t > t_l \tag{5.5}$$

Where t_l is the lag phase duration and μ is the exponential growth rate (log units/h).

The curvature observed between the lag and growth phases is a cultural characteristic from the cumulative numbers of daughter cells as the inoculum cells end their lag phases, not an accelerating growth rate by individual cells. Most of the cells in a growing culture are the daughters of the first cells to make the lag to growth phase transition.

The Baranyi model (Eq. 5.6) modified the lag phase to account for the adjustment to a new environment (Baranyi and Roberts, 1994):

$$\ln N_t = \ln N_0 + \mu_{max} A_n(t) - \ln\{1 + [\exp(\mu_{max} A_n(t) - 1)]/\exp(A)\} \tag{5.6}$$

where μ_{max} is the maximum specific growth rate and $A_n(t)$ is the adjustment function, whose value depends on a cell's physiological state and its adaptation to the new environment. Its value is initially small for large changes and increases to 1.0 when the cells are in the exponential growth phase.

How these primary level parameter values change over a range of environmental conditions (temperature, pH) can then be described by the secondary level model. Multiple regression equations are flexible and can be used with many environmental factors, such as nitrite and undissociated acid concentrations. Confidence intervals can be calculated for the estimate from the regression equation.

The square root or Ratkowski model (McMeekin et al., 1993; Ross and McMeekin, 1994) is another secondary level model based on the observation that the square root of the growth rate is proportional to the temperature in the range below the optimum growth temperature. One version of the model (Eq. 5.7) accounts for the decreasing rate of growth as the temperature increases above the optimum:

$$\sqrt{\mu} = b(T - T_{min})\{1 - \exp[c(T - T_{max})]\} \tag{5.7}$$

where T_{min} and T_{max} are the temperatures where the growth rate extrapolates to zero and b and c are parameter values specific for the microorganism and environment. The model has also been extended to include pH and water activity as shown in Eq. 5.8:

$$\sqrt{\mu} = b(T - T_{min})\sqrt{(aw - aw_{min})}\sqrt{(pH - pH_{min})} \quad (5.8)$$

where aw_{min} and pH_{min} are the extrapolated lower values of water activity and pH, respectively, where microorganism growth is zero.

The duration of the lag phase can also be modeled by taking its reciprocal to convert it to a rate term and using the square root model or a pseudo-Arrhenius format as shown in Eq. 5.9:

$$\ln(1/lag) = a_0 + a_1/T + a_2/T^2 + a_3 aw \quad (5.9)$$

where a_0 to a_3 are parameters specific for the microorganism and environment.

Another approach uses an individual factor (γ) for each environmental factor (van Gerwen and Zwietering, 1998; Eq. 5.10):

$$\mu = \mu_{opt}\gamma(T)\gamma(pH)\gamma(aw) \quad (5.10)$$

where μ_{opt} is the optimal growth rate, and $\gamma(X)$ are dimensionless gamma parameters for each environmental factor as shown below:

$$\gamma(T) = [(T - T_{min})/(T_{opt} - T_{min})]^2$$

$$\gamma(pH) = (pH - pH_{min})(pH_{max} - pH)/(pH_{opt} - pH_{min})(pH_{max} - pH_{opt})$$

$$\gamma(aw) = (aw - aw_{min})/(1 - aw_{min})$$

The optimal growth rate, μ_{opt}, represents the maximum growth rate, and the various γ values are multiplied to estimate the reduction in growth rate that their respective environmental conditions impose. This is a flexible approach for secondary level modeling and can easily accommodate additional factors. At this time, comparisons between these three approaches to secondary level modeling have not been made.

The USDA Pathogen Modeling Program (Buchanan, 1993) is an example of tertiary level modeling. The growth models utilize the Gompertz and regression equations. This spreadsheet-based software conveniently allows users to choose the organism of interest, input the environmental values and determine the predicted lag times and generation times, or observe a graph of the growth. This program can be obtained without cost via the Internet at the USDA Eastern Regional Research Center's home page (*http://www.arserrc.gov*).

The lag phase duration predicted by most growth models is based on cells first grown to the early stationary phase in favorable environments and then transferred to the designated environment. Recent research has shown that the previous environment, and stage of growth, affect the length of time for cells to adjust to a new environment and resume growth (Whiting and Bagi, 2002). Cells in the exponential growth phase adapt to the new environment most rapidly, whereas stationary and starved cells need more time and desiccated cells need the most time to adapt. Cells transferred with little temperature change,

or transferred to warm temperatures, have shorter lag times than cells that were grown at warm temperatures and transferred to low temperatures. In many food processing situations, the mass of the food and insulating effect of the packaging slows the rate of temperature change and the microorganisms continuously adjust to the changing temperatures without going into a lag phase.

Inactivation Models

Thermal death models are the most frequently applied inactivation models, but other mechanisms of microbial killing are also modeled. Irradiation, pulsed electrical fields, and ultrahigh pressure are all amenable to modeling. The classic thermal death model was developed for retorted foods in the 1920s and applied to many pasteurization and nonthermal processes and has been successfully used by the canning industry to calculate inactivation times for spores of *Clostridium botulinum*. The decrease in the log number of surviving organisms is assumed to be linear with treatment time. The D value is the time for one log unit of inactivation (90%) at a specific temperature and other conditions (Eq. 5.11; N_0 and N_t are the cell populations at time zero and time t). The z value is the slope of the linear change in the logarithm of the D value with heating temperature (Eq. 5.12; T is temperature).

$$\log_{10} N_t = \log_{10} N_0 - t/D \tag{5.11}$$

$$\log_{10}(D_1/D_2) = z(\mathrm{T}_2 - \mathrm{T}_1) \tag{5.12}$$

However, thermal inaction was shown to be nonlinear in some circumstances, particularly for pasteurization temperatures. An exponentially damped model allows for curvature.

$$\log_{10}(N/N_t) = -kt \exp(-\lambda t) \tag{5.13}$$

Where λ is the damping coefficient whose value depends on the microorganism, environment, and temperature.

Another explanation for this behavior is that the culture contains cells having a range of D values (Peleg and Cole, 1998). As the more easily killed cells (lower D values) are removed from the culture by heating, the increasing slope represents the more resistant (higher D value) cells. A population dynamics theory includes a combination of first-order (linear) processes for rapid inactivation of lower heat-resistant spores, activation of survivors to a heat-sensitive state, and subsequent inactivation (Rodriguez et al., 1992). The interaction of different rate parameters for these steps results in nonlinear survival curves.

Linearity in thermal inactivation has been assumed when designing thermal and other lethal processing operations. The desired inactivation of microorganisms in a food extends below population levels that can be detected by experimentation, forcing extrapolation from inactivation data at high inocula. Should research conclusively demonstrate situations of nonlinear inactiva-

tion, inactivation calculations (modeling) will become more complex. Future modeling will also need to account for cells that have adapted to high growth temperatures, low pH, or high-salt environments. These cells are frequently observed to have enhanced thermal survival over unadapted cells.

Survival Models

Survival models are applied to microorganisms in environments that do not permit growth, but where the microorganisms remain alive for times ranging from hours to months (Whiting, 1995). Examples include refrigerated foods and semi-preserved foods, having low water activity, high acidity, or high salt levels, such as refrigerated fresh orange juice (low temperature and pH), yogurt (low temperature and pH, lactate ion), and salami (low pH and water activity, lactate, salt). Inactivation and survival modeling are similar; inactivation is a more active rather than passive process, and the time period is generally seconds and minutes instead of days to months. Plots for primary level data may show a linear decline comparable to plots for thermal inactivation. They may also show lag or shoulder periods in which all of the microorganisms survive before the linear decline begins. The linear model is shown in Eq. 5.14:

$$\begin{aligned} N_t &= N_0 \quad T < t_1 \\ N_t &= N_0 + a(t - t_1) \quad T > t_1 \end{aligned} \tag{5.14}$$

where a is the slope and equals $-1/D$, and t_1 is the shoulder period.

More complex two-phase behavior with a longer-lived subpopulation is occasionally observed. The logistic model with a shoulder and one declining slope is shown in Eq. 5.15:

$$\log(M_t/M_0) = \log[1 + \exp(-kt_1)] - \log\{1 + \exp[k(t - t_1)]\} \tag{5.15}$$

The model can be expanded to include a resistant subpopulation. Factors that control inactivation, particularly the survival period, are not well understood. The physiological state of the microorganisms may play an important role in determining the length of time they can survive before inactivation starts (shoulder period).

Model Limitations

A model is a compromise between the situation of possessing sufficient complexity to include all the factors that affect microbial behavior and the need to keep the model simple with factors that can be readily known by the user. The appropriateness and accuracy of a given model may vary with the specific application. Most of the current models were developed in broth cultures. Experience has shown that growth in a food corresponds closely to growth in broth if the broth and food temperature, pH, and salt levels are equivalent.

However, if a food has another factor that limits microbial growth, such as high lactate concentrations or low water activities from other humectants, the model may not be appropriate for making predictions for that food. Models estimate values within the ranges of the factors used in the development of the model. Extrapolating beyond the range of the data may lead to erroneous estimates, especially for the empirical models. Comparing the behavior of a pathogen in a specific food of interest under a few conditions is essential before fully trusting a model's predictions for use in that food.

Usually models are made of cocktails containing three to six bacterial strains. Studies show that different strains of the same pathogen vary greatly in survival and thermal inactivation times and also in growth parameters. The ratio of the standard deviation to the mean for the thermal inactivation D values of 17 strains of *Salmonella enteritidis* was 0.26 at 57.2°C and 0.28 at 60°C (Shah et al., 1991). This means that to include 95% of the strains, the two-standard deviation range is from ~50% to 150% of the mean. How strains used in the model compare with the possible strains that may be present in a food is usually unknown. With a cocktail, essentially the fastest-growing or longest-surviving organism or strain is modeled, and the modeler hopes the selected cocktail includes a strain representing the fastest growing or hardiest likely to be present in a food. However, models based on cocktails do not provide information on variations between strains. The confidence intervals represent that of the regression equation and modeling process, not the variation that would be encountered between strains likely to be present in a food.

Most models do not consider the influence of the natural spoilage flora on pathogen behavior. Lactic acid-producing flora can reduce the pH, and many microbial species produce bacteriocins that inhibit growth of other species. The extent that the relatively low levels of natural flora on high-quality foods affect the low levels of pathogens that usually occur in a contaminated food is not well understood.

Deterministic versus Probabilistic Models

The models described above are determinative or point estimate models. They calculate the mean number of microorganisms expected under specified conditions. As the conditions for growth become less favorable, however, the growth rate decreases and the variation about the mean rate increases. In addition, at the extremes of the unfavorable conditions, the likelihood of growth also decreases. If a series of identical tubes are incubated at decreasing temperatures, the tubes at the favorable temperatures will all show growth. At lower temperatures some tubes will not have growth, even after extended incubation times. Eventually, as the temperature decreases toward the minimal growth temperature, only a few tubes in a set will have growth. To fully characterize the expected growth in the low-temperature range or other extreme condition, both a growth rate and a probability of growth model are needed. In addition to the environmental factors, the probability of growth is strongly dependent

on the number of cells present. An aliquot containing high numbers of spores would be more likely to have growth eventually than an aliquot with only a few spores. This situation was explored in time-to-turbidity models for *C. botulinum* (Whiting and Oriente, 1997) and growth-no growth boundary models (Ratkowsky and Ross, 1995).

REGULATORY, INDUSTRIAL, AND INTERNATIONAL IMPLICATIONS

Process Modeling and Risk Assessment

To model a series of processing steps or changing environmental conditions, a food process can be separated into a series of unit operations and the appropriate model can be used for each step. A deterministic process model for a frozen ground meat patty was presented by Zwietering and Hastings (1997). The process has 16 individual operations and includes the initial contamination of both the meat and spice mixture. The model provides for rework (defective patties are collected and added back to the beginning of the process) and dead spaces in the equipment where meat can reside for a long period of time and bacterial growth can occur before the meat falls back into the product flow. The model shows the expected microbial population at the end of the process and indicates which steps allow growth. With this information, the food technologist can change the processing parameters, such as microbial quality of the spices or temperature, and estimate the change in microbial numbers at the end of the process. With information on the occurrence of a pathogen in the raw ingredients and designation of the food safety objective (the frequency and level of pathogen determined to be acceptable in the product), the process can be designed to yield an acceptable product. A similar model estimates the increase in *Bacillus cereus* cells during the production of vacuum-packed cooked potatoes (van Gerwen and Zwietering, 1998).

Risk Assessment

Microbial risk assessments follow several paradigms of hazard identification, exposure assessment, hazard characterization (or dose-response), and risk characterization (ICMFS, 1998; NACMCF, 1998; Chapter 3). For process modeling of a food system the flow is typically the number and frequency of organisms in the raw ingredients (Marks and Coleman, 1998), linking unit operations with growth, survival or inactivation models, consumption data, and the impact on public health (Coleman and Marks, 1998).

Variation and Uncertainty, Simulation Modeling

The deterministic meat patty and cooked potatoes process models calculate single values for each step in the process with singular input parameter values.

This approach omits the inherent variation and uncertainty in both process inputs and model outputs (Vose, 1998). Variation refers to the real differences that occur about a parameter, for example, different strains of a microorganism have different growth rates and D values. Each strain could be characterized, but it is unknown which strain may be present in a food at a given time; therefore, a single growth rate or D value cannot fully describe what may happen in the future. Likewise, when thermal processes reduce the level of a pathogen to a few or less per package, their occurrence in a particular package is typically dependent on binomial and Poisson distributions. Variation can be reduced by redesign of the process or equipment; better control of the oven temperature would reduce the variation in thermal inactivation of microorganisms in the food.

Uncertainty refers to our lack of knowledge. More precise or extensive measurement and monitoring can reduce this uncertainty. Estimates for the length of time an egg is in a retail store or the degree of *Salmonella* inactivation during home cooking of an egg would be examples with high uncertainty. In practice, both variation and uncertainty are present in most parameters in microbial models.

Because of variation and uncertainty, each parameter has a distribution of values that it might achieve in any specific instance. This distribution can be described by a variety of functions such as normal, log normal, exponential, beta, or triangle and the appropriate parameter values that describe that distribution, that is, mean and standard deviation. Distributions frequently are skewed, with more of the occurrences toward one end than the other. Distributions also may be described by a frequency graph that simply summarizes experimental data.

Each parameter input value in each unit operation, such as temperature, time, pH of food, and microbial growth rate, has a distribution. Monte Carlo simulation is a computational tool to calculate a model with multiple distributions. The simulation will pick a value for each distribution, calculate each model, and proceed stepwise through the entire process operation (Cassin et al., 1998b). The simulation model repeats the process calculation many times. Each iteration will pick a value from the input distributions. These distributions will tend to cluster about the mean value but will also reflect the range in outcomes likely to occur as a result of the shapes and ranges of the various input distributions. The outputs from the simulations will be distributions instead of single values. A simulation model can indicate which parameters contribute to the absolute value of the output value and which input distributions contribute to the output distributions. Input distributions can easily be changed, the simulations repeated, and the resulting changes in outputs determined.

Several dynamic models for food processes have been reported in the literature. *Salmonella enteritidis* in pasteurized liquid eggs (Whiting and Buchanan, 1997), shell egg processing, storage, and preparation (FSIS, 1998), *E. coli* O157:H7 in ground beef (Cassin et al., 1998a), *Salmonella* in poultry (Oscar,

1998) and chicken products (Brown et al., 1998), and the presence of *L. monocytogenes* in cheese made from unpasteurized milk (Bemrah et al., 1998) are the first examples of process models intended to provide understanding of how various parameters interact to affect food safety.

HACCP

A HACCP plan is a form of process and risk control (Buchanan and Whiting, 1998). Traditional HACCP plans do not quantify the influence of multiple control points and their variations or attempt to link a critical control point to a measurable impact on public health. Each critical control point is usually evaluated separately from the other processing steps and critical control points.

The risk assessment provides the underlying support for a HACCP plan by quantitatively determining the degree of control an entire process and each individual process operation contributes to the safety of the food (Buchanan and Whiting, 1998; Serra et al., 1999). Establishing an *acceptable* or *tolerable level of risk* for a food is a social and value decision, not a scientific decision. The tolerable level of risk is not necessarily constant for different pathogens or foods. The severity of disease (*Listeria* vs. *Salmonella*), the susceptibility of various subpopulations (children for *E. coli* O157:H7), and established customs (raw oysters, sunny-side up fried eggs) affect the level of risk that is acceptable to the consumer. The dose-response relationship can establish the amount and frequency of pathogen consumption that achieves a tolerable level of risk (ICMSF, 1998). This amount and frequency is termed the *food safety objective*. The risk assessment, in consultation with risk management, will evaluate the entire process from raw ingredients to consumption and establish a series of process steps that meet the food safety objective. The risk managers will then select the specific process to be used, also taking into consideration quality, cost, and feasibility (Morales and McDowell, 1998). The selected process risk assessment specifies what each step will achieve, for example, 7 $\log_{10}$ units of inactivation or less than 1 $\log_{10}$ unit growth. These are termed *performance criteria*. Similar to the entire process, there may be multiple means to achieve a specific performance criterion. Many time-temperature combinations, for example, can result in the 7 $\log_{10}$ units of inactivation. The selection of the specific combination will again be based on quality, cost, engineering, and other criteria. The specific combination selected is termed the *process criteria* and becomes the critical control points. Thus the exposure assessment tied to an accepted food safety objective provides the mechanism to create a HACCP plan. Even without designating an acceptable level of risk, the exposure assessment can determine the equivalence of different processes. This principle of equivalence and the use of risk assessment to compare the safety of different food processes will only become more important in national and international food trade (ICMSF, 1998; Lupien and Kenny, 1998).

CURRENT AND FUTURE IMPLICATIONS

Advances in microbial modeling concepts and an increasing number of research studies that report data in a modeled format are making quantitative microbial processing modeling more feasible by providing the individual modeling components for the unit operations. There remains a need for scientific studies to describe the variation about a parameter in addition to reporting the parameter's mean.

The risk assessment will increasingly be used to provide the underlying support for a company's HACCP plan. The risk assessment approach will be used by regulators to change from the classic regulatory approach of specifying specific time-temperature combinations for pasteurization, for example, to performance standards. This will give industry greater freedom in optimizing the safety and quality of products and facilitating adoption of new technologies for microbial inactivation such as high pressure, pulsed electrical fields, UV, and intense light. The U.S. FDA in 1998 specified that nonthermally pasteurized juice manufacturers must design a process that achieves a cumulative 5 $\log_{10}$ inactivation in *E. coli* O157:H7 to avoid a safety warning label. The specific process steps and critical control points are chosen by each manufacturer. A complete risk-based regulatory approach would specify the food safety objective, and industry would be responsible for demonstrating that the entire processing system meets that objective. Adoption of this risk-based HACCP system will require public acceptance of the risk paradigm and consensus on the acceptable level of risk and food safety objective.

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INTERNET RESOURCES

http://www.arserrc.gov/mfs/pathogen.htm
Web site to download the most recent version of the USDA Pathogen Modeling Program.

CHAPTER 6

EXPOSURE AND DOSE-RESPONSE MODELING FOR FOOD CHEMICAL RISK ASSESSMENT

CARL K. WINTER

INTRODUCTION AND DEFINITION OF ISSUES

Chemicals present in food may pose potential health risks to consumers in cases where consumer exposure to the chemicals reaches levels considered to be of health concern. The determination of acceptable exposure levels and the estimation of potential exposure to chemicals in food are the primary components of food chemical risk assessment. Regulatory decisions concerning the continued or prospective use of chemicals that may enter the food supply are heavily influenced by the results of risk assessments. Risk assessments also form the basis for discussions among food and agricultural groups and consumer and environmental organizations concerning the adequacy of existing regulations of food chemicals.

The contemporary practice of food chemical risk assessment is quite complicated and often controversial. Numerous assumptions are frequently required to be made in both the determination of exposure and the determination of acceptable levels of exposure (Winter and Francis, 1997). These assumptions are frequently derived from legislative mandate and/or regulatory agency policy and often lack a strong scientific basis. The use of differing sets of assumptions on exposure or acceptable levels may lead to widely divergent estimates of risk that frequently are disseminated in the public arena (Winter, 1992). Significant improvements are needed to refine the accuracy of food chemical risk assessments, and many of the present trends to improve the process are discussed in this chapter.

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BACKGROUND AND HISTORICAL SIGNIFICANCE

Although some form of risk assessment has assisted regulatory agencies in making decisions about chemicals in food since the early 1900s, the field of chemical risk assessment is still in its infancy and is evolving rapidly. The first comprehensive guidelines for performing chemical risk assessments in the U.S. were published in 1983 (NRC, 1983). These guidelines separated the process of risk assessment into four components: 1) hazard identification, 2) dose response evaluation, 3) exposure assessment, and 4) risk characterization. Several improvements in the risk assessment process have been made since this report was published, but it still forms the basis for contemporary risk assessment approaches for food chemicals such as pesticide residues, food additives, naturally occurring toxins, hormones, antibiotics, environmental contaminants, and even novel products derived from food biotechnology applications.

Advances in food chemical safety risk assessment have frequently involved pesticide residues in foods. In 1993, a report of the National Research Council (NRC, 1993) suggested many improvements to the risk assessment policies used by the U.S. Environmental Protection Agency (EPA) to determine the acceptability of residues of pesticides in the food supply. This report recommended, among other things, that the EPA consider the potential susceptibility of infants and children to pesticide residues and also the exposure of the population to water and residential sources of pesticides in addition to dietary sources. The report also recommended that risk assessments be made for families of toxicologically related pesticides that cause their effects through a common mechanism of action rather than on a chemical-by-chemical basis.

Many of these recommendations were incorporated into law when President Clinton signed the Food Quality Protection Act (FQPA) of 1996. This law prescribed risk assessment approaches to be used by the EPA. Major provisions of the law included the so-called "10x factor" requiring the EPA to consider whether to apply up to a 10-fold additional uncertainty factor to provide greater protection for infants and children, the "aggregate exposure" provision requiring exposure to be calculated from food, water, and residential exposure, and the "cumulative exposure" provision to determine risks for families of chemicals whose members share a common mode of toxicological action. Ironically, the FQPA did not arise from documented cases of excessive exposure to pesticide residues but rather as a legislative "fix" of the anachronistic 1958 Delaney Clause that, based on recent legal decisions, called for elimination of many uses of pesticides on statutory grounds instead of health risks (Winter, 1993).

The FQPA provisions present significant new challenges to the scientific community and will help shape the processes by which the risks from all types of chemicals in food, including pesticide residues, will be determined.

SCIENTIFIC BASIS AND IMPLICATIONS

Exposure Modeling

The estimation of exposure to food chemicals requires an understanding of both the amount of chemical present in food and the amount of food consumed. The basic algorithm for food chemical exposure can be represented as follows:

$$\text{Exposure} = \text{Food Consumption} \times \text{Residue Level}$$

In the case of a chemical that may be present on more than one food commodity, the estimated exposure would represent the summation of all the individual commodity exposures.

Deterministic Exposure Modeling

Historically, exposures have frequently been calculated with a "deterministic" approach that assigns finite values to both the food consumption and residue levels to calculate a "point" estimate of exposure. As an example, a deterministic exposure estimate for pesticide A on commodity X would require knowledge of the residue level of pesticide A and the food consumption of commodity X. Frequently, with a prudent method unlikely to underestimate exposure, the level of pesticide A might be chosen to represent a maximum legal or maximum detected level rather than a more typical value. Food consumption of commodity X could be chosen to represent the per capita mean consumption or might be chosen to represent a higher level such as the upper 95th percentile of consumption. The choices of residue and food consumption levels are often, although not always, exaggerations of typical values and frequently lead to calculations of worst-case or unrealistic exposures (Archibald and Winter, 1989). Such deterministic approaches are valuable in cases in which the worst-case exposure estimates are still considered to be well within acceptable levels because refinements to improve the accuracy of the exposure assessments would not be necessary. Deterministic approaches also allow for the use of refinements such as substituting "anticipated" residues for maximum legal residues; such an approach may often drive exposure estimates below the levels of concern. Unfortunately, worst-case exposure scenarios are often communicated without reference to the potential degree of exaggeration and as such may lead to an exaggerated perception of the degree of risk (Winter, 1994).

In practice, deterministic approaches to predict long-term (chronic) exposure to pesticides in food tend to use more realistic estimates (i.e., average residue, median per capita daily consumption) than those approaches predicting short-term (acute) exposure (i.e., maximum legal or detected residue, upper 95th or upper 99th percentile consumption).

The preferred method for calculating chronic exposure is still to use a deterministic approach. For the estimation of acute exposures, however, deterministic approaches are frequently being replaced with "probabilistic" approaches that take advantage of improvements in our computational capabilities and are far more data intensive than deterministic methods.

Probabilistic Exposure Modeling

In the real world, neither residue level nor food consumption data exist as single values but are more appropriately depicted as distributions (Petersen, 2000). Monitoring of pesticide X on commodity A, for example, would likely demonstrate that the majority of samples contain little or no detectable residue of pesticide X while a lower percentage would show moderate levels and an even lower percentage would indicate high residue levels (Fig. 6.1). A similarly shaped distribution curve might be envisioned for the daily consumption level of commodity A; on most days, the commodity might not even be consumed, and moderate consumption of the commodity is more likely than a high level of consumption (Fig. 6.2).

Probabilistic approaches utilize our current computational capabilities to combine all of the data in the residue distribution with the food consumption data to develop a distribution of daily exposure (Fig. 6.3). This type of approach is frequently called a Monte Carlo simulation model, although probabilistic approaches may be conducted in a variety of different methods utilizing varying types of data, algorithms, and assumptions (Petersen, 2000).

In the simplest case for estimating acute exposure from a single pesticide on a single commodity, a Monte Carlo analysis would randomly select a residue

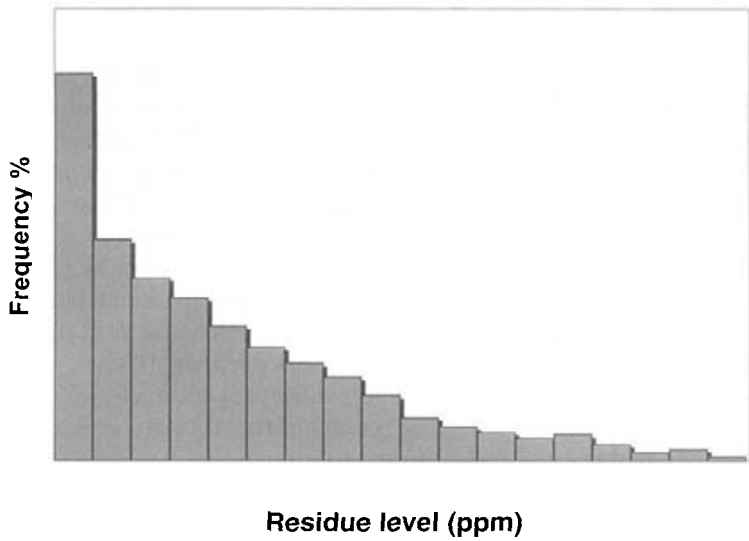

Figure 6.1. Food residue distribution.

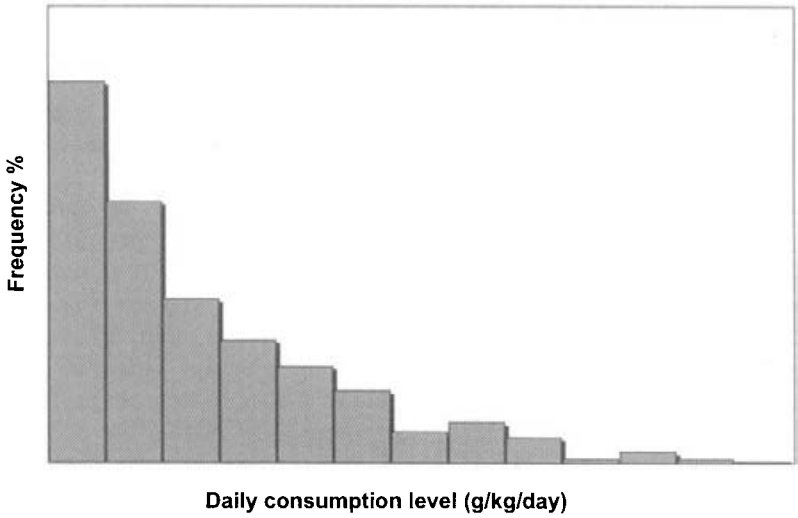

Figure 6.2. Food consumption distribution.

level value and a food consumption level value from the available residue and food consumption data sets and multiply them together to yield an exposure level. This process would be repeated for a determined number of events (often thousands or tens of thousands), and the corresponding exposure levels would be combined to yield a distribution of daily exposures.

Probabilistic approaches utilize all of the data in both the residue and food consumption data sets rather than the single point estimates that are used in

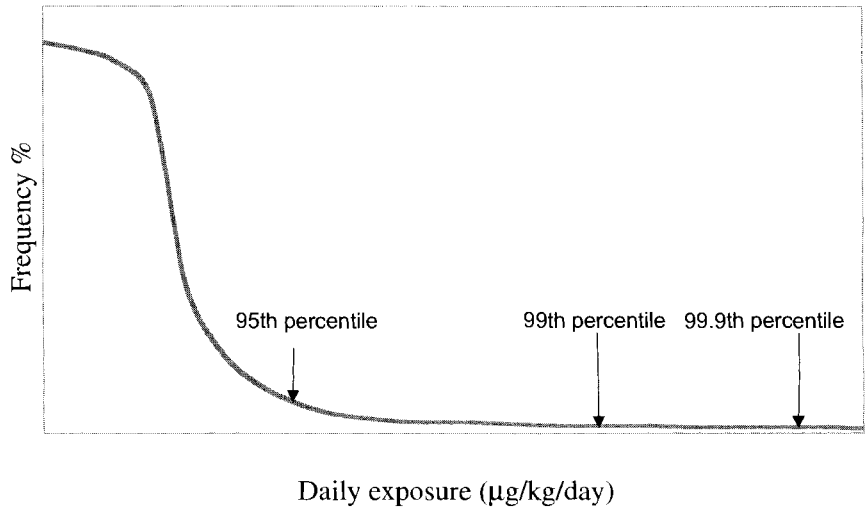

Figure 6.3. Probabilistic exposure distribution.

deterministic approaches. The corresponding distributions of exposure from the probabilistic approaches provide much more information than the exposure point estimates of the deterministic approaches. With a probabilistic approach, it is possible to estimate the median daily exposure level as well as levels corresponding to upper percentiles such as the 95th, 99th, or 99.9th percentiles (Fig. 6.3).

Although the results of acute probabilistic approaches may be significantly more useful than those obtained from deterministic methods, they also require far greater interpretation. In the case of the FQPA, the EPA is required to ensure that the levels of pesticides resulting in consumer exposure from dietary, water, and residential sources represent a "reasonable certainty of no harm." Under prior conventions, if an exposure point estimate generated from a deterministic approach were found to be below a level of toxicologically based concern such as a reference dose or acceptable daily intake, the criterion of "reasonable certainty of no harm" would likely be met. The situation is more complicated in the case of an exposure distribution developed from probabilistic methods because a science policy decision as to the desired level of population protection is required.

The current EPA approach calls for the "reasonable certainty of no harm" determination to apply if exposure to a pesticide at the 99.9th percentile for a population subgroup, as estimated by probabilistic analysis, is less than an accepted level of toxicological concern derived from the results of toxicology studies of the pesticide (EPA, 2000a). In cases where exposure at the 99.9th percentile exceeds this level, the EPA would generally conduct a sensitivity analysis to determine whether particular factors that serve to "drive" the exposure at the high end of the exposure distribution, such as high residue and/or high consumption levels, are unusual and might represent artifacts of the data sets.

The accuracy of exposure estimates at the 99.9th percentile of exposure has frequently been questioned. A comprehensive paper by Chaisson et al. (1999) assesses the consequences of bias, error, and uncertainty in the upper percentiles of exposure distributions. The focus of the paper is on food consumption issues, and the authors contend that sample data invariably contain errors that bias the higher percentiles of exposure in a manner that overestimates, for example, the true 99.9th percentile. One source of error is the inaccuracy of dietary intake surveys that rely on interviews of participants to qualitatively and quantitatively recall their food consumption patterns over selected periods of time. Errors may also arise from insufficient sample sizes, improper weighing of sample data, and reliance on subpopulation data rather than population data to characterize the population. The authors recommend that risk assessments should be performed with the broadest population base in the analysis and that the choice of the "point of regulation," or highest percentile that is not dominated by overestimation bias and error, should be used.

Consumption estimates for specific foods should not be considered independently of consumption estimates for other foods because, in reality, high con-

sumption of a particular commodity on a given day might be compensated by little or no consumption of other commodities. If consumption of commodities is considered to be independent, this raises the unrealistic potential for consumption of relatively high amounts of several food items on a given day that might significantly exaggerate exposures at the upper percentiles.

The quality and availability of pesticide residue data also influence the accuracy of the upper percentiles of exposure developed through probabilistic approaches.

Pesticide residue samples are often taken as composite samples of commodities that represent several individual servings of the commodities. Research has demonstrated that single-serving size subsamples of the composite samples may be quite variable and raises the possibility that an individual consuming a single serving of the commodity might be exposed to a residue level significantly different than that of the composite sample or of other single-serving subsamples. Andersson (2000), for example, reported that variability factors of 600, corresponding to the ratio of maximum to minimum residues found in related Swedish subsamples, were found for the insecticides methamidophos in peppers and monocrotophos in grapes. In another study, Harris (2000) indicated that the maximum levels of organophosphate insecticides in individual carrot roots could vary up to levels 25 times greater than those observed for composite samples and results from one subsample of plums showed residues present at 34 times the levels determined for the composite sample. It is clear that such residue variability issues may significantly impact the exposure findings for the upper percentile levels of exposure.

The cumulative risk provision of the FQPA requires assessment of all individual members of classes of pesticides possessing a common toxicological mechanism of action. Many of the individual members of a particular toxicologically related class of pesticides may serve as substitutes or alternatives for each other; this means that their potential to be used in combination on the same commodity unit is quite remote. If residues of specific pesticides are considered to be independent of residues of substitute pesticides, the mathematical probability of their co-occurrence on the food item could lead to an exaggeration of their actual probability of co-occurrence. Compounding this issue is the fact that some composite samples include individual food items that that may have received different pesticide treatments than other food items in the composite sampling. As an example, the Agricultural Marketing Service of the U.S. Department of Agriculture (USDA) provided comparisons between results of composite and single-serving analyses of pears obtained from its Pesticide Data Program (USDA, 2000). Composite pear samples indicated that as many as eight different pesticides (insecticides, herbicides, and fungicides) were detected while 36.4% of the samples contained residues of two pesticides, 18.1% contained residues of three, and 10.1% contained residues of four. In contrast, the maximum number of residues detected from single-serving samples was three (0.9%) and residues of two pesticides were detected only 19.5% of the time. Reliance on the composite samples could thus result in an exaggerated proba-

bility of co-occurrence of toxicologically related pesticides on single-serving amounts of specific commodities and could therefore exaggerate estimates at the upper percentiles of exposure for cumulative risk assessments.

Dose-Response Modeling

After the hazard identification step in risk assessment, a dose response evaluation is performed. This evaluation enables the relationships between the amount of human exposure to the chemical and the probability of adverse effects to be established.

Dose-response models vary based on the type of toxicological hazard that is being considered. Models evaluating the dose-response relationship for chemical carcinogens commonly assume that no threshold dose exists and that all levels of exposure to carcinogens provide at least some finite mathematical risk (Winter and Francis, 1997). For most noncarcinogenic effects, it is assumed that a threshold dose exists at low exposure levels, rendering the potential risks at these low levels of exposure to be considered as insignificant.

The evaluation of risks from chemical carcinogens in the diet is important, but the methods used for such evaluation, including deterministic exposure estimation and mathematical models to predict risks at low levels of exposure, are not receiving the current level of scientific and regulatory focus that exists for the probabilistic monitoring and dose-response evaluation for acute, noncancer effects.

For noncancer hazards, it is usually believed that adverse health effects will not be observed until a minimum, or threshold, level of exposure is attained. This toxicity threshold tends to be theoretical and is practical only in relation to the effects that occur just above and just below the threshold dose. Toxicology studies are frequently conducted to identify the lowest dose level above the threshold at which adverse effects are noted (the lowest observed adverse effect level, or LOAEL) and the highest dose at which no adverse effects are noted (the no observed adverse effect level, or NOAEL). Limitations in the number of dose levels used in toxicology studies and statistical and biological limitations make it difficult to determine just how closely the LOAEL or NOAEL may approximate the "true" threshold; in the interest of prudence, the NOAEL is generally considered as a conservative estimate of the toxicity threshold (Winter and Francis, 1997).

NOAEL values can be determined for a variety of different toxicology end points and may vary dramatically among the different animal species tested. In most cases, the most sensitive toxicological effects (those occurring at the lowest levels of exposure in the most sensitive species) are considered and the corresponding NOAEL is selected.

It should be understood that NOAEL values are developed from toxicology studies using small homogeneous groups of laboratory animals and, as such, may not adequately represent toxicity thresholds for large and nonhomogeneous human populations. In recognition of this fact, uncertainty fac-

tors (also commonly known as safety factors) are used to guide the animal-to-human extrapolation and to consider human variability. The most common uncertainty factor is 100 and is rationalized to provide a 10-fold uncertainty factor for the animal-to-human extrapolation (this assumes that humans may be 10 times more sensitive than the most sensitive animals studied) multiplied by an additional 10-fold uncertainty factor to account for human response variability (this assumes that some humans may be 10 times more sensitive than the "average" humans). In practice, overall uncertainty factors may range from 1 to 10,000 and the ultimate choice of uncertainty factors is influenced by the availability of human data, the quality of the animal toxicology data, and the nature, severity, and chronicity of the toxicological effect in question.

By dividing the NOAEL by the uncertainty factor chosen, it is possible to develop an estimate for the lowest level of toxicological concern for the chemical. Historically, this has been termed the acceptable daily intake (ADI) and is expressed as the amount of chemical exposure per amount of body weight per day. More recently, the EPA has replaced the ADI terminology with an analogous term, the reference dose, or RfD. This removes the inference of "acceptability" that may be plagued by the connotation of a nonscientific value judgment. In many parts of the world outside the U.S., the ADI terminology is still commonly used. For the purposes of this chapter, further references will be made to reference doses rather than to acceptable daily intakes.

Acute reference doses

The estimates of dietary risks posed by pesticide residues in food have typically focused on long-term (chronic) toxicity and have relied on deterministic methods to calculate exposure. A common approach used to assess chronic risks has been to assume that consumption of food items that may contain the pesticide in question is represented by the average daily intakes of the food items for a 70-year period and that the residue level point estimates frequently represent the maximum allowable residues on the food items or anticipated residues based on more realistic assumptions. The exposure estimate derived from this deterministic approach is compared with the chronic RfD to determine whether the exposure is sufficient to merit toxicological concern.

Acute risk assessments using deterministic methods take a similar approach but may use an upper percentile of food consumption rather than the average level and may consider the maximum detected residues or maximum allowable residues rather than the average anticipated residues. In the case of both chronic and acute risk assessments, however, the exposure estimates are frequently compared with the chronic RfD to determine the acceptability of the levels of exposure.

The development of probabilistic methods of exposure assessment, made possible by our improved computational capabilities and the regulatory requirements of the FQPA, may significantly limit the future use of deterministic methods to estimate acute dietary exposure to pesticides. Probabilistic methods may demonstrate instances in which exposure of a population subgroup at the

upper end of the exposure distribution curve, such as the 99.9th percentile, may exceed the chronic RfD even though deterministic approaches might demonstrate that the point exposure estimate is at levels below the RfD. In such cases, regulatory actions may be taken to limit exposure even though the prior deterministic estimates of exposure suggested no cause for further regulation.

To improve the accuracy of acute dietary risk assessments for chemicals in food, it is critical that appropriate toxicological studies are used to determine an appropriate acute RfD. Unfortunately, toxicology studies used to determine RfDs have traditionally been conducted for chronic (lifetime) or repeated shorter-term dosing (28–90 days). Comparing single-day estimates of exposure with RfDs developed from longer exposure scenarios may exaggerate the probability of acute risks. This is particularly important in cases in which the pharmacokinetic factors such as absorption, distribution, biotransformation, and excretion of a chemical are known and demonstrate that continuous repeated exposure to the chemical may lead to greater concentrations of the chemical at the toxicity target site over time compared with a single-exposure scenario. Toxicological databases normally do contain the results of single dosing studies, but such studies typically involve high doses of the chemical and focus on animal lethality rather than determination of toxicity thresholds. Relatively few single dosing studies exist for pesticides that presently allow for determination of the acute NOAEL and subsequent acute RfD, and those that do exist frequently involve insufficient numbers and ranges of dose levels to accurately determine acute NOAELs.

A relatively recent regulatory decision made by the EPA demonstrates the need for accurate acute RfDs in the assessment of acute dietary risk. In August of 1999, the EPA severely limited the uses of the organophosphate insecticide methyl parathion, citing excessive dietary risk to infants and children (EPA, 1999). Preliminary assessments of methyl parathion dietary risk relied on an acute NOAEL considered to be as low as any used for organophosphate insecticides. This NOAEL was determined from a toxicological study containing a 300-fold difference between the LOAEL dose of 7.5 mg/kg/day and the NOAEL dose of 0.025 mg/kg/day, suggesting that the "true" NOAEL would be anywhere from 0.025 to 7.5 mg/kg/day and was more likely to be closer to the LOAEL based on toxicity comparisons of methyl parathion with other organophosphate insecticides, many of which are considered to be far more toxic than methyl parathion. The EPA's reliance on this exaggeratedly low NOAEL also led consumer (Consumers Union) and environmental (Environmental Working Group) organizations to perform their own risk assessments for methyl parathion in early 1999 that alleged that hundreds of thousands of U.S. children were routinely exposed to excessive levels of methyl parathion in their food (Wiles et al., 1999: Groth et al., 1999). These organizations demanded that the EPA take actions to restrict methyl parathion use.

The EPA's regulations were announced in early August 1999, immediately before an FQPA statutory deadline. Interestingly, eight days *after* announcing the decision, the EPA made available its revised methyl parathion risk assess-

ment for public comment. In the revised risk assessment, the EPA recognized the limitations of the toxicology study it had previously relied on to determine the acute NOAEL, and modified its acute NOAEL based on the results of a *one-year* repeated-dosing study in rats to 0.11 mg/kg/day. The EPA also acknowledged receipt of a new methyl parathion single-dosing study that indicated a NOAEL of 1 mg/kg/day. If this more accurate NOAEL were used to determine the acute RfD, the exposures at the upper 99.9th percentile for all population subgroups would have been below the acute RfD and no regulatory action would have been deemed necessary based on the methyl parathion dietary risk assessment. The curious timing of the regulatory decision (8 days before the public release of the revised risk assessment and immediately before FQPA statutory deadlines) suggests that political factors as well as scientific limitations influenced the regulatory decision (Winter, 2000). Subsequent revisions of the regulatory decision or the risk estimates with the most recent methyl parathion toxicology study seem unlikely.

In recognition of the potential inaccuracies that may arise when comparing single-day exposure estimates with RfDs derived from repeated-dosing studies, the Codex Committee on Pesticide Residues is developing guidelines for conduct and assessment of short-term toxicology studies used to derive appropriate acute RfDs (Herrman, 2000). Issues considered by this committee include how to determine which pesticides require acute RfDs, what the toxicological requirements to establish an acute RfD are, and what uncertainty factors are appropriate.

Infant and child susceptibility—the 10x factor

One of the most controversial provisions of the FQPA is the so-called "10x factor" that requires consideration of the potentially greater susceptibility of infants and children to pesticides. According to Section 408(b)(2)(C)(ii)(II) of FQPA:

> In the case of threshold effects, for purposes of clause (ii)(I) an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children. Notwithstanding such requirement for an additional margin of safety, the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children.

The call for an additional uncertainty (safety) factor in the FQPA was derived from the National Research Council report (NRC, 1993) that investigated science and policy issues concerning pesticides in the diets of infants and children. The report concluded that current toxicology testing protocols might not be sufficient to address issues concerning toxicity and biotransformation of pesticides at early stages of development. A key recommendation of the report was that, because specific periods of infant vulnerability may exist during

postnatal development, an uncertainty factor of up to 10-fold should be considered when either data exist to suggest evidence of greater postnatal developmental toxicity or data concerning child susceptibility are incomplete. Thus, in the cases in which data may be incomplete, there should be a presumption of greater toxicity to infants and children.

At the same time, the report also concluded that age-dependent differences in chemical lethality were usually less than one order of magnitude and usually varied no more than two- to threefold. Another finding of the report was that infants may be more sensitive to some chemicals at high doses than adults but may also be less sensitive to others.

Bruckner (1999), who served as a NRC committee member, maintains that the existing 10-fold interspecies uncertainty factor provides adequate protection of infants and children. A similar position is taken by Renwick et al. (1999), who argue that the use of the additional 10-fold factor for infants and children is not generally justified based on the existing usual 100-fold uncertainty factor used for the animal-to-human and the human-to-sensitive human extrapolations. Under certain circumstances, however, they contend that the 10x factor may be appropriate. These include cases in which 1) reproductive and developmental toxicity data are not available, 2) testing methods for assessing reproductive and developmental toxicity are inadequate, or 3) effects on neonatal and/or young animals are irreversible and severe.

The NRC report also indicated that there might be little difference in age-related human toxicological responses to chemicals after 6 months of age. In practice, the FQPA 10x factor is applied equally to infants and to children up to 12 years of age, even though it may be argued that the major toxicological differences would primarily affect only the infants. In the EPA's revised risk assessment for methyl parathion, which utilized the additional 10x factor in addition to the usual 100-fold uncertainty factor that covers inter- and intraspecies variability, the population subgroup experiencing the greatest exposure was to children ages 1–6 (0.969 μg/kg/day at the 99.9th percentile). This exposure represented 8.8 times more exposure than was deemed acceptable (EPA, 1999). Elimination of the additional 10x factor for children ages 1–6 would result in acceptable levels of exposure at the 99.9th percentile. For infants, however, maintaining the 10x factor resulted in exposure (0.415 μg/kg/day at the 99.9th percentile) that was 3.8 times greater than the level considered acceptable.

Dose response considerations for cumulative risk assessments

The FQPA requires that risk assessments for pesticide residues be based on "available information concerning the cumulative effects on infants and children of such residues and other substances that have a common mechanism of toxicity." This provision of the FQPA is derived from the NRC report finding that children may be exposed to residues of multiple pesticide residues that possess a common toxic effect and that such simultaneous exposures should be accounted for.

The NRC report suggested that such cumulative risk assessments could be conducted by assigning toxicity equivalence factors (TEFs) for each of the pesticides having a common toxicological mechanism (NRC, 1993). This practice was justified because a similar process had already been developed by the EPA to assess the risks from dioxins and dibenzofurans.

As an example, a member of a toxicologically related family of pesticides (presumably the member that was most widely studied) would be chosen as the reference chemical for the family. Comparisons of the potency of other family members to the reference chemical would yield the TEF. If the chemical in question were determined to be 2 times more potent than the reference chemical, the TEF would be 2; if the chemical in question were determined to be one-half as potent as the reference chemical, the TEF would be 0.5. Cumulative exposure to the class of pesticides studied could be determined by multiplying the actual level of each pesticide residue by its TEF and then adding results for each pesticide.

A specific example of this approach was provided in the NRC report (NRC, 1993). This example considered five organophosphate insecticides, all considered to possess a common mechanism of toxicity through cholinesterase enzyme inhibition, and their presence on eight foods and three juices that are common in the diets of infants and children. In this example, TEFs were determined relative to the insecticide chlorpyrifos and were based on comparisons of NOAEL values for cholinesterase enzyme inhibition.

As discussed above, the value chosen for the NOAEL (and therefore the RfD) is subject to the choices of experimental design such as dose levels, test species, and routes of exposure. Comparing such values to develop TEFs is therefore subject to great uncertainty. The NRC example relied on some NOAELs derived from animal studies and others derived from humans. Comparing RfDs among different chemicals to determine TEFs raises the potential for even more uncertainty because the RfDs are based on both the NOAELs and the choices of uncertainty factors used. Interestingly, the EPA has determined that the additional 10x factor should be retained for methyl parathion, whereas, its close chemical relative, ethyl parathion, which is identical in structure with the exception of two additional methylene groups, does not require the additional 10x factor. In cases in which large differences exist between the NOAEL and the LOAEL, the "true" NOAEL may not be well approximated by the experimentally determined NOAEL; such inaccuracies are magnified when NOAELs of different chemicals are compared to determine TEFs.

The EPA defines the "point of departure" as a point estimate of the dose or exposure level that is used to depart from the observed range of empirical response (or incidence) data for purpose of extrapolating risk to the human population (EPA, 2000b). Because the NOAEL represents a single arbitrary dose, the EPA prefers to use an "effective dose," essentially similar to a benchmark dose, that is associated with some designated level or percentage of response relative to the control or baseline level of response. The EPA suggests

the adoption of a 10% effect level (ED_{10}) as the standard default point of departure.

In addition to the TEF approach, the EPA also has considered a cumulative margin of exposure (MOE) approach. The MOE is calculated by dividing the point of departure (effective dose or, suboptimally, the NOAEL) by the expected or measured human exposure. A cumulative MOE approach would sum the MOEs of the individual pesticides possessing a common mechanism of toxicological action. This same type of process, deemed the total MOE, is advocated by Sielken (2000) as the preferred method for performing FQPA cumulative risk assessments.

CURRENT AND FUTURE IMPLICATIONS

Food chemical risk assessment practices are dynamic and evolving. The passage of the FQPA has clearly presented challenges to those responsible for modeling the exposure and dose-response characteristics of pesticides that leave food residues. Regulatory implementation of the FQPA has the potential to significantly impact pest management practices, both in the U.S. and abroad, by limiting the types of pesticides allowed and/or restricting their uses. It is critical that regulatory decision making be based on the best available science and that decision makers maintain flexibility as the science evolves and improves. It is likely that models for dose response and exposure assessment for other food chemicals will incorporate the scientific advances developed for pesticide residues in foods.

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CHAPTER 7

ECONOMIC CONSEQUENCES OF FOODBORNE HAZARDS

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INTRODUCTION AND DEFINITION OF ISSUES

For both microbial and chemical hazards, the private marketplace does not automatically provide the optimal level of food safety for society because of information problems and transactions costs. Consequently, U.S. consumers delegated this oversight responsibility to the Federal government at the turn of the twentieth century. This chapter provides a brief discussion of categories of economic costs from foodborne illness borne by individuals, industry, and government. Separate sections focus on microbial and chemical hazards. The particular emphasis in the microbial section is the cost of illness method. Each year, five microbial foodborne hazards cost society an estimated $6.9 billion in medical costs, productivity losses and the value of premature death. The chemical section emphasizes the low human health risks and the limited consumer willingness to pay for food with pesticide residues reduced below current regulatory tolerance levels.

The concluding section focuses on topics for economic research that can help improve regulatory performance in this area. The relative benefits of regulation aimed at microbial and chemical hazards and the implications for government-wide food safety regulatory priority setting are assessed. Efforts underway to improve the economic valuation of foodborne risks are identified. A method to explicitly account for uncertainty in regulatory impact analyses for control of foodborne hazards is outlined. In addition, ways to harness economic incentives to improve the efficiency of public and private pathogen control strategies are discussed.

Economics of Foodborne Illness

Foodborne illness is a combination of what economists call an "experience good" and a "credence good." Consumers cannot tell the risk they run of

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incurring a foodborne illness at the time they purchase or consume a food item, because they cannot observe the extent of microbial contamination or the level of chemical residues present. As a result, they are unable to assess the health risk of buying and consuming that food item. Food is an experience good in that the consumer can determine whether it will cause illness only after it is consumed. Food is a credence good in that the consumer frequently cannot tell with certainty whether it actually caused an illness. For example, illnesses due to *Campylobacter* and *E. coli* O157:H7 typically occur several days after ingestion, and *Listeria monocytogenes* can cause illness weeks or months after ingestion. The relationship between foodborne pesticides and any possible disease risk is even more difficult to establish. This lag between consumption of the food containing the pathogen/chemical and illness means that the cause is more difficult to identify with certainty.

As is common with experience and credence goods, fear of foodborne illness can create market dysfunction. Fearing foodborne illness, some consumers may cut purchases of certain food items or avoid consuming them altogether. Measures that ensure safer foods can benefit everyone in such situations. Consumers gain because they avoid some foodborne illness, their fears are reduced, and their food choices are wider. Producers gain because the market as a whole expands. Government regulation tends to be necessary in such cases, however, because private sector initiatives tend to be ineffective in providing adequate levels of safety because of inadequate information and high transaction costs. Product liability and warranties, often the most effective private sector measures in such contexts, tend to give producers insufficient incentive to improve food safety because of the difficulty of proving causality, the cost of bringing suit, and caps on liability because of bankruptcy (Menell, 1991: also see Buzby et al., 2001).

The central question facing regulators is *how much* safety to ensure, for example, which pathogens and chemicals to regulate, what levels of contamination to allow, and what foods to target first. In general, the appropriate level of regulation can be characterized as one that minimizes the total societal costs of foodborne illness. The societal costs of foodborne illnesses affect all three major sectors of the economy: individuals/households, industry, and government (Table 7.1). People who become ill bear costs such as medical expenses, productivity losses, and pain and suffering. They may also incur costs in seeking to avoid illness by changing their behavior (e.g., cooking beef more thoroughly takes time and can adversely change its flavor and texture). Industry costs include effects of pathogens on animal productivity, development and implementation of new control options throughout the farm-to-table food chain, and costs associated with foodborne disease outbreaks (e.g., recalls of food, cleaning up production facilities, and associated legal liability suits). Government budgets pay for disease surveillance, investigation of outbreaks, and research to identify new pathogen control options from farm to table.

The views expressed in this paper are not official policy of the U.S. Department of Agriculture.

TABLE 7.1. Societal Costs of Foodborne Illness

Costs to individuals/households[1]
Human illness costs:
- Medical costs:
  - Physician visits
  - Laboratory costs
  - Hospitalization or nursing home
  - Drugs and other medications
  - Ambulance or other travel costs
- Income or productivity loss for:
  - Ill person or dying person
  - Caregiver for ill person
- Other illness costs:
  - Travel costs to visit ill person
  - Home modifications
  - Vocational/physical rehabilitation
  - Child care costs
  - Special educational programs
  - Institutional care
  - Lost leisure time
- Psychological costs:
  - Pain and other psychological suffering
  - Risk aversion

Averting behavior costs:
- Extra cleaning/cooking time costs
- Extra cost of refrigerator, freezer, etc.
- Flavor changes from traditional recipes (especially meat, milk, egg dishes)
- Increased food cost when more expensive but safer foods are purchased

Altruism (willingness to pay so that others will avoid illness)

Industry costs[2]
Costs of animal production:
- Morbidity and mortality of animals on farms
- Reduced growth rate/feed efficiency and increased time to market
- Costs of disposal of contaminated animals on farm and at slaughterhouse
- Increased trimming or reworking at slaughterhouse and processing plant
- Illness among workers because of handling contaminated animals or products
- Increased meat product spoilage due to pathogen contamination

Control costs for pathogens at all links in the food chain:
- New farm practices (age-segregated housing, sterilized feed, etc.)
- Altered animal transport and marketing patterns (animal identification, feeding/watering)
- New slaughterhouse procedures (hide wash, knife sterilization, carcass sterilizing)
- New processing procedures (pathogen tests, contract purchasing requirements)
- Altered product transport (increased use of time/temperature indicators)
- New wholesale/retail practices (pathogen tests, employee training, procedures)
- Risk assessment modeling by industry for all links in the food chain
- Price incentives for pathogen-reduced product at each link in the food chain

TABLE 7.1. *(Continued)*

Outbreak costs:
- Herd slaughter/product recall
- Plant closings and cleanup
- Regulatory fines
- Product liability suits from consumers and other firms
- Reduced product demand because of outbreak:
  - Generic animal product—all firms affected
  - Reduction for specific firm at wholesale or retail level
- Increased advertising or consumer assurances after outbreak

Regulatory and public health sector costs for foodborne pathogens

Disease surveillance costs to:
- Monitor incidence/severity of human disease by foodborne pathogens
- Monitor pathogen incidence in the food chain
- Develop integrated database from farm to table for foodborne pathogens

Research to:
- Identify new foodborne pathogens for acute and chronic human illnesses
- Establish high-risk products and production and consumption practices
- Identify which consumers are at high-risk for which pathogens
- Develop cheaper and faster pathogen tests
- Risk assessment modeling for all links in the food chain

Outbreak costs:
- Costs of investigating outbreak
- Testing to contain an outbreak (e.g., serum testing and administration of immunoglobulin in persons exposed to Hepatitis A)
- Costs of cleanup
- Legal suits to enforce regulations that may have been violated[3]

Other considerations:
- Distributional effects in different regions, industries, etc.
- Equity considerations, such as special concern for children

[1] Willingness-to-pay estimate for reducing risks of foodborne disease is a comprehensive estimate of all these categories (assuming that the individuals have included employer-funded sick leave and medical programs in their estimates). The estimate is comprehensive and covers reduced risks for everyone—those who will become ill as well as those who will not.

[2] Some industry costs may fall with better pathogen control, such as reduced product spoilage, possible increases in product shelf life, and extended shelf life permitting shipment to more distant markets or lowering shipment costs to nearby markets.

[3] In adding up costs, care must be taken to ensure that product liability costs to firms are not already counted in the estimated pain and suffering cost to individuals. However, the legal and court expenses incurred by all parties are societal costs.

Source: Reprinted from Buzby and Roberts (1997b) with permission from the World Health Organization.

Minimizing the total societal cost of foodborne illness requires equalizing the marginal costs of all affected parties, for example, the marginal cost of foodborne illness to consumers, the marginal cost to industry of increasing safety, and the marginal cost to government of enforcing regulations. In considering a single regulation, then, it is necessary to compare incremental costs. In general, economic principles suggest that a regulation should be adopted if it reduces the costs of foodborne illness to consumers more than enough to offset increases in industry compliance costs and government enforcement costs. And economic principles suggest that the regulation should not be adopted if it reduces the cost of illness but not enough to cover the increased costs of industry compliance and government enforcement.

This decision criterion can be framed equally well in terms of benefit-cost analysis, with the benefits of regulation being consumers' avoided costs of foodborne illness. The appropriate level of safety equalizes benefit and cost at the margin. Any regulation whose incremental benefit exceeds its incremental cost increases aggregate well-being.

The costs incurred (or avoided) by consumers are the most difficult to estimate. Methods for estimating these costs include both *ex ante* and *ex post* measures (before and after illness has occurred, respectively). Economists prefer to use *ex ante* measures of value, in which all the relevant costs are anticipated before a purchase takes place in the marketplace. A number of techniques are used to estimate consumers' "willingness to pay" (WTP) for greater safety in the foods being purchased. In theory, and maybe in practice, well-designed WTP studies can estimate *ex ante* values for all of the foodborne illness costs listed in Table 7.1 for individuals. In doing benefit-cost analysis, often the *ex post* measures of costs actually incurred are estimated using the cost of illness (COI) approach. Both WTP and COI measures are discussed in more detail in the sections on microbial and chemical hazards. [Golan et al. (2001) also discuss these measures more fully with particular attention paid to the evolution of the ERS COI methodology.]

BACKGROUND AND HISTORICAL SIGNIFICANCE: MICROBIAL HAZARDS

Foodborne diseases are caused by ingesting bacteria, fungi, parasites, viruses or the toxins they produce in contaminated food or water or by person-to-person contact. Each year, microbial pathogens cause as many as 76 million cases of foodborne illness, including 5200 deaths in the United States according to the U.S. Centers for Disease Control and Prevention (CDC) (Mead et al., 1999). The Economic Research Service (ERS) in the U.S. Department of Agriculture (USDA) and the Center for Food Safety and Applied Nutrition (CFSAN) in the U.S. Food and Drug Administration (FDA) have estimated the annual human illness costs for a number of foodborne illnesses. ERS estimates that the total costs of five major bacterial pathogens are $6.9 billion annually (Table 7.2). CFSAN estimates a cost of $28.1 billion for nine major causes of food-

TABLE 7.2. Estimated Annual Costs Due to Selected Foodborne Pathogens, August 2000[1]

	Estimated annual foodborne illnesses[2]			
	Cases	Hospitalizations	Deaths	Costs[3,4]
Pathogen	—Number—			Billion 2000 dollars
Campylobacter spp	1,963,141	10,539	99	1.2
Salmonella	1,341,873	15,608	553	2.4
E. coli O157:H7	62,458	1,843	52	0.7
E. coli, non-O157 STEC	31,229	921	26	0.3
Listeria monocytogenes	2,493	2,298	499	2.3
Total	3,401,194	31,209	1,229	6.9

[1] Because these new estimates of foodborne illness costs are based on new data and improved methodologies for valuing these costs, the estimates presented here are not directly comparable to earlier ERS estimates of the costs of foodborne disease.

[2] Data from the Centers for Disease Control and Prevention, Food-Related Illness and Death in the United States by Mead et al.

[3] The total estimated costs include specific chronic complications in the case of *Campylobacter* (Guillain-Barré syndrome), *E. coli* O157:H7 (hemolytic uremic syndrome), and *Listeria monocytogenes* (congenital and newborn infections resulting in chronic disability or impairment). Estimated costs for *L. monocytogenes* exclude less serious cases that do not require hospitalization.

[4] ERS currently measures the productivity losses due to nonfatal foodborne illnesses by the value of forgone or lost wages, regardless of whether the lost wages involved a few days missed from work or a permanent disability that prevented an individual from returning to work. Using the value of lost wages for cases resulting in disability probably understates an individual's willingness to pay to avoid disability because it does not account for the value placed on avoiding pain and suffering. The willingness to pay measure derived from labor market studies that ERS uses to valuc a premature death is not an appropriate measure of willingness to pay to avoid disability, because it measures the higher wages paid to workers to accept a higher risk of premature death, not disability. Methods have been suggested to adjust willingness to pay to reduce the risk of premature death downward to estimate willingness to pay to avoid disability, such as the approach based on measuring quality adjusted life years (QALYs). As yet, there is no consensus among economists about how to use these methods to value willingness to pay to avoid the disability, pain, and suffering associated with foodborne illnesses. ERS's conservative estimates of the annual costs due to foodborne illnesses (particularly the chronic conditions associated with *Campylobacter*) would be substantially increased if willingness to pay to avoid disability, pain, and suffering were also taken into account.

borne illness (Table 7.3). In their estimates for human foodborne illness costs, both ERS and CFSAN include medical costs, productivity losses from missed work, and an estimate of the value of premature deaths. CFSAN also includes an estimate of the cost of pain and suffering due to illness.

The vast majority of foodborne illnesses are classified as "acute." These are usually self-limiting and of short duration, although the cases can range from mild to severe. Gastrointestinal problems and vomiting are common acute symptoms of many foodborne illnesses. Deaths from acute foodborne illness, although rare, are more likely to occur in the very young (including the fetus), the elderly, or patients with compromised immune systems (such as those suffering from AIDS and cancer) (CAST, 1994).

TABLE 7.3. CFSAN Estimated Annual Costs Due to Selected U.S. Foodborne Pathogens, 2000[1]

Pathogen	Billion 2000 dollars
Bacterial Infections	
Salmonella	17.2
Clostridium perfringens	0.2
Shigella	0.3
E. coli O157:H7	2.2
Listeria monocytogenes	2.5
Parasites	
Giardia lamblia	0.2
Cryptosporidium parvum	0.1
Viral Infections	
Norwalk-like viruses	5.3
Hepatitis A	0.1
CFSAN total	28.1

[1] CFSAN values productivity losses and pain and suffering using quality adjusted life years (QALYs). This method uses a two-step procedure for valuing health losses. In the first step, the effect of a condition on health is estimated to be between zero (well-being in the full health state) and one (well-being in death). For example, a QALY loss of 0.14 for arthritis means that for every day of suffering with arthritis the affected individual has a level of well-being 14% lower than he/she would have had in the absence of arthritis. In the next step the value of a QALY is estimated and multiplied by expected QALY losses to calculate the value of health losses. QALYs are designed to measure the loss of well-being both from symptoms and from activity limitation. Consequently, both pain and suffering and productivity values are captured by this measure.

Data taken from Table 2 in Raybourne, Roberts, Williams and Arthritis Working Group, draft 2001.

In addition to the common acute symptoms of foodborne illness, an estimated 1–3% of all foodborne-illness cases develop secondary illnesses or complications that can occur in other parts of the body (CAST, 1994, Table 2.2). These complications, called chronic sequelae, can occur in any part of the body including the joints, nervous system, kidneys, or heart, and may afflict the patients for the remainder of their lives and/or result in premature death. For example, *Campylobacter* infections are estimated to cause 20–40% of all Guillain-Barré syndrome (GBS) cases (a major cause of paralysis unrelated to trauma) in the United States. About 1.5% of *E. coli* O157:H7 disease patients develop hemolytic uremic syndrome (HUS), which usually involves red blood cell destruction, kidney failure, and neurological complications such as seizures and strokes.

The medical literature indicates that the impact of the infection and its

complications may vary depending on the age and health status of the individual. For example, in an ERS COI study of campylobacteriosis GBS cases, the analysis was complicated by demographic differences and the broad array of possible GBS symptoms, subsequent medical costs, and final outcomes (Buzby et al., 1997a,b). Using data from Sunderrajan and Davenport (1985), ERS divided patients with GBS into two age and treatment categories:

- Mechanically ventilated patients with an average age of 47
- Those not on mechanical ventilation with an average age of 30

Those who are mechanically ventilated face more serious complications and prognoses than those who are not, including a reduced likelihood of returning to work (see Appendix to this chapter and Fig. 7A.1 for a more detailed example of this COI analysis).

SCIENTIFIC BASIS AND IMPLICATIONS: MICROBIAL HAZARDS

Traditionally, the social costs of human illness associated with microbial foodborne pathogens have been estimated with the COI method. COI analyses have typically estimated only the individual's (or household's) medical costs, lost productivity, and value of premature death from a particular illness or injury. Other costs are usually omitted because of the lack of suitable measures, often resulting in underestimation of the true societal costs. The important advantage of a COI measure is that it employs readily available and reliable economic data (such as wages and hospitalization costs). Also, these relevant data are precise enough to allow for sensitivity analyses of the response of the measure to changes in medical costs or demographic profiles of affected individuals. Because they are so tractable, COI measures have been widely used by economists and policymakers for several decades.

Malzberg developed the COI method in 1950, and Rice codified its empirical application in 1966. The application of the method to foodborne illness is limited but increasing. The method has been applied for selected foodborne pathogens in the United States (Buzby and Roberts, 1997a; Buzby et al., 1996; Cohen et al., 1978; Roberts et al., 1998; Roberts and Marks, 1995; Todd, 1989a; Sockett and Stanwell-Smith, 1986), Croatia (Razem and Katusin-Razem, 1994), the United Kingdom (Roberts and Upton, 1997), and Canada (Todd, 1989b) and for acute infectious intestinal disease in England (Djuretic et al., 1996).

Procedures for the Cost of Illness Method

The first step in any COI analysis is to determine the incidence of a specific illness. Incidence is often expressed as the number of new cases of a disease per

100,000 individuals in a 1-year period. The quantification of foodborne disease incidence is a matter of great controversy because of uncertainties about the true incidence (CAST, 1994). Because the nature and reporting of foodborne diseases result in vast undercounting of the actual incidence of illnesses, incidence rates are often estimated by expert opinion. The ERS estimates incorporate the best available estimates from CDC (Mead et al., 1999).

For each foodborne illness, cases are classified by severity. In the ERS COI presented here, four acute illness severity groups were used: those who did not visit a physician, those who visited a physician, those who were hospitalized, and those who died prematurely because of their illnesses. For some foodborne illnesses, a fifth severity group was used for patients who developed select chronic sequelae from the acute illness.

For each severity group, medical costs were estimated for physician and hospital services, supplies, medications, and special procedures unique to treating each particular foodborne illness. Such costs reflect the number of days/treatments of a medical service, the average cost per service/treatment, and the number of patients receiving such service/treatment. Hospitalization accounts for a large proportion of these costs. Data to estimate medical costs come from nationwide data bases, such as the published Medicare reimbursement rates and per capita expenditures on physician services from the Health Care Financing Administration (HCFA), the American Hospital Association's Annual Survey of Hospitals, and the National Center for Health Statistics' National Hospital Discharge Survey (NHDS) and National Mortality Follow-Back Survey.

The incidence data combined with information on severity were also used to estimate the costs of lost productivity. Most people with foodborne illnesses restrict their usual activity for just one or two days. However, some patients die and others develop chronic complications so serious that they never return to work, regain only a portion of their pre-illness productivity, or switch to less demanding and lower-paying jobs. The total cost of lost productivity is the sum of costs for all individuals affected, primarily the patient or, in the case of ill children, their parents or paid caretakers. For those cases in which work is temporarily interrupted, we estimate the productivity loss as the product of time lost from work multiplied by the corresponding wage rate published by the Bureau of Labor Statistics. The daily wage of an individual is frequently used in economic studies as a proxy for the value of output produced in a day's work. When data are not available on time lost from work due to illness, this lost time is estimated by assuming a typical ratio of the average time spent in the hospital to time lost from work.

Calculating the Value of a Statistical Life

ERS has historically used two different methods for calculating proxy values for the forgone earnings of someone who dies prematurely or is unable ever to return to work because of their foodborne illness (Table 7.4).

TABLE 7.4. Estimating the Value of a Statistical Life

(1) **Market approach:**
- Estimated from studies of market behavior. Most estimates come from hedonic-wage studies, which use labor market data on how much employers must offer workers, in terms of higher wages, to induce them to take a job with some injury risks, as opposed to a similar job with no such risks. Other estimates come from studies of seat belt use and other automobile safety features as well as costs incurred to avoid contaminated drinking water and air pollution. Still others come from contingent valuation studies that study stated behavior, that is, responses to hypothetical choice situations.
- Estimated value of saving a life is $5 million for each life (1990 dollars), regardless of age, updated to current dollars. More recent valuations updated to adjust for age.
- Estimates of willingness to pay to avoid temporary or chronic illnesses vary according to individuals' risk preferences and according to the characteristics of the illness.

The market approach excludes government and industry costs as well as other costs that individuals may not consider when making choices among specific risky alternatives.

(2) **Landefeld and Seskin's human capital/willingness to pay (WTP) approach:**
- Generates the present value of expected lifetime after-tax income and housekeeping services at a 3% real rate of return, adjusted for an annual 1% increase in labor productivity and a risk aversion factor of 1.6. The risk aversion factor is based on the ratio of life insurance premium payments to life-insurance loss payments. In most cases, life insurance premiums represent "household WTP for potential losses associated with the death of an income-earning household member."
- Estimates the value of a statistical life, depending on age, to range from roughly $15,000 to $2,037,000 in 1996 dollars.

This more conservative approach underestimates the true costs of foodborne illnesses to society because it excludes costs, such as:
- Pain, suffering, and lost leisure time of the patient and family;
- Lost business and costs and liabilities of lawsuits affecting agriculture and the food industry;
- The value of self-protective behaviors undertaken by industry and consumers;
- Resources spent by federal, state, and local governments to investigate the source and epidemiology of the outbreak; and
- The value of reducing risks for people who do not become ill.

The first approach, the *human capital approach*, was used in earlier research at ERS. The human capital approach incorporated estimates of forgone earnings, adjusted by a "risk premium" from life insurance markets. The cost of a premature death was estimated, depending on age, to range from roughly $15,000 to $2,037,000 in 1996 dollars. These estimates were calculated with a combination of human capital and willingness to pay estimates developed by Landefeld and Seskin (LS) (1982). In essence, these estimates represent the

value in today's dollars of an individual's lifetime stream of income if the illness had not occurred. The LS method generates the present value of expected lifetime after-tax income and housekeeping services at a 3% real rate of return, adjusted for an annual 1% increase in labor productivity and a risk aversion factor of 1.6. The risk aversion factor is based on the ratio of life insurance premium payments to life insurance loss payments. In most cases, life insurance premiums represent "household WTP for potential losses associated with the death of an income-earning household member" (Landefeld and Seskin, 1982, p. 562). The LS value of a statistical life lost is:

$$\text{VOSL} = \left[\sum_{t=0}^{T} \frac{Y_t}{(1+r)^t}\right]\alpha$$

where T = remaining lifetime, t = a particular age, Y_t = after-tax income including labor and nonlabor income, r = household's opportunity cost of investing in risk-reducing activities, and α = risk aversion factor. The major limitation of this approach is that it does not fully consider the value that individuals may place on (and pay for) feeling healthy, avoiding pain and suffering, or using their free time. Because the approach does not cover all of these valuable aspects of health, the approach is generally thought to understate the true societal costs of illness.

The second approach for calculating the value of a statistical life, the *market approach*, infers the value of a statistical life from behavior observed in market settings and is the foundation for ERS VOSL estimates for foodborne illness deaths. The fundamental assumption of this method is that people make tradeoffs between safety and other consumption goods in their daily lives. For example, Volvos are sold at a price premium in part because some consumers are willing to pay a higher price for goods that are safer to use, in this case, cars that provide greater protection in accidents. The increment in price attributable to the safety features reveals consumers' willingness to pay for (implicit price of) safety at the margin. The controversy over the sweetener saccharin is another example of consumers' willingness to trade safety for other goods and services. By using saccharin, weight-conscious consumers reveal a willingness to use products associated with a potentially greater risk of cancer in return for being able to eat sweet foods containing fewer calories. The majority of studies estimating the value of life in this manner use data from labor markets. Typically, employers must offer workers higher wages to induce them to take jobs with a higher risk of occupational fatalities than jobs with a lower risk.

Viscusi (1993) compared wage differentials in 24 wage-risk studies and found that the extra wages associated with the increased overall hazard of one death from risky jobs are between $3 million and $7 million (in 1990 dollars). Other studies have obtained very similar implicit values of a statistical life with information on safety features of automobiles (Atkinson and Halvorsen, 1990, Dreyfus and Viscusi, 1995). Several regulatory agencies use either Viscusi's range of estimates or the $5 million midpoint when analyzing the

benefits of proposed public-safety rules. The market approach has also been used to estimate the value of lost work time due to illness or injury [see, for example, Hersch and Viscusi (1990)]. For the current ERS estimates, this $5 million midpoint was modified by taking the age distribution of deaths from each pathogen into account, in effect treating the value of life as an annuity paid over the average U.S. life span at an interest rate of 3.0%. After age adjustment, the assumed cost of each death ranges from $8.9 million for individuals who died before their first birthday to $1.7 million for individuals who died at age 85 or older in 2000 dollars (see *http://www.ers.usda.gov/briefing/FoodborneDisease/overview.htm*).

Other studies have used costs incurred by consumers in avoiding or mitigating health risks to infer values of avoiding premature death, lost work time, or episodes of specific illness (for a survey see Cropper and Freeman, 1991). These costs include both explicit cash expenditures and implicit costs such as the value of lost time. Studies of this kind include Blomquist's (1979) investigation of seat belt use, Harrington et al.'s (1989) investigation of avoiding giardiasis from drinking water, and Abdalla et al.'s (1992) investigation of avoiding risks from industrial solvents in drinking water.

The market approach has been extended to encompass cases in which markets do not exist through use of the contingent valuation method (CVM). CVM constructs estimates of willingness to pay for nonmarket goods with data from surveys in which participants are asked to make choices in hypothetical situations. The most commonly used format is the discrete choice format in which respondents are presented with a choice between two goods (e.g., foods) differing in only two ways, a quality attribute such as risk of illness or death and the price. Alternatively, respondents may be asked to report the maximum additional amount they would be willing to pay for the less risky good. Several studies have used CVM to estimate consumers' willingness to pay for reductions in symptoms of illness such as shortness of breath, nausea, and headaches. The correspondence between CVM estimates and the costs of illness or averting behaviors has not been close, in part because the samples used in the CVM studies may not be representative and in part because CVM study participants did not bear the full cost of illness [see Cropper and Freeman (1991) for a review].

Latest COI Estimates for Five Foodborne Pathogens

The latest ERS estimates of medical costs, productivity losses, and value of premature death for diseases caused by five foodborne pathogens is $6.9 billion per year (Table 7.2). The five bacterial pathogens are *Campylobacter* (all serotypes), *Salmonella* (nontyphoidal serotypes only), *E. coli* O157:H7, *E. coli* non-O157:H7 STEC, and *Listeria monocytogenes*. ERS uses CDC estimates of the annual number of foodborne illnesses, hospitalizations, and deaths for these pathogens (Mead et al., 1999). ERS has also revised its methodology to take account of age in valuing premature deaths. Under the age-adjusted approach,

the assumed cost of each death ranges from $8.9 million for children who die before their first birthday to $1.7 million for individuals who die at age 85 or older. Because of changes in case estimates and the economic valuation of deaths, the ERS estimates are not strictly comparable with earlier ERS estimates of foodborne disease costs.

These COI estimates undervalue the true costs of foodborne illnesses to society, however, because the analyses covers only five foodborne pathogens believed to cause human illnesses. Over 250 organisms are known to cause foodborne illnesses. Because many different organisms cause similar symptoms (especially diarrhea, abdominal cramps, and nausea), it is rarely possible to say which microbe is causing a given illness unless laboratory tests are performed to identify the microbe or the illness is part of a recognized outbreak (see *http://www.cdc.gov/ncidod/diseases/food/illness.htm*). Estimated costs would also increase if the costs for all chronic complications linked to foodborne illnesses, such as arthritis and meningitis, were included. These estimates primarily include medical costs, lost productivity, and the value of premature deaths. Total costs would also increase with the inclusion of other societal costs, such as pain and suffering, travel to medical care, and lost leisure time as shown in Table 7.1.

REGULATORY, INDUSTRIAL, AND INTERNATIONAL IMPLICATIONS: MICROBIAL HAZARDS

In general, the COI estimates for illness due to foodborne pathogens can be used in three main ways:

- To evaluate the economic impact of foodborne diseases on the U.S. economy,
- To target pathogen reduction efforts towards the most costly diseases, and
- To compare benefits and costs of control efforts to determine the most cost-beneficial interventions.

Societal benefits of a food safety regulation arise from prevention of foodborne illness among individuals. From an economic perspective, these benefits include, at a minimum, savings in disease prevention and mitigation expenditures, increases in worker productivity, reductions in pain and suffering, and reductions in anxiety about foodborne health risk.

The costs of food safety regulations include expenditures associated with their design, implementation, and enforcement. In 1994, the Federal government budgeted $1.2 billion on food safety regulatory activities such as inspection and laboratory testing (GAO, March 1996). The food industry also incurs costs to comply with food safety rules and regulations.

One example of COI estimates for foodborne illness used in policymaking is the Food Safety and Inspection Service's (FSIS) 1996 Pathogen Reduction/

Hazard Analysis and Critical Control Point (HACCP) regulation to improve the current meat and poultry inspection. Earlier COI estimates by the USDA's Economic Research Service (ERS) provided the foundation for the estimated benefits of this HACCP regulation (USDA, 1995 and 1996).

To compare the impact of different assumptions on the calculated benefits of this HACCP rule, ERS constructed the four scenarios shown in Table 7.5. The net benefits were estimated with the FSIS estimates of costs of industry compliance with the HACCP regulations over a 20-year time horizon. ERS assumed that benefits begin five years after the HACCP regulations. Industry compliance costs are assumed to start in the first year. The results indicated that the benefits of implementing HACCP outweighed the costs, as long as four pathogens were reduced by 17% or more (Crutchfield et al., 1997). (Note that this ERS analysis did not include *E. coli* STEC in the publication, AER-755.) COI estimates were also used in the Food and Drug Administration's (FDA) regulation for seafood and proposed regulations for eggs (U.S. DHHS, 1995 and 1999), and the ERS COI methodology for *Listeria* was incorporated in the analysis supporting the USDA's 2001 proposed regulation for ready-to-eat meat and poultry products (e.g., hot dogs and luncheon meats). This regulation has provisions for mandatory in-plant testing for *Listeria* and higher performance standards for some pathogens as measures of process control.

The USDA's Office of Risk Assessment and Cost-Benefit Analysis (ORACBA) reviews regulations proposed by the USDA that concern human health and safety or the environment and have an estimated annual economic impact of at least $100 million dollars (see Table 7.5). For these regulations, the USDA conducts a thorough analysis that makes clear the nature of the risk, alternative ways of reducing it, the reasoning that justifies the proposed rule, and a comparison of the likely costs and benefits of reducing the risk (web site: *www.usda.gov/oce/oracba*). The FDA has a similar review process, see the FDA website for FDA regulation of food and their review process (*http://www.cfsan.fda.gov/*) as well as the U.S. government-wide web site (*http://www.FoodSafety.gov*).

BACKGROUND AND HISTORICAL SIGNIFICANCE: CHEMICAL HAZARDS

Chemicals in foods fall into two main classes: (1) substances added to prevent spoilage, improve product quality, or change color and (2) residues of pesticides used to grow crops and to prevent spoilage or damage during postharvest processing and storage. The prevalence of illness and premature death due to such chemicals in foods is difficult to ascertain. To the best of our knowledge, their incidence is extremely low, at least in developed countries with strong regulatory systems like the United States. It appears to be so low, in fact, as to be virtually undetectable from surveillance data and epidemiological studies.

TABLE 7.5. Scenarios Used to Evaluate HACCP Rule and Benefits Assumptions

Scenario/description	Pathogen reduction	Discount rate	Valuation method for premature death/disability	Annualized benefits[1] Low	Annualized benefits[1] High	Annualized costs	Net benefits
	—percentage—			—$ billion (1995) —			
Low-range benefits	20	7	Landefeld and Seskin	1.9	9.3	1.1–1.3	0.8–8.0
Mid-range benefits I	50	7	Landefeld and Seskin	4.7	23.4	1.1–1.3	3.6–22.1
Mid-range benefits II	50	3	Viscusi, VOSL[3] = $5 million	26.2	95.4	1.1–1.3	25.1–94.1
High-range benefits	90	3	Viscusi, VOSL = $5 million	47.2	171.8	1.1–1.3	46.1–170.5

[1] Benefits begin to accrue five years after the HACCP rule is enacted, and extend over 20 years.

[2] Landefeld and Seskin VOSL estimates after averaging across gender and updating to 1995 dollars using BLS usual weekly earnings.

[3] VOSL = value of a statistical life.

Source: Crutchfield et al., 1997. See *http://www.ers.usda.gov/briefing/FoodSafetyPolicy/features.htm* for updated estimates.

Instances of acute adverse reactions are extremely rare. Levine's (1991) survey of the literature on pesticides from 1930 through the late 1980s turned up 42 instances of outbreaks of pesticide poisonings related to ingestion of contaminated food and water. Almost one-third involved cases in which peasants in poor countries facing starvation knowingly ate seed treated with pesticides and marked as not fit for consumption. The majority of the remaining cases also came from poor countries and involved inadvertent consumption of pesticides under the belief that they were flour or sugar, consumption of cooking oil stored in pesticide containers, and similar instances involving poor sanitation. Consumption of meat from animals fed illegally with treated seed accounted for several cases, whereas consumption of fish from polluted waters accounted for a single case (i.e., methyl mercury in Canada). The only recent case in the United States occurred in 1986 and involved the illegal application of the insecticide aldicarb to watermelons, despite the prohibition on its use on food crops. Recent cases of acute illness in other developed countries have similarly involved illegal uses, for example, the recent cases of meat raised on feed with excessive levels of dioxin in Belgium (see Buzby et al., 2001 for more on the dioxin incident) and soft drink cans contaminated with fungicide in western Europe. Cases of acute illness involving food additives have mainly been allergic reactions, such as the sweetener aspartame causing adverse reactions in those unable to digest the enzyme phenylalanine.

A number of studies have attempted to quantify the contributions of controllable substances to known long-term health effects, notably cancer (Doll and Peto, 1981; Henderson et al., 1991; Lutz and Schlatter, 1992; Ames et al., 1995). These studies combined information from animal bioassays with epidemiological information to estimate the numbers of annual cancer deaths attributable to various causes. The principal causes of cancer associated with diet are tobacco, fat, and, possibly, overnutrition. All food additives taken together were assigned a token amount of less than 1% of annual cancer deaths because the epidemiological evidence indicated no significant correlation between ingestion of these substances and elevated rates of any cancers for which laboratory studies and physiological analyses had suggested a possible causal connection.

The low incidence of illness and death related to chemicals in foods is testimony to the stringency of regulation of food additives by the FDA and pesticides by the U.S. Environmental Protection Agency (EPA). By law, the FDA is required to ascertain that food additives are safe before approving them for use. Food additives shown to cause cancer in animals cannot receive approval. The EPA is similarly required to set tolerances (maximum allowable limits) for pesticide residues on foods that ensure a reasonable certainty of no harm. Surveillance data collected by the FDA as part of its enforcement effort indicate that most domestic fruits, vegetables, cereals, meat, eggs, and dairy products sold in the United States have no detectable pesticide residues and that only about 1% have residues exceeding tolerances (Food and Drug Administration Pesticide Program, 1987–1998).

SCIENTIFIC BASIS AND IMPLICATIONS: CHEMICAL HAZARDS

As noted above, the value of an incremental improvement in food safety is typically estimated as the product of two factors. The first factor is the change in risk, that is, the change in the probability of illness or death or, equivalently, of the incidence of illness or death in the population. The second factor is the average value of saving a life or avoiding illness. Estimation of both factors has been controversial.

Risk Assessment of Chemicals in Foods

The risk of illness or death from chemicals in foods cannot generally be estimated directly from human data. Past experience may be an insufficient guide to the risks of new chemicals. Regulation is prospective and seeks to avoid adverse consequences, so that human data may be simply unobtainable for new chemicals. Regulatory assessments of the risks associated with exposure to chemicals in foods thus tend to rely on animal studies to assess toxicity. These toxicity results are adjusted to account for physiological differences between humans and test animals and are then combined with assessments of exposure to yield an overall quantitative characterization of risk.

In general, the results of these procedures are not appropriately characterized as estimates of risk. EPA imposes a number of assumptions designed to produce "conservative" figures. Its underlying rationale is a desire to avoid type II error, that is, declaring a compound to be safe when it in fact poses a risk, possibly to an especially susceptible subpopulation. Thus, rather than using the average toxicity obtained from animal studies, EPA uses the upper limit of a 95% confidence interval of the toxicity of a substance to the most vulnerable test species. The highest physiologically defensible number is used to convert the dose from the test animal to a human equivalent. The highest possible figures are similarly used to estimate exposure.

These procedures have a number of undesirable consequences (Nichols and Zeckhauser, 1986; Lichtenberg, 1991):

- First, they tend to overestimate the benefits of regulation and understate the costs, both in total and at the margin. As a result, they indicate the desirability of levels of regulation that are actually excessively stringent.
- Second, they make it impossible to compare quantitative characterizations of risk across substances, making it impossible to determine whether substances are regulated under comparable degrees of stringency. Each quantitative characterization of risk can be characterized as an upper limit of a confidence interval, but the type of confidence interval varies in an unknown manner because of the arbitrary nature of the assumptions imposed.
- Third, they tend to overstate the net benefits of *ex ante* regulatory actions

relative to surveillance, monitoring, and other *ex post* enforcement methods (Lichtenberg, 1991).

- Fourth, they tend to exaggerate risks from chemicals in foods and thus unjustifiably undermine confidence in the safety of the U.S. food supply. The EPA refers to its quantitative characterizations of risk as risk estimates, and they enter policy discussion as such.

Thus the EPA's risk assessment procedures suggest that chemicals in foods pose much greater risks than the data indicate. Moreover, research in cognitive psychology has shown that people consistently overestimate rare events like cancer from chemicals in food (see for example Fischoff et al., 1981). This bias in risk perception lends additional credibility to the EPA's exaggerated risk estimates. Overall, concern about chemicals in foods is much more prominent in food safety policy discussions than the incidence of food safety problems attributable to them would appear to warrant.

Concern over chemicals in food may have fallen somewhat over the past decade, however, after rising during the preceding decades. A number of surveys conducted between 1984 and 1990 in localities scattered across the U.S. indicated that most Americans had serious concerns about pesticide residues on foods (Sachs et al., 1987; Jolly et al., 1989; Food Marketing Institute, 1989; Porter/Novelli, 1990; Dunlap and Beus, 1992; Weaver et al., 1992). Sachs et al. (1987), comparing the results of their survey of Pennsylvania households with those of a survey done 20 years earlier, found much greater concern over pesticides in 1985 than in 1965. A national poll conducted in 1994, however, found that a minority of Americans (35–38%) believed pesticides were very dangerous for themselves or for the environment, roughly half the percentages reporting such concerns only a few years earlier (National Opinion Research Center, 1994). Food Marketing Institute surveys of public perceptions indicate that during the mid- to late 1980s, the majority of Americans considered chemicals in foods as the top concern related to food safety. By 1995, only about 14% reported chemicals as their top food safety concern (Buzby and Ready, 1996).

Valuing Avoidance of Chemicals in Foods

The value of avoiding illness or death from exposure to chemicals in foods may differ from the general value of avoiding illness or death. It is possible, for instance, that people have special fears about the types of illness or death resulting from chemical exposure. Several different types of evidence suggest that this is not the case, suggesting that values of life saving derived from the general literature are applicable to cases involving chemicals in foods. Overall, most consumers wanted assurance that their food was safe but were willing to pay little extra for small increments in safety beyond the level set by regulators.

One recent study tackled this question directly by comparing the implicit value of saving lives from risks posed by pesticide residues on foods and auto-

mobile accidents. It found no significant difference between them (Horowitz, 1994).

A number of other studies have examined consumers' willingness to pay for lower levels of pesticide residues on foods, in particular, complete elimination of all such residues (Ott, 1990; Misra et al., 1991; Weaver et al., 1992; Eom, 1994; Buzby et al, 1995; Buzby et al., 1998). All of these studies used CVM. Eom (1994) and Buzby et al. (1998) used a discrete choice format in which survey participants were asked which of two types of produce they would purchase at a given price differential. Eom (1994) found that willingness to pay was insensitive to the level of risk participants were told they were facing. Buzby et al. (1998) found no significant difference between respondents' willingness to pay for produce that met government standards for pesticide residues on foods and produce certified to be residue-free. The remainder of these studies asked participants to report the highest premium they would be willing to pay for produce certified to be residue-free. This latter format tends to generate excessively high reports of willingness to pay. Moreover, none of the surveys were constructed to replicate actual choice situations, that is, respondents knew that the questions were hypothetical and that there was no chance their answer would have direct financial consequences such as actually paying more. Hypothetical survey formats of this kind tend to generate excessively high reports of willingness to pay. Thus one would expect these studies to generate excessively high estimates of consumers' willingness to pay to eliminate pesticide residues on produce. Even so, few consumers reported being willing to pay more than 5% more for certified pesticide residue-free produce. Between 20 and 40% of respondents were willing to pay nothing extra, whereas an additional 25–60% were willing to pay no more than 5% extra. In most studies, only about 10% of respondents reported being willing to pay 10% or more extra. Even fewer reported being willing to buy certified residue-free produce with lower cosmetic quality or more surface defects.

Baker and Crosbie (1993) obtained similar results using conjoint analysis on a small sample of produce shoppers at two San Jose, California supermarkets in 1992 to explore their relative preferences for price, cosmetic quality, and pesticide residues. Cluster analysis indicated that these shoppers could be divided into three subgroups. About 30% cared about price and quality but not pesticide residues. The majority (55%) cared about price and quality and whether the produce met government standards for residues. The remainder (about 15%) wanted stricter government regulation of pesticide use on the farm.

Other corroborating evidence comes from studies of demand for organic food. Some have argued that the growth of organic food sales is an indication of the public's willingness to pay to avoid pesticide residues on foods. Prices for organic produce average 25–35% higher than comparable conventional produce and have been observed to be as much as double or triple the prices for conventional produce in nearby stores (Hammitt, 1986; Morgan and Barbour, 1991; Thompson and Kidwell, 1998). These price premiums measure demand for reductions in chemicals in foods to the extent that demand for organic food

is driven by concerns over chemicals in foods. It appears, however, that concerns about pesticides do not account for most of the motivation for buying organic foods. Most purchasers of organic foods believe that they are more nutritious and flavorful than conventionally grown foods (Hammitt, 1986; Jolly et al., 1989), whereas others purchase organic foods for worker safety and/or environmental concerns. Certification as pesticide residue-free did not influence demand for organic broccoli, carrots, or lettuce during the period 1985–1989 (Park and Lohr, 1996).

In sum, it appears that the great majority of the U.S. population wants assurance that produce is safe but has little or no demand for additional reductions in chemicals in foods. Thus the average willingness to pay for reductions in chemicals in foods should be treated as equal to willingness to pay for other reductions in illness or death. There does appear to be a small segment of the population willing to buy organic food at a high price premium. This segment values the overall manner in which produce is grown rather than the absence of chemicals per se. Absence of chemicals appears to be a relatively small part of the motivation for buying organic food. The price elasticity of demand for organic produce appears to be extremely low, suggesting that purchasers of organic produce do not consider conventional produce as much of a substitute for it (Thompson and Kidwell, 1998). The income elasticity of demand for organic food is quite high, suggesting that organic produce is a luxury good (Park and Lohr, 1996; Thompson and Kidwell, 1998). Thus there appears to be no reason to treat this segment of the population differently than the general population in estimating the benefits (avoided costs) of reductions in chemicals in foods.

REGULATORY, INDUSTRIAL, AND INTERNATIONAL IMPLICATIONS: CHEMICAL HAZARDS

Food additives and pesticide residues on foods are regulated under the Federal Food, Drug, and Cosmetic Act (FFDCA). In both cases, regulation is driven solely by health criteria. In general, food additives can be used legally only if the FDA has determined that they are safe. However, the FDA can approve the use of additives that can cause adverse health effects if it finds them to be safe at sufficiently small concentrations. In such cases it issues a tolerance specifying the maximum allowable concentration, which is generally 1/100 of the maximum concentration at which adverse health effects are observed. The FFDCA also specifically forbids the use of additives found to cause cancer in humans or animals.

Regulation of pesticide residues on foods is carried out by the EPA under the FFDCA as amended by the Food Quality Protection Act of 1996. This legislation directs the EPA to set tolerances for pesticide residues on foods at levels that create a reasonable certainty of no harm from aggregate exposure, including all dietary exposures as well as other exposures for which reliable

information exists. It also directs the EPA to make a special determination of safety for infants and children and requires the use of an extra 10-fold margin of safety for all substances with threshold effects that pose some risk to infants and children. The EPA must take into account the vulnerability of special subpopulations (including infants and children) in estimating exposure and health effects and must use safety factors recognized by qualified experts as appropriate. Data on the actual use of the pesticide on crops and actual residue levels can be used for this purpose only if the EPA determines that the data are reliable and do not underestimate exposure for significant subpopulations. Tolerances last for five years, at which time they must be reviewed.

The legislation does allow limited use of economic criteria for determining appropriate levels of pesticide residues on food by allowing tolerances to be set at levels necessary to "avoid significant disruption in domestic production of an adequate, wholesome, and economical food supply." Even so, economic considerations can be used to assess the appropriateness of regulatory decisions ranging from approval of a tolerance to the adequacy of surveillance and enforcement programs. Moreover, economic considerations frequently enter regulatory decision making implicitly even in cases where statutes give them no explicit role.

Buzby et al. (1995) provide an example of economic analysis of changes in food safety in a case involving pesticide regulation, specifically, postharvest treatment of fresh market grapefruit with sodium orthophenylphenate (SOPP). Grower surveys were used to identify likely alternative postharvest treatment methods for grapefruit, to estimate the packinghouse level changes in treatment cost, and to estimate changes in spoilage losses. These estimated changes in treatment cost and spoilage losses were then used to estimate a shift in the supply of grapefruit provided to the fresh market (for a discussion of methodology see Lichtenberg et al., 1988). A model of grapefruit supply and demand was used to estimate changes in grapefruit consumption and price and thus changes in grapefruit consumers' and producers' incomes. Changes in price serve as a mechanism for shifting a portion of the costs of the ban from producers onto consumers. Consumers will respond to price changes in part by substituting consumption of other commodities for grapefruit. The overall cost of the regulation as measured by changes in consumer and producer incomes will generally be less than the additional cost of treating the preregulation grapefruit crop because of these substitution possibilities. CVM was used to estimate consumers' willingness to pay for the reductions in risk induced by the regulation, as estimated by the EPA. The incremental benefit of the regulation derived from the willingness to pay estimates was then compared to the losses in consumer and producer incomes, which together comprised the incremental cost of the regulation. The net impact was positive, indicating that banning SOPP would increase societal net income. This result should be taken as illustrative: The net benefits were likely lower than those estimated because the EPA's risk assessment methods overstated the reductions in risk effected by the proposed regulation.

CURRENT AND FUTURE IMPLICATIONS

Because food safety is a combination of an experience good and a credence good, the private marketplace provides less than the socially optimal level of food safety. Since the turn of the twentieth century, the U.S. government has used its regulatory powers to remedy market failures associated with food safety. It remains important to reassess these regulations, however, to improve their efficiency in light of experience and of new information about the nature and extent of food safety problems. There are a number of areas where economic analysis can help. We highlight four here.

1. Set Priorities by Ranking Relative Risks and Costs for Microbial vs. Chemical Hazards

Ideally, the limited federal budget for food safety should be spent on the most cost-effective methods of controlling significant risks. In other words, spending on food safety regulation should be allocated to achieve the greatest feasible level of safety from any given level of overall expenditure across hazards and agencies. Comparison between microbial and chemical food risks becomes relevant in this context. The literature clearly indicates that the foodborne risks from microbial hazards are much greater than the risks from chemical hazards. The ERS estimates that foodborne illness associated with five pathogens cost the U.S. society $6.9 billion (Aug. 2000 dollars) in medical charges, lost productivity, and value of premature death each year. Because the risks are so low, the economic costs of foodborne chemical risks have not been estimated. These differences in current costs to society suggest that too much chemical safety and too little microbial safety may be provided currently. Ranking risks among pathogens has been started in Tables 7.2 and 7.3 but needs to be extended to the remaining pathogens identified by CAST.

In 1998, the National Research Council Committee to Ensure Safe Food from Production to Consumption recommended that a comprehensive food safety plan be developed and that funds for food safety programs (including research and education programs) reflect science-based assessments of risk and potential benefit (Institute of Medicine, 1998, p. 11). In response, the Risk Assessment Consortium (RAC) was established as part of the President's Food Safety Initiative (*http://www.foodriskclearinghouse.umd.edu/Risk_Assessment_Consortium.htm*). The RAC has proposed a project to rank relative risks for all sources of foodborne disease and to conduct benefit-cost analyses of potential control options for the most significant foodborne disease risks.

2. Improve Economic Valuation of Microbial Risks with WTP Methods

A second area of economic research targets consumer concerns about food safety risks. As noted above, the appropriate level of safety equates the marginal benefit of reducing foodborne risk with the marginal cost of risk reduc-

tion. One important component of assessing regulation is thus the benefit of risk reduction, that is, what consumers are willing to pay for reduced food safety risks. Two federal agencies, the USDA's ERS and the DHHS's CDC, have allocated Food Safety Initiative money to develop new valuation estimates for reducing risks from microbial pathogens.

In 1998, the CDC awarded funds for a cooperative agreement to study consumer demand for food safety. The study, which may continue for up to five years, is designed to estimate the value that consumers place on reducing the risk associated with specific microbial foodborne illnesses for which interventions already exist. The effect on consumers' value of alternative combinations of private and collective risk reduction strategies is also being assessed. The study provides opportunities to advance the techniques used in risk communication, conceptual and empirical economic modeling, and value estimation in the public health setting. Another important contribution of the project is the education of consumers with respect to the risk of foodborne illness and the available public and private efforts to reduce risk. The agreement opens the way to new collaborative efforts between the CDC and the economic research community.

The ERS also is investigating techniques to develop *ex ante* values for the willingness to pay to avoid risks associated with foodborne pathogens in cooperative agreements awarded in fiscal year 1999. Several valuation techniques can be used:

- The contingent valuation method is a stated-preference technique in which the consumer's WTP for non-market goods is revealed with surveys (Buzby et al., 1998).
- Experimental auction markets use an artificial choice situation with real choices. For example, in a staged experiment, participants bid real money to buy an irradiated chicken sandwich that poses lower food safety risks (Shogren et al., 1999).

For a comparison of methods, see Buzby et al. (1999) and Golan et al. (2001). The other three objectives of the ERS program are: 1) to evaluate the validity and effectiveness of different methods that model the process by which consumers assess changes in probability and risk, 2) to test whether the presentation of distinct pathogen-specific and symptom-specific scenarios result in different consumer valuations, and 3) to examine how alternative combinations of private and collective risk reduction strategies affect consumer valuation of safer food.

The results of these studies will be used to improve valuation methods in the regulatory agencies. Many valuation issues were discussed at the conference at the University of Maryland in September, 2000 which was cosponsored by the Risk Assessment Consortium, Federal agencies, NE-165 regional research group of economists (*www.umass.edu/ne165/*), and others (for conference proceedings, see *http://www.ers.usda.gov/publications/mp1570/*).

3. Incorporate Uncertainty into Regulatory Impact Analyses for Food Safety

A third area involves the treatment of uncertainty in regulatory decision making. Quantitative assessments of risks of foodborne illness from pathogens and chemicals are subject to considerable uncertainty. Susceptibility to both pathogens and chemicals varies across individuals in the population. Some of that variability is linked to observable attributes (e.g., age, sex), making it possible to devise policies that address identifiable subpopulations. Some of that variability is not easily observable and can only be treated as random in analyzing regulatory impacts (for example, see Havelaar et al., 2000). In addition, gaps in scientific understanding of the mechanisms by which chemicals (and, in some cases, pathogens) cause adverse health effects mean that estimated cause-effect relationships are subject to considerable uncertainty. Gaps in scientific understanding of correspondences between animal and human responses to chemicals and pathogens mean that the use of animal models adds further uncertainty.

As noted above, regulators tend to be sensitive to these uncertainties, in particular, to the prospect of declaring a compound to be safe when it actually poses a significant risk. At present, they adjust quantitative characterizations of risk by using arbitrary "conservative" assumptions, with a number of negative effects discussed above. An alternative approach is to use probabilistic risk assessment methods that incorporate uncertainty formally and explicitly. Lichtenberg and Zilberman (1988a) present a method of estimating uncertainty-adjusted regulatory costs based on such probabilistic risk assessments. This Lichtenberg–Zilberman approach involves minimizing the cost of meeting a nominal risk standard while holding violations to a given (low) probability. Cost-minimizing strategies consist of combinations of measures, some of which are relatively more effective in reducing risk on average, whereas, others are relatively more effective in reducing uncertainty about risk. Monte Carlo methods can then be used to generate regulatory cost as a function of the nominal standard and probability of violation as well as to explore changes in efficient combinations of risk reduction measures. Empirical applications of this approach include cases involving the cost of reducing the risk of cancer from pesticide contamination of drinking water (Lichtenberg et al., 1989), the cost of mitigating the risk of gastroenteritis from consumption of shellfish contaminated by dairy wastes (Lichtenberg and Zilberman, 1988b), the cost of reducing farm workers' cancer risk from insecticide exposure (Harper and Zilberman, 1992); and the cost of meeting nitrate standards in well water (Lichtenberg and Penn, 2003).

There are two principal directions for extension of this approach in the context of food safety. First, the general approach can be used to take uncertainties into account in devising HACCP strategies. Factors contributing to risk differ in terms of uncertainty about (or unobserved variability in) their effects on risk. The Lichtenberg–Zilberman approach allows incorporation of that uncertainty

into formulation of cost-minimizing HACCP strategies. Second, use of the approach implies a need to consider demand for uncertainty reduction as a component of the value of life saving. The degree of reliability with which safety is attained is likely important to consumers and regulators. Methods of incorporating willingness to pay for added reliability (reduced uncertainty) would permit comparison of uncertainty-adjusted benefit and cost.

4. Use Economic Incentives in Designing Public Control Strategies

Economic incentives are an important part of any regulatory strategy. Economic theory suggests that reliance on incentives allows achievement of regulatory goals at low cost in many situations. Moreover, regulations may create incentives that give rise to unintended consequences that undermine the effectiveness of regulation. For example, both nominal food safety standards and the ways in which they are enforced alter the economic incentives facing food processing firms in ways that sometimes increase foodborne risks (see van Ravenswaay and Bylenga, 1991 for a case study of antibiotic and sulfa drug residues in veal). Improvement in the design of regulations can, in principle, increase the economic incentives for firms to produce safer food both in the short run and, via technological change, in the long run (Crutchfield et al., 1997). Gill (1999) found significant variability among beef slaughter plants in their practices and the resulting levels of generic *E. coli* on carcasses and trim destined for hamburgers. Minor modifications in worker practices in the skinning operation caused a significant reduction in generic *E. coli* levels on the carcass, suggesting that small increases in economic incentives may significantly reduce contamination in slaughter plants.

One approach is to shift from process to performance standards. Process standards specify the exact safety-enhancing procedures for firms to use, whereas performance standards allow firms to choose the mix of safety enhancement procedures that generates the regulated level of safety at least cost. In addition, performance standards encourage innovation because firms can keep any cost savings generated by technical improvements. Much of the success of the EPA's sulfur dioxide trading program, for example, can be attributed to substituting performance standards for process standards. Widespread use of low-sulfur coal, along with a number of process innovations, accounted for much of the low cost of meeting stricter sulfur dioxide emissions standards (Schmalensee et al., 1998). These measures would have been impossible under the process standards formerly used by the EPA, which mandated the use of scrubbers to meet emissions targets. Such a shift would not be entirely new for food safety, because HACCP-required testing for *Salmonella* and generic *E. coli* are performance standards (Powell et al., 2001). However, the economic incentives implicit in alternative HACCP approaches deserve further study.

Another possible use of incentives would be to create differentiated markets for safer foods through the use of certification and labeling (see Golan et al.'s

2001 paper on the economics of labeling: ⟨*http://www.ers.usda.gov/publications/aer793/*⟩). Certification is currently used to remedy problems associated with experience and credence goods in a number of markets. Underwriters Laboratories, for instance, is a private organization that certifies the safety of home electrical equipment, and shipping point inspection by the USDA's Agricultural Marketing Service, a government program that certifies the quality of fruits and vegetables. In the case of food safety, the analogy would be to label foods certified as having exceptionally low risk from microbial pathogens. The reliability of testing methods (and thus certification itself) is one key to the feasibility of this approach. If testing distinguishes risk from foodborne pathogens perfectly, then a certification program gives firms incentives to provide enhanced levels of safety—provided that the testing is conducted by a third party that is not beholden to the industry using its services (Viscusi, 1978). But if testing is imperfect, so that certification is not a reliable indicator of enhanced safety, then product differentiation will likely be infeasible (De and Nabar, 1991). In this latter case, the benefits from certification are unlikely to justify the costs. It is also possible that enhanced safety from certification may be undercut by the "lulling effect," that is, consumers taking fewer precautions because of the increased perception of safety, as has been observed in the case of safety caps on poisonous products (Viscusi, 1985). Enforcement is required to ensure that certification standards are met by industry (see, e.g., the counterfeit Underwriter Laboratories certification on electrical extension cords produced in China and illegally sold in the United States in 1999).

Research is needed to determine whether testing is sufficiently reliable to make certification a reasonable policy instrument. Research is also needed to determine the potential for certification in creating incentives for enhanced food safety, that is, on demand for food products differentiated as "safer." One aspect likely to be of major importance is consumer response to perceived risk of illness of foodborne pathogens and to uncertainty about that risk. If consumer behavior is strongly responsive to perceived risk, certification is likely to have substantial effects on demand, creating strong incentives for enhanced safety.

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APPENDIX: COSTS OF *CAMPYLOBACTER*-ASSOCIATED GUILLAIN-BARRÉ SYNDROME

This appendix provides an example of an ERS cost of illness (COI) analysis for one of the chronic sequelae, Guillain-Barré syndrome (GBS), associated

with *Campylobacter jejuni*. Campylobacteriosis is the most common cause foodborne illness in the United States. GBS is the leading cause of acute paralysis in the United States now that polio has been almost eliminated by vaccination programs. Although the causes of GBS are uncertain, many medical researchers believe that GBS is a reaction by a person's immune system responding to fight off several potential triggers, such as some gastrointestinal or respiratory infections. Medical studies all over the world have confirmed that 20–40% or more of patients with GBS had became infected with *Campylobacter* in the 1–3 weeks before the onset of GBS symptoms. Each year, an estimated 1028 patients diagnosed with GBS in the United States had a preceding *Campylobacter* infection.

Although GBS is a secondary complication in a small percentage of human *Campylobacter* infections, it is a severe illness. GBS is characterized by a rapid onset, various degrees of numbness, pain, progressive weakness, or paralysis over 1–4 weeks, and gradual recovery in the first year or two. Almost all patients are hospitalized, and some have relapses. Almost 80% of patients recover with only minor deficits and can return to normal life within a year. Others, however, are permanently bedridden or wheelchair bound or die prematurely because of the illness. Roughly 20% of GBS patients are left significantly disabled.

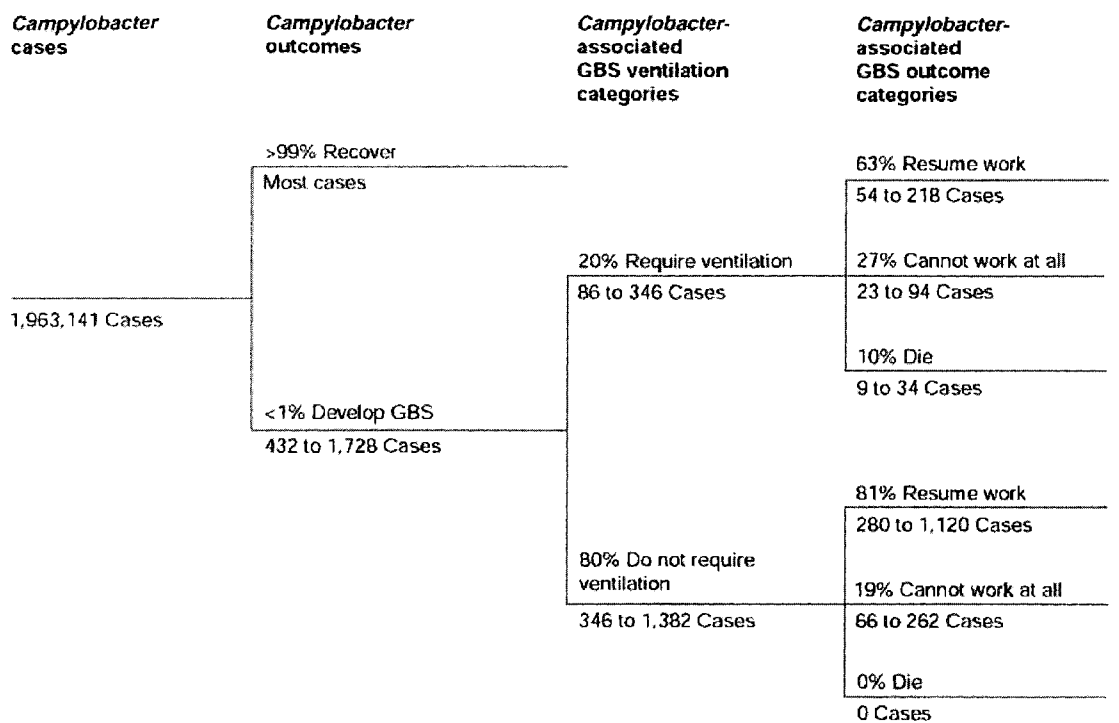
Like polio victims, some patients with GBS require mechanical ventilation to assist breathing. These patients tend to be older and tend to have a poorer prognosis. To capture differences in the prognoses for both younger and older GBS patients and the requirement for mechanical ventilation, we grouped GBS patients into two categories. On the basis of the average ages found by two physicians, Sunderrajan and Davenport, ventilated GBS patients are represented by a 47-year-old patient and patients who did not require mechanical ventilation are represented by a 30-year-old patient.

Several neurologists specializing in GBS suggested that we lower the overall death rate found by Sunderrajan and Davenport to 2% to reflect recent advances in medical care. This adjustment resulted in a total of 9–34 deaths each year from *Campylobacter*-associated GBS (Fig. 7A.1).

Annual productivity losses totaled across all six patient categories from foodborne *Campylobacter*-associated GBS in the United States are estimated at $568.8 million (Table 7A.1). These productivity losses for *Campylobacter*-associated GBS derived with the human capital approach are over six times larger than medical costs.

Annual medical costs include immunoglobulin treatments, plasma exchange, regular hospital room fees, and intensive care unit room fees. Estimated annual medical costs from foodborne sources are $88 million. Summing all medical and lost productivity costs provides an estimate of total annual costs for *Campylobacter*-associated GBS of $656.8 million.

In addition to the health burden of *Campylobacter*-associated GBS, Havelaar et al. (2000) estimated the burden of other *Campylobacter*-related diseases (e.g., *Campylobacter* enteritis, reactive arthritis). This study focused on The



[1]Percentages are rounded.
Prepared by the Economic Research Service, USDA.

Figure 7.1. Estimated annual U.S. cases and disease outcomes of foodborne *Campylobacter*-associated Guillain-Barré syndrome. *http://www.ers.usda.gov/briefing/FoodborneDisease/gallery/Diseasefig5.pdf*

TABLE 7A.1. Paralysis Caused by *Campylobacter*-Associated Guillain-Barré Syndrome Imposes High Costs on Society[1]

	Cases Number	Estimated annual foodborne illness costs Million dollars
Medical:		
Nonventilated patients	870	36.5
Ventilated patients	218	51.5
Subtotal	1,088	88
Productivity loss/premature deaths:		
Nonventilated patients:		
Resumed work	705	4
Cannot work	165	354.8
Died	0	0
Subtotal	870	358.8
Ventilated patients:		
Resumed work	137	4.4
Cannot work	59	73.9
Died[3]	22	131.7
Subtotal	218	210
Total	1,088	656.8

Source: Economic Research Service, USDA, ⟨*http://www.ers.usda.gov/briefing/FoodborneDisease/otherpathogens/index.htm*⟩.

[1] Data from the Centers for Disease Control and Prevention (Mead et al., 1999) except for physician visits, which were estimated by ERS.

[2] These estimated cases and costs are for the chronic complication, Guillain-Barré syndrome, a subset of the number who have acute campylobacteriosis.

[3] Cost calculations are based on the labor market approach for valuing the cost of premature deaths.

Netherlands and used the disability adjusted life year (DALY) approach, an approach related to quality adjusted life years. In essence, DALYs are the sum of the number of years that patients live with disability and the years of life lost by premature disability, after applying weights for the severity of illness (between 0 and 1). Findings from this study cannot be directly compared with the U.S. estimates because of differences in methodology and surveillance data on disease incidence and severity.

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Codex Alimentarius Commission: Information about the Codex Alimentarius and the Joint FAO/WHO Food Standards Program is available at *http://www.codexalimentarius.net*

Economic Research Service (ERS), USDA: Information about the economic cost of foodborne illness, benefit-cost analysis of HACCP, and other economic food safety issues is available at *http://www.ers.usda.gov/Emphases/SafeFood.*

FDA Center for Food Safety and Applied Nutrition (CFSAN): Information about FDA food safety activities, plus the *Bad Bug Book* providing descriptions of individual foodborne pathogens is available at *http://www.cfsan.fda.gov/list.html*

Fight BAC!™ Partnership for Food Safety Education: Information about foodborne illness for consumers and links to other relevant web sites are available at *http://www.fightbac.org/*

Food Safety and Inspection Service (FSIS), USDA: Consumer information, regulations and recalls, HACCP models, etc. at *http://www.fsis.usda.gov/OA/whatsnew.htm*

FoodNet CDC/USDA/FDA Foodborne Diseases Active Surveillance Network: Background information and recent results from FoodNet are available (via the CDC website) at *http://www.cdc.gov/foodnet/*

Food Safety Consortium (University of Arkansas, Iowa State University, and Kansas State University): Newsletter, list of research projects, and links to other relevant web sites are available at *http://www.uark.edu/depts/fsc/*

FSNet: Daily listserve summarizing international media coverage, government announcements, and press releases about food safety issues produced by Dr. Doug Powell, Dept. of Plant Agriculture, University of Guelph, Guelph, Ontario, Canada. To subscribe to FSnet, send mail to: *listserv@listserv.uoguelph.ca.* (Leave subject line

blank. In the body of the message type: subscribe fsnet-L firstname lastname, e.g., subscribe fsnet-L Doug Powell.)

International Food Information Council (IFIC): Information about food safety and other food-related issues is available at: *http://www.ific.org/food/safety*

Joint Institute for Food Safety and Applied Nutrition (JIFSAN) (FDA and University of Maryland): Information about research program and funding opportunities is available at: *http://www.jifsan.umd.edu*

National Academy of Sciences (NAS): The recently released NAS report on *Ensuring Safe Food: From Production to Consumption* can be ordered at a 20% discount at *http://www.nas.edu/* [Click on (1) Institute of Medicine, and then on (2) Recently Released Reports.]

National Alliance for Food Safety (NAFS): Partnership among universities and federal agencies to conduct research, set priorities, educate food handlers, and foster scientific debate at *http://www.nafs.tamu.edu*

NE-165, Private Strategies, Public Policies, and Food System Performance: Does research on the impacts of changes in strategies, technologies, consumer behavior, and policies on the economic performance of the food system, and on how private and public strategies influence improvement in food safety and other quality attributes. It has over 100 members around the world, primarily from universities and government agencies, and a core research group at the Food Marketing Policy Center, Universities of Connecticut and Massachusetts. Its web site is *http://www.umass.edu/ne165/*.

U.S. Government food safety site: Gateway to federal government food safety information with links to sites by CDC, EPA, FDA, and FSIS at *http://www.foodsafety.gov*.

PART II

FOOD HAZARDS: BIOLOGICAL

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CHAPTER 8

PREVALENCE OF FOODBORNE PATHOGENS

LEEANNE JACKSON

INTRODUCTION

Although the U.S. food supply is among the safest in the world, we face ever-changing challenges. There have been wide-scale changes in food processing and packaging technology. Forty to fifty years ago, most foods were manufactured and distributed locally. Today we have large production facilities that distribute foods nationwide, as well as internationally. The globalization of the food supply means that food can become contaminated in one country and cause outbreaks of foodborne illness in another. The centralization of the food supply also provides an opportunity for foodborne pathogens to cause illness in a large proportion of consumers. Foodborne pathogens have developed resistance to traditional preservation techniques (e.g., heat, refrigeration, acid) and with the advent of new processing and preservation technologies, foodborne pathogens will adapt to these new technologies thus becoming resistant to them as well.

The U.S. now has a larger proportion of the population that is immunocompromised or elderly. This segment of the population is more susceptible to foodborne illness. The demographics of the American population have changed with more people living in and around large cities. The dietary habits of consumers have changed as well. More people are eating fresh fruits and vegetables now than five to ten years ago. With all of these changes, one naturally expects to see a change in the prevalence of foodborne pathogens.

BACKGROUND AND HISTORICAL SIGNIFICANCE

For decades, foodborne transmission of pathogenic microorganisms has been a recognized hazard. The predominant foodborne pathogens that were known

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thirty years ago—*Salmonella*, *Clostridium botulinum*, *Clostridium perfringens*, and *Staphylococcus aureus*, have been joined by a widening array of pathogens of bacterial, viral, and parasitic origin. Those pathogens that were only seen associated with animals have presented as illness-causing agents in humans.

Traditionally, most foods were either purchased and prepared on the same day or they were removed from the cellar or cupboard as home-canned products. Also, most foods were eaten on the same day they were prepared, thrown away if there were left-overs, or fed to the farm animals. Grocery stores used to carry only locally grown produce, because that was all that was available. However, now the food supply is truly global in nature, in that at almost anytime of the year you can find an abundance of different produce items available in your supermarket as well as a variety of ethnic foods. Also, consumers used to only buy meat from the local butcher or slaughter their own farm animals. Now the meat you purchase in your local supermarket could come from thousands of miles away.

SCIENTIFIC BASIS AND IMPLICATIONS

Incidence

Recent estimates by the Centers for Disease Control and Prevention (CDC) have placed the incidence of foodborne illness at 76 million illnesses, 325,000 hospitalizations, and 5,000 deaths each year in the United States (Mead et al., 1999). These numbers present a much larger incidence of foodborne illness than previously thought. *Campylobacter* spp. and *Salmonella* spp. are the predominate causes of bacterial-related foodborne illness. *Giardia lamblia* is the most often reported foodborne parasite. However, the vast majority of foodborne illnesses are attributed to viruses. The foodborne pathogens with the highest estimated number of deaths are *Salmonella* spp. *Listeria monocytogenes*, *Toxoplasma gondii*, and norwalk-like viruses.

Foodborne Outbreaks

The regulation of the U.S. food supply is primarily divided among two federal agencies—the U.S. Department of Agriculture/Food Safety and Inspection Service (USDA/FSIS) and the U.S. Department of Health and Humans Services/Food and Drug Administration (USHHS/FDA). The FSIS regulates meat and poultry, as listed in the Meat Inspection Act and the Poultry Inspection Act, and egg products as listed in the Egg Products Inspection Act. The FDA regulates all other food commodities as well as exotic animals as listed in the Food Drug and Cosmetic Act.

Food Safety and Inspection Service (FSIS)-regulated commodities

Listeria monocytogenes *in hot dogs and possibly deli meats—1998/99* From August 1998 through early February 1999, a total of 100 illnesses caused

by *L. monocytogenes* serotype 4b were reported in 22 states. A total of 21 deaths—15 adults and 6 miscarriages/stillbirths—were associated with this outbreak. The manufacturer voluntarily recalled certain production lots of hot dogs and deli meats that might have been contaminated. The outbreak strain of *L. monocytogenes* was isolated from an opened and unopened package of hot dogs (CDC, 1998b). It was postulated that the contamination came from dust due to facility construction.

Listeria monocytogenes *in deli turkey meat* After May of 2000, 29 illnesses attributed to *L. monocytogenes* were identified in 10 states. Subtyping of the patient isolates found them to be indistinguishable by pulsed-field gel electrophoresis (PFGE). A case-control study identified deli turkey meat as the probable source of infection. The implicated manufacturer recalled implicated product in December 2000 (CDC, 2000b).

Escherichia coli *O157:H7 in fermented sausage* Commercially distributed dry-cured salami was associated with an outbreak attributed to *E. coli* O157:H7 in California and Washington in 1994 (CDC, 1995). This is the first outbreak associated with dry-cured salami as a source of *E. coli* O157:H7. A total of 23 laboratory-confirmed cases were reported. All salami associated with illness was purchased from a local grocery chain deli counter. Research conducted with inoculated salami batter determined the *E. coli* O157:H7 could survive the fermentation, drying, and storage process.

Escherichia coli *O157:H7 infections associated with frozen ground beef* In 1997, the Colorado Department of Public Health and Environment identified an outbreak of *E. coli* O157:H7 infections associated with the consumption of a nationally distributed commercial brand of frozen ground beef patties and burgers. *E. coli* O157:H7 isolates from patients and the implicated lot of product were indistinguishable by PFGE. A total of 25,000,000 pounds of ground beef were recalled by Hudson Foods (CDC, 1997).

Food and Drug Administration (FDA)-regulated commodities

Salmonella *Muenchen in unpasteurized orange juice* In 1999, an outbreak of salmonellosis was attributed to a commercially produced unpasteurized orange juice (CDC, 1999). A total of 423 confirmed cases and one death were reported in 21 states and three Canadian provinces. The death occurred with an elderly male who resided in an assisted-living facility. The unpasteurized orange juice was manufactured in Arizona and distributed to multiple states and Canadian provinces under several brand names. Analysis of juice from an unopened container, as well as a blender and some juice-dispensing equipment from selected retail stores, yielded *S.* Muenchen. A comparison of *S.* Muenchen isolates from the juice, retail equipment, and patients yielded an indistinguishable PFGE pattern. The outbreak investigation was unable to determine

the source of the *Salmonella* contamination. The contamination could have occurred in incoming juice components or within the processing establishment.

E. coli *O157:H7 in apple juice* In the fall of 1996, a cluster of *E. coli* O157:H7 infections was epidemiologically linked to the consumption of brand A unpasteurized apple juice. Upon completion of the investigation, a total of 70 people with *E. coli* O157:H7 infections were identified. Of these 70 persons, 25 were hospitalized, 14 developed hemolytic uremic syndrome, and 1 died. *E. coli* O157:H7 was isolated from an unopened container of brand A unpasteurized apple juice. Further investigation at the manufacturing facility did not determine a source for the contamination; however, it was postulated that contamination entered the manufacturing facility on incoming apples since no other juices were associated with illness (Cody et al., 1999).

Salmonella *Agona in toasted oat cereal* In 1998, an outbreak of salmonellosis was associated with a commercially prepared nationally distributed cereal (CDC, 1998a). This was the first reported *Salmonella* outbreak attributed with ready-to-eat cereal. A total of 409 confirmed cases and one death occurred in 23 states. *Salmonella* Agona was isolated from unopened boxes of cereal. Sample analysis of consumer and unopened boxes of cereal yielded an average apparent infective dose between 1 and 45 cells per 30 g serving size (Rosas-Marty and Tatini, 1999). An investigation of the manufacturing facility determined that the contamination may have been attributed to the spraying of a vitamin mix onto the dried cereal.

Escherichia coli *O157:H7 in deer jerky* In 1995, an outbreak of *E. coli* O157:H7 infection was attributed to jerky made from deer meat (Keene et al., 1997). A total of 6 confirmed and 5 presumptive cases were identified. A deer was shot on one day, eviscerated in the field, dragged to the hunters' vehicle, and hung outdoors for 5 days at ambient temperatures. After skinning, the carcass was dismembered and trimmed by hand. A portion of the meat was cut into strips and marinated in the refrigerator. Following marinating, the meat was dried in a home food dehydrator for 12 to 14 hours between 51.7 °C to 57.2 °C.

Environmental samples of the equipment used to dismember the deer and remnants of the deer skin yielded *E. coli* O157:H7. All outbreak associated *E. coli* O157:H7 isolates from the jerky, uncooked venison, equipment, deer skin, and human patient isolates were indistinguishable by Pulsed Field Gel Electrophoresis (PFGE). Recovery experiments found that *E. coli* O157:H7 could be recovered from experimentally inoculated and dehydrated venison meat.

Salmonella *Enteritidis in shell eggs* During the last 15 years, there has been a dramatic rise in the incidence of *S.* Enteritidis (SE) infections in humans worldwide. In the United States, SE emerged as an important cause of human illness in the 1980's and 1990's. Data from the CDC shows that from 1985–

TABLE 8.1. *Salmonella* Enteritidis (SE) Outbreaks (1996–1998)

	1996	1997	1998
Total # of SE outbreaks	50	44	47
Total # of SE outbreaks that implicate food or foods containing eggs or egg products	30	31	25
Total # of cases for all outbreaks	1,460	1,096	709
Total # of hospitalizations for all outbreaks	159	124	90
Total # of deaths for all outbreaks	2	0	3

1998, there were 796 SE outbreaks that accounted for 28,689 illnesses, 2,839 hospitalizations, and 79 deaths. Of the 360 SE outbreaks with a confirmed source, 279 were associated with raw or undercooked eggs (CDC, 2000a). Table 8.1 provides a compilation of the data of SE-associated outbreaks reported for 1996–1998.

A number of SE prevention measures have been put in place in recent years in order to reduce the incidence of SE egg-associated illness. On-farm control programs, egg refrigeration and labeling regulations, consumer and food worker education, adoption of the FDA Food Code in states and localities, in addition to improved surveillance, will contribute to the decrease in the incidence of SE egg-associated illness.

Salmonella spp. in cantaloupe Since 1990, six outbreaks of salmonellosis have been attributed to cantaloupe consumption (Table 8.2). The first outbreak occurred in 1990 and involved 245 cases attributed to *Salmonella* Chester reported in 30 states. The next outbreak occurred in 1991 and caused over 400 cases attributed to *Salmonella* Poona in 23 states and Canada. Twenty-four cases identified with *Salmonella* Saphra infections occurred in California in 1997 (Mohle-Boetani et al., 1999). In Ontario, Canada, 22 cases of *Salmonella* Oranienburg were reported in 1998. The next outbreak occurred in 2000, affecting seven states and yielding 43 cases of *Salmonella* Poona. The last reported outbreak occurred in 2001 and was associated with 46 illnesses and

TABLE 8.2. Melon Associated Outbreaks—1990–2001

Year	Pathogen	No. of Cases	Type of Melon	Location of Outbreak
1990	*Salmonella* Chester	245	Cantaloupe	30 states
1991	*Salmonella* Poona	>400	Cantaloupe	23 states and Canada
1991	*Salmonella* Javiana	26	Watermelon	Michigan
1997	*Salmonella* Saphra	24	Cantaloupe	California
1998	*Salmonella* Oranienburg	22	Cantaloupe	Ontario, Canada
2000	*Salmonella* Poona	43	Cantaloupe	7 states
2001	*Salmonella* Poona	46 (2 deaths)	Cantaloupe	14 states

two deaths attributed to *Salmonella* Poona in 14 states. Following the outbreak in 1991, the FDA analyzed samples of imported cantaloupe in order to determine the prevalence of *Salmonella* spp. These analyses determined that approximately 1% of the exterior of the cantaloupes analyzed harbored *Salmonella* spp. Also following the 1991 outbreak, the FDA issued guidance to the retail and food service industries that outlined safe handling practices for melons. The FDA reissued this guidance following the 2000 and 2001 outbreaks.

Sprout-associated outbreaks Since 1973, 19 outbreaks have been attributed to sprout consumption in the United States (see Table 8.3). More than 1500 cases have been associated with soy, mustard, cress, alfalfa, clover, and mung bean sprouts. In 1997, the National Advisory Committee on Microbiological Criteria for Foods (NACMCF) was asked by the FDA to investigate the issue of sprout-associated outbreaks and to provide recommendations (NACMCF,

TABLE 8.3. Reported U.S. Sprout Outbreaks—1973–2001

Year	Pathogen	No. of Cases	Location of Outbreak	Type of Sprout
1973	*Bacillus cereus*	Unknown	Texas	Soy, Mustard, & Cress
1995	*Salmonella* Stanley	242	17 states and Finland	Alfalfa
1995–96	*Salmonella* Newport	>133	7 states and Canada	Alfalfa
1996	*Salmonella* Montevideo/Meleagridis	>500	California	Alfalfa
1997	*Salmonella* Infantis/Anatum	90	Kansas, Missouri	Alfalfa
1997	*E. coli* O157:H7	108	Michigan, Virginia	Alfalfa
1997/98	*Salmonella* Senftenberg	60	California	Clover/Alfalfa
1998	*E. coli* O157:NM	8	California, Nevada	Alfalfa/Clover
1998	*Salmonella* Havana	18	California	Alfalfa
1998	*Salmonella* Cubana	22	California	Alfalfa
1999	*Salmonella* Mbandaka	73	California, Idaho, Oregon, Washington	Alfalfa
1999	*Salmonella* Typhimurium	137	Colorado	Clover
1999	*Salmonella* St. Paul	36	California	Clover
1999	*Salmonella* Muenchen	100	California, Michigan, Wisconsin	Alfalfa
2000	*Salmonella* Enteritidis	100	California	Mung Bean
2001	*Salmonella* Enteritidis	26	Hawaii	Mung bean
2001	*Salmonella* Kottbus	31	California, Nevada, Arizona	Alfalfa
2001	*Salmonella* Enteritidis	30	Florida	Mung Bean

1999). The majority of the outbreaks were attributed to contaminated seed. The FDA published guidance for the sprout industry to enhance the safety of sprouted seeds. The guidelines provided information on seed disinfection with 20,000 ppm calcium hypochlorite, as well as procedures for testing spent irrigation water for *Salmonella* spp. and *E. coli* O157:H7 (FDA, 1999).

Shigella sonnei *in parsley* Prior to 1998, parsley had not been associated with foodborne illness. In 1998, more than 400 cases of shigellosis were reported in three states and two Canadian provinces (CDC, 1998c). In each outbreak, fresh chopped parsley was sprinkled on dishes or was mixed with the food item. A traceback investigation determined that a farm in Mexico or four farms in California were possible sources for the contaminated parsley. The only reservoir for *S. sonnei* is humans or other primates; therefore, transmission occurs through the fecal-oral route.

Cyclospora cayetanensis *in raspberries, lettuce and basil* Beginning in 1996, a new foodborne pathogen and food vehicle were associated with foodborne illness. *C. cayetanensis* is a coccidian parasite that was originally classified in 1993 by Ortega et al. The oocysts of this parasite are believed to be extremely hardy and can survive harsh environmental conditions. *Cyclospora* oocyts in freshly excreted stools are noninfectious and are believed to require days to weeks outside the host, under favorable environmental conditions (heat and humidity), to sporulate and thus become infectious. In 1996, a multistate outbreak affecting 1,465 people in the U.S. and Canada was associated with Guatemalan raspberries. This clearly demonstrated that food could serve as a vehicle for this pathogen. In 1997, foods other than raspberries were associated with illness. Five outbreaks of cyclosporiasis occurred in the U.S. and Canada that were associated with mesclun lettuce, basil, and raspberries (Herwaldt, 2000). Prior to 1999, *Cyclospora* had never been detected in an epidemiologically implicated food item. An outbreak of cyclosporiasis occurred in Missouri in the summer of 1999 that was associated with the consumption of chicken pasta salad and tomato basil salad. The food item common to both dishes was basil. A leftover sample of chicken pasta salad was found to contain a *Cyclospora* oocyst (Lopez et al., 2001).

Listeria monocytogenes *in homemade Latin-style fresh soft cheese* In the fall of 2000, 12 cases of listeriosis were identified in North Carolina among Hispanics who had eaten homemade Latin-style fresh soft cheese purchased from local markets or from door-to-door vendors (CDC, 2001). Of the 12 cases, 11 were women and one was a 70-year old immunocompromised male. Ten of the women were pregnant, and the resulting *Listeria monocytogenes* infections resulted in five stillbirths, three premature deliveries, and two infected newborns. The cheese was made from raw milk illegally purchased from a local dairy farm. Fourteen isolates were obtained from patients, cheese

samples, and raw milk samples. All fourteen isolates were indistinguishable by PFGE, indicating a common link.

REGULATORY, INDUSTRIAL, AND INTERNATIONAL IMPLICATIONS

As microorganisms adapt to changing environmental conditions, the industry and government must assess whether new control measures should be pursued. Prior to 1991, it was never thought that the high acid content of unpasteurized juice would allow the survival or growth of foodborne pathogens. In response to numerous outbreaks associated with unpasteurized juice products, new regulations were implemented by the FDA to prevent future outbreaks. These new regulations involved the use of a warning labeling as well as Hazard Analysis Critical Control Point (HACCP) systems (see Part IV). The industry has also developed new means to process and produce food products. Many of these methods utilize technologies that will extend the shelf-life and maintain the fresh characteristics of the food.

International travel has increased tremendously during recent years. It was estimated that by the year 2000, the number of travellers would be in the order of 660 million people. It was also estimated that, depending on the destination, some 20 to 50% of the world travellers may acquire a foodborne infection. This means that between 130 to 330 million people per year may acquire a foodborne infection due to exposure to foodborne pathogens in countries other than their home country.

CURRENT AND FUTURE IMPLICATIONS

Consumer Education

The continued importance of consumer education cannot be overemphasized. By reinforcing simple food safety messages, the public will begin to change their food handling habits. Also, by notifying the consumer when a problem occurs, such as a foodborne outbreak or a product recall, they may change their eating or purchasing habits. Those individuals who fall into the "at-risk" category are especially vulnerable to foodborne illness and must be educated on foods that one shouldn't eat.

Surveillance

Most countries have systems for reporting notifiable disease, but very few have foodborne disease surveillance programs. On a worldwide basis, very little is known about foodborne disease. Within the U.S., foodborne disease surveillance is conducted by local, state, and federal public health agencies. By identifying outbreaks quickly and determining the source or cause for the outbreak,

surveillance allows one to determine early intervention strategies that may be applied to mitigate further illness.

Emergence/Reemergence

There are two types of emergence associated with foodborne pathogenic microorganisms. One is a true emergence—this is the emergence of a microorganism that had not previously been associated with human illness. The second type—reemergence—is much more common. A microorganism typically associated with a particular type of food, environmental condition, or geographic location will find a new way to cause disease. As food processing changes, microorganisms will continue to adapt in order to survive.

Research

To keep pace with the changing microbial world, we must continue to support and conduct research. As pathogens begin to adapt, change, and find new niches, we must conduct research to understand and control these emerging pathogens. Broad category areas for research include: detection methodology, growth and survival characteristics, microbial ecology, pathogenicity, and control.

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CHAPTER 9

PHYSIOLOGY AND SURVIVAL OF FOODBORNE PATHOGENS IN VARIOUS FOOD SYSTEMS

G.E. RODRICK and R.H. SCHMIDT

INTRODUCTION AND DEFINITION OF ISSUES

Foodborne pathogens can exist in raw or improperly processed and handled foods. Whether pathogenic microorganisms will be present in sufficient numbers to cause disease or produce toxins depends on the growth and survival characteristics of particular organisms and on the conditions to which the foods are exposed. Infectious bacteria growing in food products have varied metabolic rates and growth characteristics and are affected by nutrient composition and storage conditions, among other factors. Many bacteria are capable of growth and/or survival under extreme conditions of food processing and storage (i.e., low or high temperature, high salt, low pH), although toxigenic bacteria generally require very specific growth conditions for toxin production. Pathogenic bacteria have varied heat resistance and some produce spores, which increases their heat resistance and their ability to survive extreme conditions. Although viruses and parasites do not grow in food products, they are capable of surviving at sufficient numbers to cause infection.

BACKGROUND AND HISTORICAL SIGNIFICANCE

Efficient food safety and sanitation systems have evolved through scientifically advanced food processing and food safety surveillance technologies. Changing lifestyles have also created a demand for more convenient, shelf-stable, and ready-to-eat foods. The microbial flora of food products includes those microorganisms associated with raw materials, those acquired from food handling

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procedures, those acquired from (or those that survive) food processing and preservation treatments, and those that multiply during storage.

Because organisms are highly adaptable, technological advances, although lowering the total level of microbial contamination found in food, may also select or alter the microbial flora and create new problems. Such advances have included improved refrigeration, modified atmosphere packaging, vacuum sealing, and microwave cooking. Agricultural practices may also change the microbial flora, as with the advent of more centralization, more crowding of animals in feedlots and in transit to slaughter, altered feeding practices, and subtherapeutic antibiotic and drug use. Medical antibiotic and drug use may also play a role in the evolution of resistant strains of pathogens.

SCIENTIFIC BASIS AND IMPLICATIONS

The majority of the pathogens that contaminate food products are natural inhabitants of the environment, soil, plants, and animals. Their survival and growth in foods is affected by a wide range of factors, which have been categorized as intrinsic and extrinsic. Application of combined or synergistic effects of these intrinsic and extrinsic factors in food preservation is the basis of barrier or "hurdle" technology. Pathogen growth and survival are also affected by the relationships among the varied types of microorganisms that make up the complex microbial flora. Depending on environmental conditions, these microorganisms may grow either competitively or cooperatively.

Intrinsic Factors Affecting Growth and Survival

A number of factors intrinsic to foods affect microbial growth and survival. These include pH, moisture content, oxidation-reduction potential, nutrient content, antimicrobial constituents, and biological structure. The intrinsic factors are thought to have evolved as defense mechanisms against foreign microorganisms that can invade and multiply in plant or animal tissues, and they collectively represent nature's way of protecting and preserving the tissues. For example, most fruits—whose biological function is protection of the vital reproductive body or seed—have pH values below those tolerated by many spoilage organisms. Although the pH of living animals favors the growth of microorganisms, other intrinsic properties of animal tissue may control microbial growth and survival. By assessing the various intrinsic factors in individual foods, one can predict what general types of microorganism may be present and adjust handling and processing procedures to ensure a high-quality, safe product.

Acidity It is well established that most microorganisms survive and grow well within a pH range of 6.5–7.0. However, the pH range for microorganisms growing on food is quite wide (pH 4.0–9.5). Although few microorganisms

TABLE 9.1. Minimum pH Values for Selected Foodborne Bacteria[a]

Aeromonas hydrophila	~6.0
Alicyclobacillus acidocaldarius	2.0
Bacillus cereus	4.9
Clostridium botulinum, Group I	4.6
C. botulinum, Group II	5.0
C. perfringens	5.0
Escherichia coli O157:H7	4.5
Gluconobacter spp.	3.6
Lactobacillus brevis	3.2
L. plantarum	3.3
Lactococcus lactis	4.3
Listeria monocytogenes	4.1
Plesiomonas shigelloides	4.5
Pseudomonas fragi	~5.0
Salmonella spp.	4.1
Shewanella putrefaciens	~5.4
Shigella flexneri	~5.5
S. sonnei	5.0
Staphylococcus aureus	4.0
Vibrio parahaemolyticus	4.8
Yersinia enterocolitica	4.2

[a] From Jay (1996).

(primarily yeast and molds) grow below pH 4.0, several are capable of survival at low pH (Table 9.1). Growth and survival at low pH values are dependent on the type of microorganism and on other factors such as temperature, acid type, salt level, food composition, and the presence of preservatives (e.g., potassium sorbate or sodium benzoate). Microorganisms are generally more susceptible to pH change during early or logarithmic growth phases, in which rapid growth occurs, than during stationary or resting growth phases.

As shown in Tables 9.2 and 9.3, the acidity of food products is highly varied. Thus growth and survival of microorganisms also vary among food systems. In general, less acidic products, including meats, seafood, and vegetables, are more susceptible to bacterial spoilage as well as to pathogenic growth. High-acid products, such as fruits, fruit juices, soft drinks, vinegar, and wines, possess pH values below those at which bacteria usually grow. Therefore, it is common for these products to undergo yeast and mold spoilage and not bacterial spoilage (one exception being the spoilage of certain fruit juices by lactic acid bacteria and other acid-tolerant bacteria).

The pH of some foods is inherent, but in others the pH may be affected by the action of certain microorganisms. This effect, known as biological acidity, is seen in lactic acid-fermented products such as cheese, cultured dairy products, sauerkraut, and pickles. Some foods resist changes in pH caused by

TABLE 9.2. Approximate pH Values of Some Fresh Fruits and Vegetables[a]

Product	pH
Vegetables	
Asparagus (buds and stalks)	5.7–6.1
Beans, string and lima	4.6–6.5
Beets, sugar	4.2–4.4
Broccoli	6.5
Brussels sprouts	6.3
Cabbage, green	5.4–6.0
Carrots	4.9–5.2; 6.0
Cauliflower	5.6
Celery	5.7–6.0
Corn, sweet	7.3
Cucumbers	3.8
Eggplant	4.5
Lettuce	6.0
Olives	3.6–3.8
Onions, red	5.3–5.8
Parsley	5.7–6.0
Parsnip	5.3
Potatoes, tuber and sweet	5.3–5.6
Pumpkin	4.8–5.2
Rhubarb	3.1–3.4
Spinach	5.5–6.0
Squash	5.0–5.4
Tomatoes (whole)	4.2–4.3
Turnips	5.2–5.5
Fruits	
Apples	
fruit	2.9–3.3
cider	3.6–3.8
Bananas	4.5–4.7
Figs	4.6
Grapefruit (juice)	3.0
Limes	1.8–2.0
Melons, honeydew	6.3–6.7
Oranges (juice)	3.6–4.3
Plums	2.8–4.6
Watermelons	5.2–5.6
Grapes	3.4–4.5

[a] From Jay (1996).

TABLE 9.3. Approximate pH Values of Some Foods of Animal Origin[a]

Product	pH
Dairy	
Butter	6.1–6.4
Buttermilk	4.5
Milk	6.3–6.5
Cream	6.5
Cheese	
American mild	4.9
Cheddar	5.9
Meat and poultry	
Beef (ground)	5.1–6.2
Ham	5.9–6.1
Veal	6.0
Chicken	6.2–6.4
Fish and shellfish	
Fish, most species[b]	6.6–6.8
Clams	6.5
Crabs	7.0
Oysters	4.8–6.3
Tuna fish	5.2–6.1
Shrimp	6.8–7.0
Salmon	6.1–6.3
Whitefish	5.5

[a] From Jay (1996).

[b] Just after death.

microbial growth and are considered buffered. Meat and milk products are buffered by the various proteins they contain. In contrast, vegetables are low in protein and do not resist pH changes.

Acid has two significant effects on respiring microbial cells: It renders the food less optimal as an environment for key enzymatic reactions, and it influences the transport of nutrients into the cell. Metabolic functions such as the synthesis and utilization of deoxyribonucleic acid (DNA) and adenosine triphosphate (ATP) require a neutral pH. When microorganisms are grown below or above their optimal pH, an increase in the length of the lag time (the period just after inoculation or contamination when cells have not yet begun to grow exponentially) is observed. The lag time may be extended even more if the substrate on which the cells are growing is buffered at a low pH.

The transport of metabolites into bacterial cells can be affected by the environmental pH. Bacterial cells tend to have a residual negative charge. Therefore, nonionized (uncharged) compounds can enter the cell, but ionized (charged) compounds cannot. Specifically, organic acids in their ionized form

(at higher, i.e., neutral or alkaline, pH) do not enter microbial cells, whereas nonionized acids (at low pH) are capable of transport into microbial cells.

The other effect exerted on microorganisms by adverse pH is the interaction between the H^+ and the enzymes in the cytoplasmic membrane. Under the influence of acidity, the morphology of some microorganisms changes: For example, the hyphae of *Penicillium chrysogenum* are shortened when the organism is grown in medium whose pH is >6.0.

Other environmental factors, such as temperature and salt, may interact synergistically with pH. For example, the pH of the substrate becomes more acid as the temperature increases. Thus many microorganisms may have higher acid tolerance at lower temperatures. For most microorganisms, when salt concentrations exceed the optimal range, the pH range that permits growth is narrowed. Adverse pH also makes microorganisms more sensitive to a wide variety of toxic agents.

Because enteric pathogens must survive the acidity of the stomach before reaching the intestinal tract to cause illness, their acid survival properties are important to their pathogenicity. Certain strains of *Yersinia enterocolitica* have shown low pH stability and survival in tartar sauce (Aldova et al., 1975), cheese (Moustafa et al., 1983), and yogurt (Ahmed et al., 1986). *Listeria monocytogenes* has shown the ability to survive the manufacture of fermented products including sauerkraut, cheese products (Papageorgiou and Marth, 1989; Ryser and Marth, 1987, 1988), and sausages (Junttila et al., 1989; Glass and Doyle, 1989). The waterborne pathogen *Plesiomonas shigelloides*, which is often associated with seafood, has been shown to be both acid- and salt tolerant, with some strains exhibiting growth at pH 4.0 (Miller and Koburger, 1986). Certain strains of *Escherichia coli* O157:H7 have been shown to have exceptional tolerance for acid pH, surviving in apple cider (pH 3.7–4.1) stored for 14–21 days at 4°C (Miller and Kaspar, 1994). Further, survival of these *E. coli* O157:H7 strains in acidic trypticase soy broth (pH 2, 3, and 4) was greater at 4°C than at 25°C.

Exposure to a moderately low pH can result in cells with enhanced acid survival properties. This phenomenon, known as acid adaptation, has been observed in *E. coli* and in species of *Salmonella* (Leyer and Johnson, 1993), *Listeria* (Kroll and Patchett, 1992), *Streptococcus*, and *Enterococcus* (Belli and Marquis, 1991). The most extensively studied acid adaptation is the acid tolerance response (ATR) of *Salmonella typhimurium* (Foster, 1993). Acid-adapted *S. typhimurium* has been shown to have increased resistance to food processing and preservation treatments (i.e., heat, salt, hydrogen peroxide, and increased osmolarity; Leyer and Johnson, 1993).

Indigenous antimicrobial agents Certain naturally occurring substances indigenously found in some foods enhance their stability by killing or inhibiting microorganisms. Examples of such compounds in plants are essential oils such as eugenol in cloves, allicin in garlic, cinnamic aldehyde and eugenol in cinna-

mon, allyl isothiocyanate in mustard, eugenol and thymol in sage, and carvacrol, isothymol, and thymol in oregano.

Cow's milk contains several antimicrobial substances, such as lactoferrin, conglutinin, and the lactoperoxidase system. The lactoperoxidase system, the best-known of these agents, consists of three components—lactoperoxidase, thiocyanate, and peroxide—all of which are required for antimicrobial activity. Gram-negative bacteria such as pseudomonads are very sensitive to extremely small amounts (<1.0 ppm) of these compounds (Zapico et al., 1983). This system has been used to preserve milk in underdeveloped countries where refrigeration is rare. An interesting feature of the system is that it can alter the thermal properties of microorganisms in milk. For example, the thermal D values (decimal reduction: the time required at constant temperature to reduce the bacterial population by 1 log) of *L. monocytogenes* and *Staphylococcus aureus* may be reduced by >80% (Kamau et al., 1990). The underlying mechanism remains unclear. Among other components of milk, fatty acids and casein have been shown to have antimicrobial activity under certain conditions. Raw milk also contains a rotovirus inhibitor, but this is destroyed by pasteurization.

Eggs, milk, clams, and oysters contain lysozyme, which can act as an antimicrobial agent (Cheng and Rodrick, 1975). Fruits, vegetables, tea, molasses, and a number of plants show antibacterial and antifungal activities thought to arise from hydroxycinnamic acid derivatives, such as ferulic, caffeic, and chlorogenic acids. Cruciferous plants such as cabbage, brussels sprouts, broccoli, and turnips contain glucosinolates in their cell vacuoles. On rupture, these compounds release isothiocyanates, which possess antifungal and antibacterial activity.

Oxidation-reduction potential It is well known that microorganisms exhibit different sensitivities to the oxidation-reduction (O/R) potential of their growth media. The O/R potential of a substrate is the ease with which the substrate loses or gains electrons. When an atom or molecule loses electrons it is oxidized, and when it gains electrons it is reduced; therefore, a substrate that gives up electrons easily is a good reducing agent and one that readily takes up electrons is a good oxidizing agent. The transfer of electrons from one compound to another creates a potential difference (E) between them that can be measured with a potentiometer. E, expressed in millivolts (mV), may be positive (oxidation), negative (reduction), or zero.

The O/R potential of food systems or complex growth media (expressed as E_h) is affected by the oxygen tension of the environment, the availability of the food system to that environment, the inherent O/R characteristics of the system, and the poising capacity (resistance to E_h change). Reducing conditions in food products are maintained by reducing components that include the sulfhydryl (SH) groups in proteins and amino acids, ascorbic acid moieties, and/or reducing sugars. Oxidizing conditions are influenced by the presence of oxygen, oxidizing catalysts (e.g., iron and copper), and certain oxidation reactions (e.g.,

lipid oxidation). Because E_h measurement is dramatically influenced by pH, reported values should indicate the pH of the system. The E_h of foods varies widely. Plant foods and juice products tend to have positive E_h values ranging from 300 to 400 mV. Protein-based foods generally have negative E_h values (e.g., meat products −200 mV; cheese products −20 to −200 mV).

Generally, aerobic microorganisms require positive E_h values and anaerobes require negative E_h values for growth. The E_h requirements for the growth of strict anaerobes (such as *Clostridium*) are approximately −200 mV. Such low E_h values would be inhibitory to strict aerobes such as *Bacillus*. Other bacteria may be classified as microaerophilic—defined as aerobes that grow better at lower (reducing) E_h values—or as facultatively anaerobic (those that can grow either anaerobically or aerobically).

Moisture content One of the oldest methods of preserving food is drying or dehydration, accomplished by removing water and/or binding the water in the food so that microorganisms cannot grow. The water requirements for microorganisms are described in terms of the water activity (a_w) in their environment. This value is defined by the ratio of the water vapor pressure of a food to the vapor pressure of pure water at the same temperature (thus pure water has an a_w of 1.00). For example, the a_w of a saturated solution of sodium chloride in water is 0.75 (see Table 9.4). Water activity is related to relative humidity (RH; discussed below): $RH = 100 \times a_w$. Because all biochemical reactions require an aqueous environment, reducing water availability adversely affects enzyme activities and hence impairs biological processes. As a general rule, lowering a_w lengthens microorganisms' lag phase of growth, decreases their growth rate, and reduces the final population size.

The a_w of most fresh foods is >0.98; approximate minimal a_w values for growth of important food microorganisms are shown in Table 9.5. In general,

TABLE 9.4. Relationship Between Water Activity (a_w) and Concentration of Salt Solutions[a]

Water activity (a_w)	Sodium chloride concentration	
	Molal	Percentage (w/v)
0.995	0.15	0.9
0.99	0.30	1.7
0.98	0.61	3.5
0.96	1.20	7
0.94	1.77	10
0.92	2.31	13
0.90	2.83	16
0.88	3.33	19
0.86	3.81	22

[a]From Jay (1996).

TABLE 9.5. Approximate Minimum a_w Values for Growth of Microorganisms Important in Foods[a]

Organism(s)	a_w
Groups	
Most spoilage bacteria	0.9
Most spoilage yeast	0.88
Most spoilage molds	0.80
Halophilic bacteria	0.75
Xerophilic molds	0.61
Osmophilic yeast	0.61
Specific organisms	
Clostridium botulinum, type E	0.97
Pseudomonas spp.	0.97
Acinetobacter spp.	0.96
Escherichia coli	0.96
Enterobacter aerogenes	0.95
Bacillus subtilis	0.95
Clostridium botulinum, types A and B	0.94
Candida utilis	0.94
Vibrio parahaemolyticus	0.94
Botrytis cinerea	0.93
Rhizopus stolonifer	0.93
Mucor spinosus	0.93
Candida scottii	0.92
Trichosporon pullulans	0.91
Candida zeylanoides	0.90
Staphylococcus aureus	0.86
Alternaria citri	0.84
Penicillium patulum	0.81
Aspergillus glaucus	0.70
Aspergillus conicus	0.70
Zygosaccharomyces rouxii	0.62
Xeromyces bisporus	0.61

[a]From Jay (1996).

yeast and molds grow over a wider a_w range than bacteria, which usually require a higher water activity. For example, most spoilage bacteria will not grow below an a_w of 0.91, whereas molds can grow as low as 0.81 a_w. Among bacterial pathogens, *S. aureus* can grow as low as 0.84 a_w, but its toxin production may be reduced. *Clostridium botulinum* cannot grow below 0.94 a_w.

Relationships between a_w, temperature, pH, E_h, and nutritional factors can influence the growth of many foodborne microorganisms. For example, at any given temperature, lowering a_w reduces the ability of microorganisms to grow. The a_w range that allows growth of a specific microorganism can be extended

by the presence of certain nutrients or growth factors. Table 9.5 lists approximate minimum a_w values for some foodborne microorganisms.

Although microorganisms do not grow in dehydrated food products, they are generally capable of surviving in them. Long-term survival of *Salmonella* at low a_w is well documented. Species variability in survival characteristics has been shown for *Salmonella* during long-term (19 month) storage of chocolate and cocoa products and nonfat dry milk (Tamminga et al., 1977). *L. monocytogenes* has also been shown to survive the manufacture and long-term storage of nonfat dry milk (Doyle et al., 1985).

In general, microorganisms grown at suboptimal a_w accumulate compatible osmoprotective solutes such as K^+, glutamine, glutamate, proline, sucrose, trehalose, and polyols (i.e., glucosylglycerol) to counteract osmotic stress. Such solutes accumulate through cellular synthesis or increased transport. For example, although enteric pathogens such as *E. coli* and *S. typhimurium* exposed to adverse a_w do not synthesize proline as a protective measure, they nonetheless accumulate proline by enhanced transport into the cells (Grothe et al., 1986). *L. monocytogenes* is able to accumulate several osmoprotectants (primarily carnitine) when grown under unfavorable osmotic conditions (Beumer et al., 1994). Many researchers (see Park et al., 1995) believe that growth of *L. monocytogenes* at 4°C is caused by its accumulation of glycine betaine. *Salmonella oranienburg* grown at suboptimal water activity levels has demonstrated an elevation in respiratory activity in the presence of proline (Townsend and Wilkinson, 1992).

Overall, the effect of reduced water activity on the nutrition of microorganisms appears to be of a general nature, because cell metabolism depends on reactions in an aqueous environment. Microorganisms that can grow under extreme water activity conditions do so by virtue of their ability to concentrate salts, polyols, and amino acids to internal levels sufficient not only to prevent water loss but to allow the microorganism to extract water from its environment.

Nutrient content To grow, microorganisms require, besides water, (1) an energy source, (2) a nitrogen source, (3) vitamins (especially B vitamins) and related cofactors, and (4) minerals. Energy sources for microorganisms include simple sugars, alcohols, and amino acids. Very few microorganisms are able to metabolize polysaccharides such as starch, cellulose, and glycogen (which must first be degraded to simple sugars), and few can utilize fats. The primary nitrogen source for food microorganisms is amino acids; some species can also hydrolyze and use more complex nitrogen sources such as peptides and proteins.

B vitamins are found in most foods at levels adequate to support the growth of microorganisms (such as gram-positive bacteria) that cannot synthesize these vitamins. Gram-negative bacteria and yeast can synthesize B vitamins and as a result can grow in and on foods low in B vitamins. Fruits tend to fall into this category, which (along with their usually low pH and positive E_h) may help explain why fruits are generally spoiled by molds rather than bacteria.

Structure The coverings of many foods help prevent the entry of microorganisms and subsequent food damage and spoilage. For instance, the skin of fish and meats tends to dry out faster than the flesh it covers, retarding spoilage. Fruits and vegetables are also usually covered by skins and spoil faster when these are damaged or broken than when they are intact.

Extrinsic Factors Affecting Growth and Survival

Extrinsic factors are those factors associated with the storage environment that can affect both a food and the associated microorganisms. These include heat treatment, storage temperature, relative humidity of the environment, presence and concentration of gases, and presence and activity of other microorganisms.

Heat treatment Food products may be subjected to a variety of treatments that eliminate or reduce the potential for pathogenic microorganisms. The most common approach is heat treatment, including pasteurization, sterilization, and cooking. Microorganisms vary in their heat resistance, with the most heat stable being termed thermodurics. With exception of the spore formers (e.g., *Clostridium* and *Bacillus*), most microbial pathogens can be destroyed by high-temperature heating. However, certain bacterial toxins (e.g., the *S. aureus* enterotoxin) as well as some viruses (e.g., hepatitis A) are relatively heat stable (Cliver, 1994).

Selection of appropriate process parameters of temperature and heating time for a particular food is based on the properties of the most heat-resistant pathogen associated with the product, heat penetration and transfer characteristics, and compositional parameters. In commercial sterilization, appropriate heat treatment is applied to achieve a 12-log reduction of test spores of higher heat resistance than *C. botulinum*. Pasteurization is a milder heat treatment applied to destroy pathogens likely to be associated with a specified food system. For example, the heat treatment involved with milk pasteurization is based on the destruction of *Coxiella burnetii* (the causative agent of Q fever), and the pasteurization requirements for egg products are designed to destroy *Salmonella*.

Storage temperature Because microorganisms grow over a wide temperature range, it is important to select proper food storage temperatures to help control their growth. The general effect of temperature on microbial activity is shown in Figure 9.1. The lowest temperature at which microorganisms are known to grow is −34°C (−29°F), and the highest is slightly over 100°C (212°F). Microorganisms are generally categorized into three groups based on their growth temperature requirements. The largest category are the mesophiles, which grow well between 20°C (68°F) and 45°C (113°F). Those that grow well between 55°C (131°F) and 65°C (149°F) are called thermophiles. The foodborne thermophilic bacteria of most importance belong to the genera *Bacillus* and *Clostridium*. Finally, some mesophiles, termed psychrotrophs, are

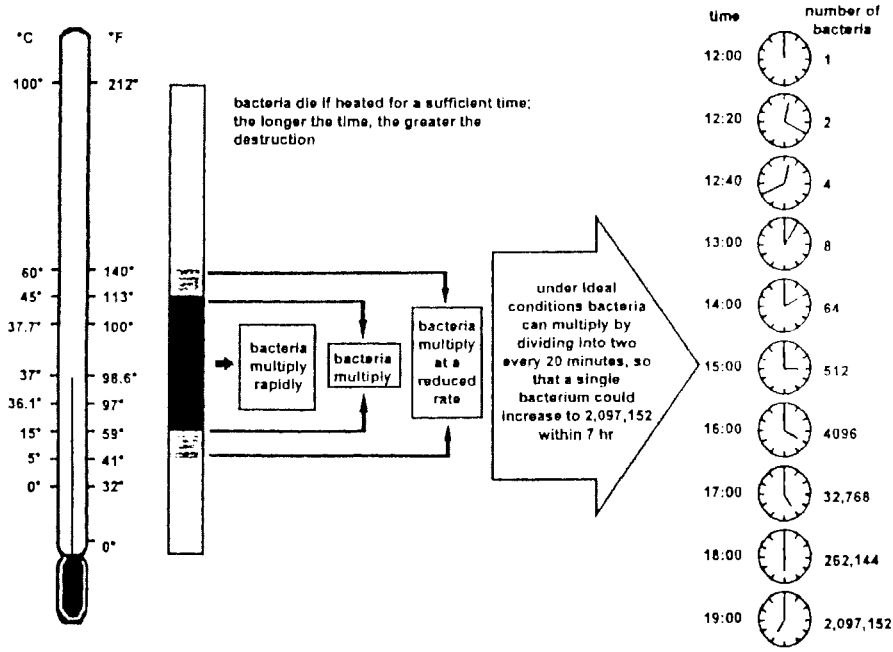

Figure 9.1. General effect of temperature on bacteria. Adapted from Jay (1996).

capable of growth at or below 7°C (45°F)—in contrast to other microorganisms, which may survive in food held at refrigeration temperatures but will not grow. Psychrotrophs grow well at refrigeration temperatures and cause spoilage of meats, fish, milk, poultry, and eggs. Psychrotrophic species include the genera *Alcaligenes*, *Shewanella*, *Brochothrix*, *Corynebacterium*, *Flavobacterium*, *Lactobacillus*, *Micrococcus*, *Pseudomonas*, *Psychrobacter*, and *Enterococcus*.

Psychrotrophic foodborne pathogens that have been shown to grow at refrigeration temperatures are listed in Table 9.6. Although other pathogens do not grow at low temperatures, they are capable of survival (CAST, 1994). Thus temperature abuse and fluctuation during storage should be avoided to prevent these organisms from growing to sufficient numbers to cause disease.

Molds are able to grow over a wide range of pH, osmotic pressure, nutrient content, and temperature. Many molds, such as *Aspergillus*, *Cladosporium*, and *Thaminidium*, are able to grow under refrigeration conditions on eggs, meats, and fruits. Yeast can grow in both the psychrotrophic and mesophilic temperature ranges.

Storage temperature may be the most important parameter affecting the spoilage and safety of highly perishable, ready-to-eat foods. Improper temperature control has been an important contributing factor in foodborne disease outbreaks. Freezing is not an effective method of killing pathogens. In fact, improper thawing temperatures can result in microorganism growth, and a

TABLE 9.6. Minimum Growth Temperatures of Selected Pathogenic Foodborne Microorganisms[a]

Pathogen	Minimum growth temperature (°F)
Bacillus cereus	42
Clostridium botulinum	38
Listeria monocytogenes	32
Salmonella spp.	43
Staphylococcus aureus	45
Escherichia coli O157:H7	32
Yersinia enterocolitica	38

[a] Adapted from CAST (1994) and Schmidt (1998).

frozen and improperly thawed food product may be an even more favorable substrate for microbial growth than the fresh food if the freeze-thaw process has caused sufficient cellular damage for nutrient release.

Relative humidity The relative humidity (RH) of the storage or packaging environment is important for maintaining an optimal a_w in the food and controlling the growth of microorganisms on the surface of the food. If a food a_w has been set, it is important that the food not pick up moisture from its environment and thereby increase its a_w and allow microorganism growth. Foods placed in low-RH environments will lose water and equilibrate with their environment. Conversely, foods with low a_w will gain moisture (increase a_w) when stored in a high-RH environment.

The relationship between temperature and RH value—in general, the higher the temperature, the lower the RH—should be kept in mind when storing foods. Foods that undergo surface spoilage by molds, yeast, and bacteria should be stored under low-RH conditions. When improperly wrapped, foods such as meats, whole chickens, and fish stored in a refrigerator tend to suffer surface spoilage before deep spoilage occurs because of the high RH of the refrigerator and the fact that surface spoilage bacteria on meats tend to be aerobic. Therefore, in selecting proper storage conditions, consideration must be given to the potential for surface growth as well as to the need to maintain desirable qualities in the food. Altering the gaseous environment of the food (as discussed in the following section) can retard surface spoilage without the need to lower the relative humidity.

Atmospheric composition Modification of the atmosphere during food storage, referred to as controlled-atmosphere (CA) or modified-atmosphere (MA) storage, has become widely accepted in certain segments of the food industry as a means to improve shelf life (see Chapter 4). Atmospheric modification can be achieved by the use of various gas mixtures that are high in car-

bon dioxide (CO_2) or nitrogen (N_2) either in the storage chamber or in the packaging, or by vacuum packaging. The use of O_3 as a preservative during storage has also received consideration in recent years. O_3 is a highly effective broad-spectrum bacteriocide. However, its strong oxidative properties have limited its use to applications where lipid oxidation and equipment corrosion are not concerns.

Increasing the level of CO_2 during fruit storage has been shown to retard fungal rotting of fruits. CO_2 also acts as a competitive inhibitor of ethylene and thus delays fruit ripening. Vacuum packaging, as well as CO_2 or N_2 enrichment, is also being used in meat storage. The overall effect of these practices is to inhibit gram-negative spoilage microorganisms (e.g., *Pseudomonas*) and molds. Growth of beneficial lactic acid bacteria is also encouraged, which enhances the shelf life of the meat products (Blickstad and Molin, 1983; see ***Presence of other microorganisms***, below). In most applications, CO_2 has been shown to be more effective than either vacuum packaging or N_2 in improving meat shelf life.

Although more research is needed, atmospheric enrichment and/or vacuum packaging are also thought to inhibit most foodborne pathogens. A notable exception is the concern for the possible germination of *C. botulinum* spores under highly anaerobic environments, which occur at extremely high pressure of CO_2 or N_2 gases and under high-vacuum conditions (Lambert et al., 1991). More typically, high CO_2 pressures have been shown to be quite lethal to *Salmonella* (Wei et al., 1991). Effects of atmosphere modification on *L. monocytogenes* vary, with CO_2 being more effective than N_2.

Presence of other microorganisms The microflora of food products consists of a mixture of microorganisms, which may include spoilage microorganisms, pathogens, and innocuous microorganisms as well as desirable microorganisms that aid in food preservation. The most notable of these desirable microorganisms are the lactic acid bacteria. These are essential to the production of a variety of fermented food products, including cheese and cultured dairy products, pickles, sauerkraut, and sausages. Furthermore, their growth and activity enhance the shelf life of packaged meat products. In addition to the direct effect of the lowered pH from the lactic acid, lactate itself is also inhibitory to other bacteria (Williams et al., 1995). Many lactic acid bacteria possess the lactoperoxidase system (see ***Indigenous antimicrobial agents***, above), and this results in synthesis of hydrogen peroxide, which inhibits other bacteria. Certain lactic acid bacteria also produce another class of antimicrobial compounds, termed bacteriocins (Klaenhammer, 1988).

Some spoilage microorganisms also inhibit the growth of pathogenic microorganisms through competition; others, however, can stimulate pathogen growth. For example, *Pseudomonas* species have been shown to stimulate *L. monocytogenes* (Marshall and Schmidt, 1988) and *S. aureus* (Seminiano and Frazier, 1966), among others, by providing more available substrates for their growth through proteolysis and lipolysis.

Although this has not been as extensively studied as bacterial effects, the presence of yeast and molds and/or their metabolites can alter the growth and activity of bacteria. For example, it is generally accepted that the yeast metabolites (such as carbon dioxide and ethanol) in alcoholic beverages and bread products are inhibitory to many spoilage and pathogenic bacteria. During the ripening of Camembert and related cheese products, the naturally occurring yeast exerts an antilisterial effect (Ryser and Marth, 1987). On the other hand, the growth of *L. monocytogenes* may in fact be stimulated by the mold *Penicillium camemberti* that is associated with Camembert manufacture (Ryser and Marth, 1988).

REGULATORY, INDUSTRIAL, AND INTERNATIONAL IMPLICATIONS

With the exception of how they may be affected by improper manufacturing techniques or poor sanitation practices, the intrinsic factors discussed above do not generally fall under regulatory scrutiny. However, many of the extrinsic factors, especially heat treatment and food storage temperature requirements, do fall under federal, state, and international regulations.

Heat Treatment

Commercial sterilization of hermetically sealed food products domestically manufactured or imported into the U.S. is regulated by the Food and Drug Administration (FDA; 1998a). These regulations cover low-acid canned foods (LACF) that have a pH > 4.6 and an a_w of ≥ 0.85 and acidified foods (AF) that have been acidified to a pH of ≤ 4.6. Although the FDA does not approve, license, or issue permits for finished food products in interstate commerce, all commercial processors and importers of LACF and AF are required to register their establishments and file processing information with the FDA.

According to the milk pasteurization regulations defined in the Grade A Pasteurized Milk Ordinance (USPHS/FDA, 1995), it is necessary to ensure that every particle of milk is heated to the appropriate temperature for the appropriate time and, furthermore, that the equipment used meets strict regulatory testing and controls to avoid any risk of cross-contamination with raw product or risk of postpasteurization contamination. Recommendations for pasteurization temperature and time parameters have not been as specifically defined for juice and other liquid food products. Recommended cooking procedures for meats, seafood, and other products prepared in retail food systems are described in the FDA Food Code (USPHS/FDA, 1997).

Temperature Requirements for Food Storage and Transportation

Maximum regulatory storage temperature requirements have been traditionally set at 7°C (45°F) by state and federal regulations for a number of commercial

food products including milk, meat, and seafood products. Because of concerns about psychrotrophic growth of certain pathogens, the FDA-recommended temperature for food storage in retail establishments has been reduced from 7°C (45°F) to the current 5°C (41°F) or below (USPHS/FDA, 1997). A proposed rule was recently issued jointly by the Food Safety and Inspection Service (FSIS) and the FDA directed at reducing the potential contamination of *Salmonella enteritidis* in eggs (FDA, 1998b). In the proposed rule, FSIS will amend its regulations to require that shell eggs packed for consumer use be stored and transported at $\leq$7°C (45°F) and that these eggs be labeled to indicate that refrigeration is required. Although some states already specify a 7°C (45°F) temperature for egg storage, others have retained the 15.5°C (60°F) traditionally required under USDA grading programs.

CURRENT AND FUTURE IMPLICATIONS

Acid Tolerance and Adaptation

In recent years, acidic food products, including mayonnaise, apple cider and other fruit juices, and yogurt, have been implicated in foodborne disease outbreaks that have primarily involved *E. coli* O157:H7 or *Salmonella* (USDA, 1998). As discussed above, the acid survival characteristics of these microorganisms are dependent on a variety of factors. In general, acid survival is greater during low-temperature storage.

Current research has primarily been directed at improved understanding of acid adaptation and its importance in food safety. Acid adaptation by prior incubation at pH 5.0 has recently been shown to greatly enhance the acid survival characteristics [especially at 5°C (41°F)] of strains of *E. coli* O157:H7 and *Salmonella* in various acidic condiments (Tsai and Ingham, 1997). In general, acid-adapted strains of *E. coli* O157:H7 survived longer than did *Salmonella* or nonpathogenic *E. coli* strains. The incidence of acid-adapted *E. coli* O157:H7 in feces of feedlot cattle has been related to the type of feed and may decrease in animals fed grass-based compared with grain-based diets (Stanton, 1997).

Heat Resistance

Foodborne illness outbreaks associated with commercial hamburger products and isolation of *E. coli* O157:H7 from ground beef have stimulated concern regarding appropriate cooking temperatures in retail and home cooking applications for destruction of this microorganism. This concern has led to redefinition of cooking recommendations and requirements for retail preparation (USPHS/FDA, 1997).

The potential association of pathogens with unpasteurized juice products discussed above has opened debate over the necessity for mandating pasteurization of fruit and vegetable juices. Short of requiring pasteurization,

FDA is proposing that all juice manufacturers develop a Hazard Analysis Critical Control Point (HACCP) system that would include validation that the processing/handling system used is capable of a 5-log reduction in a pertinent pathogen (defined as *E. coli* O157:H7 or *L. monocytogenes*; USDA, 1998).

Because of concerns regarding the alleged heat resistance of *Mycobacterium paratuberculosis* in milk, milk pasteurization requirements in the U.S. and worldwide are currently under scrutiny. This microorganism, the causative agent for Johne disease in cattle and possibly associated with Crohn disease in humans, has been isolated from raw and pasteurized milk samples in the United Kingdom (Streeter et al., 1995). Experimental data on the survival of this organism to pasteurization treatment have been conflicting and inconclusive. The heat resistance of this microorganism is related to initial population as well as its physical state (clumped vs. nonclumped). *M. paratuberculosis* may survive typical pasteurization treatments in test tube heating experiments (Stabel et al., 1997; Sung and Collins, 1998) or using laboratory scale high temperature short time (HTST) pasteurization equipment at initial inoculation levels of $>10^2$ (Grant et al., 1996; Grant et al., 1998). Other investigations using laboratory scale HTST pasteurization equipment have resulted in complete inactivation using an initial inoculation of 10^4 and 10^6 cfu/ml (Stabel et al., 1997).

Heat-inducible thermal tolerance, a property acquired after sublethal heat treatment or "heat shock," has been described for many bacteria. For example, it has recently been shown that *Clostridium perfringens* strains with acquired thermal tolerance—which are capable of surviving normal cooking treatments—can result from "heat shocking" vegetative cells at 55°C (131°F) for 30 min (Heredia et al., 1997). Exposure to low heat has also been shown to increase the heat resistance of *E. coli* O157:H7. In investigations in which beef gravy inoculated with O157:H7 was preheated to 46°C (114.8°F) for 15–30 min, the heat resistance of the microorganism at 60°C (140°F) increased by 1.5-fold (Murano and Pierson, 1993). Heat-induced thermal tolerance may have implications for manufacturers of refrigerated, cook-in-the-bag foods, such as filled pastas, gravies, or beef stews.

Resistance to Antimicrobial Agents

Subtherapeutic use of antimicrobial drugs in animal husbandry and their use in medicine may introduce selective pressures that enhance the emergence of resistant strains of enteric pathogens. For example, poultry have been suggested to be an important reservoir of antibiotic-resistant *Salmonella* strains because of selection and spread of transferable multiple resistance factors (R factors; D'Aoust et al., 1992). Antibiotic resistance profiles and R factors of *Salmonella* and *E. coli* isolates from 104 broiler carcasses have recently been characterized (Tessi et al., 1997).

Although primarily investigated in Great Britain, zoonotic infection of *S. typhimurium* [definitive type (DT) or phage type] 104 has become a well-recognized problem throughout the world (Dargatz et al., 1998). Multidrug-

resistant *S. typhimurium* (mrDT104) has known resistance to five antibiotics (ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline) and may have acquired resistance to other drugs. Although occurrence of *S. typhimurium* mrDT104, and related phage types 104b and U302, has not been well established in the U.S., it may have been present since the early 1990s. A multiresistant *S. enterica* serotype has also recently emerged in the U.S. (1998).

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CHAPTER 10

CHARACTERISTICS OF BIOLOGICAL HAZARDS IN FOODS

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INTRODUCTION AND DEFINITION OF ISSUES

For the purpose of this chapter, foodborne biological hazards are identified and discussed on the basis of their inclusion into three broad but distinct categories: bacterial, parasitic, and viral. In the United States, these hazards collectively result in millions of illnesses and thousands of deaths annually, with an economic impact estimated at approximately $8.4 billion per year (Mead et al., 1999; Todd, 1989). Clearly, the majority of foodborne diseases remain unreported and undiagnosed, because unknown agents cause an estimated 62 million illnesses and 3200 deaths annually in the United States and, in contrast, only an estimated 14 million illnesses and 1800 deaths involve identified etiology (Mead et al., 1999).

Foods that have traditionally been implicated in disease outbreaks include undercooked meat, poultry, seafood, and unpasteurized milk. More recently, other foods have emerged as vehicles of transmission including internally contaminated eggs, juices, fruits, and sprouts and other vegetables. The emergence of foodborne diseases may be the result of social, economic, and/or biological factors. Currently, the world supports an all-time high human population, including individuals possessing a wide range of susceptibility to pathogens. Variation in susceptibility within the general population has resulted from an increase in the number of persons with weakened immune systems, increases in use of immunosuppressive agents, an increase in the average population age, and a global increase in malnutrition. Additionally, increased global travel, especially in developing countries, and expanding international trade contribute to the introduction and spread of foodborne diseases, and urbanization leads to increased human crowding, resulting in more contact and subsequently increased opportunities for pathogen transmission (Hall, 1997).

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Industrial developments and changes in consumer lifestyles and consumer demand have affected food production and processing practices as well as food preparation procedures. Increased numbers of single-parent households and women in the workforce have limited the amount of time available to spend on meal preparation. In response to consumer demands, the food industry is ever increasingly producing foods that are fresher in taste and appearance, minimally processed, and "natural" or free from additives, while at the same time requiring minimal preparation before consumption (Doyle et al., 1997).

The sections that follow identify and review foodborne and waterborne biological hazards that are currently a public health concern. In addition to a brief background discussion, an overview of general characteristics and foodborne illness characteristics and a section on mechanisms of pathogenesis for each pathogen is presented. Discussions regarding regulatory, industrial, and international implications, as well as current and future implications, of foodborne/waterborne pathogens are also included.

BACKGROUND AND HISTORICAL SIGNIFICANCE

Although food microbiology is a relatively young scientific field, foodborne and waterborne pathogens have been recognized for almost 200 years. *Vibrio cholerae* consists of several serogroups, with *V. cholerae* O1 being the etiologic agent of the disease cholera, which has been documented as far back as 1817, the time of the first known pandemic. In 1854, the organism was first described and the connection between cholera and drinking water was hypothesized. The hypothesis was later proven, when in 1883 Robert Koch sampled suspect pond water and isolated the bacillus (Murray et al., 1999). In 1992, the serogroup *V. cholerae* O139 Bengal was identified during an epidemic in India. In addition to these serogroups, other non-O1/O139 *V. cholerae* have been identified and are collectively referred to as nonagglutinating vibrios (NAGs) (Jay, 2000). It is estimated that toxigenic *V. cholerae* are responsible for 49 cases of foodborne disease in the United States annually, with a case fatality rate of 0.006 (Mead et al., 1999).

In 1880, Eberth discovered *Salmonella* Typhi, the etiologic agent involved in typhoid fever. In 1884, Gaffky isolated the organism that, in 1900, Lignieres named after Dr. Salmon, in light of his work involving the isolation of *S.* Cholerae-suis from swine suffering from hog cholera (ICMSF, 1996). The first scheme for *Salmonella* classification, based on antigenic variation, was proposed in 1926 and was expanded in 1941 into the Kauffmann–White scheme (Doyle et al., 1997). Between 1988 and 1992, *Salmonella* was implicated in 69% of documented bacterial foodborne disease outbreaks in the United States; 60% of those outbreaks involved *S.* Enteritidis (Centers for Disease Control and Prevention, 1996a). *Salmonella* is currently the second most common bacterium implicated in foodborne disease outbreaks in the United States, with nontyphoidal strains causing an estimated 1.3 million cases annually and having a case fatality rate of 0.0078 (Mead et al., 1999).

Originally known as *Bacterium coli*, *Escherichia coli* was isolated by Theodor Escherich over a century ago and by the mid-1940s was implicated as a cause of gastroenteritis and significant mortality among infants (ICMSF, 1996). The recognition of Shiga toxin-producing *E. coli* (STEC) as its own individual class of diarrheagenic *E. coli* resulted from two observations in 1982. The first was the observation of characteristic symptoms associated with patients from two outbreaks involving restaurants of a fast-food chain in two states, where the etiologic agent was a previously rarely isolated serotype, O157:H7. The second observation involved sporadic cases of hemolytic uremic syndrome (HUS) in individuals that produced stools containing cytotoxin-forming *E. coli* (Blaser et al., 1995). Currently, diarrheagenic *E. coli* is estimated to be implicated in over 170,000 cases of foodborne disease annually in the United States; the case fatality rate for O157:H7 and non-O157:H7 STEC is 0.0083 (Mead et al., 1999).

The name "staphylococcus" originated from the Greek root *staphyle*, referring to grapes, and in 1882 was used for taxonomic designation of pathogenic, cluster-forming cocci. The association between staphylococci and foodborne illness was suggested in 1884, while in 1914, Barber reported illness symptoms in individuals after the ingestion of milk containing *Staphylococcus aureus*. The role of toxins in staphylococcal food poisoning (intoxication) was demonstrated in 1930, when ingestion of *S. aureus* cell-free filtrates led to development of clinical symptoms (Jay, 2000; Lund et al., 2000). It is estimated that *S. aureus* is responsible for 185,000 cases of foodborne disease annually in the United States, with a case fatality rate of 0.0002 (Mead et al., 1999).

Although *Bacillus cereus* was first isolated and described in 1887, and despite the longstanding recognized relationship between aerobic, endospore-forming bacteria and foodborne illness, it was not until the early 1950s that it became established as an etiologic agent of foodborne disease (Doyle, 1989; ICMSF, 1996). Currently in the United States, *B. cereus* is estimated to cause approximately 27,000 cases of foodborne illness annually, although the number of deaths attributed to this agent is extremely low (Mead et al., 1999).

In 1894, Yersin isolated the etiologic agent of plague, and in 1944, Van Loghem defined the genus *Yersinia*, proposing the inclusion of *Pasteurella pestis* and *P. pseudotuberculosis*; *Pasteurella* X, or *Bacterium enterocoliticum*, was included in the genus *Yersinia* in 1964 (Murray et al., 1999). Only since 1976 has the transmission of *Y. enterocolitica* to humans through food been recognized in the United States, despite the fact that it was first isolated and identified as a human pathogen in the 1930s and as a cause of gastroenteritis in 1965 (Mossel et al., 1995). It is estimated that currently in the United States, *Y. enterocolitica* is involved in nearly 87,000 cases of foodborne disease annually, with an estimated case fatality rate of 0.0005 (Mead et al., 1999).

Clostridium perfringens has been associated with gastroenteritis since 1895, although it was first recognized as an important cause of foodborne disease in the 1940s (Jay, 2000). It is responsible for causing two different types of human disease: *C. perfringens* type A food poisoning and necrotic enteritis, the latter being the least prevalent of the two (Doyle et al., 1997; Lund et al., 2000).

Currently in the United States, *C. perfringens* is estimated to cause approximately 250,000 cases of foodborne illness annually, with a case fatality rate of 0.0005 (Mead et al., 1999).

The bacterium *Clostridium botulinum* was first isolated from food and implicated as the etiologic agent in a foodborne outbreak in 1897, although a botulism-type illness had been associated with the consumption of sausage in the early 1800s. Infant botulism was recognized in 1976 and has since become the most common form of the disease in the United States (Lund et al., 2000). Currently in the United States, it is estimated that *C. botulinum* is responsible for 58 foodborne disease cases annually with a case fatality rate of 0.0769 (Mead et al., 1999).

The genus *Shigella* has been identified as a cause of bacillary dysentery since 1898 when it was first described by Shiga during an epidemic in Japan (Murray et al., 1999). In 1900, Flexner surmised the presence of a toxin, associated with *Shigella* infection, which was later confirmed in 1903 by Conradi (Blaser et al., 1995). Foodborne *Shigella* infections are more common than waterborne infections, and it is estimated that currently in the United States, *Shigella* spp. are involved in nearly 90,000 cases of foodborne disease annually, with a case fatality rate of 0.0016 (ICMSF, 1996; Mead et al., 1999).

Campylobacter (formerly known as *Vibrio fetus*) was first isolated in culture in 1909, and in 1957 King first described the group as "related vibrios," so named because of their morphology and their association with acute enteritis in humans (Blaser et al., 1995; Doyle, 1989). Species of *Campylobacter* have been recognized as agents of foodborne gastroenteritis, known as campylobacteriosis or *Campylobacter* enteritis, since the late 1970s, and in the past 10 years *Campylobacter jejuni* has become well established as the most common cause of bacterial foodborne illness in the United States, resulting in 2.0 to 2.5 million cases annually and having a case fatality rate of 0.001 (Altekruse et al., 1999; Mead et al., 1999).

Listeria monocytogenes was first described during the 1910s and 1920s, and in 1924 the first reported human case involved a soldier inflicted with meningitis during World War I (Ryser and Marth, 1999). Foodborne transmission was not recognized until 1981, when the first confirmed foodborne outbreak occurred in Nova Scotia, Canada (Doyle et al., 1997). Because of its high case mortality rate, listeriosis has emerged as a major foodborne disease concern to the food industry as well as health and regulatory agencies. Current estimates suggest that *L. monocytogenes* is responsible for approximately 2500 cases of foodborne disease in the United States annually, with an estimated case fatality rate in excess of 0.2 (Mead et al., 1999).

Vibrio parahaemolyticus was first implicated in 1950 as the etiologic agent in an outbreak of gastroenteritis in Japan and subsequently identified in the United States in Maryland in 1971 (Janda et al., 1988). It has become one of the more common causes of *Vibrio*-induced diarrhea in the United States, and between 1973 and 1987 more than 20 outbreaks were reported (Doyle et al., 1997). Between 1981 and 1993, *V. parahaemolyticus* was responsible for 88 hospitalizations and 8 deaths in the state of Florida (Hlady and Klontz, 1996).

Another *Vibrio* species, *V. vulnificus*, also referred to as *Beneckia vulnifica* or the "lactose-positive *Vibrio*," was first studied in detail by researchers in 1976 (Janda et al., 1988). It was identified as a new species and named *V. vulnificus*, meaning wound inflicting, and in 1982 a second biotype (biotype 2) was discovered (Doyle et al., 1997). Currently, it is estimated to cause 47 cases of foodborne disease annually in the United States, with a case fatality rate of 0.39 (Mead et al., 1999).

SCIENTIFIC BASIS AND IMPLICATIONS

There are two distinct categories in which a disease can be classified on the basis of the role that the pathogen plays during the disease-causing process. An infection ensues when a host is invaded directly by a microorganism, which, after being established, proliferates in the host. In contrast, intoxication ensues after the introduction of a specific, preformed toxin into the body of a host, subsequently inducing disease in the presence or absence of the toxin producer. A food source may serve as a vehicle of transmission for the biological hazard itself (infection) and/or any metabolic products including various toxins (intoxication). Typically, the clinical symptoms involved in the majority of foodborne diseases include acute diarrhea, vomiting, and/or some other manifestation of the gastrointestinal tract. However, syndromes involving the central nervous system or various organs, in addition to other chronic sequelae, may be the direct or indirect result of foodborne pathogenic microorganisms.

Bacteria

It is estimated that bacterial agents are responsible for approximately 30% of all foodborne illnesses involving known etiology, resulting in more than four million cases annually in the United States. Despite causing only 30% of all foodborne illness, bacterial agents in foods result in approximately 1300 deaths annually, or 72% of total deaths attributed to the consumption of contaminated foods (Mead et al., 1999).

The following is a brief overview of foodborne/waterborne bacterial pathogens. Gram-negative pathogenic bacteria examined include species of the genera *Campylobacter*, *Salmonella*, *Escherichia*, *Shigella*, *Yersinia*, and *Vibrio*. Pathogenic species of gram-positive bacteria examined include those of the genera *Listeria*, *Staphylococcus*, *Clostridium*, and *Bacillus*. Additionally, other bacterial pathogens transmitted less frequently in foods are mentioned to a lesser extent.

Campylobacter

General characteristics *Campylobacter* and *Arcobacter* are members of the family Campylobacteraceae, which includes 18 species and subspecies within the genus *Campylobacter* and 4 species within the genus *Arcobacter* (Murray et

al., 1999). Ecologically, *Campylobacter* are associated with poultry and migratory birds, rodents, natural water sources, and insects that may carry the organism on their exoskeleton and have been identified as important reservoirs within the poultry environment (Altekruse et al., 1999).

Campylobacter are slender, curved, gram-negative non-spore-forming rods (0.2–0.5 μm wide and 1.5–5.0 μm long) that are motile by means of a single polar unsheathed flagellum located at one or both ends and demonstrate a characteristic "corkscrew-type" motility (Lund et al., 2000). In general, they are microaerophilic, growing optimally in an environment containing 2.0–5.0% oxygen and 5.0–10.0% carbon dioxide, because growth is inhibited in the presence of 21% oxygen (Altekruse et al., 1999). The optimum temperature range for *Campylobacter* growth is 37–42°C; however, under favorable nutritional, atmospheric, and environmental conditions, growth occurs between 30 and 45°C (ICMSF, 1996). Furthermore, they can grow in culture media between pH 4.9 and 8.0 but prefer pH 6.5 to 7.5 (Doyle, 1989). *Campylobacter* are sensitive to drying and require a water activity (a_w) above 0.912. They are also quite sensitive to sodium chloride, because deviation from the optimum (i.e., 0.5%) results in decreased growth rates or increased rates of death depending on temperature, although higher sodium chloride concentrations are tolerated better at increased temperatures (Lund et al., 2000).

Characteristics of foodborne illness *Campylobacter jejuni* and *C. coli* are the most common *Campylobacter* species associated with foodborne diarrheal illness. Campylobacteriosis or *Campylobacter* enteritis may result from as few as 500 viable cells, but because not all individuals are equally susceptible to infection and differences in virulence factors exist among *Campylobacter* isolates, there are probably considerable infectious dose differences (Lund et al., 2000). Typically requiring 2–5 days of incubation before the onset of gastroenteritis, clinical symptoms may persist for up to 10 days. Infection frequently includes the onset of acute colitis combined with fever, malaise, abdominal pain, headache, watery or sticky diarrhea with minor traces of (occult) blood, inflammation of the lamina propria, and crypt abscesses (ICMSF, 1996; Lund et al., 2000). In addition to gastrointestinal symptoms, infection may result in acute cholecystitis, urinary tract infections, reactive arthritis, bursitis, meningitis, hemolytic uremic syndrome (HUS), endocarditis, peritonitis, pancreatitis, abortion, and neonatal sepsis (Murray et al., 1999). Furthermore, *C. jejuni* is the most recognized cause of an acute paralytic disease of the peripheral nervous system known as Guillain–Barré syndrome; some serotypes, specifically O:19, have been implicated more often than others (Nachamkin et al., 1998).

Milk, eggs, red meats, water, and primarily poultry meats have been implicated as vehicles of transmission in outbreaks. Unpasteurized raw milk was involved as the vehicle of transmission in the largest outbreak of *Campylobacter* enteritis, which infected 2,500 school children (Jones et al., 1981). Additionally, pets (e.g., puppies and kittens) have been implicated in human cases of campylobacteriosis (Altekruse et al., 1999).

In 1996 *Campylobacter* species accounted for 46% of all confirmed cases of bacterial gastroenteritis reported to the CDC, and it was estimated that of those cases in which *C. jejuni* was implicated, 5–10% were caused by *C. coli* (Altekruse et al., 1999). The Foodborne Diseases Active Surveillance Network (FoodNet) reported the incidence of campylobacteriosis per 100,000 population to be 23.5, 25.2, and 21.7 for 1996, 1997, and 1998, respectively (Centers for Disease Control and Prevention, 1998; 1999).

Mechanisms of pathogenicity Although little is known regarding pathogenesis of infection, the presence of *C. jejuni* or *C. coli* results in extraintestinal interaction with cellular constituents as indicated by high serum IgG and IgM antibody levels after infection (Murray et al., 1999). Host humoral immunologic response may be stimulated by various mechanisms including the enterotoxigenic mechanism, which involves mucus colonization of the small intestinal surface and subsequent enterotoxin production, thereby leading to an efflux of fluids producing acute watery diarrhea (Lund et al., 2000).

Proposed virulence determinants of *Campylobacter* include motility, adherence, invasion, and toxin production properties. *Campylobacter jejuni/coli* produce three types of toxins: an enterotoxin, which is heat labile (i.e., denatured by heating at 56°C for 1 h) and destroyed at pH 2.0 or 8.0; a cytotoxin, which is sensitive to trypsin but more heat stable than the enterotoxin (i.e., denatured by heating at 60°C for 30 min); and a cytolethal distending toxin (CDT) (Doyle, 1989; Lund et al., 2000). Another possible mechanism of pathogenesis may include actual bacterial cell penetration in the small intestine or colon, explaining the presence of blood in stools observed in individuals with *Campylobacter* enteritis (Blaser et al., 1995). Iron is an essential element of *Campylobacter* pathogenesis, and in its presence the organism produces iron-binding compounds known as siderophores. Toxin production appears to be enhanced under conditions of excess iron, which may induce typical nonproducers to subsequently produce toxins (Doyle, 1989). Symptom differences reported by various individuals suffering from campylobacteriosis might result from the employment of different mechanisms by different *Campylobacter* strains for illness induction; nonetheless, *Campylobacter* is excreted in diarrheic stools in sufficient enough numbers to prove that it is efficient at colonizing and proliferating within the human intestinal system (Lund et al., 2000).

Salmonella

General characteristics *Salmonella*, belonging to the family Enterobacteriaceae, are gram-negative, facultatively anaerobic, non-spore-forming rods. The two species currently recognized within the genus are *S. enterica*, possessing six subspecies, and *S. bongori*. *Salmonella enterica* subspecies I strains are typically found in warm-blooded animals, whereas subspecies II, IIIa, IIIb, IV, and VI strains and *S. bongori* are typically found in cold-blooded animals or in the environment (Collier et al., 1998). There are approximately 2463 *Salmonella*

serotypes, and in the United States the two most prevalent are *S.* Typhimurium and *S.* Enteritidis (Brenner et al., 2000). This zoonotic pathogen is most commonly isolated from the intestines of mammals, and although most serotypes do not demonstrate host specificity, several do (e.g., *S.* Pullorum and *S.* Gallinarum to poultry, *S.* Cholerae-suis and *S.* Typhi-suis to pigs, and *S.* Dublin and *S.* Typhimurium to cattle) (ICMSF, 1996).

Salmonella can grow at temperatures ranging from 5.2 to 46.2°C, but prefer 35–43°C. They can grow at pH 3.8–9.5, although they grow best at pH 6.5–7.5. Additionally, *Salmonella* require a a_w above 0.93 and under ideal conditions can grow in sodium chloride concentrations as high as 4% (Cary et al., 2000; ICMSF, 1996).

Characteristics of foodborne illness *Salmonella* inhabit the intestinal tracts of infected hosts or carriers, where cells are subsequently sloughed and excreted in the feces. Salmonellosis can result from the ingestion of contaminated food or water, contact with host animals, and even contact with infected humans. This organism is widely distributed throughout the environment and is usually associated with human illness transmitted by foods of animal origin, such as beef, pork, poultry, eggs, raw milk, and milk products, although outbreaks of salmonellosis have involved consumption of other foods, including fruits and vegetables (ICMSF, 1996). Typhoidal strains, including *S.* Typhi, *S.* Paratyphi A, *S.* Paratyphi C, and *S.* Sendai, can cause a serious bloodstream infection known as typhoid fever. Although this condition has been virtually eradicated in the United States (approximately 400 cases annually), it results in many more deaths in developing countries (Blaser et al., 1995).

Nontyphoidal *Salmonella* strains typically cause an intestinal infection after an incubation period ranging from 5 h to 5 days, resulting in symptoms of diarrhea, nausea, mild fever, chills, vomiting, and abdominal cramping. Symptoms typically last 1–2 days, but may persist longer, and affect individuals of all ages, with the highest incidence occurring in infants (Murray et al., 1999). Infectious doses in foods have been found to be less than 10^3, depending on the serotype and vehicle of transmission, and even as low as 10^0–10^2, depending on individual deficiencies in host defenses (Blaser et al., 1995).

Mechanisms of pathogenicity *Salmonella*, in general, invade and multiply in the lumen of the small intestine, where they colonize and enter intestinal columnar epithelial and M cells overlying Peyer's patches (Lund et al., 2000). Contact between the pathogen and target epithelial cells induces the formation of temporary attachment/adhesion mechanisms (i.e., proteinaceous appendage development). During this temporary attachment period, the host epithelial cell undergoes massive structural rearrangement in the vicinity of the adherent pathogen, resulting in the formation of membrane "ruffles" and eventually induced internalization of a pathogen-containing pinocytotic vacuole (Doyle et al., 1997).

Salmonella enterotoxin, a thermolabile protein, is released into the cytoplasm of host cells, where it activates adenyl cyclase, leading to increased cytoplasmic concentrations of cyclic AMP. In addition to the enterotoxin, a thermolabile cytotoxic protein is generally produced and released extracellularly in response to environmental stress. The cytotoxin inhibits protein synthesis and promotes cell lysis in an attempt to facilitate pathogen dissemination through host tissue (Lund et al., 2000).

There are three virulence determinants located within or on the external outer membrane. Capsular polysaccharide Vi antigen, as well as serotypic lipopolysaccharides, protrude from the outer cellular membrane and function in defending the organism from lytic attack by inhibiting the host complement system. Porins are transcribed in response to microenvironmental changes (e.g., low osmolarity, low nutrient availability, low temperature) and regulate the influx of small molecules (Doyle et al., 1997).

Diarrheagenic *Escherichia coli*

General characteristics Diarrheagenic or enterovirulent *E. coli*, belonging to the family Enterobacteriaceae, are gram-negative, facultatively anaerobic, nonspore-forming rods that are mostly motile. There are four major categories or groups in which diarrheagenic *E. coli* can be placed. The first is known as Shiga toxin-producing *E. coli* (STEC) and includes the enterohemorrhagic *E. coli* (EHEC) strains (approximately 112 recognized serotypes). STEC produce Shiga-like toxins, or verocytotoxins, and in North America and Europe the most common serotypes isolated from individuals with diarrheagenic *E. coli* are O157:H7 and O157:nonmotile. The second category is enterotoxigenic *E. coli* (ETEC), which includes approximately 32 recognized serotypes. ETEC can produce a heat-labile (LT) enterotoxin and/or a heat-stable (ST) enterotoxin. The third category of diarrheagenic *E. coli* is known as enteropathogenic *E. coli* (EPEC) and includes approximately 23 recognized serotypes that are noninvasive and do not produce Shiga-like toxins or enterotoxins. The fourth category is enteroinvasive *E. coli* (EIEC) and includes approximately 14 recognized nonmotile serotypes, which have the ability to leave the intestinal lumen by invading peripheral host tissues (Murray et al., 1999; Nataro and Kaper, 1998). Additionally, there are other diarrheagenic or enterovirulent *E. coli* categories or groups, including enteroaggregative *E. coli* (EAEC), diffusely adherent *E. coli* (DAEC), necrotoxic or cell-detaching *E. coli* (NTEC or CDEC), and cytolethal distending toxin (CLDT or CDT)-producing *E. coli*, but the extent of their clinical or foodborne significance remains unclear (Lund et al., 2000; Nataro and Kaper, 1998).

Diarrheagenic *E. coli* can grow at temperatures as low as 7–8°C and as high as 44–46°C but prefer 35–40°C. Although they grow best at pH 6.0–7.0, diarrheagenic *E. coli* can grow at pH 4.4–9.0. Diarrheagenic *E. coli* require a a_w of at least 0.95, and unlike most foodborne pathogens they are tolerant to acidic

environments and have demonstrated resistance to acetic, citric, and lactic acids applied at concentrations as high as 1.5% (Cary et al., 2000; Doyle et al., 1997; ICMSF, 1996).

Characteristics of foodborne illness Diarrheagenic *E. coli*, found in the gastrointestinal tracts of mammals, are fairly ubiquitous throughout the environment. They usually are associated with human illness resulting from fecal-oral transmission by contaminated hands, water or foods of animal as well as plant origin. Although the majority of outbreaks have involved the consumption of undercooked or underprocessed food products, especially those of bovine origin, other foods have served as vehicles for transmission, including water, cantaloupes, apple juice/cider, potatoes, coleslaw, and radish and alfalfa sprouts (Jay, 2000).

After ingestion ($>10^1$ cells) and a 3- to 9-day incubation period, STEC serotypes (e.g., O157:H7, O157:NM, O11:H8, O111:NM, and O26:H11) can cause a wide range of symptoms persisting for 2–9 days and including mild diarrhea, severe bloody diarrhea (hemorrhagic colitis) or, in some cases, hemolytic uremic syndrome (HUS), which is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure (Cary et al., 2000; Lund et al., 2000). Approximately 6% of individuals infected with STEC serotype O157 develop HUS, and it is thought that O157 is the etiologic agent involved in 80% of the HUS cases in North America (Murray et al., 1999; Blaser et al., 1995). Although O157:H7 is the most prevalent diarrheagenic STEC in the United States, there are other serotypes associated with HUS and related syndromes or conditions.

After an incubation period of 14–50 h, an ETEC infection may result in clinical symptoms that include nausea and a headache, but typically the infected individual experiences watery diarrhea, abdominal cramping, and low-grade fever, which may last for 3–19 days (ICMSF, 1996). ETEC are associated with a large infective dose ($>10^7$ cells) and are a frequent cause of weanling and traveler's diarrhea in developing countries (Nataro and Kaper, 1998). In developed countries, the case fatality rate for ETEC is 0.0001 (Mead et al., 1999).

EPEC has traditionally been associated with infantile diarrhea, with outbreaks occurring in day care centers and hospital nurseries. The infective dose is presumed to be low in infants and young children and high in adults ($>10^6$ cells). Symptoms of infection, after an incubation period of 2.9–72 h, include severe, prolonged diarrhea accompanied by vomiting and fever in children (Nataro and Kaper, 1998). EPEC serotypes typically cause diarrhea, which may occasionally contain blood, and an infected individual may experience symptoms for 6 h to 3 days while continuing to shed the organism for up to 2 weeks after cessation of symptoms (Murray et al., 1999).

EIEC, a form of bacillary dysentery, has an incubation period of 8–24 h, after which time an infected individual may be asymptomatic or may experience watery diarrhea followed by dysenteric stools containing some blood. In

most infected individuals, the only phenotypic symptom is watery diarrhea, which may last from a few days to weeks (ICMSF, 1996; Nataro and Kaper, 1998). The infectious dose is believed to be high ($>10^6$ cells), and the resulting mild dysentery may be confused with dysentery caused by members of the genus *Shigella* (Collier et al., 1998).

Mechanisms of pathogenicity Enterovirulent *E. coli* strains follow a specific infection sequence that includes colonization of a specific mucosal site, evasion of host defense mechanisms, proliferation of the organism, and damage to the host. After colonization, pathogenetic processes differ among the various strains. STEC produce Shiga-like toxins, or verocytotoxins, which are their major virulence factor, resulting in death in certain infected individuals. STEC have the capacity to produce either Shiga toxin 1 (Stx1), which is essentially identical to the *Shigella dysenteriae* type 1 toxin, Shiga toxin 2 (Stx2), or a combination of both toxins, of which the latter is less conserved, possessing several different variants, including Stx2c, Stx2e, Stx2v, Stx2vhb, etc. (Nataro and Kaper, 1998). It should be noted that recent evidence suggests that there are typical STEC serovars that do not possess the Shiga toxin-producing gene (Schmidt et al., 1999). Other virulence factors, in addition to Shiga toxins, that may be involved in the pathogenesis of STEC-related disease include a plasmid encoded enterohemolysin; a heat-stable enterotoxin (EAST1); plasmid-encoded catalase-peroxidase and serine protease enzymes; an outer membrane protein synthesized in response to a low-iron environment; an intestinal adherence factor (e.g., intimin), which plays a vital role in the adherence to epithelial cells; and the presence of O157 (LPS), which may enhance the cytotoxicity of Shiga toxins (Nataro and Kaper, 1998; Paton and Paton, 1998).

As indicated, ETEC possess plasmids that encode for the production of heat-labile (LT) and/or heat-stable (ST) enterotoxins, but most of the outbreaks reported in the United States have resulted from serotypes producing ST, either by itself or in combination with LT (Murray et al., 1999). After colonization, ETEC secrete their enterotoxins, which gain entry into intestinal epithelial cells via endocytosis, where their presence results in elevated intracellular cyclic AMP and GMP levels and intestinal lumen fluid accumulation (Nataro and Kaper, 1998).

EPEC colonization is identified by the effacement of microvilli, resulting in adherence with the epithelial cell membrane. The ability to adhere is dependent on the presence of a plasmid, known as the EPEC adherence factor (EAF) plasmid, and an outer membrane protein called intimin, which is encoded by the *eae* gene (Nataro and Kaper, 1998). Signal transduction causes the release of intracellular calcium stores, inducing a calcium-dependent actin-severing protein, resulting in cytoskeletal rearrangements that may include the concentration of polymerized actin resulting in the formation of a "pedestal" (Nataro and Kaper, 1998). In addition to pedestal formation, increased intracellular Ca^{2+} inhibits uptake and stimulates fluid efflux into the intestinal lumen.

EIEC pathogenesis consists of the penetration of the cellular epithelium in the colonic mucosa and entrance into the cell through endocytosis, which depends on the production of several outer membrane polypeptides that are mediated by both plasmid and chromosomally contained genes. Lysis of the surrounding endocytic vacuole is followed by production of one or more secretory enterotoxins, which occurs in conjunction with intracellular replication. Finally, EIEC migrate through the cytoplasm, where they extend into adjacent epithelial cells (Nataro and Kaper, 1998).

Shigella

General characteristics The genus *Shigella* is a member of the family Enterobacteriaceae and possesses four serogroups that have been traditionally treated as species: serogroup A as *S. dysenteriae*, serogroup B as *S. flexneri*, serogroup C as *S. boydii*, and, serogroup D as *S. sonnei*. Whereas serogroups A, B, and C consist of 38 serotypes, serogroup D possesses only one (Murray et al., 1999; Doyle et al., 1997). *Shigella* are nonmotile, non-spore-forming, facultatively anaerobic gram-negative rods. They can grow at temperatures ranging from 6 to 48°C, but prefer 37°C, and *S. sonnei* appears to be able to tolerate lower temperatures better than the other serogroups. Optimum growth occurs between pH 6.0 and 8.0, although growth has been reported between pH 4.8 and 9.3 (Jay, 1996; ICMSF, 1996).

Characteristics of foodborne illness *Shigella* are closely related to *E. coli* in their DNA homology and share some biochemical characteristics as well as reactivity to some of the same antibodies, but despite these similarities, their differentiation should be considered clinically significant based, at least in part, on differences in symptoms expressed by infected individuals (Lund et al., 2000). *Shigella* are found most frequently in environments of compromised sanitation and poor hygiene, and although the primary route of transmission is by person-to-person contact, shigellosis can occur after the ingestion of fecally contaminated water or food. *Shigella* have not been associated with one specific type of food; foods associated with outbreaks of shigellosis have included milk, salads, chicken, shellfish, and other fresh produce served at a wide range of establishments including restaurants, homes, schools, sorority houses, commercial airlines, cruise ships and military mess halls (Doyle et al., 1997; ICMSF, 1996). Approximately 20% of all shigellosis cases in the United States are related to international travel, with *S. sonnei* being the most prevalent and *S. flexneri* being the second most common in developed countries. However, in developing countries, *S. flexneri* and *S. dysenteriae* type 1 are the most common serogroups, with *S. dysenteriae* type 1 having been involved in a lengthy epidemic in southern Africa and major epidemics in other parts of Africa, in Asia and in Central America. These epidemics have resulted in high morbidity and mortality rates, especially in malnourished children, immunocompromised individuals, and the elderly (Murray et al., 1999; ICMSF, 1996).

The infectious dose (ID_{50}) of *Shigella* is low, with 50% of individuals developing disease after ingestion of approximately 5000 organisms for *S. flexneri*, *S. sonnei*, and *S. dysenteriae*, although some individuals have become ill after ingestion of doses as low as 10–200 organisms (Jay, 2000; Lund et al., 2000). All *Shigella* serogroups can cause gastrointestinal infections after an incubation period of 12–50 h, after which time individuals experience watery diarrhea in conjunction with fever, fatigue, malaise, and abdominal cramps, potentially progressing to classic dysentery characterized by scant stools containing blood, mucus, and pus (Blaser et al., 1995). Despite its severity, shigellosis is self-limiting, with clinical symptoms generally lasting 1–2 weeks, although they may persist for up to a month (Doyle et al., 1997). Although dysentery can be caused by all four *Shigella* serogroups, *S. dysenteriae* type 1 is the most frequent cause of epidemic dysentery and is associated with a particularly severe form of the illness that may be accompanied by other complications including HUS. In addition to the association of *S. dysenteriae* with HUS, *S. flexneri* infection has also been associated with additional complications such as Reiter chronic arthritis syndrome (Blaser et al., 1995).

Mechanisms of pathogenicity Classic dysentery results from the extensive colonization and invasion of the colonic mucosal by inducing phagocytosis and subsequently triggering an acute inflammatory response. After cellular entry, *Shigella* escape from the vacuole and proliferate while spreading through surrounding epithelial cells without ever leaving the intracellular environment. After penetration as far as the lamina propria, *Shigella* coalesce, producing abscesses and mucosal ulcers leading to the presence of blood, pus and mucus in stools after the sloughing of dead mucosal surface cells (Doyle et al., 1997; Blaser et al., 1995).

Shigella virulence is regulated by growth temperature, and after sensing of host ambient temperature (i.e., 37°C in humans), gene expression of multiple chromosomal and plasmid-encoded genes is triggered and virulent strains are able to invade mammalian epithelial cells (Lund et al., 2000). In addition to the Shiga toxins produced by *S. dysenteriae* type 1, *S. flexneri* type 2a has been described as producing two enterotoxins, explaining the watery diarrhea observed before the onset of dysentery (Vargas et al., 1999). Additionally, *Shigella* possess an endotoxin lipopolysaccharide (LPS) that functions in host immune system protection (ICMSF, 1996).

Yersinia enterocolitica

General characteristics The genus *Yersinia* belongs to the family Enterobacteriaceae and includes 10 established species, although only 3 are considered pathogenic to either humans or animals. *Yersinia pestis* is the causative agent of plague, *Y. pseudotuberculosis* is primarily an animal pathogen but may infect humans after the ingestion of contaminated food or water, and *Y. enterocolitica* has surfaced as a cause of foodborne gastroenteritis in humans (Cary

et al., 2000). *Yersinia* are gram-negative or gram-variable, non-spore-forming rods that grow under both aerobic and anaerobic conditions but are considered facultative anaerobes. With the exception of *Y. pestis*, all *Yersinia* species possess peritrichous flagella and are motile at 22–30°C but not at 37°C (Lund et al., 2000).

Yersinia enterocolitica are widely distributed throughout the environment and have been isolated from raw milk, sewage-contaminated water, soil, seafood, humans, and many warm-blooded animals such as poultry and, most importantly, pigs (Lund et al., 2000). As a psychrotroph, *Y. enterocolitica* may pose a health hazard in contaminated refrigerated foods, although under refrigeration temperatures the pathogen is usually outgrown by other competing psychrotrophs (Mossel et al., 1995).

Yersinia enterocolitica grow at temperatures between 0 and 45°C but prefer an optimum temperature between 25 and 30°C. This psychrotroph can survive alkaline conditions as well as any other gram-negative bacterium but does not survive well in acidic environments, because growth occurs between pH 4.0 and 10.0, with pH 7.6 being optimum. Additionally, *Y. enterocolitica* can grow in the presence of sodium chloride at concentrations as high as 5% (Doyle et al., 1997; ICMSF, 1996; Murray et al., 1999).

Characteristics of foodborne illness Not all serotypes of *Y. enterocolitica* are enteropathogenic, and the specific serotypes of *Y. enterocolitica* involved in human yersiniosis are prevalent primarily in swine. Ingestion of contaminated water or food, more specifically raw or undercooked pork, is a source of foodborne infection in humans, resulting in symptoms appearing after an incubation period of a few days to a week. Intestinal yersiniosis may persist for 1–2 weeks in adults and as long as 4 weeks in children and may include symptoms such as watery, sometimes bloody, stools or bloody diarrhea in conjunction with fever, vomiting, and abdominal pain, which may mimic appendicitis and mesenteric lymphadenitis (Lund et al., 2000; Murray et al., 1999). Immunocompromised individuals and children under the age of 15 are most commonly infected, and extraintestinal infections associated with yersiniosis include septicemia, meningitis, Reiter syndrome, myocarditis, glomerulonephritis, thyroiditis, and erythema nodosum (Cary et al., 2000; Mossel et al., 1995).

Mechanisms of pathogenicity The pathogenic serotypes of *Y. enterocolitica*, primarily O:3, O:5, O:8, and O:9, produce an enterotoxin and travel through the bloodstream to target lymphatic tissues, where they enter the lymph nodes and proliferate (Murray et al., 1999). *Yersinia enterocolitica* toxin is heat stable, resists enzymatic degradation, remains stable during prolonged storage, and is of similar pH stability as the thermostable enterotoxin (ST) produced by ETEC. However, there is indication that this toxin plays a relatively unimportant role in pathogenesis (ICMSF, 1996).

Although some *Y. enterocolitica* genes involved in pathogenicity reside on the chromosome, the majority are located on virulence plasmids producing

adhesin/invasin proteins, antiphagocytic proteins, processing- and excretion-related proteins, and regulatory proteins. The absence of the virulence plasmids or plasmid function results in decreased pathogenicity and the subsequent inability to cause disease (Lund et al., 2000).

Vibrio parahaemolyticus

General characteristics The genus *Vibrio*, belonging to the family Vibrionaceae, contains more than 35 species, of which nearly half have been described in the last 20 years and more than one-third are pathogenic to humans. Organisms in this genus are non-spore-forming, primarily motile, facultatively anaerobic, gram-negative straight or curved rods. All pathogenic *Vibrio* species, including *V. cholerae*, *V. parahaemolyticus*, and *V. vulnificus*, require sodium for optimum growth. They are found primarily in brackish or marine environments located in tropical or temperate areas, because their incidence decreases significantly as water temperature falls below 20°C (Murray et al., 1999). Food sources implicated as vehicles of transmission for *V. parahaemolyticus* include crabs, prawns, scallops, seaweed, oysters, and clams (Jay, 2000).

Vibrio parahaemolyticus grow at temperatures between 5 and 44°C, with an optimum temperature and pH for growth between 30 and 37°C and 7.6 and 8.6, respectively. The organism will grow in an environment at pH 4.8–11.0, in sodium chloride concentrations of 0.5–10.0%, and in environments with a minimum a_w of 0.94; however, it prefers a concentration of sodium chloride in the range of 2 to 4% and a a_w of 0.981 (ICMSF, 1996; Jay, 1996).

Characteristics of foodborne illness *Vibrio parahaemolyticus* is the *Vibrio* species most frequently isolated from clinical samples obtained in the United States. Gastroenteritis is typically associated with consumption of raw, inadequately cooked, or cooked but recontaminated seafood. After a 4- to 96-h incubation period, symptoms of *V. parahaemolyticus*-induced gastroenteritis include nausea, vomiting, headache, abdominal cramps, slight fever, chills, and watery diarrhea that is occasionally bloody. Additional symptoms, after exposure to contaminated water, may include infected wounds, eyes, and ears. Although symptoms are usually self-limiting, lasting only 2–3 days, severe cases may result in fulminant dysentery, primary septicemia, or cholera-like illness with the possibility of death (Janda et al., 1988; Lund et al., 2000). The presence of a preexisting condition (e.g., liver disease, alcoholism, diabetes mellitus, antacid medication, peptic ulcer disease, immune disorder, etc.) greatly enhances the likelihood of developing a clinical syndrome such as gastroenteritis, wound infection, or septicemia.

Mechanisms of pathogenicity *Vibrio parahaemolyticus* possess four hemolytic components, including a thermostable direct hemolysin (TDH), a thermolabile direct hemolysin, phospholipase A, and lysophospholipase (Doyle et

al., 1997). Most strains are TDH-negative, although virulence is related to the presence of the chromosomal TDH gene and subsequent production of the enterotoxin. After interaction with cellular receptors in the intestinal mucosa, TDH induces intestinal lumen fluid accumulation through the use of Ca^{2+} as an intracellular messenger. *Vibrio parahaemolyticus* are invasive and can penetrate the lamina propria and enter circulation, as they have been found in the heart, spleen, pancreas, and liver (Doyle et al., 1997; Mossel et al., 1995).

Vibrio vulnificus

General characteristics *Vibrio vulnificus*, also belonging to the family Vibrionaceae, are motile by means of a single polar-sheathed flagellum. *Vibrio vulnificus* is environmentally distributed in a similar manner as the other pathogenic *Vibrio* species, and is primarily found in temperate or tropical, marine or brackish water sources, especially around estuaries. It has been isolated from the Gulf of Mexico, the east and Pacific coasts of the United States, and from around the world (Lund et al., 2000). In addition to oysters, *V. vulnificus* has been isolated from crabs, clams, seawater samples, and the intestinal tracts of bottom-feeding fish (Doyle, 1989).

The optimum temperature for growth of *V. vulnificus* is 37°C, but the organism can grow at temperatures ranging from 8 to 43°C. *Vibrio vulnificus* can grow in pH 5.0–10.0 environments with a minimum a_w of 0.96 but prefer pH 7.8 and a a_w of 0.98. Additionally, although a sodium chloride concentration of 2.5% is optimum, growth can occur in sodium chloride concentrations between 0.5 and 5.0% (ICMSF, 1996).

Characteristics of foodborne illness *Vibrio vulnificus* infections are highly correlated with water temperature, as most cases occur between April and October, and are associated with the consumption of contaminated raw oysters (Doyle et al., 1997). *Vibrio vulnificus*, compared with other pathogenic *Vibrio* species, causes the most severe disease, with infections of wounds, gastroenteritis, and septicemia occurring rapidly and frequently ending in death. *Vibrio vulnificus* accounts for 95% of the deaths caused by seafood in the United States and is the leading cause of foodborne illness-related death in Florida (Cary et al., 2000). Almost all *V. vulnificus* systemic infections after oyster consumption occur in individuals with a preexisting liver or blood-related disorder, such as cirrhosis of the liver; the subsequent increase in available iron caused by liver damage is considered a high risk factor for infection (Janda et al., 1988). Other preexisting risk factors include hematopoietic disorders, chronic renal disease, gastric disease, the use of immunosuppressive agents and diabetes; the infective dose in sensitive individuals may be as low as 100 cells (Doyle, 1989).

Vibrio vulnificus has an incubation period ranging from 7 h to several days, after which time symptoms may include fever, chills, nausea, hypotension, abdominal pain, vomiting, diarrhea, and the development of secondary lesions

on extremities (Doyle et al., 1997). Primary septicemia resulting from infection has a fatality rate of 60%, which is the highest fatality rate of any foodborne disease agent in the United States, and death usually occurs within a few days (Todd, 1989). Wound infections as a result of exposure to a contaminated water source are associated with a 20–25% fatality rate, and in a surviving individual surgical debridement of the affected tissue or amputation is often required.

Mechanisms of pathogenicity Some strains of *V. vulnificus*, specifically the pathogenic strains, produce a polysaccharide capsule essential for initiation of infection because it protects the pathogen from phagocytosis. In addition to the capsule protection, a serum resistance factor helps to reduce complement-mediated cell lysis. *Vibrio vulnificus* are highly invasive and produce a heat-labile cytolysin that is believed to cause the severe tissue damage associated with infection (ICMSF, 1996). As suggested above, elevated levels of serum iron facilitate proliferation within the host, as they will not grow in normal human serum because of an inability to compete with serum transferrin for iron (Lund et al., 2000). *Vibrio vulnificus* produce many extracellular compounds including hemolysin, protease, elastase, collagenase, DNase, lipase, phospholipase, mucinase, chondroitin sulfatase, hyaluronidase, and fibrinolysin. Whereas some of these factors may play a role in pathogenesis, they may not all be essential to the virulence of *V. vulnificus* (Doyle, 1989).

Vibrio cholerae

General characteristics Another species of the family Vibrionaceae is *Vibrio cholerae*, which are also motile by means of a single polar-sheathed flagellum. These curved rods thrive in their environmental reservoir as part of the microflora found in estuaries. In addition to its primary environmental source, *V. cholerae* has been isolated from areas not associated with a marine or brackish water supply, including freshwater lakes and rivers and from birds and herbivores (Murray et al., 1999). *Vibrio cholerae* O1 is composed of the classic biogroup that has been isolated during previous pandemics and El Tor, which is the predominant biogroup of the current pandemic (Kaper et al., 1995). It has been suggested that the emergence of *V. cholerae* O139 Bengal may be the start of the next pandemic (Murray et al., 1999).

The optimum temperature for growth of *V. cholerae* is between 30 and 37°C, although growth can occur between 10 and 43°C. *Vibrio cholerae* grow at pH 5.0–9.6 but prefer a pH of 7.6. They grow at a a_w of at least 0.97 but prefer 0.984. Optimum growth occurs in an environment with a sodium chloride concentration of 0.5%, although *V. cholerae* growth can occur at concentrations of 0.1–4.0% (ICMSF, 1996).

Characteristics of foodborne illness *Vibrio cholerae* typically gain entrance into the human body through ingestion of a contaminated food, such as mol-

lusks (raw oysters) or crustaceans eaten raw, undercooked, or even contaminated after cooking, or exposure of an open wound to a contaminated water source. Conditions resulting from *V. cholerae* O1 infection range from asymptomatic to the most severe form known as "cholera gravis" and in part depend on which biogroup is involved, because 75% of the El Tor biogroup and 60% of the classic biogroup lead to asymptomatic infections. Additionally, the El Tor biogroup results in severe disease in 2% of the infected individuals and mild or moderate disease in 23%, whereas the classic biogroup produces severe disease in 11% of individuals and mild or moderate disease in 30% (Kaper et al., 1995).

After an incubation period of several hours to 5 days, depending on inoculum size and the amount of food ingested, typical symptoms include muscle cramping caused as a result of severe dehydration (fluid loss up to 500–1000 ml/h) resulting from vomiting, increased peristalsis followed by loose stools progressing to watery stools, and mucus-flecked diarrhea that is characteristic of cholera. In addition to dehydration, other complications may include hypovolemic shock, hypoglycemia, and metabolic acidosis (Kaper et al., 1995).

The disease caused by *V. cholerae* O139 Bengal is clinically identical to the symptoms exhibited by *V. cholerae* O1-infected individuals. Other *V. cholerae* serogroups, in addition to *V. cholerae* O1 and *V. cholerae* O139 Bengal, are known as nonO1, nonagglutinating vibrios or noncholera vibrios and are not known to cause epidemic disease. However, noncholera vibrios are known to cause self-limiting gastroenteritis and also may cause wound infections, bacteremia, and septicemia when associated with a preexisting liver condition (Janda et al., 1988). The infectious dose of *V. cholerae* is approximately 10^{11}, but with the ingestion of food, the infectious dose is reduced to about 10^6 depending on the buffering capacity of the food (Kaper et al., 1995).

Mechanisms of pathogenicity Cholera symptoms, associated with *V. cholerae* O1 and *V. cholerae* O139 Bengal, are the result of the production and action of cholera toxin, which binds to receptors on the membranes of intestinal epithelial cells and subsequently, through the activation of adenylate cyclase, produces elevated cAMP levels resulting in the accumulation of water and electrolytes in the intestinal lumen (Kaper et al., 1995). Cholera toxin is a chromosomally mediated, heat-labile enterotoxin that resembles the plasmid mediated, heat-labile enterotoxin produced by *E. coli* (Kaper et al., 1995). Non-O1 strains do not produce cholera toxin. Instead, they produce two types of hemolysins, a heat-stable enterotoxin, and produce a capsule that functions to cause bacteremia, most likely by blocking the bactericidal activity of serum (Kaper et al., 1995).

Listeria monocytogenes

General characteristics The genus *Listeria* encompasses six species that follow two lines of descent. The first line includes, among others, the species *L.*

innocua, *L. ivanovii*, and *L. monocytogenes*. The other line of descent includes the species *L. grayi*, and up until recently, *L. murrayi*, which is now included with *L. grayi* (Ryser and Marth, 1999). *Listeria monocytogenes* are non-spore-forming, psychrotrophic, aerobic, microaerophilic or facultatively anaerobic, gram-positive rods that are motile at 28°C by means of up to five peritrichous flagella (Ryser and Marth, 1999).

This hardy organism is widely spread throughout various environments and has become a large concern to the food industry, where it is most often found growing under conditions of high humidity and limited nutrient levels, such as in floor drains, condensed and stagnant water, floors, and food residues on processing equipment (Ryser and Marth, 1999). Approximately 11–52% of animals are carriers, and 45% of pigs and 24% of cattle harbor *L. monocytogenes* in their tonsils and retropharyngeal nodes, respectively (Doyle et al., 1997). *Listeria monocytogenes* have also been reported in 2–5% of raw milk bulk tanks, 2–10% of soft cheeses, 0.3–2.0% of ice cream, <1–70% of whole and processed red meats, up to 60% of ready-to-eat poultry, 80–90% of raw or processed poultry, and up to 25% of raw and ready-to-eat fish and seafood products and are often present in fresh vegetables at a low level (Doyle et al., 1997).

Listeria monocytogenes grow at temperatures as low as −0.4°C and as high as 45°C, with an optimum of 30–37°C. Growth occurs in environments of pH 4.39–9.4, but pH 7.0 is preferred. *Listeria monocytogenes* growth requires a a_w above 0.92 and the organism survives at sodium chloride levels of up to 30% and at currently approved nitrite levels for foods (ICMSF, 1996; Murray et al., 1999).

Characteristics of foodborne illness Listeriosis is not a typical foodborne disease and is characterized by a variety of severe syndromes. The disease is nonenteric in nature, and in individuals with no underlying condition, infections of the central nervous system (meningitis and meningoencephalitis) are the most typical; individuals with an underlying condition frequently experience bacteremia (Doyle et al., 1997). Pregnant women may experience a flulike illness simultaneously with a fever, myalgia, or a headache, whereas fetal symptoms may include meningitis, neonatal septicemia, stillbirth, fetal death, or spontaneous abortion (Murray et al., 1999; Ryser and Marth, 1999).

Listeriosis is frequently associated with a long incubation time, anywhere from a few days to 2–3 months, and a preference to infect the immunocompromised, resulting in a high case fatality rate of 20–30% for both epidemic and sporadic cases and 38–40% among immunocompromised individuals and individuals with an underlying condition. Additional complications of listeriosis have been reported in as many as 30% of individuals surviving a central nervous system infection (Ryser and Marth, 1999). Data from epidemic and sporadic foodborne cases indicate infectious doses greater than 100 CFU/g, but it has been suggested not to ignore the possibility of infection resulting from lower doses, because of variations in enumeration procedures (Doyle et al., 1997; Ryser and Marth, 1999).

Mechanisms of pathogenicity *Listeria monocytogenes* possesses 13 serovars, and it is the only species of the genus *Listeria* that is of public health concern. Of the 13 serovars, 1/2a, 1/2b, and 4b account for 95% of human isolates collected, with serovar 4b strains implicated in 33–50% of sporadic human cases worldwide and most large outbreaks (Lund et al., 2000). There are considerable differences in virulence potential among strains, and no correlation between virulence and origin (human, animal, food, etc.) or strain characteristics (serovar, etc.) has been observed as yet. Nonetheless, at this time, all strains of *L. monocytogenes* are considered capable of causing listeriosis (Doyle et al., 1997).

After ingestion of contaminated product, the organism crosses the intestinal barrier, where it is internalized by macrophages and subsequently transported to lymph nodes via the bloodstream and eventually to the liver, which is the primary site of infection. Once internalized, the intracellular organism causes lysis of the vacuole and is released into the cytosol, where it begins proliferating. Although it requires the polymerization and redistribution of actin, bacteria can spread directly from one cell to another, thus spreading through tissue without leaving the intracellular environment and subsequently remaining protected from host antibodies (Ryser and Marth, 1999).

Staphylococcus aureus

General characteristics *Staphylococcus aureus* are nonmotile, gram-positive cocci that appear singly or in pairs, tetrads, short chains, or characteristic "grapelike" clusters. Staphylococci are facultative anaerobes that, with the exception of *S. saccharolyticus* and *S. aureus* subspecies *anaerobius*, grow more rapidly under aerobic conditions. *Staphylococcus* are widespread throughout nature and can be found on the skin and skin glands of mammals and birds, in addition to the mouth, blood, mammary glands, and intestinal, genitourinary, and upper respiratory tracts of infected hosts (Murray et al., 1999). Outside the body, *S. aureus* can survive for long periods of time in a dry state, and have been isolated from air, dust, sewage, and water, making it one of the most resistant non-spore-forming pathogens (Doyle et al., 1997). In addition to environmental sources of infection, some reported *S. aureus*-containing foods include ground beef, pork sausage, ground turkey, salmon steaks, oysters, shrimp, cream pies, milk, and delicatessen salads (Lund et al., 2000).

Staphylococcus aureus grow, depending on the strain, at temperatures ranging from 6.1 to 47.8°C and produce enterotoxins between 10 and 46°C but prefer an optimum temperature between 40 and 45°C. The bacterium grows between pH 4.0 and 9.8, with an optimum between 6.0 and 7.0, and is very tolerant to high levels of salt (>10% sodium chloride). Enterotoxin production requires a minimum a_w of 0.86, whereas growth has been demonstrated at a a_w of 0.83 (Jay, 2000; Lund et al., 2000).

Characteristics of foodborne illness *Staphylococcus aureus* typically causes infections involving the skin, such as boils, cellulitis, impetigo, and postopera-

tive wound infections, but can also be associated with more serious infections like bacteremia, pneumonia, osteomyelitis, cerebritis, meningitis, and abscesses of muscle, urogenital tract, central nervous system, and various abdominal organs (Lund et al., 2000; Murray et al., 1999). Toxic shock syndrome, a condition resembling septic shock and resulting from the production of toxic shock syndrome toxin 1, has been attributed to *S. aureus* infection.

Currently, staphylococcal food poisoning ranks worldwide as one of the most prevalent causes of gastroenteritis without requiring entrance or growth of the organism within the host (Doyle et al., 1997). Humans are the major reservoir for *S. aureus*, and contamination of food can occur through direct contact, indirectly by skin fragments, or through respiratory tract droplets, with most staphylococcal food poisoning cases being traced to food contamination during preparation because of inadequate refrigeration, inadequate cooking or heating, or poor personal hygiene. After ingestion of the enterotoxin and an incubation period of less than 6 and up to 10 h, symptoms may include vomiting, nausea, abdominal cramps, headache, dizziness, chills, perspiration, general weakness, muscular cramping and/or prostration, and diarrhea that may or may not contain blood. Symptoms persist for an average of 26 h, and although death resulting from staphylococcal food poisoning is not common, mortality rates of 4.4% have been reported among children and the elderly (Doyle et al., 1997).

It is difficult to predict the population needed to cause staphylococcal food poisoning because many variables affect the degree of enterotoxin production and the extent to which they cause illness, such as food type and composition, temperature, chemical parameters, and presence of inhibitors, in addition to the health of the person, susceptibility to the toxin, total amount of food ingested, and the toxin type, because enterotoxin A staphylococcal food poisoning is much more common but enterotoxin B tends to produce more severe symptoms (Doyle et al., 1997). Growth to populations greater than 10^5 organisms per gram of food product has been reported sufficient to produce effective doses of enterotoxin, although smaller populations have sometimes been implicated in illness. Ingested enterotoxin levels of 1–5 μg are not uncommon in many outbreaks, but staphylococcal food poisoning can be caused by doses of <10 ng (Doyle et al., 1997).

Mechanisms of pathogenicity The presence of *S. aureus* in food may be considered a public health hazard because of its ability to produce enterotoxin and the risk of subsequent food poisoning. Although there are nine identified staphylococcal enterotoxins, designated as A, B, C1, C2, C3, D, E, F, and G, types A and D are responsible for the majority of the outbreaks (Mossel et al., 1995). Staphylococcal enterotoxins are included in a larger family of toxins, known as pyrogenic toxins, that have the unique ability to act as superantigens, thereby stimulating an extraordinarily high percentage of T cells. They are difficult to inactivate with heat, because temperatures required to inactivate them are higher than those needed to kill the organism. Staphylococcal enterotoxin A is more heat sensitive than enterotoxins B or C and requires heating at 80 or

100°C for 180 or 60 s, respectively, to cause a loss in serological reactivity (Jay, 2000). Information on the histologic effects of oral doses of enterotoxin in humans is limited, as is information regarding specific cells and associated receptors acted on by the enterotoxin. Nonetheless, interaction between the enterotoxin and target cell receptors, whether direct or indirect, results in the production of inflammatory mediators inducing staphylococcal food poisoning symptoms (Doyle et al., 1997).

Clostridium botulinum

General characteristics The spore-forming genus *Clostridium* belongs to the family Bacillaceae and includes obligately anaerobic or aerotolerant, spore-forming rods that do not form spores in the presence of air and, at least in early stages of growth, are usually gram-positive. In most species, vegetative cells appear as straight or curved rods, varying from short coccoid rods to long filamentous forms with rounded, tapered, or blunt ends, that occur singly, in pairs, or in various chain lengths. Clostridia are found throughout the environment but are most prevalent in the soil and in the intestinal tract of animals. Typical soil species include *C. subterminale*, *C. sordellii*, *C. sporogenes*, *C. indolis*, *C. bifermentans*, *C. mangenotii*, and *C. perfringens*, in addition to *C. botulinum* and *C. tetani*, which are found to a lesser extent. Species commonly found in the intestinal tract of animals include *C. innocuum*, *C. ramosum*, *C. butyricum*, *C. sporogenes*, *C. bifermentans*, *C. tertium*, *C. paraputrificum*, and *C. putrificum* (Murray et al., 1999).

Clostridium botulinum are motile by means of peritrichous flagella and produce botulinum neurotoxins, the most lethal poison known. There are seven types of botulinum neurotoxin, A through G, with types A, B, E, and F causing botulism in humans, types C and D causing botulism in birds and mammals, and type G, which has yet to be clearly implicated in a botulism case (Murray et al., 1999). Group I *C. botulinum* is proteolytic and includes all type A strains and those proteolytic strains of types B and F; group II includes all type E strains and those nonproteolytic strains of types B and F; group III includes type C and D strains; and group IV includes type G strains (Lund et al., 2000).

Groups I and II receive the most attention, because they include the strains most commonly implicated in human cases of botulism. Group I proteolytic strains grow at temperatures between 10 and 48°C, with optimum growth at 37°C. Group I spores are very heat resistant, as indicated by a $D_{100°C}$ value of 25 min. Furthermore, group I strains grow above pH 4.6 and in sodium chloride concentration below 10% and require a minimum a_w of 0.94 (Doyle et al., 1997). Group II nonproteolytic strains grow at temperatures as low as 3.3°C but prefer an optimal temperature of 30°C. In contrast to group I spores, group II spores are not as resistant to high temperatures, having a $D_{100°C}$ value of less than 0.1 min. Group II strains grow above pH 5.0 and in sodium chloride concentrations of less than 5% and require a minimum a_w of 0.97 (Doyle et al.,

1997). Toxins, much like the spores, are resistant to freezing but are inactivated by heat (75–80°C) (ICMSF, 1996).

Thermal processing is the most common method used to produce shelf-stable, low-acid, moist foods by inactivating *C. botulinum* spores, and because group I spores tend to be the most heat resistant, they have been traditionally used as the target organism in this process. The presence of other organisms can greatly affect growth of *C. botulinum* (Lund et al., 2000). Acid-tolerant yeasts and molds can enhance growth conditions, whereas some organisms (e.g., *Lactobacillus*) inhibit growth by changing local environmental conditions, such as reducing pH, or producing bacteriocins (Doyle et al., 1997).

Characteristics of foodborne illness *Clostridium botulinum* is present in soils, freshwater, marine sediments, and the intestinal tracts of animals. Food sources commonly sampled include primarily honey, which should not be fed to infants less than 1 year of age, as well as fish, meats, vegetables, and infant foods. Traditionally, foodborne botulism has been associated with underprocessed and abused sausages or home canned foods; however, in recent years botulism has been acquired through the consumption of contaminated foods such as potato salad, sautéed onions, garlic sauce, cheese, yogurt, bean paste, and olives (Lund et al., 2000).

Symptoms of botulinum neurotoxin ingestion appear 12–36 h after consumption of contaminated food and initially may include nausea and vomiting. However, these symptoms are followed by the more characteristic neurological signs including visual impairment and acute flaccid paralysis that begins with the muscles of the face, head, and pharynx, descending to involve muscles of the thorax and extremities and leading to possible death from respiratory failure caused by upper airway or diaphragm paralysis (Murray et al., 1999, Lund et al., 2000). The minimum toxic dose of *C. botulinum* neurotoxin has not been determined, but from a human health and food safety standpoint, there should be no tolerance either for the neurotoxin itself or for conditions allowing growth of the organism in foods.

Mechanisms of pathogenicity Botulinum neurotoxin is synthesized during cellular growth and is subsequently released during cell lysis, where proteolytic cleavage activates the molecule. There are four categories of botulism, which include the classic foodborne botulism derived from the ingestion of preformed toxin in foods, wound botulism resulting from toxin production after organism growth in an infected wound, infant botulism from toxin elaboration in the intestinal tract of infants, and botulism due to intestinal colonization in older children and adults with intestinal disorders or complications resulting in a lack of microbial competition (Doyle et al., 1997). Botulinum neurotoxin introduced in any of these categories is transported via the bloodstream to neuromuscular junctions, where the toxin irreversibly binds to receptors on peripheral nerve endings and subsequently is internalized into the nerve cell. Once inside, the toxin interferes with the release of neurotransmitter (i.e., acetylcho-

line), thereby blocking synapses to muscle fibers and eliminating muscle response (Lund et al., 2000).

Clostridium perfringens

General characteristics *Clostridium perfringens*, previously known as *Clostridium welchii*, belongs to the family Bacillaceae and is an important cause of foodborne disease. They are nonmotile, encapsulated rod-shaped cells that produce protein toxins and form spores resistant to various environmental stresses such as radiation, desiccation, and heat (Doyle, 1989). Vegetative cells grow at temperatures ranging from 6 to 50°C but prefer an optimum temperature between 43 and 47°C. Growth requires a minimum a_w of 0.93, a sodium chloride concentration less than 5–8% depending on the strain, and a pH of 5.0–9.0, although 6.0–7.2 is preferred (Doyle, 1989; ICMSF, 1996; Lund et al., 2000).

Characteristics of foodborne illness *Clostridium perfringens* is the most prevalent *Clostridium* species found in human clinical specimens, excluding feces, and has been implicated in simple wound infections to myonecrosis, clostridial cellulitis, intra-abdominal sepsis, gangrenous cholecystitis, postabortion infection, intravascular hemolysis, bacteremia, pneumonia, thoracic and subdural empyema, and brain abscesses (Lund et al., 2000; Murray et al., 1999). The spores and cells of the organism are frequently associated with dust contamination on many surfaces, including foods such as meat and shellfish, as a result of its ubiquity throughout the environment.

Clostridium perfringens can cause rare foodborne necrotic enteritis, otherwise known as Darmbrand or Pig-Bel, as well as type A food poisoning. Type A food poisoning typically requires the ingestion of a highly contaminated food ($>10^6$–10^7), because many of the cells are killed from exposure to the acidic environment of the stomach (Doyle et al., 1997). Foodborne illness almost always is a result of temperature abuse, and in many instances, the food vehicle has been improperly cooked meat or meat product that has been left to cook and/or cool too slowly or has undergone insufficient reheating, allowing surviving spores to germinate leading to vegetative cell proliferation. After ingestion and an incubation period of 7–30 h, symptoms typically include cramping and abdominal pain, although nausea and vomiting may also ensue, persisting for 24–48 h (Murray et al., 1999).

Mechanisms of pathogenicity Five toxin-producing types of *C. perfringens* have been identified (A through E), and all produce an alpha-toxin (phospholipase) that plays a role in myonecrosis (Lund et al., 2000). Type B strains produce beta- and epsilon-toxins, type D strains also produce epsilon-toxin, and type E strains produce an iota-toxin (Murray et al., 1999). Almost all reported cases of foodborne gastroenteritis in the United States that involve *C. perfringens* are a result of type A infection after the ingestion of highly con-

taminated foods with greater than 10^6–10^7 viable vegetative cells, which undergo sporulation in the small intestine and produce enterotoxin (Doyle et al., 1997). The enterotoxin produced during sporulation is released with the spores during cell lysis. After release, the enterotoxin binds to epithelial cells, causing cytotoxic cell membrane damage and subsequent alteration of permeability, leading to diarrhea and abdominal cramping (Doyle et al., 1997). Significant histopathologic damage, including necrosis of villus cells, has been reported after exposure of animal models to *C. perfringens* enterotoxin (Lund et al., 2000).

Bacillus cereus

General characteristics *Bacillus cereus* belong to the family Bacillaceae and are gram-positive, motile rods, and although vegetative cells can grow anaerobically, the most defining characteristic is the ability to sporulate freely, forming subterminal, central or paracentral endospores in the presence of oxygen (Doyle, 1989; Lund et al., 2000). Most *Bacillus* species are found throughout the environment, including soils and fresh and marine water environments. Endospores often survive and are redistributed from the environment in many dried foods such as spices and farinaceous products (Murray et al., 1999).

Spores produced by *B. cereus* possess appendages and/or pili and are more hydrophobic than any other *Bacillus* spore. These properties enable the spores to adhere to many different types of surfaces and to resist removal during cleaning and sanitation (Andersson et al., 1995). Vegetative cells of *B. cereus* grow at temperatures ranging from 4–15 to 35–55°C but prefer 30–40°C, depending on the strain (ICMSF, 1996). The organism grows at pH 4.9–9.3, but the inhibitory effect of pH is reduced in foods as evidenced by limited growth on meat at pH 4.35 (Jay, 2000). The minimum a_w for growth has been established at 0.93, but it has been suggested to use 0.912 as the minimum required for growth, because fried rice tends to have a_w values ranging from 0.912 to 0.961 and readily supports *B. cereus* growth (ICMSF, 1996). Germination of *B. cereus* spores typically occurs at temperatures ranging from 5 to 50°C when held in cooked rice and trypticase soy broth, although under laboratory conditions, spore germination has occurred between −1 and 59°C, with optimum germination occurring at 30°C (Johnson et al., 1983).

Characteristics of foodborne illness With the exception of *B. anthracis*, *B. cereus* is the most important animal and human pathogen in the genus, and it is a significant cause of foodborne illness, accounting for 1–23% of reported outbreaks of known bacterial cause (Doyle, 1989). Ingestion of contaminated food may lead to one of two distinct clinical forms (i.e., diarrheal or emetic) of gastroenteritis. Both syndromes (i.e., diarrheal and emetic) are a result of *B. cereus* endospores surviving the cooking process, after which germination and subsequent proliferation of vegetative cells occurs at some point during storage. The diarrheal syndrome is associated with the ingestion of a wide array of con-

taminated foods including meats, vegetables, pastas, and soups and is characterized by abdominal pain, nausea, and diarrhea after an incubation period of approximately 8–16 h (Jay, 2000). Diarrheal syndrome symptoms generally persist no longer than 12–24 h (Doyle, 1989). The emetic syndrome is primarily associated with the ingestion of contaminated foods containing rice, although other foods including cream, potatoes, and vegetable sprouts have been implicated (Jay, 2000). After a 1- to 5-h incubation period, emetic syndrome symptoms include primarily nausea and vomiting and persist for 6–24 h. Additionally, emetic toxin has been reported to be associated with fulminant liver failure (Murray et al., 1999).

Mechanisms of pathogenicity The diarrheal syndrome type of food poisoning results from the action of a thermolabile enterotoxic complex, whereas the emetic syndrome type involves the action of a thermostable toxin. The diarrheal enterotoxin is a protein with optimum activity at temperatures between 32 and 37°C and is inactivated by exposure to 56°C for 5 min. The enterotoxin is sensitive to the activity of proteases (i.e., trypsin and pepsin) and is unstable outside the range of pH 4.0–11.0 (Doyle, 1989). The emetic toxin has optimum activity at temperatures ranging from 25 to 30°C, but remains active at 126°C for 90 min, is stable between pH 2.0 and 11.0, and exhibits resistance to trypsin and pepsin (Doyle et al., 1997).

Studies with outbreak-associated foods have estimated that illness results from ingestion of *B. cereus* populations ranging from 200 to 10^9 cells/g, with calculated infective doses in the range of 5×10^4–10^{11} cells/g (Doyle, 1989). Variation in infective dose (10^5–10^8 viable cells or spores/g) can be attributed to differences in enterotoxin production by different strains, and therefore, food containing *B. cereus* cells at a level of 10^4 cells/g should not be considered safe for human consumption (Lund et al., 2000).

Other bacterial hazards In addition to the bacteria described above, other pathogenic species may be associated with foodborne illness, although their involvement has not been well documented. These may include, among others, members of the genera *Aeromonas*, *Arcobacter*, other *Bacillus* species, *Brucella*, *Citrobacter*, *Edwardsiella*, *Enterobacter*, *Helicobacter*, *Klebsiella*, *Mycobacterium*, *Plesiomonas* (*P. shigelloides*), *Proteus*, *Providencia*, *Pseudomonas*, *Serratia*, and *Streptococcus*. The sections that follow briefly highlight important characteristics associated with some of these additional bacterial hazards.

Aeromonas Members of the genus *Aeromonas*, belonging to the family Vibrionaceae, are gram-negative, facultatively anaerobic, primarily motile rod-shaped organisms. *Aeromonas* are typically found in aqueous environments and have been implicated in cases of foodborne illness involving products that include raw meats, poultry, fish, milk, and produce (ICMSF, 1996). The presence of *Aeromonas* spp. in an individual may result in an intestinal infection, resembling a dysentery-like illness with diarrhea, abdominal pain, nausea,

chills, and headache, or an extraintestinal infection, such as septicemia, meningitis, endocarditis, peritonitis, endophthalmitis, or the infection of wounds (ICMSF, 1996). They can grow at temperatures ranging from 0 to 45°C, at pH 4.5–9.0, at a minimum a_w of 0.95, and in an environment with a sodium chloride concentration of 0.0–4.5% (ICMSF, 1996).

Brucella Members of the genus *Brucella* (*B. abortus*, *B. canis*, *B. melitensis*, *B. neotomae*, *B. ovis*, *B. suis*, and probably *B. maris*), are gram-negative, aerobic, nonmotile cocci or short rods (Murray et al., 1999). Human brucellosis typically results from infection acquired through the handling of an infected animal but has also been associated with transmission through foods. Brucellosis is rarely fatal and may be accompanied by several symptoms including fever, chills, weakness, body aches, headaches, sweating, and weight loss (Murray et al., 1999). The organism is strictly aerobic, although some strains grow best in 5–10% CO_2, with growth occurring at temperatures ranging from 6 to 42°C, at pH 4.5–8.8, and in environments with sodium chloride concentrations less than 4.0% (ICMSF, 1996).

Helicobacter *Helicobacter* are gram-negative spiral or curved bacilli that are motile and microaerophilic, growing best in environments with low oxygen levels (5–10%) and increased amounts of carbon dioxide (5–12%), although *H. westmeadii* is a strictly anaerobic exception (Murray et al., 1999). They have been isolated from the gastrointestinal tract of various animals and can be classified as gastric or enteric *Helicobacter*, depending on where the organism primarily colonizes within the host. Gastric *Helicobacter* rarely invade the bloodstream and primarily colonize within or beneath the mucous gel layer next to the epithelium in the stomach. In contrast, enteric *Helicobacter* have been isolated from blood, colonize the lower gastrointestinal tract, and are associated with gastroenteritis (Murray et al., 1999).

A specific gastric helicobacter, *H. pylori*, is the primary cause of peptic ulcer disease and has been estimated to currently infect 50% of the world's population (Dunn et al., 1997). A chronic active gastritis develops in the majority of individuals with sustained infections, producing various abdominal symptoms such as nonulcer dyspepsia, duodenitis, duodenal ulcers, gastric ulcers, and even chronic atrophic gastritis and subsequent gastric ulcer disease and gastric adenocarcinoma, one of the most common human cancers worldwide. Additionally, *H. pylori* infection has been associated with a rare gastric disease known as Ménétrier disease (Dunn et al., 1997).

Mycobacterium The family Mycobacteriaceae consists of only one genus, *Mycobacterium*, with the species divided into two groups based on rates of growth. The "rapidly growing" species require less than 7 days to form colonies, whereas the "slow-growing" species can require 6 weeks or more under optimum conditions. In general, the slow-growing species, which include *M. leprae*, *M. tuberculosis*, and *M. paratuberculosis*, have the ability to cause

disease in animals and humans, whereas the faster-growing species do not, although there are exceptions. *Mycobacterium* are considered gram-positive, nonmotile, straight or slightly curved, aerobic or microaerophilic bacilli that grow best between 30 and 45°C (Collier et al., 1998; Murray et al., 1999). Humans can be infected with mycobacteria several ways, including through the consumption of contaminated water, which has been implicated as the vehicle of transmission in several outbreaks. More recently, concerns regarding the transmission of *M. paratuberculosis*, the causative agent of a chronic infectious ileitis in ruminants known as Johne's disease or bovine paratuberculosis, in milk-containing foods have surfaced, and there has been much speculation regarding the association between *M. paratuberculosis* and Crohn's disease, a debilitating inflammatory bowel disease in humans (Lund et al., 2000).

Plesiomonas shigelloides *Plesiomonas shigelloides* are gram-negative, facultatively anaerobic rods that are primarily motile and have the ability to grow at pH 4.0–8.0, in environments containing sodium chloride concentrations between 0.0 and 5.0%, and in the temperature range of 8–45°C (Murray et al., 1999). They are primarily associated with fresh and estuarine water located in more tropical, temperate environments, where fish, mollusks, and crabs most frequently harbor the organism, although the organism has been isolated from pigs, poultry, and cattle (Doyle, 1989). *Plesiomonas shigelloides* typically infect humans after the consumption of contaminated water or undercooked seafood. After an incubation period of 24–48 h, symptoms include severe abdominal pain, cramping, nausea, vomiting, fever, headaches, and dehydration and may persist for a period of 2–14 days and possibly longer (Murray et al., 1999).

Pseudomonas Pseudomonads are gram-negative, motile rod-shaped aerobes, although some isolates can grow under specific anaerobic conditions (Doyle, 1989). These organisms are found in a wide range of moist environments including water, soil, fruits, vegetables, and the human gastrointestinal tract. With respect to human illness, the most significant species is *P. aeruginosa*. Infected individuals may exhibit symptoms that include a skin infection, ear infection, nosocomial respiratory and urinary tract infections, and among others, bacteremia (Murray et al., 1999). *Pseudomonas aeruginosa* grow at temperatures ranging from 0 to 42°C, at pH 5.6–9.0, and in an environment with a minimum a_w of 0.94 (Banwart, 1989).

Streptococcus Streptococci are gram-positive, facultatively anaerobic cocci that colonize the mucous membranes of humans and animals and are divided into categories based on their hemolytic properties, colony size, and responses to Lancefield serological testing (Doyle, 1989). Strains that produce large colonies, are beta-hemolytic, and react with Lancefield's group A antibodies, are included in the species *S. pyogenes*, which after infection can induce fever, pharyngitis, respiratory, skin, and soft tissue infections (necrotizing fasciitis),

endocarditis, meningitis, puerperal sepsis, and arthritis; severe infections can lead to shock and organ failure, termed toxic shock syndrome (TSS), resulting in 30–70% mortality (Murray et al., 1999). Strains that react with Lancefield's group B antibodies and are beta-hemolytic are included in the species *S. agalactiae*, which is a major cause of mastitis and can be transferred to humans through the consumption of raw milk, resulting in sepsis, meningitis, infant pneumonia, and postpartum infections (ICMSF, 1996; Murray et al., 1999). Strains that produce large colonies and are positive for the C and G antigens are similar to group A, *S. pyogenes*, and possess virulence traits that can contribute to infection leading to bacteremia, endocarditis, meningitis, septic arthritis, and respiratory tract and skin infections (Murray et al., 1999). Small-colony-forming strains that possess antigen to Lancefield group A, C, F, or G antibodies typically fall under the species *S. milleri* (Murray et al., 1999), and tend to be less virulent than the aforementioned species.

Streptococcus can grow at temperatures ranging from 10 to 44°C, at pH 4.8–9.2, at a minimum a_w of 0.92, and in environments with sodium chloride concentrations less than 6.4% (ICMSF, 1996; Banwart, 1989). Currently in the United States, *Streptococcus* is estimated to cause approximately 51,000 cases of foodborne illness annually (Mead et al., 1999).

Parasites

Parasites associated with foodborne disease fall into three groups: intestinal protozoa, tissue protozoa, or tissue helminths. Foodborne disease-causing parasites require a host (obligate parasites) to complete their life cycle. The environmental stage of the parasite can be ingested via the fecal-oral route, or the tissue stage (helminths) can be ingested with contaminated food (e.g., undercooked meat) or water.

Parasites in foods can be controlled through good sanitation, hygiene, proper cooking, frozen storage, salt, and radiation treatments. It is estimated that parasitic agents are responsible for approximately 2.6% of all foodborne illnesses involving known etiology, resulting in more than 350,000 cases annually in the United States. Despite being implicated in only 2.6% of foodborne illness cases, parasitic agents in foods cause an estimated 383 deaths annually, or roughly 21% of total deaths attributed to the consumption of contaminated foods (Mead et al., 1999).

Parasites of importance regarding foodborne disease include, among others, *Acanthamoeba* spp., *Anisakis simplex*, *Ascaris lumbricoides*, *Cryptosporidium parvum*, *Cyclospora cayetanensis*, *Diphyllobothrium* spp., *Entamoeba histolytica*, *Eustrongylides* spp., *Giardia lamblia*, *Nanophyetus* spp., *Sarcocystis hominis/suihominis*, *Taenia solium*, *Toxoplasma gondii*, *Trichinella spiralis*, and *Trichuris trichiura*. Some of these are discussed briefly in the sections that follow.

Cryptosporidium parvum *Cryptosporidium parvum* is a protozoan parasite belonging to the family Cryptosporidiidae and has been isolated from a wide range of warm-blooded animals including poultry, rodents, pigs, horses, calves, sheep, dogs, cats, and nonhuman primates as well as humans (Jay, 2000; Doyle et al., 1997). The life cycle of *C. parvum* occurs in only one host, and human cryptosporidiosis can be acquired through zoonotic, person-to-person, nosocomial, and contaminated food or water routes (Jay, 2000). *Cryptosporidium parvum* can infect the immunocompromised as well as the immunocompetent, where it inhabits the intestinal mucosa, resulting in diarrheal illness (Ackers, 1997). The organism spends its asexual life cycle stages in the brush border of the intestinal epithelium where it develops "intracellularly, but extracytoplasmically," resulting from the presence of a parasite-containing vacuole that possesses an exterior feeder organelle (Jay, 2000). Oocysts produced by *C. parvum* differ from those produced by other parasites in that the oocysts directly contain sporozoites without the presence of the sporocysts. Additionally, two types of oocysts are produced, with 80% being thick-walled cysts that are shed possessing environmental protection and 20% being thin-walled cysts that are shed and excyst immediately, resulting in autoinfection (Doyle et al., 1997; Murray et al., 1999). This recycling of the thin-walled oocysts appears to play a role in the severe disease seen in immunosuppressed individuals, where thick-walled oocysts are no longer present in the immediate environment.

After an incubation period of 6–14 days, *C. parvum* causes a self-limiting infection in the immunocompetent that may persist for up to 23 days and be accompanied by watery diarrhea associated with epigastric cramping, nausea, and anorexia. However, in the immunocompromised, a life-threatening infection may result in profuse diarrhea (3–17 liters/day) lasting for weeks, months, or even years (Garcia and Bruckner, 1997). Additionally, *C. parvum* can infect other epithelial cells, like those located in the respiratory tract and biliary tree (Murray et al., 1999).

In 1993, the largest waterborne outbreak to date occurred in Milwaukee, resulting in 403,000 cases of cryptosporidiosis and several deaths (Centers for Disease Control and Prevention, 1996b). Currently in the United States, *C. parvum* is estimated to cause approximately 30,000 cases of foodborne illness annually, with a case fatality rate of 0.005 (Mead et al., 1999).

Cyclospora cayetanensis *Cyclospora cayetanensis* are protozoan parasites, belonging to the family Eimeriidae, that inhabit the small intestine, where they spend the intermediary life cycle stages in the cytoplasm of enterocytes and subsequently produce oocysts containing two sporocysts encapsulating four sporozoites (Doyle et al., 1997). After subsequent shedding of the oocysts, 7–15 days are required for sporulation to occur (Murray et al., 1999). *Cyclospora cayetanensis* is capable of causing prolonged illness (6 weeks or longer) in both immunocompromised and immunocompetent individuals, with characteristic symptoms including nonbloody diarrhea, nausea, vomiting, anorexia, bloating, abdominal cramping, malaise, fever, and fatigue (Doyle et al., 1997).

Between 1996 and 1998 *C. cayetanensis* was identified as the etiologic agent in several outbreaks in the United States and Canada involving raspberries, baby lettuce, and basil (Murray et al., 1999). Currently in the United States, *C. cayetanensis* is estimated to cause about 15,000 cases of foodborne illness annually, with a case fatality rate of 0.0005 (Mead et al., 1999).

Giardia lamblia The flagellate *Giardia lamblia*, belonging to the family Hexamitidae, is currently the most common cause of human intestinal parasitosis in the world (Jay, 2000). When the flagellate gains entry into the human or animal body via fecal-oral transmission, typically associated with the consumption of contaminated water or food, it is in the cyst form. The organism excysts, releasing trophozoites that firmly attach to the mucosal epithelium inside the intestine. The attachment of the trophozoite is accomplished with a ventrally located suction disk that maintains flagellate attachment but does not penetrate the mucosa. After binary fission, yielding two identical daughter flagellates, the flagellates encyst and the life cycle is completed as the new cysts are re-released into the environment during fecal excretion by the host (Garcia and Bruckner, 1997). Individuals most commonly infected include children at day care centers, the immunocompromised, and hikers and campers, primarily because of consumption of untreated water (Murray et al., 1999). Although the majority of the infections are asymptomatic, after an incubation period of 12–20 days, individuals can experience subacute or chronic infections with symptoms including nausea, chills, low-grade fever, watery diarrhea, abdominal discomfort and distention, heartburn, malabsorption, and reduced pancreatic function (Murray et al., 1999).

Between 1984 and 1994, *G. lamblia* was implicated in 34 outbreaks producing 3994 cases of giardiasis in the United States (Marshall et al., 1997). Currently in the United States, *G. lamblia* is estimated to cause about 200,000 cases of foodborne illness annually (Mead et al., 1999).

Sarcocystis hominis/suihominis The family Sarcocystidae includes six genera of cyst-forming coccidia (Dolezel et al., 1999). Within the 13 species currently described, two species of the genus *Sarcocystis* are known to cause sarcocystosis in humans. Humans are the primary host for both species; however, the secondary hosts for *S. hominis* and *S. suihominis* are cattle and pigs, respectively (Jay, 2000). Ingestion of sarcocysts results in the release of bradyzoites that target and invade the mucosal epithelium of the small intestines, penetrating into the lamina propria, where sexual reproduction occurs and new sarcocysts are formed and subsequently shed by the host (Jay, 2000). In the primary host, ingestion of sporocysts (the infective stage) results in the release of sporozoites that travel throughout the body, where they reproduce asexually and form sarcocysts in both skeletal and cardiac muscle, reaching as much as 1 cm in diameter (Doyle et al., 1997). After an incubation period of 3–6 and 6–48 h for *S. hominis* and *S. suihominis*, respectively, symptoms may include nausea, stomachache, and diarrhea (Jay, 2000). Additionally, symptoms in

animals may include abortion, weight loss, suppressed milk production, wool breakage, lameness, and even death (Murray et al., 1999).

Toxoplasma gondii *Toxoplasma gondii* are obligate intracellular protozoan parasites that use cats as their primary reservoir and any other warm-blooded animal as an intermediate host (Doyle et al., 1997). The protozoan may be present as tachyzoites, bradyzoites, or sporozoites, which are the three stages of its life cycle. Tachyzoites and bradyzoites occur in body tissues, where the tachyzoites proliferate and destroy infected host cells and the bradyzoites multiply within tissue cysts. Sporozoites are shed, within oocysts, in cat feces where they sporulate after 1–5 days, surviving for months by utilizing their ability to resist disinfectants, freezing, and drying (Murray et al., 1999).

In humans, *T. gondii* can be acquired in several ways, including the ingestion of contaminated food or water containing the oocyst, contaminated blood transfusion or organ transplantation, transplacental transmission, or accidental tachyzoite inoculation. *Toxoplasma gondii* infections typically result from the ingestion of cysts in raw or undercooked meat, with fresh pork and beef appearing to be the primary sources (Murray et al., 1999). Toxoplasmosis can result from the ingestion of as few as 100 tissue cysts or oocysts, at which time cyst walls rupture, releasing the sporozoites or bradyzoites to move through the intestinal epithelium and circulate throughout the body (Jay, 2000). Sporozoites and bradyzoites transform into tachyzoites and begin to rapidly multiply intracellularly, and after host cell death, the tachyzoites invade adjacent cells and repeat the reproduction process. These tachyzoites, by means of the host immune response, are forced to transform back into bradyzoites and form cysts in the local tissue, where they can remain throughout the life of the host organism (Doyle et al., 1997; Murray et al., 1999).

Toxoplasmosis symptoms include fever, rash, headache, muscle aches and pain, and swelling of the lymph nodes and may persist for more than a month (Jay, 2000). *Toxoplasma* oocysts can be inactivated by high temperature, 61°C for 3.6 min, or by freezing at −13°C (Doyle et al., 1997). Currently in the United States, *T. gondii* is estimated to cause about 113,000 cases of foodborne illness annually (Mead et al., 1999).

Trichinella spiralis *Trichinella spiralis*, belonging to the family Trichinellidae, is the common roundworm implicated in human trichinosis and is typically associated with the ingestion of undercooked pork or pork products contaminated with the encysted larvae (Murray et al., 1999). Adult nematodes live in the duodenal and jejunal mucosal epithelium, where they can exist for up to 8 weeks before they are expelled. During this transient period, adult female nematodes can release approximately 1500 larvae into the bloodstream to travel around the body and subsequently enter muscle tissue, where they can survive for several years (Jay, 2000). In skeletal muscle, larvae develop, mature, and undergo encapsulation in a calcified wall 6–18 months later. Both the larval and the adult stages are passed from the same host. Encysted larvae

remain viable for up to 10 years and are freed by the stomach enzymes of the new host after the ingestion of the encysted flesh (Jay, 2000).

Symptoms, after an incubation period of 3–14 days, include nonspecific gastroenteritis, nausea, vomiting, headaches, fever, visual deficiencies, difficulty breathing, chills, night sweating, eosinophilia, myalgia, and circumorbital edema (Murray et al., 1999). The nematode can be thermally inactivated, and therefore the USDA recommends cooking pork products to an internal temperature of 76.7°C (Jay, 2000). Currently in the United States, *T. spiralis* is estimated to cause about 52 cases of foodborne illness annually, with a case fatality rate of 0.003 (Mead et al., 1999).

Viruses

In the past several decades, viruses have joined bacteria and parasites as organisms that cause gastroenteritis and are involved in medically important diarrheal disease. Viruses in foods are controlled through proper sanitation, hygiene, cooking, and avoidance of cross-contamination before consumption. It has been estimated that in the United States foodborne pathogenic viruses are responsible for approximately 67% of foodborne illnesses involving known etiology, resulting in more than 9 million cases annually. Although viruses are implicated in 67% of foodborne illness cases, their presence in foods results in only 129 deaths, or approximately 7% of total deaths attributed to the consumption of contaminated foods (Mead et al., 1999). Viruses of importance regarding foodborne illness include, among others, hepatitis A, Norwalk and Norwalk-like, rotavirus, astroviruses, and enteroviruses. The following sections highlight characteristics and potential roles that some of these medically important pathogens may play in foodborne disease.

Hepatitis A Hepatitis A, belonging to the family Picornaviridae, is an icosahedral, nonenveloped virion that is resistant to heat and pH extremes (Doyle et al., 1997; Murray et al., 1999). Hepatitis A infection is associated with the fecal-oral route of transmission and is most prevalent in underdeveloped areas with poor sanitation. It is responsible for 20–25% of hepatitis cases worldwide and can be transmitted by contaminated food or water or by direct contact with contaminated blood. Raw or partially cooked shellfish harvested from polluted waters have been implicated as vehicles of transmission in several outbreaks, with symptoms of infection ranging from mild illness to a severe hepatitis infection with jaundice (Jay, 2000; Murray et al., 1999). After a dose-dependent incubation period ranging from 10 to 50 days, the onset of a preicteric phase may be associated with fever, fatigue, malaise, myalgia, anorexia, nausea, and vomiting (Lund et al., 2000). Icteric phase symptoms include a yellowish discoloration of the mucous membranes, conjunctivae, sclera, and skin, in addition to the excretion of dark, golden brown urine and stool that is pale in color (Murray et al., 1999). Additional complications associated with hepatitis A infection may include skin rash, Guillain–Barré syndrome, renal

failure, meningoencephalitis, cryoglobulinemia, arthritis, and hematologic and cardiovascular complications (Murray et al., 1999). Clinical symptoms associated with preicteric and icteric phases of hepatitis A infection typically persist for 4–8 weeks; however, fecal shedding of hepatitis A can continue months after symptoms have recessed (Murray et al., 1999). Currently in the United States, hepatitis A is estimated to cause over 4000 cases of foodborne illness annually, with a case fatality rate of 0.003 (Mead et al., 1999).

Norwalk Norwalk and Norwalk-like viruses, or small, round structural viruses (SRSV), belong to the family Caliciviridae. Human caliciviruses are divided into three groups: the Norwalk virus group, the Snow Mountain agent group, and the Sapporo virus group (Murray et al., 1999). Raw or slightly cooked shellfish and other foods not cooked after contamination, in addition to contaminated water, have been implicated as vehicles of transmission in outbreaks occurring in institutions, restaurants, and homes and on cruise ships (Doyle et al., 1997). After ingestion of contaminated food and an 18- to 48-h incubation period, symptoms may include nausea, vomiting, diarrhea, and other gastroenteritis-associated symptoms (ICMSF, 1996). Although symptoms persist for 24–72 h, the virus continues to be shed for about a week (Jay, 2000). The agent targets mucosal epithelial cells, leaving lesions in the small intestine where progeny are produced and eventually shed by the host. These organisms are resistant to acid, ether, and heat and can survive freezing (ICMSF, 1996). They are more resistant to chlorine than any other enteric virus and have remained active in drinking water with a chlorine concentration of 5–6 ppm (Jay, 2000). Currently in the United States, Norwalk and Norwalk-like viruses are estimated to cause approximately 9.2 million cases of foodborne illness annually (Mead et al., 1999).

Rotaviruses Rotaviruses, belonging to the family Reoviridae and possessing a double-stranded ribonucleic acid genome (dsRNA), are subdivided into six groups (A through E), although only three (A, B, and C) infect humans (Murray et al., 1999). Group A is associated most frequently with infants and children throughout the world, and in developing countries it is a significant cause of infant death. Group B causes diarrhea primarily in adults, whereas group C causes disease primarily in older children (Blaser et al., 1995). Children are most susceptible during the winter months, and rotaviruses are responsible for approximately one-third of diarrheal hospitalizations involving children under the age of 5 (Jay, 2000). The primary mode of transmission is the fecal-oral route, which can occur directly, through contact with an infected individual, or indirectly, by means of contaminated water or food (Jay, 2000). Rotaviruses infect the absorptive villous epithelium associated with the upper two-thirds of the small intestine, where after an incubation period lasting 1–3 days, the agents target enterocytes. After target cell entrance, the virus is transported to the lysosomes and subsequently uncoated (Doyle et al., 1997). Symptoms may include vomiting in conjunction with watery diarrhea induced by a nonstruc-

tural protein (NSP-4) possessing enterotoxin-like activity (Murray et al., 1999). Symptoms, typically persisting for 3–8 days, may also include abdominal pain or fever, or any other gastroenteritis-associated symptom (Blaser et al., 1995). Currently in the United States, rotavirus is estimated to cause about 39,000 cases of foodborne illness annually (Mead et al., 1999). However, worldwide rotavirus infection is the most common cause of diarrhea among children, resulting in approximately 800,000 deaths per year (Parashar et al., 1998).

REGULATORY, INDUSTRIAL, AND INTERNATIONAL IMPLICATIONS

An understanding of foodborne biological hazard characteristics and properties associated with specific food sources has important regulatory, industrial, and international implications. Consideration of intrinsic and extrinsic factors, and how these influence growth and/or survival of microorganisms, is imperative in the establishment of effective mandatory or advisory performance criteria. Establishment of a microbiological criterion requires an understanding of the properties of the specified organism, including microbial ecology (prevalence among food and other environmental sources), mode(s) of transmission, virulence factors (e.g., preformed toxin production), and metabolic characteristics, among others. Furthermore, this information is critical to the establishment of an effective sampling plan and analytical procedure.

Although it is clearly better to err on the side of caution when decisions are made regarding public health, error in itself can be costly. For example, additional insight into the characteristics regarding pathogenicity among specific strains of *L. monocytogenes* could result in an amendment to the general assumption that all strains be considered capable of causing listeriosis, thereby potentially reducing the likelihood of unnecessarily recalling and/or destroying otherwise biologically safe foods. Furthermore, the development and/or implementation of various techniques or technologies to preserve or increase the microbiological quality of foods by effectively and efficiently eliminating, reducing, or inhibiting individual or groups of microorganisms, to comply with performance criteria or otherwise, requires an understanding of the characteristics of the target organism(s), as well as preservation/decontamination methods and antimicrobial properties or mode(s) of action (e.g., modified atmospheres, radiation, low- and high-temperature treatment, drying, organic and nonorganic compound application, etc.) (Jay, 2000). These considerations have a wide base of applications including, among others, the systematic approach of HACCP, which encourages proactive, repeated assessments and strategy implementations during the food manufacturing process. It is through this increasingly mandated approach that microbiologically safe foods are produced and marketed not solely based on end product testing but through closely monitoring manufacturing processes contributing to acceptable product hygiene (Jay, 2000; NACMCF, 1998). This system involves the identification of critical control points (CCPs), or points in the food manufacturing process

where control over a hazard can be exerted, and associated measures at those process locations that achieve the desired level of control (e.g., cooking, chilling, etc.). CCPs are accompanied by critical limits, or operating parameters (e.g., time and temperature), that ensure that implemented measures associated with CCPs effectively control the desired hazard. HACCP, on an international level, illustrates one way of achieving consistent product manufacturing on a global basis, in an attempt to "harmonize" the worldwide production of safe food.

Despite the debate surrounding the establishment of performance criteria or microbiological limits as indicators of food safety or process control/hygiene, their development and implementation have certainly influenced, and undoubtedly will continue to influence, methods by which foods are produced, harvested, processed, and marketed.

CURRENT AND FUTURE IMPLICATIONS

As they have done in the past, microorganisms continue to evolve, and their large genetic variability and short generation times increase their potential for survival in less than favorable environmental conditions (Hall, 1997). The emergence of antibiotic-resistant bacteria as a result of the ubiquity of environmental antimicrobials has led to public health concerns centered around increased morbidity and mortality associated with failing antimicrobial treatment regimes (Morse, 1995). For example, in 1997 the United States experienced its first pentadrug-resistant outbreak involving a strain of *S.* Typhimurium phage type 104 (DT104), previously seen in the United Kingdom, that exhibited resistance to ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline (Centers for Disease Control and Prevention, 1997). In addition to pentadrug-resistant *S.* Typhimurium, there has been a general emergence of quinolone-resistant nontyphoidal *Salmonella* (Herikstad et al., 1997). Isolation of antimicrobial-resistant *Salmonella* has been on the rise since 1979–1980 when 16% were resistant, to 1989–1990 when 29% were resistant and in 1996 when 37% of isolates were resistant to at least one agent (Murray et al., 1999). In addition to *Salmonella*, other examples include antimicrobial resistance in the genera *Shigella* and *Staphylococcus*. *Shigella* have developed resistance to sulfonamides, ampicillin, trimethoprim-sulfamethoxazole, tetracycline, chloramphenicol, and streptomycin, and in areas of Africa and Asia, *S. dysenteriae* type 1 serotypes have been reported as being resistant to all locally available agents (Murray et al., 1999). Similarly, methicillin-resistant *S. aureus*, emerging during the 1980s and early 1990s, has impacted human health, especially in hospital settings.

In addition to the emergence of antibiotic resistance, common foodborne pathogenic bacteria have demonstrated resistance and cross-protective capabilities to food preservation stresses as well as increased virulence. For a foodborne pathogen to cause disease, it must survive exposure to a wide range of

stresses associated with both the vehicle of transmission and host immune defenses. Foodborne infection illustrates a pathogen's ability to adapt and survive exposure to environmental stresses. The induction of bacterial resistance to environmental stresses such as temperature and pH extremes involves the production of "protective" shock proteins, some of which possess cross-protective capabilities or the ability to confer protection to more than one type of stress. For example, the ability of acid-induced *E. coli* O157:H7 to resist the antimicrobial effects of acid is increased after heat shocking. In addition to increased heat tolerance after shocking, *L. monocytogenes* express increased tolerance to ethanol and NaCl. *Listeria monocytogenes* also demonstrate increased tolerance to low pH and H_2O_2, after adaptation to ethanol (Sheridan and McDowell, 1998). Exposure to sublethal stress during the food manufacturing process may result in stress-hardened pathogens. These pathogens may more readily survive subsequent antimicrobial treatment applications aimed at improving microbiological food quality, potentially resulting in persistent microbiological populations possessing elevated virulence factor expression (Sheridan and McDowell, 1998). The ability of an organism to resist environmental stresses, both individually or in combination and with or without previous exposure, is an important consideration when developing future systems aimed at improving microbiological quality within a particular food and, furthermore, deserves consideration during predictive microbiology and modeling efforts to ensure food safety.

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CHAPTER 11

CONTEMPORARY MONITORING METHODS

JINRU CHEN

INTRODUCTION AND DEFINITION OF ISSUES

To ensure the safety of the global food supply, contemporary methods are needed for rapid, effective, and accurate monitoring of environmental hygiene, identification of biological hazards, and assessment of product quality. These methods include adenosine triphosphate (ATP) bioluminescence, polymerase chain reaction (PCR), and enzyme-linked immunosorbent assay (ELISA).

ATP is a nucleotide consisting of an adenine, a ribose, and a triphosphate unit. The phosphanhydride bonds in the triphosphate unit make ATP an energy-rich molecule. In water, ATP is hydrolyzed to adenosine diphosphate (ADP) and adenosine monophosphate (AMP), with the subsequent release of energy.

One way to determine the level of ATP is by measuring bioluminescence, as registered on a luminometer. Bioluminescence is the light emitted from living organisms that have the ability to produce luciferase enzymes. The most extensively studied luciferase is from *Photinus pyralis*, a common firefly in North America. Firefly luciferase is a protein with a molecular weight of 62,000. It catalyzes an oxidative reaction of luciferin, in which one of the end products is left in an unstable state that subsequently decomposes to give light. The peak emission of firefly bioluminescence is 560 nm, with the emission wavelengths ranging from 560 to 630 nm.

PCR is a technique used for *in vitro* DNA amplification. The assay is carried out in an instrument known as DNA thermocycler, invented by Perkin Elmer, Inc. (Norwalk, CT). The thermocycler provides repeated cycles of temperature change. During these cycles, low levels of DNA extracted from a pathogen are amplified into millions of copies within short period of time. The

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amplification makes it possible to detect pathogens from food sensitively, specifically, and rapidly.

ELISA is an immunological assay that uses polyclonal or monoclonal antibodies to detect target microorganisms. For pathogenic microorganisms, unique surface structures or toxic metabolites are used as antigens to produce specific antibodies. These antibodies, in the ELISA, identify their corresponding antigens, whose presence is the indication of pathogen contamination of a tested sample. For microorganisms with unknown pathogenicity, heat- or chemical-killed whole cells are sometimes used to produce antibodies.

When an antibody encounters its corresponding antigen, an antigen-antibody complex is formed. However, if the antigen molecules are too small or too diluted, this reaction may not be visible. Therefore, a secondary antibody, that is, an antibody against the primary antibody, conjugated with an enzyme, is needed for the generation of a detectable signal.

SCIENTIFIC BASIS AND IMPLICATIONS

Bioluminescence Reactions

ATP is an immediate provider of free energy, meaning that an ATP molecule is consumed soon after its formation and that the energy associated with the molecule cannot be stored. As a result, ATP is present only in living cells and disappears shortly (about 2 h) after cell death. Therefore, the presence of ATP can be used as an indication of cell viability.

The firefly bioluminescence reaction is an energy-consuming process. As in many other biochemical reactions, ATP is the donor of such energy. In addition to ATP, firefly luciferase requires luciferin, molecular oxygen, and magnesium as substrates. In the initial step of the firefly bioluminescence assay, an adenyl moiety is transferred from ATP to the carboxyl group of luciferin to form luciferyl adenylate, with the elimination of inorganic pyrophosphate (Reaction 1). The luciferase-AMP complex subsequently reacts with molecular oxygen (Reaction 2) to yield light (McElroy and Deluca, 1985).

Reaction 1:

$$E + LH2 + ATP + Mg \rightarrow E \cdot LH2\text{-}AMP + ppi$$

Reaction 2:

$$E \cdot LH2\text{-}AMP + O_2 \rightarrow \text{oxyluciferin} + CO_2 + AMP + \text{light}$$

E stands for luciferase enzyme; LH2 stands for the luciferase substrate luciferin.

The amount of ATP consumed in the firefly bioluminescence assay is proportional to the amount of light generated. Because the level of ATP in certain microbial cells is fairly consistent (10^{-18} to 10^{-17} mol/bacterial cell), light gen-

erated in a reaction quantitatively reflects the level of metabolically active cells in a system.

The ATP bioluminescence assay was first developed in the 1960s for finding life in space (Chappelle and Levin, 1968). The technique was adapted years later for the detection of microorganisms in foods (Sharpe et al., 1970). Currently, ATP bioluminescence is widely used for rapid assessment of processing conditions and microbial contamination of food. It has also been used for monitoring critical control points (CCPs) during Hazard Analysis and Critical Control point (HACCP) management. Distinct from traditional monitoring methods, the ATP bioluminescence assay is rapid and the test results can be available in minutes. The assay can be conducted on-site because luminometers, the equipment that measures emitted light, have been made portable. In contrast to swabbing techniques commonly used for hygiene monitoring, the ATP assay measures not only the level of microbial contamination but also the cleanliness of food processing surfaces and equipment.

Polymerase Chain Reaction (PCR)

PCR was first described in 1971 (Kleppe et al., 1971) but gained prominence in the 1980s and 1990s as a diagnostic tool. After two decades, the technique is more popular than ever and has been used in many disciplines of life science. In the field of food microbiology, PCR is primarily used for rapid detection or identification of microorganisms from food.

As with higher plants and animals, the genetic traits of microorganisms are determined by the information stored in their deoxyribonucleic acid (DNA). This information includes genetic determinants that encode for enzymes and proteins involved in metabolic pathways and constituting structures and virulence factors of microbial cells. PCR identifies unique regions of DNA, known as templates, of a target microorganism. The positive amplification of these regions in PCR suggests microbial contamination of a tested sample. As a contemporary detection method, PCR is more sensitive and specific, and less intensive and cumbersome, than standard microbiological assays.

In PCR, new DNA is synthesized according to the template by *Taq* DNA polymerase, an enzyme isolated from the themophilic bacterium *Thermus aquaticus*. The *Taq* DNA polymerase is stable and remains active at the elevated temperatures used for DNA denaturation. In addition to the DNA template and enzyme, the assay needs the participation of several other components: 5′ and 3′ specific primers, deoxynucleotide triphosphates (dNTPs), and salts. The nucleotide sequences of the two primers are homologous to the 3′ and 5′ sites of the template, respectively. In PCR, the segment of DNA that lies between the two primers is amplified. Salts provide an optimal condition for the reaction to proceed, and the dNTPs serve as substrates for *Taq* DNA polymerase.

The process of PCR is shown in Figure 11.1. There are three temperatures in a PCR cycle: 95°C for DNA denaturation, during which a double-stranded DNA template dissociates to become single-stranded; 55°C for primer anneal-

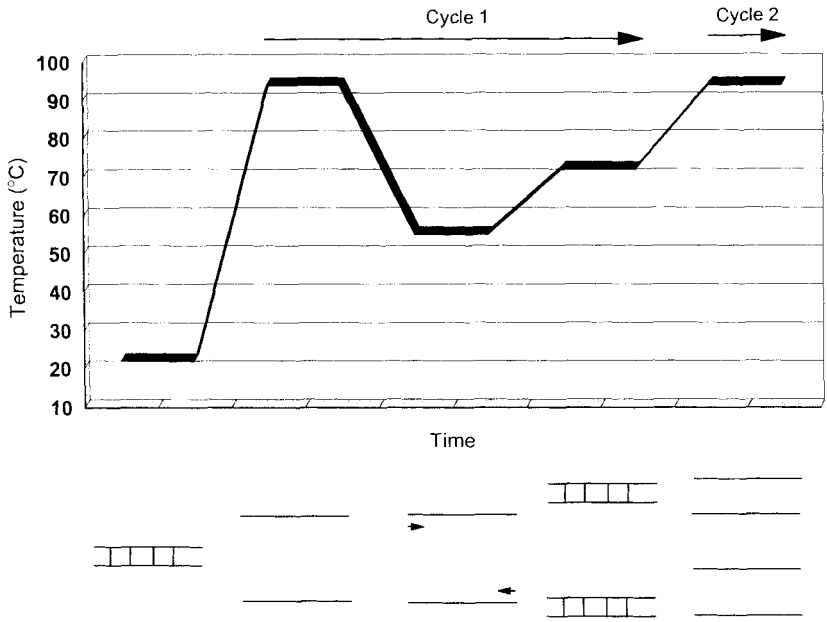

Figure 11.1. The Process of PCR.

ing, during which the two primers bind specifically with the single-stranded template; and 72°C for primer extension, during which the region of DNA between the two primers is synthesized. Results of PCR are analyzed by fluorescent staining of amplified products separated by electrophoresis on an agarose gel.

Enzyme-Linked Immunosorbent Assays (ELISA)

ELISA was first introduced in the 1960s and has been around for quite some time. However, the availability of more sensitive dyes and substrates in recent years has enhanced the utility of ELISA. ELISA differs from PCR in that it detects phenotypic characteristics of pathogenic microorganisms. By using a commercial ELISA reader, the assay is semiautomatic and handles up to 96 samples per assay.

There are different formats of ELISA. The most common type uses a polystyrene microtiter plate as a solid phase. The wells of the microtiter plate are coated with antigen by overnight incubation in a coating buffer. Two antibodies are involved in ELISA (Figure 11.2). The primary antibody, usually produced in rabbits or mice, binds specifically with the antigen and determines the specificity of the assay. A secondary antibody is enzyme-labeled goat anti-rabbit or goat anti-mouse IgG, depending on the origin of the primary antibody. Enzyme-conjugated secondary antibody is applied for detection and can be used for the identification of different pathogens as long as the primary

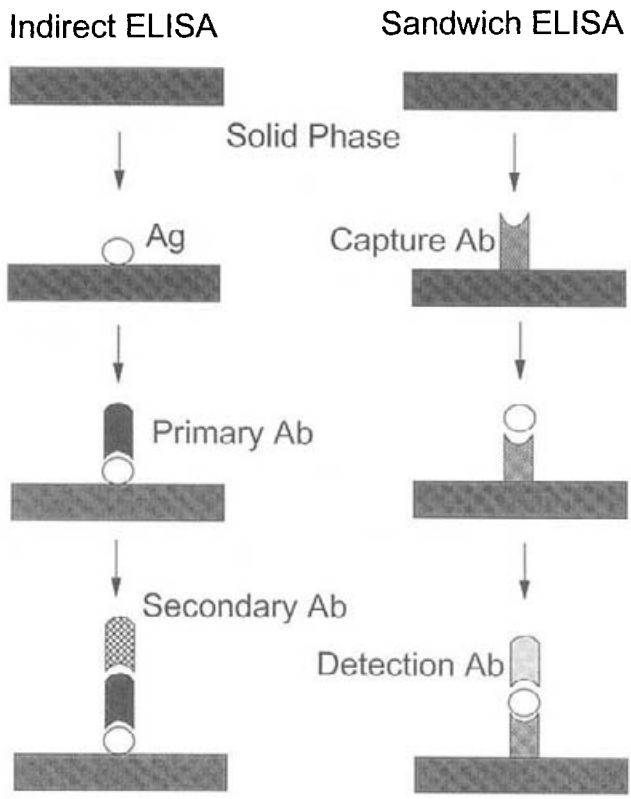

Figure 11.2. Principles of ELISA.

antibodies belong to the same animal source. Horseradish peroxidase or alkaline phosphatase is commonly used in ELISA. These enzymes produce chemical changes in their corresponding substrates and provide detectable color or chemiluminescence signals.

Another format is the sandwich ELISA, in which the antigen must have more than one binding site. One antibody is bound to the solid phase to capture the antigen, and an enzyme-labeled secondary antibody provides a detectable signal. In some assays, however, the same antibody is used in both capture and detection steps.

REGULATORY, INDUSTRIAL, AND INTERNATIONAL IMPLICATIONS

Bioluminescence Monitoring Techniques

Although the food industry depends heavily on Standard Sanitary Operation Procedure (SSOPs) and HACCP (see Chapter 20) to enhance product quality

and safety, the adequacy of these programs is not always ensured. Therefore, postsanitation inspection and routine hygiene monitoring are used to confirm effectiveness. ATP bioluminescence is a rapid and sensitive tool for monitoring the operating conditions in food processing plants. When used to evaluate the efficacy of sanitation treatments, ATP bioluminescence offers a strong correlation with traditional swabbing techniques. The occasional disagreement between the results of the ATP bioluminescence assay and those of traditional microbiological tests are caused by the presence of food residue or the occurrence of nonreplicating spores and injured microorganisms (Griffiths, 1996).

There are four basic steps in the ATP bioluminescence assay: sample collection, separation of microbial cells from food, extraction of microbial ATP, and light measurement. The reagents for the ATP bioluminescence assay are commercially available and are listed in Table 11.1.

TABLE 11.1. Commercial Reagents Used in ATP Bioluminescence Assay [Adapted from Griffiths (1996) with modifications]

Instrument/test	Manufacturer	Canadian distributor	U.S. distributor
Bio-Orbit®	Bio-Orbit Oy, Turku, Finland	Diagnostix Inc., Mississauga, ON	Diagnostix Inc., Burlington, NC
BioProbe® ATP Detection System & BIOPROBE	Contamination Sciences LLC, Madison, WI	—	Contamination Sciences LLC, Madison, WI
GEM	GEM Biomedical Inc., Hamden, CT	—	GEM Biomedical, Inc. Hamden, CT
Hy-Lite®	E. Merck, Darmstadt, Germany	Glengarry Biotech, Cornwall, ON	E. M. Science, Gibbstown, NJ
Inspector®/System Sure™	Celsis International plc, Cambridge, U.K.	—	Celsis Inc., Evanston, IL
Lightning®	Idexx Labs, Inc., Westbrook, ME	—	Idexx Labs., Inc., Westbrook, ME
Lumac®	Lumac bv, Landgraaf, The Netherlands	—	Perstorp Analytical, Silver Springs, MD
Luminator®/ PocketSwab™	Charm Sciences Inc., Malden, MA	—	Charm Sciences Inc., Malden, MA
Uni-Lite®/UniLite® Xcel	Biotrace Ltd., Bridgend, U.K.	Klenzade Ecolab, Mississauga, ON	Biotrace, Inc., Plainsboro, NJ

ATP bioluminescence has been used to assess the microbial quality of raw milk and meats. After treatment with the milk-clarifying solution Enliten (Promega, Madison, WI), milk was filtrated or centrifuged to collect bacterial cells that would be subsequently lysed and assayed for ATP activity (Pahuski et al., 1991). Poultry and meat samples, however, had to be rinsed or swabbed to collect microbial cells (Bautista et al., 1995; Siragusa and Cutter 1995; Siragusa et al., 1995). Separation of microbial cells from meat was accomplished by repeated centrifugation at different velocities (Chen and Griffiths, 1998), initially at slow speeds to recover meat particles and later at high speeds to sediment bacterial cells. Two-step filtration was an alternative (Griffiths, 1996). Tested samples were filtered first through a coarse filter to remove meat tissues and then through a fine membrane to collect bacterial cells. ATP was subsequently extracted from the bacterial cells and assayed with commercial firefly luciferase and luciferin complex.

Monitoring and record keeping are important steps in HACCP management (see Chapter 20) that provide information on whether potential hazards are under control and if corrective actions are necessary. In poultry processing plants, the microbial quality of poultry processing waters as indicated by ATP bioluminescence was used in CCP monitoring (Bautista et al., 1996). Samples were collected from different CCPs identified in poultry processing plants by swabbing chicken carcasses. ATP was extracted from chicken-rinsing waters and assayed with a 2-min bioluminescence assay. It was found that ATP levels on chicken carcasses increased after evisceration but decreased to low levels after prechill and chill treatments.

Yeasts and lactobacilli are often the cause for beverage and juice spoilage (Griffiths, 1996). The quality of carbonated beverages can be accurately assessed by the ATP bioluminescence assay because they contain low levels of nonmicrobial ATP (Willianms, 1971). The natural components in beers, however, contain abundant ATP and quenching substances that can influence the results if the tests are performed without proper filtration to separate microbial cells (Kyriakides and Patel, 1994). The results of an ATP detection method used to assay the microorganisms in fruit juice were disappointing; the poor performance of the assay was attributed to the low pH of the product and the presence of nonmicrobial ATP (Griffiths, 1996).

PCR Monitoring Techniques

Since the early 1990s, more than 200 PCR protocols have been published for the detection of foodborne bacteria, molds, yeasts, viruses, and parasites. Selected information is summarized in Table 11.2.

BAX™ is a commercial PCR system marketed by Qualicon for screening of important foodborne bacterial pathogens such as *Salmonella*, *Escherichia coli* O157:H7, *Listeria monocytogenes*, and *Campylobacter jejuni* (Table 11.3).

PCR detection of pathogens directly from food can be difficult because food components, such as proteins and lipids, often inhibit the activity of *Taq* DNA

TABLE 11.2. PCR Detection of Foodborne Pathogens

Pathogen	Target sequences	Assay
Bacillus	hemolysin B; hemolysin BL; cold shock protein and lecithinase	PCR
Campylobacter jejuni	*fla*A, *fla*B; 16S rRNA; 23S rRNA; *ceu*E and pDT1720	Seminested PCR; nested PCR
Canobacterium	16S rRNA; *fla*A and *fla*B	PCR
Cryptosporidium	genes encoding a surface protein; 18S rRNA; hsp70; a repetitive oocyst protein	PCR
Escherichia coli	*slt*1; *slt*2; *eae*; p60; *st*1a; *st*1b; and *inv*	5′ nuclease assay; Qualicon BAX™ System; multiplex PCR; PCR and hybridization
Listeria monocytogenes	*iap*; *prfA*; *hlyA*; *plcB*; 16S rRNA and internal transcribed spacer	RT-PCR; 5′ nuclease assay; Qualicon BAX™ System; PCR-ELISA
Molds and yeasts	*ver*-1; *omt*-1; *apa*-1; *nor*-1 and elongation factor	PCR
Salmonella spp.	*fimA*; *invA*, *IS*200, *hns*, *him*A and 16S rRNA	Qualicon BAX™ System; 5′ nuclease assay; PCR-ELISA; FD-PCR
Shigella	*spa*; *vir*A; 16S rRNA and invasive plasmid	Multiplex PCR
Staphylococcus aureus	*ent*A, *ent*B, *ent*C, *ent*D, *ent*E; thermonuclease	Most probable number (MPN)-PCR
Small round viruses	RNA	Antigen-capture (AC)-PCR and RT-PCR
Yersinia enterocolitica	*Yad*A; 16S rRNA; 23S rRNA; *vir*F; *yst*B;	PCR and hybridization; multiplex PCR;

TABLE 11.3. Commercial PCR Kits

Manufacturer	Country	Kit
BioControl System	U.S.	Probelia PCR system for *C. jejuni* and *C. coli*
		Probelia PCR system for *C. botulinum*
		Probelia PCR system for *E. coli* O157:H7
		Probelia PCR system for *L. monocytogenes*
		Probelia PCR system for *Salmonella*
Qualicon, Inc.	U.S.	BAX® for screening *E. coli* O157:H7
		BAX® for Genes *Listeria*
		BAX® for screening *L. monocytogenes*
		BAX® for screening *Salmonella*

polymerase during DNA amplification. Before PCR, ether extraction or column purification can be used to remove food inhibitors (Simon et al., 1996). Alternatively, bovine serum albumin, protease inhibitor (Powell et al., 1994), or Tween 20 (Simon et al., 1996) is sometimes added into the PCR mix to overcome the inhibition. With differential centrifugation or filtration, microbial cells can be successfully separated from food. If the cells are properly washed, DNA present in the supernatants of heat-killed cells is good enough for PCR amplification.

Since DNA persists a relatively long time after cell death. DNA released from dead cells can sometimes be amplified during PCR resulting in false positive results. However, this problem can be solved if microbial messenger RNA (mRNA) is used as the initial template during amplification. The technique, known as reverse transcription PCR (RT-PCR), adds a reverse transcription step, the conversion of mRNA to copy DNA (cDNA) into a conventional PCR assay. Microbial mRNA is relatively unstable—several minutes after cell death, mRNA degradation occurs because of intracellular RNase activity (Sheridan et al., 1998). During RT-PCR, reverse transcriptase catalyzes the synthesis of cDNA that subsequently serves as the ultimate template for DNA amplification. Because mRNA is a good indicator of cellular viability, RT-PCR avoids the false positive results occasionally generated by conventional PCR due to dead cells. RNA extraction and RT-PCR are slightly more complicated than DNA isolation and conventional PCR. However, commercially available kits make the assay less challenging.

The numbers of pathogens in food are usually lower than in clinical samples. To improve the sensitivity of the assay, immunomagnetic separation (IMS) is often used to concentrate cells before PCR. Pathogens are captured by paramagnetic particles coated with pathogen-specific antibodies. Microbial DNA is subsequently extracted and tested by PCR. IMS is proven to be effective (Goodridge et al., 1999), and immunomagnetic particles for capturing important foodborne pathogens are commercially available.

PCR-ELISA is a commercially available procedure marketed by Boehringer Mannheim (Indianapolis, IN). The assay combines PCR with hybridization to omit post-PCR gel electrophoresis and to improve sensitivity. During PCR, digoxigenin (dig), a steroid hapten, is cooperated into PCR products by using a dig-dUTP-labeled dNTP mix. Amplified PCR products are bound to a microtiter plate by hybridizing with an internal DNA probe, the biotin label of which binds with streptavidin coated on the wells of the microtiter plate. When dig reacts with an alkaline phosphatase-labeled anti-dig antibody in the presence of a appropriate substrate, a chemiluminescent signal is generated.

Another means of increasing the sensitivity of PCR is to use nested or semi-nested primers in a PCR assay (Wegmuller et al., 1993). A primer or a set of primers internal to a primary PCR product is included in the second-round PCR amplification. The technique is often used for the detection of low concentrations of target DNA sequences.

When first described, PCR was more promising for detection than enumeration of pathogens from food. However, recent developments have made it possible to quantitatively measure pathogens. The 5′ nuclease PCR assay marketed by PE Applied Biosystems (Foster City, CA) includes an internal TaqMan probe labeled with a fluorescent reporter dye and a quencher dye at the 5′ and 3′ ends, respectively. Because of spatial proximity on the probe, the quencher dye suppresses the fluorescence emission of the reporter dye before PCR amplification. However, during PCR, *Taq* DNA polymerase uses its 5′ exonuclease activity to hydrolyze the probe that anneals to the amplified products, causing cleavage of the quencher dye, and emission of the fluorescence reporter. Because the emission of the fluorescence signal occurs only during a positive PCR amplification, the detection of a particular DNA sequence can be accomplished by measuring the fluorescence in the PCR reaction. A positive or negative result can be available approximately 15 minutes after PCR amplification without the necessity of performing DNA gel electrophoresis.

ELISA Monitoring Techniques

ELISA has been used for the detection of various foodborne pathogens by targeting their surface structures, toxins, or whole cells. Information collected from recent literature is summarized in Table 11.4.

Commercial immunodiagnostic kits available for the detection of foodborne pathogens are shown in Table 11.5. Some of the kits are suitable for the detection of microbial toxins such as aflatoxins, *Clostridium difficile* toxin A, *Staphylococcus* enterotoxins, and *E. coli* verotoxins. Other kits target microorganisms, for example, *Salmonella*, *E. coli* O157:H7, *L. monocytogenes*, *C. jejuni*, and *C. botulinum*.

CURRENT AND FUTURE IMPLICATIONS

ATP bioluminescence is an enzymatic reaction and is therefore sensitive to temperature and pH (Griffiths, 1996). Firefly luciferase is also sensitive to detergents. Cleaners and sanitizers either enhance or quench bioluminescence signals, causing false results (Velazqaez and Feirtag, 1997). Food residue often contains ATP from nonmicrobial sources. To differentiate microbial from nonmicrobial ATP, different extractants can be applied in a two-step lysis procedure to selectively lyse prokaryotic or eukaryotic cells (Siragus and Cutter, 1995; Siragus et al., 1995).

Firefly luciferase can detect ATP released from 10^3–10^4 CFU/ml. To improve the sensitivity, a modified ATP bioluminescence assay can be used. The assay targets adenylate kinase, the enzyme that converts ATP and AMP to two molecules of ADP. By adding ADP into the assay, the reaction is driven into the opposite direction, resulting in the generation of ATP that can then be detected by firefly bioluminescence. Studies (Squirrell and Murphy, 1997) have

TABLE 11.4. Detection of Foodborne Pathogens with ELISA

Pathogen	Antigen target	Antibodies
Campylobacter jejuni	Cellular proteins	Monoclonal
	Flagellins	Monoclonal
	Major outer-membrane protein	Polyclonal
Clostridium difficile	Toxin A; toxin B	polyclonal
Clostridium botulinum	Toxin A, B, D, and E	polyclonal
Clostridium perfringens	Alpha, beta, epsilon, iota ib toxins	Polyclonal
	Enterotoxins	Monoclonal capture Ab and polyclonal detection Ab
Cryptosporidium	Surface antigens	Polyclonal
	Oocysts	Polyclonal
Escherichia coli O157:H7	H7 flagellin	Monoclonal
	Verotoxins	Monoclonal
	O157	Polyclonal Ab for capture and monoclonal Ab for detection
Listeria monocytogenes	Live cells	Monoclonal
	Formalin-killed cells	Monoclonal
	Antigen 4b	Monoclonal
Pseudomonas fluorescens	Live cells	Same antibody for capture and detection
	Protein F of cell envelope	Polyclonal
Pseudomonas spp.	Thermostable protease	Polyclonal
Salmonella enteritidis	LPS	Polyclonal for capture and monoclonal for detection
	Flagellins and LPS	Monoclonal
Salmonella spp.	Outer core polysaccharide	Monoclonal
Salmonella typhimurium	Dulcitol 1-phosphate dehydrogenase	Monoclonal
	Heat-attenuated cells O5 antigen of B serogroup	Monoclonal
	Flagellins	Polyclonal and monoclonal
Staphylococcus aureus	Protein A	Same antibody was used for both binding and detection
Vibrio parahaemolyticus	Outer membrane proteins	Shared binding and detection antibody

revealed that by targeting adenylate kinase rather than ATP, a 10- to 100-fold improvement in the sensitivity of bioluminescence assay is obtained.

By combining this reaction with IMS, it is possible to make the firefly bioluminescence assay measure ATP released from specific pathogens. However, development of paramagnetic beads coated with antibodies against individual foodborne pathogens can be cumbersome. An alternative is to allow commer-

TABLE 11.5. Commercial Immunodiagnostic Kits for the Detection of Foodborne Pathogens

Manufacturer	Country	Kit
BioControl System, Inc.	U.S.	Assurance EHEC EIA
		Assurance *Listeria* EIA
Bioline	Denmark	*Salmonella* ELISA Test
BioMérieux Inc.	France	VITEK Immunodiagnostic Assay System
		Vidas CAM (for *Campylobacter*)
		Vidas ECO (for *E. coli*)
		Vidas ICE (for *E. coli* O157:H7)
		Vidas LIS (for *Listeria*)
		VIDAS SLM (for *Salmonella*)
		VIDAS SET (for *Staphylococcus* enterotoxins)
Clinpro International Co. LLC	U.S.	*Helicobacter pylori* IgA-ELISA
		Helicobacter pylori IgG-ELISA
		Helicobacter pylori IgM-ELISA
Diffchamb AB	France	Transia Aflatoxin B1
		Transia Plate *Clostridium* spp.
		Transia Plate *E. coli* O157:H7
		Transia Plate *Listeria*
		Transia Plate *Salmonella*
		Transia Plate *Staphylococcus* enterotoxins
ELISA Systems	Australia	Mycotoxin Test Kits
		ELISA kit for *Salmonella*
		ELISA kit for *E. coli* O157:H7
		ELISA kit for verotoxins
Foss North America, Inc.	U.S.	EIAFoss *Campylobacter*
		EIAFoss *E. coli* O157:H7
		EIAFoss *Listeria*
		EIAFoss *Salmonella*
International Bio Products	U.S.	TECRA *Bacillus* Diarrheal enterotoxin VIA
		TECRA *E. coli* O157:H7 VIA
		TECRA *Listeria* Visual Immuno Assay
		TECRA *Salmonella* Unique
		TECRA *Salmonella* Visual Immunoassay
		TECRA *Staphylococcus aureus* visual immunoassay
		TECRA *Staphylococcus aureus* enterotoxins (SET)
Intracel Corporation	U.S.	Antigen ELISA *Clostridium difficile* toxin A
Lionheart Diagnostics	U.S.	RIDSCREEN verotoxins
		RIDSCREEN SET (used to identify *S. aureus* enterotoxins)
Meridian Diagnostics	U.S.	Premier *E. coli* O157:H7
Neogen Corporation	U.S.	Reveal® Microbial Screening Test for *E. coli* O157:H7
		Reveal® Microbial Screening Test for *Listeria*
		Reveal® Microbial Screening Test for *Salmonella*
		Mycotoxin Kit

TABLE 11.5. *(Continued)*

Manufacturer	Country	Kit
Organon Teknika Corporation	U.S.	EHEC-Tek™ for *E. coli* O157:H7 *Listeria*-Tek™ *Salmonella*-Tek™
Oxoid, Inc.	U.S.	*Listeria* Rapid Test

cial paramagnetic beads coated with goat anti-rabbit or goat anti-mouse IgG to react with rabbit or mouse antiserum against individual pathogens. This procedure has been used successfully for the capture of *Mycobacterium paratuberculosis* from milk (Grant et al., 1998).

The correlation between automated PCR, especially semiautomated, quantitative procedures, and standard plate counts needs to be investigated and evaluated. PCR procedures should be further simplified for industrial applications, and portable PCR equipment capable of handling multiple samples will be helpful for routine industrial testing.

ELISA-based tests are relatively inexpensive and easier to perform. However, false positive and negative results are often associated with immunoassays. Therefore, development of high-quality pathogen-specific antibodies is crucial to the success of this technique.

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PART III

FOOD HAZARDS: CHEMICAL AND PHYSICAL

Edited by AUSTIN R. LONG and G. WILLIAM CHASE

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CHAPTER 12

HAZARDS FROM NATURAL ORIGINS

JOHN J. SPECCHIO

INTRODUCTION AND DEFINITION OF ISSUES

Many hazards from natural origins are found in most staple foods of the human diet. The extent of the risks to human health associated with ingesting naturally toxic substances remains a scientifically debatable matter (Watson, 1987). All human food is a complex matrix of chemicals including carbohydrates, amino acids, fats, oils, pigments, enzymes, minerals, and vitamins, some of which may be toxic if consumed in large quantities (Strong, 1974). Plants, in particular, contain some chemicals that are known to be toxic to both animals and humans. Some of these chemicals evolved in plants to protect them from insects, plant pathogens, and other organisms (Pimentel, 1988). A small number of these chemicals, such as the hydrazines found in several mushrooms, are highly carcinogenic. Debate on this subject has been clouded by limited systematic approaches to defining and, in particular, quantifying human hazards. In general, however, the adverse effects of toxic chemicals in plants are related to interference with nutrient availability, metabolic processes, detoxification mechanisms, and allergic reactions in particular animals and humans. Some of these are discussed in this chapter. Although data have been accumulated on the chemical properties and functional properties of most of these compounds, their long-term risks to public health have not been established. In fact, the National Research Council has concluded that the current data on human dietary exposure is insufficient and has recommended the need for new studies with larger sample sizes and refined testing methods (NAS, 1996). Above all, it is important to emphasize that there is presently no firm evidence to correlate a link between long-term ingestion of natural toxins in commonly eaten foods and any type of chronic human illness (NAS, 1989; NAS, 1996).

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BACKGROUND AND HISTORICAL SIGNIFICANCE

Plants do contain many chemicals—hydrazines and mycotoxins, for example—that are highly toxic to animals and humans. Although these compounds may play important roles in influencing the incidence of certain types of human cancer, the exact proportion of cancers that are due to "natural" versus synthetic carcinogens is not known (Perera et al., 1991). However, there is strong evidence to suggest that synthetic chemicals present in food may increase cancer risk over that which may be posed by the presence of natural toxins alone. For example, laboratory rodent diets also contain many of the same naturally occurring toxins present in the human diet. Nevertheless, compounds such as aflatoxin, 2,3,7,8-Tetrachloro benzo-p-dioxin (TCDD), and 1,2-dibromo-3-chloropropane (DBCP), when added to the diet of mice and rats, significantly increase tumor incidence, even when present at very low levels. This suggests that, in several cases, the risk of tumorigenesis from certain synthetic food contaminants is increased in the animal over any risk presented by the background level of "natural pesticides" (Weinstein, 1991). No study has directly demonstrated that implementing dietary changes in a given individual inhibited the onset of cancer or kept an established cancer from spreading. Lacking contrary evidence, there is no reason to assume that there is a difference in humans. However, important caveats should be noted in drawing conclusions from risk analyses of dietary exposure to toxins. Short-term screens such as the "Ames test," whether for genetic damage or increased cell proliferation, are far from 100% accurate in predicting carcinogenicity and are not a replacement for long-term bioassays (Cohen and Ellwein, 1991). Also, no matter how suggestive epidemiological or experimental studies may be, they cannot provide unequivocal proof that a certain diet will increase the risk of cancer.

Heredity and environmental factors are extremely difficult to control. Data from laboratory animal tests and epidemiological studies with humans must serve as guides for assessing the safety of the food supply. Consequently, it is extremely difficult in the absence of further information to predict the sensitivity of humans to the tumor-promoting, mutagenic, or cytotoxic potential of a target compound. Thus risk extrapolation under conditions in which individuals are exposed to multiple factors and in heterogeneous populations (the situation in the real world) is much more involved and confusing than envisioned by some authors (see, e.g., Ames and Gold, 1990).

The most potent natural toxins responsible for human health risks are the mycotoxins. These are not strictly plant compounds but toxic metabolites produced by fungi infesting foodstuffs, especially cereals and nuts, that have been stored under conditions of elevated temperature and high humidity (NAS, 1989). Among the ailments caused by these mycotoxins the most notable historically is ergotism, or "St. Anthony's fire," which afflicted people centuries ago. This was caused by ergot alkaloids produced by *Claviceps purpurea* growing on cereal grains (NAS, 1973). Although some mycotoxins have been iden-

tified as potent liver carcinogens in experimental animals, their role as human carcinogens has not been established.

Mycotoxins are produced by fungi that infest foods including cereals and nuts that have been stored at high temperature and humidity. Aflatoxin is a mycotoxin found in peanut butter and corn. It can cause cancer and cirrhosis of the liver, as well as impaired immune function. To avoid aflatoxin contamination, avoid peanut butter and cornmeal from questionable manufacturers. For example, don't buy grind-your-own peanut butter from stores whose storage conditions may be questionable.

Cyanogenic glycosides occur in many food plants like cassava, lima beans, and the seeds of some fruits—peaches, for example. Because of their cyanide content, ingestion of large amounts of cassava and, to a lesser extent, lima beans can be fatal if these foods are eaten raw or are not prepared correctly (Strong, 1974). Cassava toxicity is much reduced by peeling, washing in running water to remove the cyanogens, and then cooking and/or fermenting to inactivate the enzymes and to volatilize the cyanide. In regions like Africa where cassava is a staple food, care is taken in its preparation for human consumption.

Goitrogens (glucosinolates), which inhibit the uptake of iodine by the thyroid, are present in many commonly consumed plants. They are estimated to contribute approximately 4% to the worldwide incidence of goiters in humans (Liener, 1986). Cabbage, cauliflower, brussels sprouts, broccoli, kale, kohlrabi, turnip, radish, mustard, rutabaga, and oil seed meals from rape and turnip all possess some goitrogenic activity (Coon, 1975). Effects of thyroid inhibition are not counteracted by the consumption of dietary iodine. The nature and extent of toxicity of glucosinolates are still the subject of debate. Although there are few, if any, acute human illnesses caused by glucosinolates, chronic and subchronic effects remain a possibility (Heaney and Fenwick, 1987).

Lathyrogens, found in legumes such as chickpeas and vetch, are derivatives of amino acids that act as metabolic antagonists of glutamic acid, a neurotransmitter in the brain (NAS, 1973). When foods containing these chemicals are eaten in large amounts by humans or other animals, they cause a crippling paralysis of the lower limbs and may result in death. Lathyrism is primarily a problem in some areas of India.

Lectin proteins (phytohemagglutunins) are present in varying amounts in legumes and cereals and in very small amounts in tomatoes, raw vegetables, fruits, and nuts. Ricin, a lectin that is extremely toxic and can be fatal to humans, was used as an insecticide at one time. When untreated lectins are eaten, they agglutinate red blood cells and bind to the epithelial cells of the intestinal tract, impairing nutrient absorption. Fortunately, heat destroys the toxicity of lectins.

Protease inhibitors are widely distributed throughout the plant kingdom, particularly in the Leguminosae and, to a lesser extent, in cereal grains and tubers. These substances inhibit the digestive enzymes trypsin and chymo-

TABLE 12.1. Food, Natural Toxin, Amount, and Effect

Food	Natural toxin(s)	Amount (1)	Effect (2)
Alfalfa sprouts	Canavanine	15,000 ppm	Toxin
Basil	Estragole		Carcinogen
Beer	Ethyl carbamate	1–5 ppm	Tumor
Black pepper	Piperine	10% by wt	Tumor
Black pepper	Safrole		Carcinogen
Bracken fern	Tannins		Carcinogen
Bread	Ethyl carbamate	1–5 ppb	Tumor
Bread, fresh	Formaldehyde		Carcinogen
Bread	Urethane		Carcinogen
Broccoli	Allyl isothiocyanate		Carcinogen
Butter	Diacetyl		Mutagen
Cauliflower	Allyl isothiocyanate		Carcinogen
Celery	psoralens		Mutagen
Chicken, grilled	Carcinogenic nitro-pyrenes	100 ppb	Carcinogen
Cinnamon	Safrole		Carcinogen
Coffee	Benzo(*a*) pyrene (4)		Carcinogen
Coffee	Caffeine		Toxin
Coffee	Chlorogenic acid		Mutagen
Coffee	Diacetyl		Mutagen
Coffee	Hydrogen peroxide		Carcinogen
Coffee	Methyl glyoxal		Mutagen
Coffee	Tannins		Carcinogen
Coltsfoot	Senkirkine	150 ppm	Tumor
Comfrey (5)	Symphytine		Tumor
Fennel	Estragole		Carcinogen
Fiddlehead greens	Ptaquiloside		Carcinogen
Horseradish	Allyl isothiocyanate	50–100 ppm	Carcinogen
Mace	Safrole		Carcinogen
Morel, false (6)	Methyl hydrazine	14 ppm	Carcinogen
Morel, false (6)	Myromitrin	500 ppm	Carcinogen
Morel, false (6)	*N*-methyl-*N*-formylhydrazine	500 ppm	Carcinogen
Mushroom, common	Parahydrazinobenzoic acid	10 ppm	Carcinogen
Mustard, brown	Allyl isothiocyanate	50–100 ppm	Carcinogen
Nutmeg	Safrole		Carcinogen
Parsnips	Psoralens	40 ppm	Mutagen
Potatoes	Chaconine	75 ppm	Toxin
Potatoes	Solanine		Toxin
Red wines	Tannins		Carcinogen
Rocket (arugula)	Allyl isothiocyanate		Carcinogen
Sake	Urethane		Carcinogen
Shrimp (7)	Formaldehyde		Carcinogen
Soy sauce	Ethyl carbamate	1–5 ppb	Tumor

TABLE 12.1. *(Continued)*

Food	Natural toxin(s)	Amount (1)	Effect (2)
Star anise	Safrole		Carcinogen
Tarragon	Estragole		Carcinogen
Tea	Tannins		Carcinogen
Tomato puree	Methylglyoxal		Mutagen
Wine	Ethyl carbamate	1–5 ppb	Tumor
Yogurt	Ethyl carbamate	1–5 ppb	Tumor

Ames et al., 1990

trypsin (Bender, 1987). For example, raw soybeans contain a protein that inactivates trypsin and results in a characteristic enlargement of the pancreas and an increase in its secretory activity. It is this latter effect, mediated by trypsin inhibition, that depresses growth. Clearly, soybeans and other related legumes should be properly cooked and processed before being eaten.

Potatoes—which contain two major glycoalkaloid fractions, α-solanine and α-chaconine—that have been exposed to sunlight show a significant increase in their alkaloid content (NAS, 1973). Solanine is a cholinesterase inhibitor and can cause neurological and gastrointestinal symptoms (Oser, 1978), potentially including fatal depression of the activity of the central nervous system.

Additional foods with the potential for antithyroid activity include plants in the genus *Allium* (onion group); other vegetables such as chard, spinach, lettuce, celery, green pepper, beets, carrots, and radishes; legumes such as soybeans, peas, lentils, beans, and peanuts; nuts such as filberts and walnuts; fruits such as pears, peaches, apricots, strawberries, and raisins; and animal products such as milk, clams, oysters, and liver (Coon, 1975). However, it has not been proven that a diet of these foods would be goitrogenic unless they comprised an excessively high proportion of the diet, a substantial amount of them were eaten raw, or they were not well cooked. Although goitrogens in foods are largely destroyed by thorough cooking, it must be acknowledged that many of the foods listed above are eaten uncooked (Coon, 1975).

In addition to microbes, other potentially dangerous contaminants in plants used as food can originate from the uptake of chemicals such as nitrate from soil and drinking water (Coon, 1975). Nitrates are not considered a human carcinogen, but nitrosamines, which are formed from nitrates and nitrites in the stomach, are carcinogenic in animals. Nitrates are added to food (as in curing meats) but also occur naturally in spinach, beets, celery, radishes, and rhubarb. Because of their low stomach acidity, young babies who ingest too many nitrates can suffer from methemoglobinemia, a condition in which nitrite is substituted for oxygen in hemoglobin. Therefore, feeding these types of foods to babies younger than 4 months should be avoided (NAS, 1989). Other hazardous chemicals like lead, iodine, mercury, zinc, arsenic, copper, and selenium are found in varying quantities in foods, and if consumed in large amounts, can cause human health problems or death.

Solanine, which is toxic in high concentrations, is identified with the greening of potatoes. When harvested potatoes are exposed to light, the surface of the potatoes may turn green from chlorophyll production. The concentration of solanine is highest directly beneath the peel, so peeling deeply will remove most of the toxin. Cooking in steam or water reduces solanine about 40%. Solanine can cause gastric upset and respiratory problems. The body converts solanine into a poison called solanidine, which has caused spontaneous abortions in laboratory animals. Pregnant women (or those hoping to become pregnant) should be careful about removing all green splotches on potatoes.

The level of risk involved in eating natural toxins is a contentious matter, and not enough scientific research has been evaluated to settle it. But as long as we avoid abnormally large quantities of any one food, there seems little need to be overly concerned. People have been eating these foods for centuries with few adverse consequences.

SCIENTIFIC BASIS AND IMPLICATIONS

The causes, treatment, and epidemiology of chronic food illnesses, including cancers, are extremely complex. Over a lifetime, individuals who differ in genetic makeup and susceptibility are exposed to a wide variety of carcinogens. Some food chemicals by themselves are safe but may act as synergists or promoters in concert with other chemicals to cause illness. Research as to how human health is affected by increasing exposure to all food chemicals, especially natural pesticides and other natural toxins, will be of vital importance in this century. The following sections present several common food toxins:

Ciguatera

The term "ciguatera" was derived from a name used in the eighteenth century for intoxication by the ingestion of *cigua* or turban shell. Ciguatera was recorded in the West Indies by Peter Martyr and in the Pacific as early as 1606 (Krogh, 1998). The toxins originate from several dinoflagellates that are common to coastal regions. Toxic outbreaks of ciguatera are sporadic and affect both tropical and subtropical coastal regions. An estimated 10,000–50,000 individuals are affected yearly (Sahrma and Salunke, 1991). Ciguatera is mainly found in marine finfish and may include groupers, barracudas, snappers, jacks, mackerel, triggerfish, goatfish, sea bass, parrot fish, white eel, moray eel, porgy, and surgeonfish. Because the occurrence is sporadic, not all fish from a given species or from a certain locality will be toxic.

Symptoms and course of the disease Initial symptoms occur within 6 hours after the ingestion of toxic fish and include paresthesia, nausea, vomiting, and diarrhea. Other symptoms may include intensified paresthesia, arthralgia, myalagia, headache, temperature sensitivity, heart arrhythmia, and reduced

blood pressure (Hu et al., 1994). The typical course of the disease is gastroenteritis for 1–2 days, then general weakness for 2–7 days, with parethesia lasting from 2 days to 3 weeks or longer. In rare cases neurological symptoms have persisted for several years, and in some cases recovered patients have experienced recurrence of neurological symptoms months to years after recovery (Keeler and Tu, 1983).

Ciguatera is sometimes fatal, and in acute cases, death may be caused by respiratory failure due to paralysis of the respiratory musculature. Severe dehydration in the early stages of intoxication can result in death, especially in malnourished children who do not receive treatment (Hauschild and Dodds, 1993).

Diagnosis of ciguatera intoxication Diagnosis is based solely on symptoms because no clinical test is available. However, an enzyme immunoassay designed to detect toxic fish in field situations is under evaluation by the Association of Office Analytical Chemists (AOAC) and may provide some measure of protection to the public in the future (Hu et al., 1994).

Treatment There is no specific antidote for ciguatera poising, and treatment is symptomatic and supportive only. Treatment has included gastric lavage, calcium gluconate, magnesium sulfate, pain medication, oxygen and ventilation assistance, aspirin, and antidiarrheal agents (Hu et al., 1994).

Epidemiology Approximately 10,000–50,000 people contract ciguatera each year. The region with the highest incidence is the South Pacific area. There are also reported ciguatera poisonings in the United States and Canada from imported fish. This number is growing, as the symptoms of ciguatera are becoming more familiar to clinicians. Administrative bans on the sale of suspected fish exist in only a few locations (Keeler and Tu, 1983). An estimated 2,300 cases per year occur in the United States and Canada, costing up to $20 million in time off work and hospitalization (Culliney and Pimentel, 1992).

Pyrrolizidine Alkaloid Poisoning

Pyrrolizidine alkaloid intoxication is caused by the consumption of plant material containing these alkaloids. The plants are usually consumed as food; however, they may be taken for medicinal purposes. These alkaloids may find their way into flour, milk, and other foods because of contamination by pyrrolizidine-producing weeds. The Leguminosae family contains over 100 hepatotoxic pyrrolizidine alkaloids (Davidek, 1995). Some alkaloids used for medicinal purposes include morphine, vincristine, vinblastine, quinine, atropine, cocaine, pilocarpine, reserpine, and colchicines.

Approximately 40% of plant families contain alkaloid-bearing plants and in a given species alkaloid content can vary widely depending on the part of the plant, its maturity, the time of year, the geographic location, and the type of

soil (Culliney and Pimentel, 1992). Plants are most frequently implicated in pyrrolizidine poisoning. Alkaloids tend to be bitter tasting and are therefore, rarely consumed intentionally in foods. Exceptions include the monoamines, such as tyramine, present in cheese and beer. However, if the food is contaminated it is often evident from the taste (Moy et al., 1994).

People can be affected by alkaloids in foods or herbs for a number of reasons. Intentional exposure occurs if the plant is ingested for the pharmacological properties of the alkaloids such as coffee or tobacco. They could accidentally expose themselves to alkaloids because of food contamination or because a misidentified plant was consumed. (Moy et al., 1994).

There has been an increase in the number of alkaloid-containing plants sold as tea, herbs, herbal remedies, and food supplements in the United States, where they are largely unregulated. This can and has caused public health problems in the United States and other countries.

Symptoms and course of alkaloid intoxication When alkaloids are eaten, gastrointestinal symptoms are usually the first sign of intoxication. However, in most cases bioactivation in the liver is required for toxicity and results in moderate to severe liver damage. In these cases gastrointestinal toxicity is minimized and toxicity is expressed in the liver, lungs, and kidneys, where the alkaloids are concentrated and excreted (Ames and Gold, 1990). Because of the toxic effect of alkaloids on major body organs the course of illness may run from 2 weeks to permanent damage to the liver, lungs, or kidneys. Death may ensue from intoxication anywhere from 2 weeks to 2 years after poisoning. Patients may recover almost completely if the alkaloid intake is discontinued and the liver damage has not been too severe. Chronic illness from ingestion of small amounts of alkaloids over a long period of time results in cirrhosis of the liver (Ames and Gold, 1990).

Diagnosis of alkaloid intoxication Early clinical signs of alkaloid ingestion include nausea, acute upper gastric pain, and acute abdominal distension with prominent dilated veins on the abdominal wall, fever, and biochemical evidence of liver dysfunction. Fever and jaundice may also be present. When the lungs are affected pulmonary edema and pleural effusions are present. Lung damage has proven to be fatal (Cohen and Ellwein, 1991).

Treatment Discontinue alkaloid intake and treat the patient for any damage that may have occurred to the liver, kidneys, and lungs (Cohen and Ellwein, 1991).

Epidemiology All humans are believed to be susceptible to the pyrrolizidine alkaloids. There have been few reports of human poisonings in the United States. However, worldwide, a number of cases have been reported and documented. Most of the intoxication in the United States involves the consumption of herbal teas or herbal remedies (Ames and Gold, 1990).

Aflatoxin Intoxication

Aflatoxins are a group of structurally related toxic compounds produced by certain strains of the fungi *Aspergillus flavus* and *A. parasiticus*. When temperature and humidity are favorable, aflatoxins grow on certain foods and feeds. The most common commodities contaminated are tree nuts, peanuts, and corn and cottonseed oil. The major aflatoxins of concern are B1, B2, G1, and G2. These toxins are usually found together in various proportions; B is usually predominant, and it is the most toxic and carcinogenic. (NAS, 1996).

When a food or feed is analyzed by thin-layer chromatography, the aflatoxins separate into the order given above. The first two aflatoxins fluoresce blue and then two fluoresce green when viewed under a microscope. A major metabolic product of aflatoxin B1 is aflatoxin M, and it is usually excreted in the milk of dairy cattle that have consumed aflatoxin-contaminated feed (Salyers, 1994). Animal species respond differently in their sensitivity to the acute and chronic toxicity of aflatoxins. However, for most species, the LD_{50} ranges from 0.5 to 10 mg/kg body weight (Ames and Gold, 1990).

Environmental factors, levels and duration of exposure, age, health, and nutritional status can affect toxicity. Aflatoxin B1 is a potent carcinogen in many species, with the liver being the primary target organ. Studies show that aflatoxin requires metabolic activation to begin its carcinogenic effect (Ames and Gold, 1990).

Symptoms and course of aflatoxin intoxication Aflatoxins produce acute necrosis, cirrhosis, and carcinoma of the liver in many mammals, fish, and birds. Because no animal species is resistant to the acute toxic effects of aflatoxins, it is therefore logical to assume that humans may also be affected (Ames and Gold, 1990). However, aflatoxicosis has rarely been reported in humans and often is not recognized. An aflatoxicosis outbreak has the following characteristics: The cause is not readily identifiable. The condition is not transmissible. The syndromes may be associated with certain batches of food. Treatment with antibiotics or other drugs has little effect, and the outbreak may be seasonal (Ames and Gold, 1990).

The effects of aflatoxins in animals, and possibly humans, have been categorized as follows. A. Acute aflatoxicosis is produced when moderate to high levels of aflatoxins are eaten. Acute episodes of the disease may involve hemorrhage, acute liver damage, edema, alteration in digestion, absorption, and/or metabolism of nutrients, and possibly death (Ames and Gold, 1990). B. Chronic aflatoxicosis is produced from eating low to moderate levels of aflatoxins. The effects are usually subclinical and therefore difficult to recognize. The more common symptoms are impaired food conversion and slower rates of growth (Cantor et al., 1992).

Treatment There is no specific treatment for aflatoxin. However, if a person is infected with acute aflatoxin and fully recovers, there are usually no long-term effects (Ames and Gold, 1990).

Epidemiology Little information is available on outbreaks of aflatoxicosis in humans because they usually occur in less developed areas of the world. In underdeveloped countries, human susceptibility can vary with health, age, and level and duration of ingestion.

The frequency of aflatoxicosis in humans in the United States is unknown. Although sporadic cases have been reported in animals, no outbreaks have been reported in humans (Ames and Gold, 1990).

Phytohemagglutinin—Plant Lectin Toxin

The presence of heat-labile toxic factors in plant products, mainly legume seeds for lectins, makes them unsuitable for human consumption unless they are properly cooked (NAS, 1996). Lectins were discovered in the nineteenth century when evidence was found that the extreme toxicity of castor beans could be attributed to a protein fraction that agglutinated red blood cells (NAS, 1996). The binding of lectins to the cells lining the intestine may interfere with their defense mechanisms, which prevent normal bacteria from passing from the intestines throughout the body (NAS, 1996).

To have toxic actions lectins must resist digestion, be thermostable in cooked foods, and interact with the brush border membrane of the intestinal mucosa. Cooking the beans does not necessarily destroy their toxic effects. However, cooking beans at 100°C for 20 minutes will deactivate toxic activity (Davidek, 1995).

Symptoms and course of phytohemagglutinin intoxication When raw or undercooked lectins are consumed, the onset of symptoms usually starts within 1–3 hours of consumption. Symptoms usually include acute gastroenteritis, nausea, and some abdominal pain. Symptoms may be severe enough to require hospitalization. Diagnosis is made based on the symptoms, the food history, and the exclusion of other foodborne illnesses or poisoning agents. Treatment may require intravenous fluids. The disease only lasts about 3–4 hours, and recovery is usually rapid and spontaneous (Minyard and Roberts, 1991).

Epidemiology All people appear to be equally susceptible to lectin intoxication. The only variable is the severity of the intoxication, which is due to the amount of raw or undercooked beans a person has ingested (Davidek, 1995). There have been no major outbreaks in the United States; however, in the United Kingdom, it is more common. Intoxication is sporadic, affects small numbers of persons and is easily misdiagnosed or never reported because of its short duration (Davidek, 1995).

Mushroom Toxins

Mushroom intoxication is caused by the high content of amatoxins in mushrooms. Other toxins found in mushrooms may include amanitin, gromitrin,

orellanine, muscarine, ibotecic acid, muscimol, psilocybin, and coprine. Mushrooms identified as containing amatoxin toxins are the species *Amanita*, *Galerina*, *Lipiota* and their genera such as *A. bisporigera*, *A. temifolia*, *A. ocreata*, *A. suballiacea*, *G. autumnalis*, and *L. brunneolilacea* (Keeler and Tu, 1983).

There are four categories of mushroom toxins:

1. Neurotoxins—neurotoxins cause neurological symptoms such as profuse sweating, hallucinations, depression, spastic colon, excitement, convulsions, and coma.
2. Protoplasmic poisons—Protoplasmic poisons cause generalized destruction of cells, which is followed by organ failure.
3. Gastrointestinal irritants—Gastrointestinal irritants produce rapid, transient nausea, abdominal cramping, vomiting, and diarrhea.
4. Disulfiram-like toxins—Disulfiram-like toxins are usually nontoxic and produce no symptoms. However, if alcohol is consumed within 72 hours after eating them, they may produce vomiting, nausea, headache, flushing, and cardiovascular disturbances. These symptoms are of short duration and usually only last from 2 to 3 hours (NAS, 1996).

The toxins are produced naturally by the fungi themselves, and each specimen of a toxic species should be considered equally poisonous. Therefore, the only way to avoid poisoning is avoid eating the toxic species (Casey and Vale, 1994).

Symptoms and course of mushroom poisoning The first symptoms of mushroom poisoning occur within 6–24 hours after ingestion of the mushrooms. This long incubation period is one of the most important indications of amatoxin poisoning (Davidek, 1995). This period is usually called phase one. Phase two, also called the gastrointestinal phase, involves severe vomiting and abdominal cramps, nausea, and watery diarrhea. Phase three lasts about 12–24 hours and is characterized by improved clinical symptoms; however, it is also the beginning of liver necrosis. Phase four, the last phase, results in hepatic failure, encephalopathy, internal bleeding, and, often, acute renal failure. Internal bleeding is usually observed and may cause complications and death. Patients usually die within 5–20 days after ingestion of the mushrooms. Although each poisonous species of mushroom produces its own unique symptoms, these are the most common symptoms (NAS, 1996).

Treatment Treatment usually involves making the patient comfortable and giving fluids intravenously. Liver transplants may be required to save the person's life. There is no known antidote to mushroom poisoning (Keeler and Tu, 1983).

Epidemiology All humans are susceptible to mushroom intoxication. Poisonous mushrooms are not restricted to one geographic location. The toxic

content of the individual mushrooms may vary by geographic location because of genetics and growing conditions. Therefore, intoxications may be more or less serious depending on the dose of toxin in the mushrooms that are consumed. Most cases of accidental poisoning are in adults, because they actively search for and consume wild mushrooms. However, the very old, the very young, and debilitated persons are more likely to become seriously ill from all types of mushroom poisonings (Egmond and van Speijers, 1994).

Frequencies of mushroom poisonings are hard to obtain. From 1976 to 1981, 16 outbreaks involving 44 cases were reported to the Centers for Disease Control in Atlanta. Cases of mushroom poisoning have been sporadic, and there are no known large outbreaks. Most cases are reported during the spring and fall, when mushrooms are at the height of their production. Although the actual incidence of mushroom poisoning is rare, the potential exists for grave problems. Dangerous species grow in many locations including urban lawns. With the increase in Americans' interest in organic foods, they may become too adventurous and poisonings are likely to occur (Colborn et al., 1996).

Chemical Stressors and Sensitivities

Food is full of extra substances that must be processed in the body and then excreted, but which have no nutrient value and may have drug and toxic effects. Chemical stressors can be found in foods as native ingredients and are not necessarily additives or contaminants. These substances have complex chemistry; they include inorganic and organic salts, toxic minerals, alcohols, aldehydes, alkaloids, polyphenolic compounds, salicylates, nonnutrient amino acids, and peptides.

A food chemical stressor becomes toxic when ingested too often or in too large a dose or when ingested by a person who lacks the metabolic machinery to detoxify it. Molecular stressors may simply require the body to handle and excrete it without harm. The metabolic work of this activity is the "cost" of ingesting these substances. When we consume stressors in excess, the effect becomes toxic. Our capacity to handle chemical stressors is limited and varies from individual to individual (NAS, 1996).

Chemical "sensitivity" is reported when exposure to airborne chemicals, such as cigarette smoke, engine exhaust, perfumes, household detergents, and solvents causes symptoms. Patients who are recovering from food allergy illnesses will often report increased awareness of airborne chemicals; this seems to represent a generalized hypersensitivity. Part of the recovery strategy is to avoid chemical exposure as much as possible.

Many chemical stressors compete for the same metabolic pathways for excretion. The liver is responsible for removing toxins. One of its actions is to attach acetyl groups to toxic molecules, which makes them more soluble for kidney excretion. Some people are "poor acetylators" and report intolerance to a wide range of drugs, foods, and airborne chemicals. If many molecules compete for the same excretion pathways, it is easy to imagine that overloading

occurs regularly in modern people who are exposed to a wide range of chemicals in food, water, and air. Once overload occurs, even small amounts of extra chemical stressors become toxic and produce symptoms and dysfunction (Ames and Gold, 1990).

Chemical stressors are inhaled and ingested simultaneously. Air pollution will reduce tolerance for food pollution and vice versa. A typical dinner in a pleasant restaurant may be biochemically and metabolically stressful, as inhaled smoke and ingested alcohol, coffee, tea, spices, and sugar combine with the complexes already in food. You may be in more trouble if you are also coping with the effects of prescription drugs taken to relieve your symptoms of chemical overload (Ames and Gold, 1990).

Safety and Toxicity of Food Additives

Several chemicals used as food additives are also found naturally in many foods. Nitrates and nitrites are ubiquitous in plants. They form part of the essential chemistry of soil and plants. As every gardener knows, nitrogen is essential for plant growth; nitrogen fertilizers, containing nitrates, are the most abundant agricultural chemicals. Beets, radishes, spinach, and lettuce contain the highest levels of nitrates. Consumption is estimated to be in the range of 100 mg/day (Davidek, 1995).

Aromatic Substances

All plants contain molecules that have an impact on our chemical senses. Aromatics attract us to a food. The food industry uses large quantities of aromatics from both natural and synthetic sources. The chemistry of these substances is widely known. The basic ring is a six-sided molecule, benzene. Different side chains attached to the ring change its color, taste, and smell. If benzene rings are linked together, a variety of ring structures give rise to different classes of substances. Molecules based on the benzene ring structure are common in nature. The usual term for many of the substances is "phenolics."

Molecules with aromatic ring structures include the food drugs caffeine and salicylic acid; the flavors camphor, cinnamic acid, eugenol (nutmeg and cloves), safrole, anethole (anise), tannin (tea), gallic acid, and vanillin (vanilla); and the vitamins ascorbic acid and niacin. Phenolic compounds are very varied in foods; some are toxic and others appear to be beneficial (Davidek, 1995).

Anther group of plant chemicals includes the essential oils of plants, which are also aromatic. Terpenes are used in perfumes, garnishes, and teas. Common aromatic terpenes in food plants include complex terpenes, such as lanosterol (in lanolin), a form of cholesterol, and squalene, found in yeast, wheat germ, and olive oil. Some terpenes are toxic but remain in our food supply as flavors, Alcohol extracts of plants often contain toxic terpenes. Other terpenes are beneficial molecules or at least benign (Ames and Gold, 1995). Vitamin A is not one substance; it is a family of related terpenes with shared biological

activity. Beta-carotene is the yellow pigment in carrots that can be converted into active vitamin A (retinols) after we ingest it. Lycopene is a similar red terpene found in tomatoes. Excessive consumption of tomatoes and carrots may induce a color change in complexion but appears to do little harm and may have benefits such as the prevention of cancer (NAS, 1996).

Garlic and onions Garlic (*Allium sativum*) and onions (*Allium cepa*) are both members of the lily family. Both contain strong aromatic substances that we use as flavoring for food. The medicinal properties of these foods have been used for centuries. Allicin is the principal aromatic of garlic. Allicin is a sulfur-containing terpene. An intact garlic bulb has little odor. The strong odor of allicin appears only after a garlic bulb is cut or crushed. The air exposure excites an enzyme that changes a precursor odorless molecule, alliin, to allicin (Davidek, 1995).

The medicinal properties of the combined chemicals in garlic include antiseptic activity and an anticlotting (reduced platelet-stickiness) activity. The anticlotting factor is ajoene (4,5,9-trithiadodeca-1,6,11-triene 9-oxide). This ajoene or anticlotting activity has not been found in proprietary garlic preparations, including garlic oil or garlic tablets. Ingestion of freshly crushed garlic seems to be necessary for this drug effect (NAS, 1996). The anticlotting effect of ajoene is similar to the effect of aspirin (ASA). The unpleasant breath odors following ingestion of garlic are the volatile sulfur-containing metabolites of allicin.

Onions are known for their tearing effect. The substance that promotes tearing is propanethial S-oxide. The tearing effect can be reduced by chilling the onion before cutting or by processing the onion under running tap water (Moy et al., 1994).

Spices Herbs and spices tend to be chemically complex and druglike in their activity. Most native cultures are reluctant to eat nonfood plants for good reason. Most people are not affected by herb and spice ingestion only in small doses eaten infrequently. Nutmeg, a common spice favored in desserts and drinks, yields many chemicals such as eugenol, isoeugenol, safrole, myristicin, elemicin, and limolene. Therapeutic use of eugenol as an antidiarrheal, anticlotting, and anti-inflammatory agent could be suggested; however, if we were to use nutmeg oil as therapy, we would face the drug and toxic effects of the other chemicals in nutmeg. The hallucinogenic effects of the psychotropic myristicin and the ability of safrole to induce liver cancer in mice are of some concern. The proper pharmaceutical approach would be to isolate the medicinal substance, eugenol, and to decide, after careful testing of its efficacy versus its toxicity, whether it is therapeutic (Davidek, 1995).

Peas and beans are common edible legumes. These foods are staples worldwide and possess desirable nutritional properties, but several biochemical problems may arise with their use. Soybeans contain indigestible carbohydrates and inhibitors of digestive enzymes (soybean trypsin inhibitor). Both problems con-

tribute to difficulty digesting beans, excessive gas, and, occasionally, abdominal pain and diarrhea (Bender, 1987).

Uncooked, lima and kidney beans are toxic. Both beans contain cyanide-producing compounds (cyanogenic glycosides), which can be destroyed by heating. Small amounts of cyanogenic glycosides will be detoxified by the liver. Cyagonic glycosides are also found in fruit pits, millet, sprouts, yams, maize, chickpeas, and cassava root (Bender, 1987).

Cassava (manioc) is an common vegetable of South East Asia, Africa, and South America and is inherently toxic. These tubers contain linamarin, which can be converted to a hydrocyanic acid. They must be processed by soaking, boiling, drying, and fermentation to reduce toxic cyanide effects. Neurological disorders and thyroid enlargement occur in African populations who eat large amounts of inadequately processed cassava (Tu, 1997).

An unusual genetic condition, "favism," makes some people sensitive to vicine, a nucleotide in fava beans; these people develop red blood cell damage (hemolytic anemia) after eating the beans. Cooking the beans thoroughly can reduce this effect. This is a specific example of the cytotoxic mechanism of food molecules and illustrates the advantages of cooking foods (Culliney and Pimentel, 1992).

Nightshades Plants of the nightshade family contain toxic substances. "Deadly nightshade" refers to the toxicity of the leaves of this plant group, which includes tomato, potato, peppers, eggplant, and tobacco. All the nightshades contain nicotine; tobacco has the highest concentration, and eggplant is next. Usually, solanine is in high concentration in green potatoes. The green potato contains toxic compounds (glycoalkaloids) similar to those found in the leaves. Solanine poisoning from green potatoes will produce throat burning, weakness, diarrhea, and even convulsions. Adverse and allergic reactions to tomatoes and peppers are common, and these vegetables are not on our most favored food list. Nightshades have often been implicated in arthritis (Culliney and Pimentel, 1992).

The occurrence of toxic nonnutrient amino acids is not unusual in plants that produce toxic compounds to deter predators from eating them. Over 150 nonprotein amino acids derived from plant materials have been chemically characterized. One of the problems with these amino acids is their ability to imitate and replace normal amino acids in protein synthesis. Canavanine in alfalfa seeds and sprouts may a cause hypersensitivity illness. The toxic agent in inky cap mushrooms (*Coprinus atramentarius*) that produces alcohol intolerance is the amino acid coprine. The toxic amino acid BMAA in cycad seeds are thought to cause a severe neurological disease in Guam; this amino acid resembles BOAA in the grass pea, *Lathyrus sativam*, which can cause a paralytic illness. Carnosine and its methylated form, anersine, in skeletal muscle and brain are associated with seizures, and carnosinemia may lead to mental retardation (Davidek, 1994).

Some vegetables also become undesirable when they are damaged or dis-

eased. Fungal growth is a major cause of toxic alteration of plant tissue. Sweet potato, for example, supports a fungal growth (*Fusarium solani*), especially when the tuber's surface is damaged. The fungus alters the potatoes' metabolism, and toxic stressors are produced. Ipomeanol is one such chemical that is liver- and lung toxic. Lung disease in cattle is caused by infected sweet potatoes. No similar human syndrome has been described.

Brassicas The common and popular cabbage or Brassica family can contain natural toxins as well. The gas-producing properties of brassica vegetables are well known. Some brassicas (broccoli) have high vitamin K content. The therapeutic effect of anticoagulant drugs that interfere with the conversion of vitamin K to prothrombin may be reduced by brassica ingestion. Brassicas also contain high levels of chemicals that may interfere with thyroid function, promoting thyroid enlargement (goiter). Cabbage, brussels sprouts, and kohlrabi contain progoitrin (in the range of 65–140 mg per 100 g of fresh vegetable). Cooking reduces the goiter effect of these vegetables. Goitrogens are also found in turnips, soybeans, radishes, rapeseed, and mustard. On the plus side of the brassica profile, there is some evidence that regular ingestion of brassicas may offer protection against bowel cancer (Ames and Gold, 1990).

Herbs and Teas Many people inquire about the use of herbal teas and herbal treatments. Most if not all plant materials are potentially allergenic. From a biochemist's point of view, plant materials contain many active substances in complex combinations whose body effects are generally not known. Beneficial effects of plant materials can be associated with negative metabolic and toxic effects that need to be considered when any plant is used with increasing intensity, especially on a daily basis (Davidek, 1995).

Medicinal herbs are drug-containing plants. Like other drugs, medicinal herbs have side effects, toxic effects, and allergenic effects and they may be harmful. The problem with whole plant medicines is that the active ingredients are mixed with everything else in the plant. This means that the control over the drug effect that is achieved with purified substances is not possible with plant preparations. The safety of these products is in question (Minyard and Roberts, 1991).

Cathartic teas, including those with senna leaves, flowers, and bark, buckthorn bark, dock roots, or aloe leaves, have been shown to cause diarrhea. These herbs may induce laxative-independence, often with abdominal discomfort, bowel dysfunction, and malabsorption of nutrients (NAS, 1996).

Herbal allergenic teas, such as those from chamomile, goldenrod, marigold, and yarrow, can cause allergic reactions in persons that are sensitive to ragweed, asters, chrysanthemums, and other related plants. Delayed allergic reactions and sun sensitivity can follow consumption of tea from the leaves of many plant products. St. John's wort is known to be photosensitizing. Tannins in tea, including ordinary tea and peppermint tea, are surface irritants to the gastrointestinal tract and have been linked to cancer of the liver (NAS, 1996).

Diuretics are present in teas made from buchu, quack grass, and dandelion. Diuretics increase urine production, with water and mineral losses. Coffee and tea are potent diuretics; the other plant teas are similar in their stressful diuretic effects. A variety of brain-active chemicals are also found in catnip, juniper, hydrangea, jimson weed, lobelia, and wormwood. Teas made from the petals of flowering plants (rose, hibiscus, hydrangea) are also neurotoxic and cause headaches, thinking disturbances, irritability, and depression. Alfalfa tea contains saponins that can disrupt digestion and respiration. Although the saponins of alfalfa have been found experimentally to clear the arteries of fatty plaques in monkeys, the ingestion of alfalfa teas may have adverse effects (FDA, 1998).

Liver toxicity has been linked with a number of herbal teas.

Comfrey is a popular herb that is potentially hepatotoxic because of pyrrolizidine alkaloids, known to cause hepatocellular adenomas and increased incidence of bladder tumors in rats. Sassafras contains safrole (as in nutmeg), another potentially hepatotoxic substance. Ginseng has caused breast enlargement in men (gynecomastia) due to the presence of an estrogen-like substance.

Licorice has been found to have substances that aid healing of stomach ulcers; however, it also causes sodium and water retention and loss of potassium. High blood pressure may result from excessive consumption of licorice (FDA, 1998).

Mistletoe contains alkaloids, small proteins (viscotoxins), and lectins (which collectively have hypotensive, diuretic, and antispasmotic properties). Mistletoe has been used by some herbal therapists as an anticancer drug. The complex of alkaloids may be cytotoxic. Hepatitis has also been reported with mistletoe ingestion.

Pennyroyal extract has long been recommended to produce abortions, a doubtful effect, but death due to liver damage has been blamed on regular pennyroyal ingestion.

There are many possible interactions of herbal medicines and prescription drugs. Lily of the valley contains cardiac glycosides and may lead to digitalis toxicity in a person taking adequate doses of the prescription drug. Horse chestnut contains natural anticoagulants. Ink cap is a natural source of disulfiram, with the risk of an "Antabuse" reaction with alcohol. Disulfiram interferes with the metabolism of alcohol and increases the accumulation of a toxic metabolite, acetaldehyde (FDA, 1998).

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CHAPTER 13

CHEMICAL AND PHYSICAL HAZARDS PRODUCED DURING FOOD PROCESSING, STORAGE, AND PREPARATION

HEIDI RUPP

INTRODUCTION AND DEFINITION OF ISSUES

Processed foods have become a way of life in the modern world. Manipulation of chemical and physical properties has created food products that offer the consumer greater convenience, variety, and safety. However, with processing of food comes the opportunity for more instances of mishandling or creation of intentional or accidental chemical/physical changes that may render a food hazardous. Hazards can result from poor nutritional quality due to processing and be more of a chronic dietary concern, or they can be from unintentional contamination and pose immediate risks. Production trends have shifted to a smaller number of food processing and preparation facilities providing products to a large number of consumers. This magnifies the harm possible from any adverse event (Institute of Medicine/NRC, 1998).

In the last two decades, chemical hazards in the food supply have been of notable concern, especially for their long-term carcinogenic potential. However, current trends are showing that microbiological hazards are of much more immediate concern and pose substantial acute risks. Regulatory focus is now centered on dealing with pathogenic hazards and will continue to do so into the foreseeable future. Microbiological hazards can effectively be minimized through current Good Manufacturing Practices (cGMPs) and by following an adequate Hazards Analysis and Critical Control Points (HACCP) plan. Coupled with education and a sense of responsibility on behalf of the producer, transporter, preparer, and consumer, this science-based approach will go a long way toward keeping food safe from pathogens.

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On the other hand, many chemical hazards are the result of intentional processing steps or additives. Often they are unavoidable or are a trade-off for a product with bacterial resistance, extended shelf life, and/or lower cost. Many times they are a trade-off for a more attractive or convenient product. In these cases, it is left up to the consumer to weigh the advantages or disadvantages of the offered benefits. This is often difficult, because risks from chemical hazards are not always easily definable, usually contributing to disease after ingestion over long periods of time.

The definition of chemical and physical hazards associated with food processing, storage, and preparation is inherently broad. These hazards can be acutely toxic, promoters of disease states, or contributors to poor nutrition. They include undesirable chemical changes and residues associated with processing, synthetic macronutrient replacements, intentional additives for preservation, flavor, and appearance, formulation errors and oversights that introduce allergens, and gross contamination with foreign matter ranging from machinery residues to filth. Unwanted hazardous chemicals can also find their way into food from agricultural and industrial practices that are part of the food production chain.

BACKGROUND AND HISTORICAL SIGNIFICANCE

Over the years, food regulations have focused extensively on direct chemical residues, including various food and color additives. Additives are used in foods for five main reasons: to maintain product consistency, to improve/maintain nutritional value, to maintain palatability and wholesomeness, to provide pH control, or to enhance flavor and color (FDA/IFIC, 1992). Inclusion of food additives in the food supply is a trade-off for no longer growing and processing our own food as well as being a part of a global marketplace.

All food additives are carefully regulated for safety by governmental authorities or international organizations. In 1958 the Food Additives Amendment (to the Food Drug & Cosmetic Act of 1938) was enacted, requiring FDA approval for the use of an additive in food and proof by manufacturers of an additive's safety for its intended use. However, two classes of additives were exempted from this amendment: prior-sanctioned and generally-recognized-as-safe (GRAS) substances. Additives that were considered safe before 1958 by the Food and Drug Admin. (FDA) and The U.S. Department of Agriculture (USDA) were designated as prior-sanctioned substances (like sodium nitrite). Additives were generally recognized as safe (GRAS) (like salt, sugar, and spices) by experts on the basis of a history of safe use or current scientific evidence. FDA and USDA continue to monitor these prior-sanctioned and GRAS substances for safety in light of evolving scientific information. A suspect substance can be prohibited or can require further studies according to governmental review. The amendment includes a provision (known as the Delaney Clause, named for its congressional sponsor, Rep. James Delaney) that pro-

hibits the approval of any additive if it is found to cause cancer in humans or animals at any level. Additionally, cGMPs limit the amount of additives used in foods, allowing only that amount necessary to achieve the desired effect (FDA/IFIC, 1992).

Before 1900, hundreds of colorants were available, and there were no regulations on their use in foods. Food poisoning was common, as many of the colorants were acutely toxic (e.g., lead compounds, mineral pigments, and coal-tar dyes). Colors were often used to mask adulteration or to defraud the consumer. Color additives are either derived from natural animal, vegetable, and mineral sources or synthesized in the laboratory from petrochemicals. In 1904, a division of the USDA (from which later came the FDA) embarked on studying and testing the safety of the most common colorants. By 1906 the Food and Drug Act listed only seven synthetic dyes for use in foods. Newly discovered colorants were added over the years, but ultimately the list has been narrowed down to only nine listed certifiable/synthetic colorants (not counting both dye and lake forms) and a fair number of natural colorants in use today. In 1938, the Federal Food, Drug and Cosmetic Act superseded the 1906 act, established three categories for synthetic colors, and required certification of each batch of colorant for purity. In 1960, the Color Additives Amendments prohibited the use of any colorant found to induce cancer in humans or animals and allowed the use of existing colorants (both natural and synthetic) under a provisional listing until scientific studies proved their safety for permanent listing. Natural colorants were also required to undergo testing but not certification. At this time, *color additive* was legally defined as "any dye, pigment or other substance made or obtained from a vegetable, animal or mineral or other source capable of coloring a food, drug or cosmetic or any part of the human body." Outside the United States, regulation of food colors has not received as many years of attention. There is no international policy—what may be allowed in one country may not be allowed in the next. Some countries permit the use of any colorants, whereas some prohibit the use of any synthetic colorants (Ghorpade et al., 1995). Although establishment of tolerances for color additives was part of the foundation on which the practice of food regulation was built, concern today has turned toward emerging food processing issues that are more challenging to the modern scientific community.

In today's marketplace of prepackaged "convenience" foods, the safety of packaging materials is of great interest to both consumers and manufacturers. Packaging is made of many materials, including plastic, paper, glass, and metal. The business of packaging has turned into a science, as "food contact materials" have become a multi-million dollar industry. Packaging serves to prevent filth and microbial contamination of food to aid in its preservation, or to ease preparation. Because of the intimate contact of food with its packaging, the safety of food contact materials is the object of much research and regulation. The concern is related to the potential for the migration of harmful chemical components from the food contact materials into the food. These migrants are legally considered food additives and are subject to FDA regula-

tion. In the past, the concern was with contaminants like lead leaching from tin can solder into the food or environmental PCBs making their way into paperboard cartons and then into the food. Those contaminants were not essential components of the packaging material structure and could be avoided. However, current concern is focused on plastics, because they have essential chemical components that have the most potential for contaminating the food they were designed to protect.

In the last two decades nutritional replacement products have been introduced into the marketplace, and many common products have been "reengineered" for both nutritional content and functionality (e.g., the amount of *trans* fats in hydrogenated products has decreased). This is a result of the marketplace responding to consumers' interest in choosing foods as part of a plan toward improving health. Advances in medical science have prompted Americans to realize that dietary factors are associated with health. Advances in chemical engineering and food science have led to a greater understanding of manufacturing processes and to improvements in production. For example, factors affecting the hydrogenation process include choice of source fat, temperature, pressure, duration, and catalyst. The composition and function of the final product can be determined by adjusting these factors (ASCN/AIN, 1996). Of course, the question remains whether the new science has created improved products or new hazards.

Advances in food science have also given us the ability to recognize and detect the creation of undesirable reaction products. These are the chemical changes associated with processing or mishandling during storage. Some changes are desirable from an organoleptic point of view, whereas some changes are unavoidable by-products from necessary or desired reactions. Processing and storage reaction products can be a result of improper practices, and they have played their part in prompting regulations for cGMPs and HACCP programs.

SCIENTIFIC BASIS AND IMPLICATIONS

Undesirable Reaction Products

Chemical changes from processing Processing food usually means altering its form, appearance, sensory qualities, or ability to stay fresh and wholesome. Through a combination of physical manipulation, chemical additives, or treatment with heat/cold, the molecules of a foodstuff are changed, giving it characteristic chemical/physical properties. These properties may be the very reason the product was developed or is desirable, but they may be formed at the cost of coproperties that are not so desirable. It is a situation of give and take, in which the benefits must be weighed against the risks.

Chemical carcinogenicity studies are typically conducted with high levels of compounds fed over a relatively short period of time in animal models. This

may or may not correlate to human risk from years of low-level ingestion. However, it is postulated that the high levels in a study make up for the short time span and small test population and thus correlate to typical human exposure that would induce a disease state.

Regulation of undesirable general chemical changes is difficult at best, as they may be intrinsic to the product. It is easier to monitor for specific chemical indicators, because they can be identified and quantified. Hard data are needed to support legal action. There are limits for some process residues, and product surveys may be conducted to enforce these limits. Ultimately, industry concern for public rejection of a product or consideration of public health issues prompts manufacturers to search for ways to minimize unwanted residues or to minimize publicity associated with a contaminant, making this issue self-limiting in most instances.

Formation of trans *fatty acids* In recent years there has been increased scrutiny of the health implications associated with *trans* fatty acids and the source of their dietary intake. *Trans* fatty acids are commercially produced by the hydrogenation of oils. Hydrogenation of oil molecules (usually from a vegetable or seed source) raises the melting point, effectively saturating the molecules and resulting in fat that is solid at room temperature, such as margarine. Thus a solid product is achieved without the nutritional expense of incorporating cholesterol as in animal-derived fats like butter.

The predominant source of *trans* fats in the American diet is hydrogenated vegetable oil, which contributes 80–90% of the *trans* fats. *Trans* fats as a whole are about 8% of the fat intake (ASCN/AIN, 1996). This is about 8–13 g of *trans* fats in the U.S., versus 4–6 g in the U.K. and 8–10 g in Europe (IFST, 1996a). Hydrogenated fat products offer a healthier source of solid fat than traditional animal-derived saturated fats containing cholesterol and higher levels of saturated fat. Ingestion of hydrogenated and *trans* fats versus a diet with saturated fats leads to lower total and low-density lipoprotein (LDL) cholesterol concentrations in blood. However, both *trans* and saturated fats increase total and LDL blood cholesterol versus *cis* fats or unsaturated fats (ASCN/AIN, 1996). Studies have shown that as long as diets include sufficient essential fatty acids, *trans* fatty acids have negligible adverse effects (ASCN/AIN, 1996).

The digestion and metabolism of *trans* fatty acids are reported to be essentially the same as for *cis* isomers (IFST, 1996a). However, a recent article in the *New England Journal of Medicine* reports that instead of lowering overall fat intake, replacing saturated and *trans* fats with unhydrogenated monounsaturates and polyunsaturates was more effective in lowering heart disease in women (Hu et al., 1997). The 1996 American Society of Clinical Nutrition/American Institute of Nutrition Task Force on *Trans* Fatty Acids recommends that more research be conducted on biomedical effects and cautions against assuming that all *trans* isomers have the same effects or losing focus on the effect of saturated fats in the diet. However, they advise that it may be prudent

to limit *trans* fat in one's diet (preferably by limiting fats overall) and that manufacturers should continue their efforts to reduce *trans* fats in their products. They also indicate the importance of product labeling to accurately describe the fat content of foods down to the level of classes of fats so consumers can make an educated choice in planning their diets (ASCN/AIN, 1996).

Formation of pyrolytic and thermal decomposition products Cooking is the oldest form of food processing—it makes food more palatable and prevents microbial growth. This processing can result in the desirable and tasty browning of meat and bread, the bitter charred edges on a barbequed steak, or tasteless chemical changes that can cause a product to taste less than fresh.

The juices at the surface of a food are rich in amino acids, sugars, and fats. High temperatures decompose these compounds into smaller, more reactive molecules that combine to form stable compounds in a process known as pyrolysis (Janssen, 1997). Many of these are responsible for the desirable flavors and aromas associated with cooked food. Cooking temperatures over 200°C can promote the formation of compounds that have been shown to be mutagenic and carcinogenic, such as polycyclic aromatic hydrocarbons (PAHs) and heterocyclic amines. Temperatures well over 300°C can easily be reached on the surfaces of foods during cooking. The kind and amount of pyrolysis products formed depends on the parent compounds and the temperature. Modification of cooking techniques can help reduce their formation.

Each amino acid has its own set of pyrolysis products, as does each combination of amino acids. So there are numerous types of PAHs that can be produced from one product (NRC, 1996). The most potent PAH is benzo[*a*]-pyrene (3,4-benzpyrene), and it has been identified in roasted coffees, broiled/barbecued meat and fish, and charred bread crusts. Fat plays an important role in the formation of PAHs. For example, broiled fatty hamburgers have 43 ppb of PAHs whereas lean burgers only have 3 ppb (Janssen, 1997). PAHs are also abundant in smoked foods, where they originate from the combustion of the fuel. Because pyrolytic products are fundamental to many cooking processes and are not overly abundant, there is no way to sensibly regulate their presence. Their avoidance is left to the consumer's dietary choices. 5-hydroxymethyl furfural (HMF) is a thermal decomposition product of sugars and carbohydrates in the presence of acid. It is formed in cooking, heat sterilization, or elevated temperatures during storage. It is common and virtually unavoidable in products containing high amounts of fructose. Apple juice and honey often have elevated HMF levels, but HMF can also be found in milk, other fruit juices, spirits, and cigarette smoke. The U.S. Public Health Service's National Toxicology Program has HMF on its list to conduct toxicological studies. The National Institute of Environmental Health Sciences nominated HMF for study based on its structural similarity to other potential carcinogens, its potential for widespread exposure in the diet, and the fact that little is known about its toxicity (PHS/NTP, 1996). The presence of high levels of HMF in apple juice, for

example, may also be an indicator of added invert sugar. In some apple juices, HMF levels reach into the parts per millions. HMF can contribute to an "off taste" in a product. Canadian agricultural regulations limit HMF levels in honey to <15–40 mg/kg, depending on concomitant diastase levels.

Formation of urethane in alcoholic beverages The health benefits of moderate alcohol consumption or the benefits of drinking wine periodically surface in media reports. What is not as well known is that urethane (ethyl carbamate) is a chemical substance that forms naturally during the fermentation process of some alcoholic beverages and fermented foods and that it may be a potential carcinogen. The wine and spirits industry has been aware of this for almost 20 years and has studied ways to minimize the production of urethane through modifications of agricultural and manufacturing processes. The University of California at Davis, a center for the study of viticulture and enology, recently published the *Ethyl Carbamate Preventative Action Manual* (1997), which recommends actions that producers can take to minimize urethane levels in wines. Urethane is found in the highest concentration in fruit brandies (up to 1200 ppb, according to an FDA-ATF survey in 1987), followed by sake (300 ppb), bourbon (150 ppb), dessert wines and liqueurs, and finally table wines (13 ppb). Voluntary industry effort has brought about a decrease in domestic urethane levels to well below 100 ppb, with foreign products showing slightly higher levels according to a 1991 FDA-ATF survey (Foulke, 1993).

The World Health Organization suggests a level of 10 ppb of urethane for soft drinks, and the Canadian government suggests 30–400 ppb for various alcoholic beverages; however, most countries have no set limit (Janssen et al., 1997). With the successful industry effort to reduce urethane, there is no need for alarm over urethane levels in most alcoholic products.

Wine yeast use the amino acid arginine (abundant in grape juice) as a nutrient. Yeast metabolism of excess arginine naturally produces urea during the fermentation process. Urea is released from the yeast cells during or at the end of fermentation—whenever it accumulates above a critical level where it no longer can be metabolized. Urea in turn spontaneously combines with ethyl alcohol to produce ethyl carbamate (urethane). Elevated temperatures exponentially accelerate this reaction. That is why distilled spirits contain more urethane than plain table wine. Because many factors effect the production of urethane, levels can be reduced through a number of approaches, including modification of the distillation process, adjustment of the fertilizer used to grow raw products, addition of urease enzymes, use of different strains of yeast, or precise timing of fortification of dessert wines (Butzke and Bisson, 1997; Segal, 1988).

Chemical changes from storage Raw food ingredients or finished products being kept in storage are not to be forgotten about as in the old adage "out of sight, out of mind." Not only is storage the most likely place for contamination by rodents or insects or for spoilage by bacteria and growth of patho-

genic organisms, but it is the most likely place for mold to rot products and produce mycotoxins. Mold itself is not necessarily a hazard (vegetative cells can be killed during cooking), but its toxic metabolites are chemical hazards that can survive the cooking process. Improper storage conditions can also contribute to the endogenous formation of scombrotoxin in susceptible species of fish. These toxins are considered "natural" toxins because of their genesis from natural sources, which is the topic of Chapter 12. However, mycotoxins and scombrotoxin are included here because of their importance as chemical contaminants related to mishandling during processing or storage, the topic of this chapter. The bacterial toxins produced by *Staphylococcus aureus* and *Clostridium botulinum* are also associated with mishandling during processing and storage, but are discussed at length in Part 2 on biological food hazards.

Mycotoxins Contamination of foodstuffs with mycotoxins is common in most parts of the world, especially in hot, humid climates. Chronic exposure to mycotoxins is a worldwide concern. In countries where contaminated crops are raised and serve as domestic dietary staples, exposure can be frequent and severe. Cooler countries that import these products can also be exposed [NRC, 1996]. Tragically, it is typically the less advanced countries—those who can only afford to consume domestic products—that rely on mycotoxin-susceptible products as the basis for their diets.

The formation of mycotoxins requires both the presence of toxigenic fungi and appropriate growth conditions. There are hundreds of known mycotoxins, but several species of *Aspergillis*, *Penicillium*, and *Fusarium* are responsible for most of the common mycotoxins. These include aflatoxins, ochratoxins, patulin, fumonosins, deoxynivalenol, zearalenone, sterigmatocystin, and ergot alkaloids. They are typically heterocyclic multiringed molecules. Mycotoxin production can occur at any stage during the production of foodstuffs—in the field, during harvest, processing, storage, or shipment (Janssen et al., 1997). Plants environmentally stressed in the field are more susceptible to mold growth. Harvested crops or even finished products that are stored in unclean facilities or at improper temperature and humidity are excellent breeding grounds for mold growth. Improper drying of harvested foodstuffs can be a significant factor in the formation of mycotoxins. Because conditions must be optimal for mold to produce toxin, the presence of mold in a product does not necessarily indicate that toxins have been produced. And because mycotoxins can be chemically stable to processing, products devoid of viable mold do not indicate the absence of toxins (Janssen et al., 1997).

Mycotoxin-induced diseases have had a long history but were only identified in the 1960s. The "Holy Fire" prevalent in Europe in the Middle Ages was from ergot poisoning (causing neurological and tissue damage leading to gangrene) from *Claviceps*-contaminated rye, and "yellowed rice disease" caused by *Penicillium* contamination was still occurring in the twentieth century in Japan (Janssen et al., 1997). Mycotoxins can induce both acute and chronic toxic effects. They can damage organs (especially the liver, kidneys, and central ner-

vous system) and can be carcinogenic, teratogenic, or mutagenic. Some mycotoxins are more toxic than others, and some are more prevalent than others. Aflatoxins are the most prevalent and acutely toxic, and are commonly found in grains, corn, oil seeds, and nuts (especially peanuts)—all dietary staples. At the other end of the (relative) toxicity spectrum is patulin, commonly found in fruit and vegetable products. It is frequently present (at low ppb levels) in apple juice. Patulin's presence is a good indicator of poor manufacturing practices—indicating use of moldy material or unclean facilities. Because food staples are eaten on a regular basis and can form a significant percentage of the daily diet, long-term exposure to mycotoxins can easily lead to physiological damage.

Scombrotoxin Scombroid poisoning is otherwise known as histamine poisoning. The name "scombroid poisoning" was coined because histamine ("scombrotoxin") is produced in fish species of the families *Scombridae and Scomberesocidae*, as well as some nonscombroid fish like *Coryphaena* and *Pomatomus*. Histamine-producing species include tuna, mahi mahi, escolar, bonito, yellowtail, bluefish, sardine, pilchard, abalone, and mackerel, to name a few. Fresh product typically has barely detectable levels of histamine. Histamine can be present in fresh, canned, and cooked products—the toxin survives processing. The formation of histamine is typically associated with decomposed products. However, decomposed products (determined organoleptically) do not always produce histamine and the presence of histamine does not always occur in decomposed products—thus sensory analysis cannot ensure the presence or absence of histamine. However, histamine can reliably be quantitated by chemical analysis down to 5 ppb (an acceptable level often found in fresh fish) (CPG 7108.24).

The aforementioned species of fish are high in levels of free L-histidine, from which histamine is formed in the muscle after death. The amino acid L-histidine is decarboxylated by histidine decarboxylase, an enzyme produced by certain bacteria common in fish. Because the associated bacteria are found in the fish gut, fillet from the anterior section is more likely to be contaminated as the intestine decomposes. Formation of histamine is dependent on the growth of these bacteria, which is a function of time and temperature. Excess L-histidine may also be produced by proteolysis during spoilage, which can further contribute to the formation of histamine. Interestingly, histamine can also be found in cheeses (such as Swiss cheese) that rely on the action of bacteria to form the product. The distribution of histamine within an individual fish fillet is not necessarily consistent. One portion of the fish may cause poisoning while another causes no reaction. It follows then that cans of processed products can have inconsistent histamine levels even within the same case lot (FDA, 1998).

Scombrotoxin formation is associated with fish that were inadequately refrigerated after being caught or inappropriately handled during subsequent storage or processing. In restaurant situations, storage of "good" fillets at improper temperatures can result in histamine formation. Other chemical

markers of decomposition have been found in spoiled fish, but their relationship to scombroid poisoning has not been determined. Histamine can form in both high- and low-temperature storage conditions, and even before the associated odors of decomposition are apparent. Histamine-forming bacteria seem to be more sensitive to freezing than spoilage-producing bacteria. According to the FDA's Compliance Policy Guide 7108.24, significant decomposition and histamine formation can be avoided by following good handling practices. This includes icing or rapid immersion of the fresh catch in chilled water (at $-1°C$) followed by continuous frozen storage. Leaving fresh catch lying about on the deck of a fishing vessel for an extended period of time or interruption of frozen storage are common occurrences in the histories of histamine-contaminated products. The canning of fish provides additional opportunity for problems associated with poor handling. Frozen fish are received at the cannery and thawed before processing, at which point temperature abuse (letting the product get too warm or inadvertently allowing it to thaw) has another chance to occur. Additionally, temperature abuse can occur during transportation or retail display if cooling equipment is not held at the correct temperature.

The seafood industry is in the process of implementing programs to establish HACCP plans to help producers prevent cases of contamination and foodborne illness. HACCP plans delineate the most likely locations and scenarios for something to go "wrong" in a process that would result in the food product becoming unfit for consumption. The HACCP theory can be simply summarized as holding that if it is known where the problems are most likely to occur, then a prevention and monitoring plan can be put in place to effectively control them. It is a proactive approach that places the burden on industry, not a reactive approach to be countered by the government and tax dollars.

Histamine poisoning manifests as an allergic reaction. Onset of the reaction can be immediate to within 1 hour. Symptoms may include tingling/burning mouth and lips, rash, headache, or nausea and vomiting. The symptoms may last for several hours, and recovery is generally rapid. Antihistamine drugs are an effective treatment; however, sensitive individuals may need further medical treatment. The suspect food must be analyzed within a few hours to confirm the presence of histamine. A good indicator of undesirable fish is a sharp, metallic, or peppery taste. Also, fish with an "off smell" should be avoided (FDA, 1998).

Scombroid poisoning knows no geographic boundaries. The network for harvesting, processing, and distributing fisheries products is worldwide. Finished seafood products are sold fresh, frozen, or processed to homes, restaurants, or various institutions. That adds up to a lot of opportunities for spoilage to occur. The FDA monitors fresh, frozen, and canned seafood for decomposition through organoleptic analysis. Products that might form histamine can be subjected to further chemical testing. Aside from the results of organoleptic analysis, a product is also considered decomposed if it contains at least 50 ppm of histamine. However, regulatory action is considered on a case by case basis (CPG 7108.24).

Direct and Indirect Chemical Residues

Food additives Food additives are an integral part of modern foods, but their role is often misunderstood. Food additives make possible year-round safe, convenient, and tasty foods. Although such familiar ingredients as salt, baking soda, and vanilla are technically food additives, consumers tend to think of additives as complex (and even sinister) chemical compounds.

A food additive is any substance added to food during production, processing, treatment, packaging, transportation, or storage. Legally, a food additive is defined as "any substance the intended use of which results or may reasonably be expected to result—directly or indirectly—in its becoming a component or otherwise affecting the characteristics of any food" (FDA/IFIC, 1992). Direct additives are added to a food for a specific purpose and are identified on the ingredient label of the food. Indirect additives unintentionally become part of the food in trace amounts because of its handling, packaging, etc.

Excessive levels of an additive or inclusion of an undeclared additive may be directly dangerous in some instances, but food additives themselves, when used properly, pose little health risk given current scientific evidence. However, this does not negate their possibility of inducing disease from years of ingestion at low levels. Such a disease state would most likely be one stemming from poor nutrition. The ubiquitous additives, sugar and salt, are well documented for their disease potential. Their addition to a product may be important to prevent harmful bacterial growth, but usually they are just for improving taste. For the health-conscious consumer, a good rule of thumb to follow is to avoid the foods that contain the more questionable additives, as they are used primarily in foods of low nutritional value (e.g., artificial color and flavor to hide the lack of real fruit). Consumer and scientific interest, government supervision, and industry compliance are keys to the safe use of food additives.

Migration of packaging residues I—plastics A plastic is not only composed of its polymer, but also plasticizers, antistatic agents, stabilizers, and antioxidants, to name a few possible components. Some components are more likely to migrate into foods than others, especially residual plastic monomers and plasticizers. Although ethylene, propylene, and vinyl chloride are the most volatile monomers and usually decrease with time, low levels may persist indefinitely. Acrylonitrile and styrene residues are unavoidable (Deshpande and Salunkhe, 1994). The plastic monomers of most health concern are vinyl chloride, acrylonitrile, styrene, and vinylidene chloride, which have known potential toxicity (CSIRO, 1994; Deshpande and Salunkhe, 1994). Vinyl chloride monomer (VCM) has a long latent period for tumor development, as would be suspected for low-level exposure over many years. VCM causes liver cancer and brain, lung, and lymphatic tumors. Acrylonitrile is metabolized into a mutagen and can be metabolized into cyanide. Styrene is a potent mutagen, but little toxicological information is available concerning vinylidene chloride (Deshpande and Salunkhe, 1994).

Important plasticizers include phthalic acid esters, which have low acute toxicities but appear to be nongenotoxic carcinogens (Janssen, 1997). In contrast, processing adjuvants are likely to be present in greater amounts than polymerization residues and should be subject to stringent quality control. However, these compounds are usually restricted to approved food-contact chemicals (Deshpande and Salunkhe, 1994). Interestingly, the polymers themselves, being of very high molecular weight, are inert and virtually insoluble in aqueous or aliphatic foods, and their migration into foodstuffs is of little concern. Furthermore, ingested plastic fragments are not digestible (Deshpande and Salunkhe, 1994).

Styrene prefers to leach into fats. Deli packaging and yogurt cups are typical sources of styrene. Vinyl chloride (the monomer of polyvinyl chloride or PVC) leaches into both water and fats. Bottled mineral water and cooking oils are typical products that absorb vinyl chloride (CSIRO, 1994). VCM is the most available for migration from the "cling" films that are used for all kinds of foods. Different plastics and forms are designed for specific product containment situations, for which their safety has been tested. Use of this plastic packaging in a manner other than that for which it was designed may result in significant migration of plastic components into the food (CSIRO, 1994). For example, situations that can promote contaminant migration include heating containers (such as in a microwave oven) designed solely for chilled foods, overheating "heat-resistant" containers, coming close to laminating leftovers covered with cling wrap in the microwave, or storing leftovers in an empty food container (that was not designed to safely hold food of that chemical composition). Packaging for microwavable entrees is quite complex; not only does it have to protect freshly frozen food but it also has to serve as a cooking container. Having been specially designed for microwave heating, this packaging is safe when manufacturers' instructions are followed (CSIRO, 1994).

The plastics industry recognized the potential for monomer and plasticizer migration from packaging to food and has made and continues to make a concerted effort to reformulate products to reduce migration to low ppb or negligible levels. This shows that optimizing manufacturing processes can increase purity. These low residue levels are not acutely toxic, but little is known about their accumulative health effects. These chemicals are also present in other materials in our daily environments: those involved in transportation, construction, clothing, and medicine, as well as in packaging (Janssen, 1997). The health effects from the widespread use of polymers have gained scientific concern over the years, but most attention has been paid to their use as food contact materials—probably because they are the easiest to study and regulate in this context.

Migration of packaging residues II—lead Lead is still a hazard associated with food packaging. Although U.S. food canners stopped using lead solder in 1991, some foreign producers may still be using lead solder. In 1996, wine capsules (coverings for the neck and cork area) were prohibited from being

made with lead, although old tin/lead-wrapped bottles of wine may still be available from aging cellars. Prevention of lead in ceramic ware is given international attention, but some small craft producers may unwittingly still produce products with high leachable levels of lead. Although background levels of lead from the environment are expected to contribute to the food supply, excessive amounts of lead can sometimes be found in products incorporating dried produce. This is likely in countries where leaded gasoline is still predominant and where farms have drying tables outdoors relatively near to a road. Despite these broad modes of lead contamination, the most significant, because children are so often the victims, is the little-known threat of lead contamination from the lead ink used on some candy wrappers or from the glaze in the small ceramic pots in which some regional treats are packaged.

One of the most common routes of contamination is from lead-printed plastic films. Packaging film is usually delivered to the food manufacturer in a roll in which the outside and inside surfaces of the film are in contact with each other. Thus the inside surface that contacts the food will have been in contact with the exterior lead inks. Luckily, most inks today are not lead based. Problems also arise when the plastic wrapper of a candy sticks to the product and is difficult to remove. In these cases a child may then suck on the wrapped candy, use his teeth to remove the wrapper and abrade the lead-containing pigments, or may inadvertently ingest pieces of wrapper adhered to the product. Other products may be packaged in such a way that lead actually migrates from the paper wrapper to the product inside. For example, an acidic powdered candy, under conditions of high relative humidity, could leach lead from the outer printed wrapper.

Children absorb ingested lead more efficiently than adults do—approximately 30–75% absorption by children versus only 11% by adults. Little lead (<1%) is absorbed through skin contact. Lead accumulates in the bone and can also disrupt the function of neurotransmitters by wreaking havoc with calcium channels. Lead poisoning can manifest itself as learning and behavioral problems, organ damage, and even seizures. The Centers for Disease Control and Prevention (CDC) consider a blood lead level of 25 mcg/dl to be a health concern in adults and 10 mcg/dl to be the level of concern in children. The FDA considers the tolerable daily lead intakes to be 75 mcg for adults, 25 mcg for pregnant women, and only 6 mcg for young children (Farley, 1998). Over the past 20 years, lead has been restricted from being used in house paint, food can solder, and gasoline. This has done much to lower blood lead levels in the American population, which have dropped 85%. An FDA study conducted after lead was banned from food can solder revealed a 93–96% reduction in blood lead levels in the population since a similar survey ten years before (Farley, 1998).

Nitrates, nitrites, and N*-nitroso compounds* Nitrates and nitrites are used to preserve ("cure") meat products such as bacon, ham, hot dogs, and cold cuts. When meat is cured with nitrite, the purple myoglobin is oxidized to pink

nitrosomyoglobin, which is temperature stable but sensitive to light and oxygen (therefore cured meats are often vacuum-packed). Curing also retards fat oxidation and imparts a desirable flavor and color. Originally a trace mineral in curing salt, nitrite was intentionally added to meat beginning in the sixteenth or seventeenth century.

Nitrite also helps to prevent bacterial growth, especially that of *Clostridium botulinum*, the bacterium that produces the deadly botulinum toxin. Nitrite is believed to inhibit the bacterial production of chemical energy by inhibiting certain enzymes within the microbe and on its cell membrane. Even though the decrease in cases of botulism results in increased exposure to nitrites, the risk is deemed acceptable versus the acutely lethal alternative. The very name *botulism* is evidence of the risk from cured meats: It derives from the Latin word for "sausage" (*botulus*) and translates to the German word for "sausage-poisoning." Cured pork, salt fish, and canned vegetables are still the most common source of botulism. Botulinum spores can easily survive boiling temperatures. Under conditions of room-temperature storage and oxygen-free food containers, the spores can germinate and produce toxin. Although heat (e.g., boiling for 10 min or cooking 30 min at 176°F) can denature the toxin, cold cuts and canned fruit are not usually cooked before eating and the center of a baked ham may not get that hot. Nitrite weakens the bacterial spores, reducing the likelihood of germination without the need for pressure cooking, which would change the flavor and texture of the food (McGee, 1984).

Nitrate (NO_3) itself is not considered toxic because of its low reactivity. It is even found naturally in human saliva (where the bacteria in the oral cavity can reduce it to nitrite) and is commonly found in water and vegetables (especially those grown with high-nitrate fertilizer)—so it is an unavoidable part of the human diet. However, nitrate becomes a hazard when it is reduced to nitrite (NO_2). Nitrite is very reactive and can be directly toxic or form carcinogenic *N*-nitroso compounds. Nitrite has the ability to oxidize blood oxyhemoglobin (ferrous form) to methemoglobin (ferric form). Whereas oxyhemoglobin is a good transport for oxygen throughout the body, oxygen cannot bind to methemoglobin and is thus unavailable for respiration. Excessive nitrite intake can lead to cyanosis and suffocation. The average lethal dose of nitrite is approximately 4 g as sodium nitrite. The toxic effects of sublethal doses of nitrite may lead to abnormalities in the body's biochemical processes (Sofos and Raharjo, 1995).

Because dietary nitrates can be converted to nitrites during digestion, it has been argued that the small amount of residual nitrite in cured meat is insignificant when compared with the amount gained from eating vegetables. Couple this amount with endogenous nitrite formation and the argument gets stronger. There have been cases of life-threatening "methemoglobinemia" (especially in children) when the patient's diet contained too many nitrate sources (like drinking water and spinach) within a short time span (Verhagen, 1997). Ingested nitrates have a half-life of about 5 hours before being eliminated in the urine. About 25% of blood nitrate is secreted in the saliva, where one-fifth of

that amount is reduced to nitrite by bacteria and reconsumed. Interestingly, when nitrite is acidified in the stomach to nitric oxide, it provides antimicrobial activity and protection against gut pathogens. However, if the nitrites react with amines under acidic conditions, carcinogenic nitrosamines may be formed (CAST, 1997).

N-nitroso compounds (including nitrosamines and nitrosamides) are formed when a nitroso group replaces a hydrogen attached to a nitrogen, in a process called *nitrosation.* Nitrosamines are generally stable, whereas nitrosamides can become unstable as the pH rises above 2. Furthermore, nitrosamides can decompose at mildly alkaline pH and can be destroyed by cooking. Formation of nitroso compounds is more rapid at high temperatures and can be catalyzed directly by nucleophilic anions or stomach acid or by bacteria that create a conducive chemical environment. Nitrosamines quickly equilibrate throughout the body but require metabolic activation for expression of mutagenic and carcinogenic activity (NRC, 1996). On the other hand, nitrosamides are believed to be direct mutagens. The mutagenic/carcinogenic potential of nitroso compounds in vitro and in animal models is well documented; however, the toxicity to humans at everyday levels is not proven but can reasonably be assumed (NRC, 1996). Besides the typical cured meat products, nitrosamines have been found consistently in malt products, such as beer. Although only at very low levels, the nitrosamines in beer could pose a more significant health threat (than eating bacon, for instance) because of the greater overall exposure (Sofos and Raharjo, 1995). But perhaps the most insidious and surprising source of nitrosamines is from rubber baby bottle nipples and pacifiers. The incidence of nitrosamine in these products were highlighted in a German study presented at the American Chemical Society meeting in 1981. Subsequent governmental and industry concern prompted manufacturers to alter their production processes to achieve rubber products with low ppb levels of nitrosamines. The FDA considers nitrosamine levels over 10 ppb in nipples to be avoidable contamination and includes such products (along with malted barley and malted beverages) on its sampling list for nitrite food additives.

Exposure to nitroso compounds can be minimized through the concomitant use of ascorbic and erythorbic acids in curing solutions. These antioxidants also speed curing and stabilize both color and flavor, as well as improving the bacteria-inhibiting properties of nitrite. They reduce the formation of nitroso compounds during both cooking and digestion. Because of their synergistic effect on nitrite, it may be possible to use smaller amounts of nitrite in the presence of such acids (McGee, 1984; Sofos and Raharjo, 1995). A food manufacturer wanting to use nitrites must show that nitrosamines will not form in hazardous amounts in the product under the additive's intended conditions of use. The USDA requires the addition of sodium ascorbate (550 mg/kg) together with sodium nitrite (100–120 mg/kg) in bacon products. Alternately, less nitrite can be used (40 mg/kg) if sugar and lactic acid bacteria are also added (which reduces nitrosamine formation and inhibits botulism). The USDA also monitors nitrite levels in fried bacon, setting a limit of 10 μg/kg

nitrosamines and an action level of 17 μg/kg (Sofos and Raharjo, 1995). The FDA also requires the use of antioxidants in the presence of nitrite and is responsible for monitoring nitrite levels in smoked fish. To prevent botulism in vacuum-packed smoked fish (such as salmon) nitrite should be at least 100 ppm, but it should also be less than 200 ppm to prevent nitrite poisoning or excessive formation of nitroso compounds (Foulke, 1993).

Sulfites Sulfites are used as antioxidants to prevent or reduce enzymatic browning in light-colored produce. They are also used in wine making to inhibit bacterial growth without interfering with the desirable yeast metabolism. Less familiar uses for sulfites in food processing include bleaching food starches, as a rust scale preventative in boiler water used for making steam that will come in contact with food, as a dough "conditioner," to prevent melanosis on shrimp, and in the production of some food packaging (Foulke, 1993; Papazian, 1996). Sulfites can be found in food in the form of sulfur dioxide, sodium sulfite, sodium metabisulfite, sodium bisulfite, etc. (Madhavi & Salunkhe, 1995).

Sulfites are safe for most people but can pose a hazard to others. Sensitive individuals, especially those with asthma, can react to sulfites with unpredictable and even life-threatening severity. Sulfites have been GRAS since 1959, but the FDA banned their use on raw produce in 1986 after numerous reported adverse reactions to grocery store or restaurant fresh salad ingredients. In these cases, sulfites were used to maintain the color and crispness of the salad greens. The agency had also wanted to ban the use of sulfites on dehydrated or frozen fresh potatoes intended to be cooked and served to consumers without packaging or labeling (such as restaurant french fries). However, the "fresh" potato industry challenged the FDA in court and won on procedural grounds. Sulfites sprayed onto foods produce the most rapid allergic reactions; however, the most severe reactions occur when the sulfites are incorporated into the food (Papazian, 1996). The FDA requires that product labels declare sulfites in excess of 10 ppm (because that is the amount that can be detected, not necessarily the amount to cause a reaction) or sulfites at any level that have a technical or functional effect in the food. The exact sulfite used need not be declared; however, the function of the sulfite must be noted. Additionally, food that is sold unpackaged in bulk form should have an accompanying sign stating that sulfites were used. Also, because sulfites destroy thiamin, the FDA prohibits their use in foods that are important sources of the vitamin (such as enriched flour) (Foulke, 1993). Sulfites are also not permitted to be used in meats, and their limit in shrimp is 100 ppm. Although the majority of food processors and providers honor the regulations, sulfite-sensitive individuals "shouldn't take anything for granted" (Papazian, 1996).

Undeclared and excessive sulfites may be due to lack of knowledge of regulations on the part of the manufacturers, lack of technical knowledge or quality control, or use of sulfites in excess to mitigate a poor-quality product. A most unexpected case of widespread undeclared sulfite contamination occurred

in 1997 when the National Food Processors Association and the U.S. tuna industry advised the FDA that canned tuna contained sulfites not declared on the product label. The sulfites were inadvertently added to the product, without the canned tuna manufacturers' knowledge. Sulfites found their way into the tuna through one of the raw ingredients—the hydrolyzed vegetable protein added to the tuna to enhance flavor (FDA, 1997). In this case, the manufacturers should not have taken for granted the composition of their raw ingredients. The canned tuna manufacturers subsequently discontinued use of raw materials containing sulfites.

Phenolic antioxidants Antioxidants are used to protect fats against oxidation. Oxidation of fat-containing foods causes changes in color, odor, taste, and nutritional value. Degradation products (lipid peroxides) can induce toxic effects. Antioxidants prevent their formation by removing destructive radicals. Phenolic antioxidants, like butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT), are radical scavengers and interfere with the propagation step during lipid peroxidation (Verhagen, 1997). Curiously, these antioxidants can exhibit both antitumorigenic *and* tumorigenic effects, and both are known to alter enzymatic activity affecting the activation/detoxification of xenobiotics (NRC, 1996).

BHA and BHT have relatively low acute toxicities, and because of many years of safe use, hold GRAS status with the FDA. However, later studies conducted during the 1980s suggest carcinogenic potential for BHA in animal models. Because the carcinogenicity is suspected to be nongenotoxic, BHA is assumed to have a threshold dose (Verhagen, 1997). Obviously, an acute toxic dose of BHA would not be intentionally added to a food—the concern would be for the effects of years of chronic ingestion (at which point the cause and effect relationship is obscured by the effects of all the other hazards in one's diet). BHT metabolism is more complex and slower than BHA and is reported to have toxic effects on organ systems (Madhavi and Salunkhe, 1995).

Although these additives may have possible carcinogenic properties, they are permitted in foods because they were affirmed as GRAS by the FDA after evaluation of toxicity and carcinogenicity data, and their usage levels were limited. Regulations limit BHA and BHT to 0.02% (or 200 ppm) of the fat or oil content of the food product. Where these additives are used in dry low-fat products, such as cereal or potato flakes, the limit is 50 ppm (combined BHA + BHT) of total product (Foulke, 1993).

Salt Consumers are generally not aware that common salt (sodium chloride) is considered a food additive or that it is the most common food additive in food processing. Salt is so ubiquitous, that most consumers do not give a second thought to its presence or health effects. Although both sodium and chloride ions are important in physiological processes, excess sodium has been implicated in the direct development of hypertension or in the increase of

hypertension that is associated with aging. The typical modern consumption of sodium (especially from prepared foods and snacks) is 10–20 times the amount needed for physiological balance. The reduction of sodium chloride content in a food or its replacement with potassium chloride is not a panacea. Salt can be an important food additive for necessary technical reasons or for prevention of bacterial growth; however; it is often primarily used for flavor. On the other hand, too much potassium in one's diet can lead to life-threatening incidences of hyperkalemia. Potassium-containing tabletop salt substitutes do not bear dosage information or warnings concerning overuse, leading consumers to believe that they are harmless (Sofos and Raharjo, 1995). Because of their generally bland flavor, low-salt products are not very popular except with that segment of the population that must decrease salt intake for medical reasons. The best way for consumers to reduce their salt intake is to take charge of their own diet—read labels, make educated choices, and follow the USDA guidelines for a balanced diet and the FDA guidelines for salt intake (which limit sodium to 2400 mg daily for a 2000-calorie diet).

Nonnutritive sweeteners Nonnutritive sweeteners, like saccharin and aspartame, have had a lot of controversial press over the years. However, both compounds have undergone extensive scientific studies and have been pronounced safe when properly used. They have become very popular as sweeteners in "low-calorie" products designed for special dietary needs. Diet products constitute a multi-million dollar industry, and low-/no-calorie sweeteners are the cornerstone.

The discovery of saccharin was a happy accident. Over a hundred years ago, a chemist working on the synthesis of toluene derivatives ate his lunch with unwashed hands and noticed a strong sweet taste ... the rest is history. Saccharin is 300 times sweeter than table sugar and has zero calories. Saccharin is a nonnutritive sweetener that is not metabolized and therefore contributes no calories. It usually comes in the forms of pure saccharin, ammonium saccharin, calcium saccharin, and sodium saccharin.

Although saccharin has low direct toxicity (for which a threshold can be set), it had been implicated as a potential human carcinogen (officially since 1981). A congressional moratorium protecting saccharin's use had been renewed periodically by Congress despite saccharin's carcinogenic potential (Verhagen, 1997; Greeley, 1992), while at the same time (up through 1998) the National Toxicology Program continued to list it as "reasonably anticipated to be a carcinogen" (Food Chemical News, 2000). In April of 2000, saccharin was delisted as a possible human carcinogen, in large part because of a petition by the Calorie Control Council. The National Toxicology Program agreed to the delisting "because the rodent cancer data are not sufficient to meet the current criteria to list this chemical as reasonably anticipated to be a carcinogen," because the rat tumors "arise by mechanisms not relevant to humans," and because of "the lack of data in humans suggesting a carcinogenic hazard" (NTP, 2000).

The delisting has prompted a strong outcry from Center for Science in the Public Interest (CSPI) Executive Director Michael Jacobson, who states that "the government is making a serious mistake" and that the NTP's dismissal of the human studies is wrong because "the best human study, conducted by the National Cancer Institute, correlated bladder cancer with exposure to saccharin (and other artificial sweeteners)" (Jacobson, 2000). He goes on to state further that "the delisting of saccharin sets a dangerous precedent for delisting other chemicals that cause cancer in animals, but have not been proven to do so in humans" (Jacobson, 2000).

In the meantime, saccharin-containing products are still required to bear the following warning statement on their labels: "Use of this product may be hazardous to your health. This product contains saccharin which has been determined to cause cancer in laboratory animals." Manufacturers may now have grounds to challenge the existing labeling requirements. Before being delisted, saccharin was allowed as a beverage additive at not more than 12 mg per fluid ounce, as a processed food additive at not more than 30 mg per serving of designated size, and as a sugar substitute in amounts not to exceed 30 mg of saccharin for each expressed teaspoonful of sugar sweetening equivalency (21 CFR 180.37). The Acceptable Daily Intake (ADI) for saccharin is 2.5 mg/kg body weight (Verhagen, 1997) [The ADI is the level of consumption that has been determined to be safe for human consumption every day over an entire lifetime].

Approved in 1981, aspartame (marketed as Nutrasweet or Equal) is also a popular artificial sweetener, probably even more so than saccharin. It is 200 times sweeter than sugar and has the same number of calories per teaspoonful (but one would only use a fraction of the amount of regular sugar, thus the calorie-reducing effect). Aspartame is a dipeptide consisting of L-aspartic acid and the methyl ester of L-phenylalanine. During digestion, it is hydrolyzed into its three components, aspartic acid, phenylalanine, and methanol. Chronic methanol exposure can cause visual impairment, whereas acute ingestion of just 30 ml can be fatal. Phenylalanine may interfere with amino acid transport, leading to nervous system disturbances. However, this is only a problem in people with the rare genetic disease phenylketonuria (PKU), who are unable to properly metabolize phenylalanine (Verhagen, 1997). When aspartame-containing products are heated or stored for long periods of time, aspartame can partially decompose into diketopiperazine (DKP), a suggested tumor agent. The ADI for DKP is 30 mg/kg body weight (21 CFR 172).

The ADI for aspartame is 50 mg/kg body weight. The FDA estimates that the daily intake of aspartame would be 8.7 mg/kg body weight if it were used as a general-purpose sweetener (that is, if all sucrose in the diet was to be replaced with aspartame). For a 60-kg individual, this would be a daily dose of 522 mg. Aspartame is only allowed in food at a level not more than what would accomplish its intended purpose (this follows current GMPs). Therefore, the FDA has generally not set food levels, except in ready-to-bake products, where aspartame is limited to 0.5% by weight (21 CFR 172).

Because nonnutritive artificial sweeteners are profitable products, industry will continue to research and develop new compounds. New or planned products include acesulfame K (approved in 1988), alitame, and sucralose. Alternately, research is being done on the use of stevioside extract (from the *Stevia rebuadiana* plant) as a natural sweetener that is 200–300 times sweeter than sugar and adds no calories. Stevia has had a history of use in its native South America, and is currently used as a common sweetener in Japan. Although popularly used in herbal teas in this country during the 1980s, it was deemed an unsafe food additive and banned in 1991 because of the lack of formal toxicological evaluation proving its safety (as required in the 1958 Act for "new" additives). It is also not allowed in Canada or the European Union. Actually, several studies indicate that steviol, a metabolite of stevioside, may have toxic effects (EC, 1999). Ironically, stevia is allowed as a nutritional supplement (FDA Import Alert 45-06, 1996). At the time of this writing, no petition has yet been filed with the FDA for the use of stevia as a sweetener—not surprising because the cost of research is unlikely to be recouped from a nonpatentable natural commodity.

Fat substitutes With the marketing success of low-/no-calorie sweeteners, the food industry also began researching ways to reduce that other dietary villain, fat. It has been much more difficult for scientists to synthesize a product that provides few or no calories and at the same time feels and acts like fat. Fat is an important nutrient that serves a number of functions, including providing calories for energy, providing essential fatty acids, and carrying fat-soluble vitamins (Kurtzweil, 1996). Because fat is a major dietary component, fat substitutes have the potential to be a significant part of the diet, unlike other food additives. Synthetic fat substitutes have only recently been introduced into the market. One of the first approved synthetic fats was Simplesse (in 1990), introduced by the Nutrasweet Company. This was followed by petitions for Salatrim (filed in 1994 by Nabisco) and Proctor & Gamble's olestra (approved in 1996).

Simplesse is made of microparticulated egg white and milk protein. It obtained GRAS status because its components have had a history of safe use. Simplesse is primarily used in frozen dairy products as a thickener or texturizer, but not in cooked products, where it would lose its creaminess (Segal, 1990). Simplesse contains less than half the calories of regular fat. It is entirely safe to eat, except perhaps for those individuals with egg or milk allergies who may not realize that this "fat" is actually made of protein ingredients. (However, because Simplesse is used in dairy and creamy egg-based products, those individuals would not likely come across it.)

Salatrim (short and long-chain acid triglyceride molecules) is a true fat, but it only provides 5 calories per gram and is partially absorbed by the body. Although (at the time of this writing) the FDA has yet to act on Nabisco's petition to gain GRAS status for Salatrim, Nabisco is able (as the law allows) to market and use Salatrim in its own products. The consumer group CSPI

calls for the FDA to deny Salatrim's GRAS petition on the grounds that Nabisco's submitted research supporting Salatrim was insufficient (according to CSPI) and that the documented gastrointestinal effects of Salatrim (when ingested at high levels) may pose a health hazard (Jacobson, 1998). Nabisco recently sold Salatrim to another company, Cultor, who will market it under the name Benefat.

The most celebrated yet controversial fat substitute has been olestra (trade name Olean), a sucrose polyester. It too is fat based, but instead of a glycerin molecule at its core, sucrose is the core molecule to which up to eight (instead of the usual three) fatty acids are attached. The olestra molecule is not digested, which makes it unlike the customary sugars and fatty acids of which it is comprised, so it needed approval to be a new food additive. Because olestra is not absorbed, it passes through the body, adding no fat or calories (Segal, 1990). Olestra passes through the gastrointestinal track because digestive enzymes are prevented from breaking down the sucrose core by all of the surrounding fatty acids (FDA, 1995). However, as more of the other nutrients are absorbed out of the intestines, the relative concentration of olestra increases (21 CFR 172). And just like an indigestible laxative, olestra can cause cramps, bloating, loose stools, and diarrhea. The "laxative" nature of olestra has prompted concern over its interference with the body's absorption of fat-soluble nutrients, such as vitamins A, D, E, and K and the carotenoids, from foods eaten at the same time as those containing olestra. To counter the loss of these vitamins from the diet, olestra-containing products are required to be enriched in these vitamins and must carry the following warning on their label: "This product contains olestra. Olestra may cause abdominal cramping and loose stools in some individuals. Olestra inhibits the absorption of some vitamins and other nutrients. Vitamins A, D, E and K have been added" (Kurtzweil, 1996).

Olestra is used in a variety of deep-fried savory snack products like chips and puffs. Olestra's particular physical properties depend on the specific fatty acids used and the degree of esterification. Manipulation of these factors can create variations in olestra tailored to the needs of specific food product formulations (IFST, 1996). Unlike other fat replacements, olestra is stable to baking and frying temperatures. Assuming olestra to be a 100% replacement for all the fat in savory snacks, the FDA estimates that the daily consumption of olestra would be 7 g/person/day (90th percentile eaters) and that a short-term binge eater may consume 20 g/person/day (21 CFR 172). Because of olestra's broad marketing demographics, Proctor & Gamble has submitted over 150 studies on its safety (FDA, 1995). The FDA did not feel that possible gastrointestinal disturbances precluded olestra from being approved because they "do not represent significant adverse health consequences," and because the issue of vitamin loss can easily be addressed by supplementation. Furthermore, olestra was determined to have no toxic, carcinogenic, genotoxic, or teratogenic potential (21 CFR 172).

The use of synthetic fat substitutes has met with the criticism of being "unnatural"—and the argument that the logical way to avoid fat is by chang-

ing eating habits. Nutritionists worry that consumers will feel more free to eat larger portions of foods made with fat replacements or of other high-fat foods, rationalizing that by "saving" fat they can eat more and come out equal. And because they eat more of these snacks, they may not have enough room left for more nutritious foods. The low-fat label may inadvertently become a license to overeat. However, eating specially manufactured low-fat foods is psychologically easier to do than giving up fats. Because of this, processed low-fat foods do have a place in the American diet as long as consumers remember that fat-free does not mean calorie-free (Kurtzweil, 1996).

Color additives The categories established for certified colors are *FD&C colors* (safe for foods, drugs, and cosmetics), *D&C colors* (safe for drugs & cosmetics that may be ingested), and *external D&C colors* (safe for drugs and cosmetics that may not be ingested). Being synthetically derived, certified colors, as compared with natural colors, are typically very pure and have higher tinctorial strength and are more uniform, brighter, and cheaper to manufacture. Certified colors are available as dyes or lakes, depending on their compatibility with the chemical/physical composition of the food to be colored. The FDA considers the lakes to be toxicologically equivalent to their dyes but has not established regulations for their use and continues to list the lakes provisionally. Chemically, certified colors belong to four classes: azo dyes, triphenylmethane dyes, xanthene dyes, and sulfonated indigo dyes. It is suggested that certified dyes should be used at less than 300 ppm, according to cGMPs [however, when considering the tolerances of other chemical "residues," 300 ppm is considered high] (Ghorpade et al., 1995).

Today's natural colorants generally tend to be very safe, some possibly having minor pharmacological effects in high concentrations, but not being disease-inducing. It is the certifiable synthetic dyes that are a health concern. The carcinogenic potential of a number of dyes has led to their delisting in the United States, but they remain a concern in imported food from countries where they are still allowed. For example, FD&C Red No. 1 was delisted in 1961 because of its hepatocarcinogenic nature. FD&C Red No. 2 was delisted in 1976 but is still used in other first-world countries because of what is considered insufficient toxicological evidence of a health threat. FD&C Red No. 4, originally used as a butter/margarine colorant, was delisted in 1976 because of its toxicity. FD&C Red No. 40 is allowed in the United States (where it is quite popular) but not in many EEC countries (including the United Kingdom, Switzerland, Sweden, The Netherlands, and others), who felt the validity of the safety studies was questionable. Citrus Red No. 2 is only allowed for coloring orange skins (which are not expected to be eaten), although it has been implicated as an animal carcinogen. FD&C Yellows No. 3 and No. 4, originally used as margarine colorants, were delisted in 1959 because of their hepatotoxicity. Yellows No. 5 and 6 are not believed to be toxic but are associated with allergic reactions and are specifically required to be declared on ingredient

labels. Orange B is permanently listed, but is restricted to use on the surfaces of sausage casings at a level of no more than 150 ppm (Ghorpade et al., 1995).

Because typically a little colorant goes a long way, one portion of a colored food consumed now and then provides minimal exposure and is not a health concern. In a 1979 National Academy of Sciences (NAS)/National Research Council survey, the average concentrations of certified colors in some common processed foods were found to be 75 ppm in beverages, 100 ppm in candy, and 350 ppm in cereals, for example. The average daily intake of each of the certified colors ranges from less than 10 to 100 mg/kg/person (99th percentile)—FD&C Red No. 40 and Yellows No. 5 & 6 being the highest. However, because of the complexity of the food supply, the NAS estimates the actual intake to be much less, perhaps only one-fifth (Ghorpade et al., 1995). Over years of habitual consumption of a favorite colored food product, the dose of colorant received may be of concern as carcinogenic potential is typically exacerbated by chronic exposure to toxins. Cause and effect is not clear in cases of chronic exposure; that is why regulation and public concern are warranted—to "play it safe."

As colorants are not technically essential to a food product, why aren't they just left out? Color plays perhaps the most important role in making an impression on the consumer. It dramatically influences the ability to identify the flavor and also its strength and quality. One study revealed that given uncolored sherbets, taste-tasters had difficulty identifying (and in some instances even failed to identify) the common flavors. Thus color indicates the identity or character by which foods are recognized and emphasizes or identifies associated flavors. Colorants enhance product acceptability by providing uniform appearance and correcting for color variations due to processing and storage.

Introduced allergens During the processing of food, it is not uncommon for formulation errors or oversights to occur. These errors could just end up being a labeling issue, or they could become a serious health threat. Formulation problems usually consist of one of several errors: cross-contamination from another product/line, inclusion of undeclared components in the raw materials, unlabeled recipe change, or the use of the wrong recipe or ingredient. Product contaminations are not always gross errors in formulation that would definitely be noticed at the production plant and thus not distributed. The most hazardous errors are those that introduce a visually undetectable amount of "contaminant" that would not be noticed as unusual by the consumer, causing them to refrain from eating the offending food. For the average consumer the consumption of a different food ingredient in their usual food is not a health problem. However, it can be a life-threatening problem when the contaminant is a major allergen for sensitive individuals. Typically these cases involve contamination with peanuts, although milk, egg, and soy contamination are very common, too.

Food allergy is an abnormal response of the immune system to an otherwise harmless food. The allergenic moiety of the food is usually a protein. When the food is ingested, the body recognizes it as an invader and produces an immune response. The response can include a few or many sites on the body: the mouth (swelling of lips or tongue), the skin (hives, rashes), the gastrointestinal tract (vomiting, diarrhea), or the airways (wheezing, constriction). The response can occur immediately or within an hour. If the response is extreme and involves several body systems, as in anaphylaxis, death is even possible. As little as 1/5 to 1/5000 of a teaspoon of a major serious allergen has caused death in highly sensitive individuals (Hingley, 1993). Not only is this a heartbreaking human tragedy, but for a manufacturer it could mean a very serious liability claim.

The major serious allergens (MSAs) include peanuts, tree nuts, soy, milk, eggs, crustacea, fish, and wheat. These eight foods cause 90% of the food allergic reactions. Other foods can produce allergies, but not as often (e.g., strawberries). Food-sensitive individuals will often have underlying asthmatic conditions or other environmental allergies. Someone with a peanut allergy, for instance, may also be sensitive to tree nuts—multiple sensitivities are common. These individuals must always be vigilant when grocery shopping or eating out (imagine ordering a side salad at a nice restaurant and finding out that it is unexpectedly topped with toasted almonds and strawberries). Correct product labeling (as well as education of restaurant personnel) is extremely important, because it is often an allergic consumer's only tool for determining a food's safety.

Allergies may develop at any point in one's life and usually come on gradually. Interestingly, as noted by Hefle et al. (1996), "the prevalence of allergic sensitivities to specific foods varies from one country to another depending on the frequency with which the food is eaten in that country and the typical age at its introduction into the diet." In the U.S. peanuts are a significant allergen, probably because of the prevalence of peanut butter in children's diets (it's an "easy" food that kids actually like). In Japan, soy, which is very popular, causes the most allergies. Following this line, the general U.S. population may see a rise in both soy and fish allergies as soy gains popularity as a cheap protein supplement and as people eat more fish and exotic seafood (Hingley, 1993).

Food manufacturers are generally responsible about posting alerts concerning allergen contamination and recalling their products. Consumers can check the website of the Food Allergy Network [*http://www.foodallergy.org*] for product alerts, or sign up to be on their mailing list. Examples of allergen contamination involve yogurt-covered peanuts included in yogurt-covered raisins, cashew butter containing almost one-quarter peanuts, cross-contamination of "plain" chocolate coins with nuts from a "chocolate and peanut" version, peanut butter cracker sandwiches included in what is labeled cheese cracker sandwiches, and undeclared egg white and dry milk in breaded chicken nuggets. For some of these contaminations, the offending ingredient was immediately noticeable,

but for most of them it was not. Formulation errors, oversights, and labeling omissions can occur with small production operations as well as with the big-name manufacturers.

The U.K. Institute of Food Science and Technology (IFST) provides an informative position paper on the responsibilities of food manufacturers concerning food allergens (1997). The IFST states that manufacturers should formulate foods to avoid the MSAs if possible, provide appropriate warnings on food labels, and "organize production, production schedules and cleaning procedures so as to prevent cross-contamination of products by 'foreign' allergens." In theory, problems can be avoided by following strict cGMPs. Misformulation stems from inattention and/or inadequate quality control. Cross-contamination stems from residues in shared equipment, airborne dust, or the incorporation of re-work material without consideration of the allergen problem. Preferably, separate production equipment should be used for MSA-containing products and non-MSA products. If the company is big enough to have multiple buildings or sites, designating an "MSA-only" site is an ideal way to prevent both physical and airborne contamination. If production equipment must be shared, then the MSA-containing product should be run as the last production of the day, just before cleaning. The IFST notes that even cleaning may not remove all traces of allergen, especially with dry products. Small amounts may be trapped and then carried over to the first production run of the next day. This product may have to be segregated if cleaning is not sufficient. Incorporation of re-work material calls for a strict quality assurance plan. If re-work material is received as a raw ingredient, it is the responsibility of the manufacturer of the finished product to ensure that what it receives is what it assumes it is. This problem is common in the chocolate industry, where scrap chocolate-nut product is turned into commercially viable re-work material. In these cases of contamination, if left unnoticed and distributed to consumers, the products' current labeling obviously would not indicate the presence of the unintentional MSAs.

The IFST emphasizes the need for appropriate warnings for MSAs on food labels. Tragedy can result when a consumer checks the label and finds no mention of an MSA that is actually present in the food. This can happen from oversight in listing the ingredients or when the wording for an allergenic ingredient is not obvious, such as when the term "vegetable oil" really denotes peanut oil, or when the scientific term "calcium caseinate" is used instead of the common term "milk protein." In addition to listing MSAs within the ingredients list, the IFST strongly encourages manufacturers to separately, prominently, and legibly state their presence so that the consumer will clearly see the warning under normal conditions of display. Suggested terminology includes "Contains PEANUT," "May contain traces of PEANUT," and "to which some people may be allergic." Also possible is a warning such as "Produced in a factory where PEANUT is also handled." The regulatory requirement of the inclusion of a warning statement is still a topic of contention. The

argument against these statements is that manufacturers may then hide behind them and be lax in their GMP responsibilities or that they may label all their products as "may contain traces of . . ." to cover themselves legally.

REGULATORY IMPLICATIONS

The FDA monitors a multitude of products for food additive violations. Often, the violation takes the form of the additives not being declared on the product label or some other labeling error. Other times, it is the use of nonpermitted additives, the use of permitted additives in an unapproved amount, or the use of permitted additives on an unapproved food. Most violations have to do with curing agents, preservatives, colors, or nutrient substitutes. Because the products to be examined for food additive violations are chosen based on past experience, the violation rate can be significant—up to 30% (CPGM 7309.006).

Lead inks on product packaging have always been a health concern. Products are subject to regulatory action if lead inks are used on a food package and if the lead contaminates the product or if it can reasonably be expected to contaminate the product while in the package or during the act of opening the package and eating the product.

Regulations to control plastic migration residues are relatively recent and not uniform between countries; however, both government and industry agree on the need to keep levels low. Some regulations define the use of specific additives, whereas others set limits on potentially harmful migrating substances in general (CSIRO, 1994). For consumer safety, extraction and migration tests are required for food-package and package-process compatibility, and the FDA also requires manufacturers and processors to provide toxicological data for the migrants (Deshpande & Salunkhe, 1994).

International agencies and governments recognize the serious health threat that mycotoxins pose to world health and are active in monitoring and preventing the occurrence of these toxins. Some populations enjoy better protection than others: The U.S. population consumes approximately 2.7 mg/kg body weight/day of aflatoxin, whereas in some areas of China the consumption rate is over 2000 mg/kg body weight/day (NRC, 1996). Countries generally impose a limit of 50 ppb or less for aflatoxins or patulin in foodstuffs. At the time of this writing, the tolerance level for patulin was still under consideration by the FDA but is expected to be 50 ppb as well. Ochratoxin is limited to very low ppb levels because it is associated with common staple foods. Many industries have established quality-control procedures to help their member producers avoid mycotoxin contamination. The FDA compliance program 7307.001/2 lists the regulatory guidance for mycotoxins in domestic and imported foods. The FDA regularly monitors for aflatoxins, fumonosins, deoxynivalenol, ochratoxins, and patulin. The British government also actively monitors for mycotoxins (and publishes its findings on the Internet) (MAFF, 1997).

Under the FDA's recent (1998) Food Safety Initiative the focus of food regulation has turned toward pathogens in foods because of their immediate health threat (like *E. coli* in undercooked hamburgers). In the same spirit, chemical monitoring has shifted toward detection of biogenic toxin residues like mycotoxins and scombrotoxin (histamine). Furthermore, the presence of antibiotic residues in foods of animal origin has also come under regulatory attention because of the possibility of chronic antibiotic ingestion fostering bacterial resistance to the drugs.

FUTURE IMPLICATIONS

Chemical and physical hazards in the food supply are rarely of an immediate life-threatening nature (except, for example, in cases of allergen contamination). For this reason, concern over these hazards is secondary to concern over acute contamination with pathogenic bacteria. However, in the future, science may (or may not) reveal that long-term exposure to small doses of ingested chemicals does indeed pose a health risk and may even contribute to many of our common debilitative diseases. Clear correlation over a long time span may be impossible to determine because of the presence of other mitigating factors. It is becoming clear, though, that foods of low nutritional value (such as some of the processed foods containing chemicals mentioned in this chapter) play a factor in disease processes related to poor nutrition. Because the government can only impose and enforce food regulations based on sound science supported by hard data, it may be up to consumers' purchasing decisions to shape the direction of the processed food industry. But this will only come about through public awareness, education, and interest.

Elimination or minimization of chemical and physical hazards may be partly achieved by following cGMPs. Industry commitment to producing high-quality products can go far toward reducing unwanted exogenous contaminants. Modifications of manufacturing processes can affect the presence or amount of process residues. To illustrate, alternative processes to create hydogenated fats are being developed that still create solid products without creating unwanted *trans* fatty acids. Interesterification decreases the *trans* fatty acid content of processed vegetable oils by rearranging the fatty acids on the glycerol molecule. It raises the melting point of the product without affecting the degree of saturation (IFST, 1996a). Another approach is to combine solid and liquid fats, giving a heterogeneous product with the consistency of a hydrogenated oil product. However, because of the incorporation of solid fat, this method increases the saturated fatty acid content of the product. A third approach is to genetically engineer seed oil plants to modify the fatty acid composition of their oils, reducing the need for hydrogenation (ASCN/AIN, 1996).

Rethinking product formulations (where possible) can minimize the need for

additives, the development of residues, or the allergenicity of a product. In the future, scientific developments may lead to new, safer food additives or foodstuffs that require less chemical/physical processing. For instance, foodstuffs could be bioengineered to resist bacteria without the need for preservatives, or to display more desirable colors and flavors. Because colors are vital to consumers' acceptance of processed foods yet at the same time carry perceived negative health implications, color science is a field ripe for development of new approaches. One such approach is to bind a chromophore onto a polymer that is of such high molecular weight that it would not be absorbed through the gut and metabolized. The colorant would pass right out of the body without affecting the consumer's health (however, it may be a bit shocking to notice one's unusually colored excrement). Natural colors, although virtually without safety concerns, have been expensive to harvest and are practically and technically inferior to the synthetic certified colors. However, plant tissue culture may be the answer to these problems. Cultured plant tissue can be manipulated and controlled to provide an easily available harvest and genetically engineered to produce a higher-quality product (Ghorpade et al., 1995).

The chemical basis of some additives may be approached in the future from a totally different perspective offering novel chemicals and processes with less toxicity. The future chemistry of food processing, storage, and preparation provides much material for further research and development.

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INTERNET RESOURCES

http://www.fda.gov
U.S. Food and Drug Administration. Provides links to the Center for Food Safety and Nutrition for latest information on food and nutrition issues. Link to past issues of FDA Consumer.

http://www.cspinet.org
Consumer Safety in the Public Interest. Focuses on health hazards in the food supply.

http://www.cast-science.org
Council for Agricultural Science and Technology.

http://www.easynet.co.uk/ifst
British Institute of Food Science and Technology.

CHAPTER 14

HAZARDS ASSOCIATED WITH NUTRIENT FORTIFICATION

ANNE PORADA REID

INTRODUCTION AND DEFINITION OF ISSUES

Fortification is a term that describes how nutrients are added to foods and indicates the addition of nutrients at levels higher than those found in the natural food product. Nutrient fortification of some foods is traditionally used to correct nutritional deficiencies. Typical examples include adding water-soluble vitamins to breakfast cereals, vitamin C to fruit drinks, vitamin A to margarine, and vitamins A and D to nonfat dry milk and evaporated milk. Nutrient fortification has been effective in public health, virtually eradicating beri beri, goiter, anemia, and pellagra (Sloan and Steidemann, 1996). Nutrient fortification can add life-giving properties to foods deficient in that nutrient and prevent disease or even death (Giese, 1995).

Nutrients are defined as physiologically important (body oriented) chemicals necessary for growth, maintenance, and reproduction of living organisms (Rutten, 1998). Typically they are placed into two main groups, these being macronutrients and micronutrients. The macronutrients are fats, carbohydrates, and protein. The micronutrients are vitamins, minerals, and trace elements (Rutten, 1998). The National Academy of Sciences' Food and Nutrition Board has set Reference Daily Intakes (RDIs; formerly known as RDAs) for the micronutrients (Geise, 1995). Although nutrients are necessary for life and growth (over 40 are required in human nutrition that must be obtained from food or supplements), too little or too much of any given nutrient may have health implications. For example, a lack of vitamin C can cause scurvy, a lack of iodine can result in thyroidism, and too much of a fat-soluble vitamin can cause liver damage. Generally, most problems are associated with nutrient deficiencies; however, a high intake of some nutrients may cause toxic effects or

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even death (Rutten, 1998). These toxic effects will vary from nutrient to nutrient and may lead to an immediate reaction or an accumulative response.

Self-improvement by nutrient supplementation is a recent trend in the United States. Dietary supplements are the tenth largest-selling food-related category across all food, drug, and mass merchandising outlets in the United States (Sloan, 1998). A dietary supplement is defined as a substance intended for ingestion as a supplement to the diet (Kurtzeil, 1998). The data supporting ways in which vitamins, minerals, herbs, and phytochemicals can combat disease are compelling (Kuhn, 1998), whereas data on nutrient-drug, nutrient-nutrient, and botanical-nutrient interactions are marginal (Marriott, 1997).

Information on dietary supplements is widely available, and each supplement may be purchased through many outlets (Cerulli et al., 1998). One of the newest categories of food items on the market are functional foods (nutraceuticals). Although not strictly a supplement, functional foods are defined as processed foods containing specific ingredients that aid specific bodily functions in addition to being nutritious (Hasler, 1998). As with supplements, safety is becoming an issue with functional foods, which are thought to have a detrimental effect on diet because they are often chosen over a balanced diet (Kuhn, 1998). Dr. Dean Ornish of Golden Valley Foods feels that people should be taking dietary supplements instead of eating fortified foods to control the nutrient intake (Kuhn, 1998). Some supplements and functional foods are labeled as natural. Unfortunately, although many consumers believe that "natural" and "harmless" are synonymous, this is not necessarily true. Natural substances that are considered harmless can be harmful when consumed in large amounts (Butterworth, 1994). Cyndi Thomson of the American Dietetic Association describes a study at the University of Arizona in which beta carotene supplements, which are thought to be harmless at high levels, actually interfered with vitamin E levels in the participants (Kuhn, 1998). Other examples are discussed in this chapter.

BACKGROUND AND HISTORICAL SIGNIFICANCE

Food fortification has been in effect in the United States for a half a century since the introduction of standards of identity for enriched flour. The fortification of flour, which dates to the 1940s, included three water-soluble vitamins (thiamin, riboflavin, niacin) and iron. Subsequent regulations allowed fortification of other cereal and bakery products. Salt has been fortified with iodine since 1924. The Michigan salt fortification program reduced the rates of goiter in school children by more than 50,000, resulting in a widespread voluntary fortification program (Mertz, 1997). The fortification of whole milk with vitamin A is voluntary, whereas fortification of low-fat and skim milk is mandatory because of the removal of fat-soluble vitamins during processing (Tanner et al., 1988). The fortification of vitamin D_2 in milk began in 1932 and was the

second major fortification program. The milk program was widely recommended in 1933 by the AMA. Before fortification, up to 75% of babies under 1 year old in large eastern U.S. cities showed some degree of rickets. Government and private agencies worked together on the vitamin D fortification project and by 1947 rickets had almost disappeared (Shank and Wilkening, 1986).

Another fortification issue involves iron, because it remains a worldwide nutritional problem. The best solution to the iron deficiency problem remains fortification of foods, but problems may exist because of sensory and bioavailability problems. Foods that are currently fortified with iron include flour, breakfast cereals, chocolate drink powders, and beverages (Hurrell and Cook, 1990).

The Food and Nutrition Board of the NAS/NRC and the AMA's Council on Foods and Nutrition in 1973 issued a policy statement with seven conditions for fortification: 1) The intake of a nutrient considered for addition to a food should be judged to be below the desirable level in the diets of a significant number of people. 2) The food that is used to carry the nutrient should be consumed by the segment of the population in need, and the added nutrient should make an important contribution to the diet. 3) The addition of the nutrient should not create a dietary imbalance. 4) The nutrient added should be stable under customary conditions of storage and use. 5) The nutrient should be physiologically available from the food. 6) There should be reasonable assurance that an excessive intake to a level of toxicity will not occur. 7) The additional cost should be reasonable for the intended consumer (Shank and Wilkening, 1990).

SCIENTIFIC BASIS AND IMPLICATIONS

Vitamins

Vitamins are generally classified as fat soluble or water soluble. Fat-soluble vitamins require proper lipid digestion, absorption, and liver functions for utilization. Water-soluble vitamins are more rapidly absorbed and eliminated. Vitamins serve as essential components of enzymes or coenzymes, which are necessary for proper metabolism and life. Vitamins may be important in preventing chronic diseases including cancer, heart disease, and cataracts (Butterworth, 1994). Vitamins are instrumental in preventing spina bifida and neural tube defects and lowering cholesterol levels (Butterworth, 1994). Most vitamins or vitamin precursors must be supplied by diet, because the body is unable to synthesize them (Geise, 1995).

Vitamin A Vitamin A is a fat-soluble vitamin and represents a group of substances necessary for reproduction, cellular differentiation, the immune system, gene regulation, and eyesight (Rutten, 1998). Typical natural sources in-

clude fruits and vegetables: lettuce, spinach, chard, escarole, carrots, and sweet potatoes. Vitamin A is the generic term for any compound with beta-ionone structure having the biological activity of all-*trans* retinol (Gerster, 1997). Precursor forms of vitamin A are carotenoids that take on the biological activity of vitamin A after intestinal conversion to retinol (Gerster, 1997). The most significant carotenoids include beta carotene, alpha carotene, and cryptoxanthin (Gerster, 1997). The conversion of beta carotene to vitamin A (in the intestine) is regulated; excess vitamin A is not absorbed. Preformed vitamin A includes retinol, retinal, and various retinyl esters (Bendich and Langseth, 1989). One result of vitamin A deficiency is xerophthalmia, whose main symptom is night blindness (Bendich and Langseth, 1989).

Ingestion of high levels of vitamin A can have adverse effects. An example of vitamin A toxicity was documented in Arctic and Antarctic explorers who consumed polar bear liver, which can contain up to 600 mg of retinol per 100 g of liver. When the explorers consumed this high level of vitamin A they demonstrated symptoms of vitamin A hypervitaminosis. The symptoms included drowsiness, headache, vomiting, and extensive peeling of the skin (Rutten, 1998). The potential for overexposure to vitamin A exists because high-dose dietary supplements are available without prescription. For example, dietary supplements can contain up to 25,000 IU per capsule (Bendich and Langseth, 1989). Therefore, toxicity associated with vitamin A can result from high intakes of dietary supplements or from the consumption of liver from animals or fish (Gerster, 1997). Toxicity is based on the ingestion of retinol or retinyl esters and not from provitamin A forms such as beta-carotene (Hathcock, 1997).

Vitamin A toxicity can be acute or chronic. Acute vitamin A toxicity is defined as a single dose of >150,000 μg RE (retinol equivalents) in adults. Acute hypervitaminosis cases usually result from overuse of dietary supplements (Bendich and Langseth, 1989). Chronic intake, which occurs with long-term intake at 30,000 μg RE and above in adults, can produce symptoms of hypervitaminosis; for children the level is 3600 μg (15,000 RE) (Gerster, 1997). Chronic hypervitaminosis is more commonly diagnosed as acute exposures and often goes unrecognized (Bendich and Langseth, 1989). The symptoms of hypervitaminosis include loss of appetite, dry, itchy skin, hair loss, weakness, headache, bone thickening, enlarged liver and spleen, nausea, vomiting, and blurred vision (Gerster, 1997). The symptoms may be reversible unless the abuse has been of extensive duration. High intakes of vitamin A in early (first 3 months) pregnancy increases the risk of birth defects (Butterworth, 1994), which can include malformations of the cranium, face, heart, thymus, and central nervous system (Rutten, 1977).

Individuals with kidney or liver disease can be more prone to vitamin A's toxicity because the liver and kidneys are involved in the intermediary metabolism, storage, biotransformation, and excretion of many nutrients (Russell, 1997). Also, excess stores of vitamin A in the liver increase the risk of hyper-

vitaminosis during liver disease (Bendich and Langseth, 1989). In acute liver disease, serum vitamin A levels can become elevated because of the release of retinyl esters from hepatic stores (Russell, 1997). Decreased transport of vitamin from the liver could cause local tissue intoxications (Russell, 1997). Hypervitaminosis is also found in individuals who are alcoholics or are malnourished (Gerster, 1997). Alcohol induces cytochrome P450 IIC8, which has been shown to increase the catabolism of vitamin A to 4-hydroxyretinol, which is toxic to cell membranes (Russell, 1997).

Vitamin D Vitamin D is a fat-soluble vitamin that exists in two major forms: ergocalciferol (D_2), which is found in foods, and cholecalciferol (D_3), which is synthesized in the body after exposure of the skin to ultraviolet light (Butterworth, 1994). Vitamin D is considered a hormone as well as a vitamin. Vitamin D is necessary for bone growth and mineral homeostasis (Rutten, 1997) because it functions in the regulation of rapid stimulation of intestinal calcium absorption and mobilization of calcium and phosphorus stores from bone (Marriott, 1997). Fortified foods (margarine, butter, milk) are the major sources of vitamin D (Rutten, 1997). Milk fortification in the United States has played a role in the elimination of rickets, which is the childhood form of vitamin D deficiency that causes a malformation of bones (Butterworth, 1994). Rickets was a serious health problem from the seventeenth century to the early twentieth century. Early in the twentieth century, several researchers discovered the link between vitamin D and rickets and fortification programs began with the fortification of milk.

Vitamin D toxicity occurs in adults when intake exceeds 50,000 IU/day but can also occur at levels as low as 25,000 IU/day (Butterworth, 1994). Excessive vitamin D intake can result in hypercalcemia resulting from the vitamin D-dependent increase in intestinal absorption of calcium and resorption of the bone (Barger-Lux et al., 1996). This condition can lead to deposition of calcium in soft tissues, heart damage, blood vessel damage, and irreversible renal damage (nephrocalcinosis) (Rutten, 1997). The deposition of calcium in the soft tissues leads to a metastatic calcification of the tissues. A severe depressive illness has also been noted in hypervitaminosis (Keddie, 1987). In Massachusetts, eight people suffered from vitamin D intoxication after consuming milk that was incorrectly fortified at levels approaching 232,565 IU/quart (580% of label declaration) (Butterworth, 1994).

Niacin Niacin is a water-soluble vitamin that exists in two forms, nicotinic acid and niacinamide (nicotinamide) (Butterworth, 1994). Niacinamide is a compound made up of two factors (1-to-1 ratio): nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) (Rutten, 1997). In these forms, niacin functions in intracellular respiration and reductive biosynthetic processes such as fatty acid and steroid synthesis. Nicotinic acid in large doses (3–6 g/day) has been found to lower cholesterol (But-

terworth, 1994). Niacin is found in liver, kidneys, meat, fish, wheat bran, grain germ, and yeast (Rutten, 1997). Niacin is associated with the deficiency disease pellagra (Giese, 1995), which is characterized by dermatitis, diarrhea, inflammation of mucous membranes, and dementia.

Niacinamide is not shown to have any harmful side effects at high levels. However, nicotinic acid is a peripheral vascular dilator, and many people taking large doses experience flushing of the skin (Butterworth, 1994). Some people can develop gastrointestinal reactions and liver toxicity at gram levels (Hathcock, 1997). The gastrointestinal effects include indigestion, nausea, vomiting, and diarrhea (Hathcock, 1997). The liver toxicity is associated with the release of enzymes because of liver cell damage, and the side effects can include jaundice, fatigue, and liver failure (Hathcock, 1997). Liver toxicity effects are at extremely high levels.

Folic Acid Folic acid is a water-soluble vitamin; in the body it functions as a coenzyme that transports single-carbon fragments from one compound to another in amino acid metabolism and nucleic acid synthesis. Folic acid is widely distributed in foods such as liver, yeast, leafy vegetables, legumes, and fruits. Since January 1, 1998 the Food and Drug Administration has required that most cereal grain products (bread, flour, cornmeal, pasta, rice, etc.) be fortified with a synthetic form of folic acid (Nutrition Reviews, 1996). The levels will range from 0.43 to 1.4 mg/lb; the levels are designed to keep daily intakes below 1 mg (Glenn, 1997). The grain products were chosen for fortification because of their history of success with fortification with other nutrients (Nutrition Reviews, 1996). The emphasis on food fortification is based on many studies suggesting the prevention of neural tube defects (spina bifida or anencephaly) in pregnancy (Dickinson, 1995). The suggested levels for women of childbearing age is 400 μg/day (Kelly et al., 1997). The decision to fortify foods was made to reach groups of people, in particular poor and uneducated people, to ensure that folate requirements are ingested (Kelly et al., 1997).

Three major problems may arise from excessive folic acid intake: 1) masking of pernicious anemia, 2) disruption of zinc function, and 3) antagonism of medications (Hathcock, 1997). Excessive intake is described as >1 mg/day (Glenn, 1997). Pernicious anemia is a severe anemia associated with the reduced ability to absorb vitamin B_{12} because of the absence of the intrinsic factor—if untreated, it may lead to permanent nerve damage. Pernicious anemia mainly affects older people (Glenn, 1997). High folate levels have been shown to mask anemic manifestations and to allow posterolateral spinal cord degeneration to progress (Hathcock, 1997). Another effect of excessive intake is the disruption of zinc function. Studies have suggested that high concentrations of folic acid may interfere with the absorption of zinc from the intestine (Butterworth, 1994). If a high dose of folic acid is necessary, it has been suggested that zinc supplementation should be administered (Butterworth, 1994). Elevated levels of folic acid (5–30 mg) have been shown to interact with certain drugs. For example, folic acid has been shown to interfere with anticonvulsant

drugs such as Dilantin (diphenylhydantoin), causing some epileptics to experience seizures when ingesting high levels of folic acid (Hathcock, 1997). Other drugs that can potentially interact with folic acid include methotrexate, trimethoprim, and sulfa-salazine (Butterworth, 1994).

Minerals

Minerals comprise a group of elements essential for growth and maintenance of the cellular and metabolic systems; in food they are present as complex salts (Rutten, 1998). Minerals have many biological functions. They are components of bones and teeth, they are also electrolytes that function to maintain water balance in the vascular system and tissues, and they are components of enzymes (Lehninger, 1982). A list of essential minerals includes arsenic, calcium, chlorine, chromium, copper, fluorine, iodine, iron, magnesium, manganese, molybdenum, nickel, phosphorus, potassium, selenium, silicon, sodium, tin, vanadium, and zinc (Lehninger, 1982). A major factor in mineral toxicity is the mineral's solubility in an aqueous environment (Rutten, 1998). Sodium and potassium are readily soluble, but iron, calcium, and phosphorus (in complex salts) are relatively insoluble and not readily absorbed from the gut (Rutten, 1998).

Iron

Iron is involved in many metabolic processes. It is required for heme-containing and non-heme-containing proteins, including enzymes involved in DNA synthesis and oxidative metabolism (Crowe and Morgan, 1996). Iron is a constituent of hemoglobin and myoglobin. The amount of iron in the body is regulated through absorption (intestinal mucosa), and this absorption is influenced by body stores. Iron is highly reactive and can lead to damage of cellular systems if the ions are free in the cell or body. Iron is often complexed by proteins such as ferritin, which is a widely distributed biological protein and is thought to prevent such cell damage (Aust, 1995). Iron deficiency causes anemia, reduced physical performance, decreased immune function, and increased premature births.

The iron compounds currently used in food fortification include 1) water-soluble compounds (ferrous sulfate, ferrous gluconate, ferric ammonium citrate, and ferrous ammonium sulfate), 2) compounds with poor water solubility but soluble in dilute acids (ferrous succinate, ferrous fumarate, and ferric saccharate), 3) compounds insoluble in water and in acid (ferric orthophosphate, ferric pyrophosphate, and elemental iron), and 4) experimental compounds (sodium iron EDTA and bovine hemoglobin) (Hurrell and Cook, 1990). The factors determining selection of the form of iron for fortification include bioavailability, cost, and safety.

There are several problems associated with iron fortification, including iron overload, cancer development, and impaired trace metal absorption. Iron over-

load is a significant safety issue. Iron-depleted individuals who are subjected to raised levels of iron can accumulate stores in the body, and this can lead to cirrhosis of the liver or heart failure (Hurrell and Cook, 1990). People with iron balance disorders (e.g., thalassemia major and idiopathic hemochromatosis) are especially at risk, whereas the risk is low in healthy individuals. Individuals with Parkinson and Hallervorden diseases have elevated levels of iron in the brain (Crowe and Morgan, 1996). Iron can interfere with the absorption of certain trace metals that share a common absorptive pathway (Hurrell and Cook, 1990). For example, aqueous ferrous iron impairs the absorption of zinc when the ratio of iron to zinc is 2:1 or greater and when the amount of the minerals exceeds 25 mg (Hurrell and Cook, 1990). Iron is important in cellular growth and multiplication. A concern in the health community is that excess stores of iron will enhance the proliferation of malignant cells or promote carcinogenesis by the formation of free radicals. Hurrell and Cook (1990) described an iron-associated increase in primary liver cancer and idiopathic hemochromatosis. Another study looked at 14,000 adults and showed a relationship between iron intake and cancer in men but not women.

CURRENT AND FUTURE IMPLICATIONS

A new trend in fortification involves minerals. Minerals are becoming a stronger force in the nutraceuticals industry, with sales in 1998 reaching $1.13 billion (Madley, 2000). Calcium is being added to breakfast cereals, orange juice, candies, and cookies. Calcium is important in the diet for the formation of bones and teeth, and it regulates heartbeat and proper transmission of nerve impulses. Adults may intake large quantities of calcium with little or no effects; however, intakes higher than 2500 mg calcium/day can cause hypercalcemia and decreased renal function and may interfere with absorption of iron and zinc (Rutten, 1988). Copper is essential for the absorption of iron in the body as well as enzyme functions. Copper toxicity can lead to hemolytic anemia, personality changes, eczema, and nephritis (Rutten, 1988). Zinc is essential as a co-factor for many enzymes. Megadoses of zinc can lead to copper deficiency, impairment of immune system, gastro-intestinal irritation, and vomiting (Rutten, 1998).

The following minerals are not currently used in food fortification programs; however, both are used in medical foods, infant formulas, functional foods, and dietary supplements. Their current popularity as dietary supplements is evident in the media. Chromium and selenium can have definite benefits as well as posing certain risks.

Chromium

Trivalent chromium [chromium (III)] is a trace element required for normal glucose metabolism, acting as a cofactor for insulin. Chromium is natu-

rally occurring in brewer's yeast, fruits, vegetables, and whole grains. Over-the-counter (OTC) chromium compounds are used for weight loss and glycemic control (Cerulli, 1998). The current recommended daily allowance for chromium is 50–200 μg/day and is regarded as safe in normal quantities. Cerulli et al. (1998) describe cases of chromium picolinate toxicity; for example, a 49-year-old woman consumed 600 μg/day for 6 weeks and suffered chronic renal failure. After treatments, her chromium levels returned to normal but she suffered residual renal dysfunction. Also, a 33-year-old woman went to an emergency room after 1–2 weeks of severe fatigue. Her symptoms included fever, chills, jaundice, renal failure, anemia, hemolysis, thrombocytopenia, and hepatic dysfunction. Many routine tests were run on the woman and blood transfusions were given. Before the onset of symptoms the woman had been consuming six to twelve 200-μg chromium picolinate tablets per day for 4–5 months. After 26 days of hospitalization the woman was discharged.

Selenium

Selenium is a naturally occurring trace element distributed widely and unevenly in the earth's crust. Selenium functions as a component of enzymes involved in antioxidant protection and thyroid hormone metabolism. Recent research has suggested that high levels of selenium may have antitumorigenic effects. Natural sources of selenium include food (grains, cereals, meat, and seafood) and drinking water. The RDA for selenium was set at 150 μg; the toxic dose is about 4500 μg (Rutten, 1998). Acute intoxication can occur after the ingestion of 30 mg. The symptoms of acute intoxication include nausea, abdominal pain, diarrhea, nail and hair changes, peripheral neuropathy, fatigue, and irritability (Rutten, 1998). Hathcock (1997), describes a case of poisoning resulting from a supplement manufacturer adding 182 times the amount of selenium declared on the label. After several weeks the symptoms included adverse effects on hair, nails, and the liver. Chronic intake of 1 mg/day can result in hair loss, fingernail breakage, and garliclike odor of dermal excretions (Rutten, 1998).

CURRENT AND FUTURE IMPLICATIONS

New trends in fortification also include nontraditional nutrients. The Food and Drug Administration in October, 1999 decided to allow products with soy protein to carry health claims. The ruling allows foods with at least 6.25 g of soy protein per serving to carry the claim that soy protein, combined with a diet low in saturated fat and cholesterol, may reduce the risk of coronary heart disease (Neff, 2000). Many products currently contain soy, and the trend is toward fortification of traditional foods such as pastas and breads (Neff, 2000). Another fortification trend includes isoflavones. Soybeans contain isoflavones, which are reported to reduce the risk of heart disease and several cancers. The

main focus has been genistein and daidzein, because they are considered phytoestrogens because they look and act like estrogen (Pszczola, 1988). The soy phytochemicals, while boasting cancer fighting qualities, may also be a contributing factor in breast cancer in some women (Kuhn, 1998). The nutraceutical and functional food markets are growing at a steady pace as is the fortification of foods that traditionally were unfortified. Research in the areas of phytochemicals, herbal extracts, and ligands is still in its infancy (Kuhn, 1998). More work will have to be done in the future to determine the safety and efficacy of these new nutrients.

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An excellent, timely source of information on the subject of nutrient hazards.

CHAPTER 15

MONITORING CHEMICAL HAZARDS: REGULATORY INFORMATION

DAPHNE SANTIAGO

BACKGROUND AND HISTORICAL SIGNIFICANCE

From the beginnings of civilization, people have been concerned about the quality and safety of foods. For example, King John of England proclaimed the first food law in 1202: The *Assize of Bread* prohibited adulteration of bread with ingredients such as ground peas or beans. In the United States regulation of food dates from early colonial times. The first food adulteration law in this country was enacted in 1785 in Massachusetts. These concerns have motivated legislative actions through the years, and in the 1950s the "Delaney Committee" congressional investigation on the safety of chemicals in foods provided the foundation for laws approved later to effectively control pesticides, food additives, and colors. Subsequent initiatives through the years have resulted in laws that ensure that our food is safe to consume (*FDA, 1995b*).

This country has one of the safest food supplies in the world because of the complementary roles of the different agencies involved in monitoring food production and distribution systems locally, at state level, and nationally. Food inspectors, chemists, microbiologists, and scientists working for the different state health agencies and federal departments and agencies provide continuous monitoring at all levels. Local, state, and national laws, guidelines and other directives describe their duties. Some monitor only one kind of food, such as milk or seafood, whereas others work strictly within a specified geographic area. They can be also responsible for only one type of food operation, such as restaurants or meat packing plants. Together they make up the U.S. food safety team.

The government's Food Safety Initiative, which began in 1997, strengthens the efforts of the nation's food safety team in the fight against foodborne illness (*FDA, 1998*). These illnesses afflict between 6.5 million and 33 million

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Americans every year, causing astronomical expenses to everyone involved. The losses extend from spoiled or contaminated products to severe sickness and even death.

The potential hazards that can cause these health problems have three basic forms, biological, physical, and chemical. Although biological hazards comprise over 95% of the risk in the food supply, an understanding and knowledge of chemical residues is important for all individuals, whether they are agricultural producers, food processors, handlers, or consumers. The term "chemical hazards" usually refers to metals, pesticides, and other chemical residues (e.g., antibiotics) that are sources of potential foodborne illness or chemical poisoning. Chemical foodborne illness is normally the result of preventable human error (*Snyder, 1998*).

Agencies Involved

Three federal agencies are primarily involved in monitoring the nation's food supply. The Food and Drug Administration (FDA) oversees all domestic and imported food sold in interstate commerce, including shell eggs, and with the exception of meat and poultry (*FDA, 1998*). It enforces food safety laws by inspecting food production establishments and food warehouses and collecting and analyzing samples for physical, chemical, and microbial contamination. It is involved in establishing good food manufacturing practices and other production standards, such as plant sanitation, packaging requirements, and Hazard Analysis and Critical Control Point (HACCP) programs. It works with foreign governments to ensure safety of certain imported food products. It requests manufacturers to recall unsafe food products and monitors those recalls. It takes appropriate enforcement actions. It is involved in educating industry and consumers on safe food handling practices and conducts research on food safety.

The Food Safety and Inspection Service (FSIS), a service of the U.S. Department of Agriculture (USDA), oversees domestic and imported meat, poultry, and processed egg products (generally liquid, frozen, and dried pasteurized egg products). It enforces laws by inspecting food animals for diseases before and after slaughter. The FSIS works with the USDA's Agricultural Marketing Service (AMS) to monitor and inspect processed egg products. They collect and analyze samples of food products for microbial and chemical contaminants and infectious and toxic agents. The FSIS is in charge of establishing production standards for use of food additives and other ingredients in preparing and packaging meat and poultry products, plant sanitation, thermal processing, and other processes. It makes sure all foreign meat and poultry processing plants exporting to the United States meet U.S. standards, seeking voluntary recalls by meat and poultry processors of unsafe products. It sponsors research on meat and poultry safety and educates industry and consumers on safe food-handling practices.

The Environmental Protection Agency (EPA) has jurisdiction over foods made from plants, seafood, meat, and poultry. The EPA determines the safety of new pesticides, sets tolerance levels for pesticide residues in foods, and publishes directions on safe use of pesticides. The agency also establishes safe drinking water standards and regulates toxic substances and wastes to prevent their entry into the environment and food chain. The EPA also assists states in monitoring quality of drinking water and finding ways to prevent its contamination (*U.S. EPA, 1991*).

State and local governments oversee all foods within their jurisdictions. Working with FDA and other federal agencies, they implement food safety standards for fish, seafood, milk, and other foods produced within state borders. They inspect restaurants, grocery stores, and other retail food establishments, as well as dairy farms and milk processing plants, grain mills, and food manufacturing plants within local jurisdictions. They also take part in the embargo (stop the sale of) unsafe food products made or distributed within state borders (*California, 1994*).

Other government agencies are also involved in these efforts. The Consumer Product Safety Commission (CPSC) enforces the Poison Prevention Packaging Act. The Federal Bureau of Investigation (FBI) enforces the Federal Anti-Tampering Act. The U.S. Department of Justice oversees all foods and prosecutes companies and individuals accused of violating food safety laws. The U.S. Marshals Service seizes unsafe food products not yet in the marketplace, as ordered by the courts. The U.S. Department of Transportation enforces the Sanitary Food Transportation Act. The U.S. Postal Service enforces laws against mail fraud, and the U.S. Customs Service ensures that all goods entering and exiting the United States do so according to U.S. laws and regulations.

Regulatory Actions

The chemical residues most commonly found in the food supply come from pesticides, animal drugs, or environmental contaminants like trace metal elements. Monitoring the presence of these substances requires a complex residue control system with rigorous processes for approval, sampling and testing, and enforcement by the different agencies involved.

The number of potential residues is impressive. However, it is not necessary to monitor for residues of all chemicals, because they differ greatly in their ability to produce a residue, their hazard to health, and the potential for exposing the human population to their residues. The samples are collected and analyzed for violative residue concentrations. Violative residue concentrations are determined by reference to residue limits (tolerances or action levels) established by the EPA for pesticides and by the FDA for animal drugs and environmental contaminants. Action levels and tolerances are limits at or above which FDA will take legal action to remove products from the market.

Where no established action level or tolerance exists, FDA may take legal action against the product at the minimal detectable level of the contaminant. The action levels are established and revised according to criteria specified in Title 21, Code of Federal Regulations (CFR) Parts 109 and 509 and are revoked when a regulation establishing a tolerance for the same substance and use becomes effective. They are established based on the unavoidability of the poisonous or deleterious substances and do not represent permissible levels of contamination where it is avoidable. The blending of a food or feed containing a substance in excess of an action level or tolerance with another food or feed is not permitted. The final product resulting from blending is unlawful regardless of the level of the contaminant

The FSIS has had the National Residue Program (NRP) in place since 1967 to sample meat and poultry for concentrations of residues that exceed the tolerances set by the EPA and the FDA (*USDA, 1998*). This initiative has as specific objectives: to assess and communicate the exposure potential from residues in the meat and poultry supply of the nation; to prevent live animals with violative concentrations of residues in their tissues from being slaughtered; and to prevent contaminated edible tissues from slaughtered animals from entering the food supply. The residue limits of potential contaminants is based on tolerances and action levels developed by the EPA for pesticides and by the FDA for animal drugs and unavoidable contaminants. These limits are derived in most cases from the CFR: pesticide limits from 40 CFR 180, animal drugs from 21 CFR 556, and unavoidable contaminants from 21 CFR 520, 522, 524, 526, 529 (new animal drug not subject to certification), 540, 544, 546, 548 (antibiotic drugs for use with animals), and 558 (new animal drugs for use in animal feed).

The FDA uses three approaches for pesticide residue monitoring: 1) incidence/level monitoring, 2) regulatory monitoring, and 3) the Total Diet Study (*Gunderson, 1995*). Incidence/level monitoring is conducted to obtain information on specific commodities, pesticides, or combinations thereof. The samples are collected from packing sheds, wholesale facilities, or otherwise as close as possible to the point of production. Regulatory monitoring is applied to enforce EPA tolerances. If tests confirm that any food contains pesticide residues exceeding the tolerance level, the FDA can enforce legal action such as seizure of the shipment, prevention of further shipments, recalls, and criminal penalties. The same happens in case of residues for which no tolerance is established. The Total Diet Study provides estimates of the intakes of pesticide residues in foods as consumed or prepared. In the Total Diet Study, foods are collected four times a year, once from each of the four U.S. geographic regions (*FDA, 1998; Yess et al., 1993*).

Formal tolerances are not established in all cases. For example, the EPA and the FDA have granted tolerance exemptions in approving the use of some pesticides and new animal drugs. For some unavoidable contamination situations, the EPA and the FDA, on request, recommend action levels to the FSIS; however, tolerances or action levels have not been established for all such

situations. The FSIS permits concentrations of residues in meat and poultry that do not exceed the residue limits allowed.

The residue limits for poultry and livestock species are published in the CFR or the Federal Register (FR) citations for tolerances and notations of action levels. Entries for animal drugs with "zero" or "no residue" tolerances report the limits of quantification considered by the FDA in approving those drugs in food-producing animals. These limits are used by the FDA for enforcement purposes, and are applied by the FSIS in determining whether the product is adulterated. All tolerance and action level units are stated in parts per million (ppm). Any residue of an animal drug found in the edible tissues of a species for which the drug is not approved is considered an adulterant. A substance endogenous to the animal tissue is not considered an adulterant.

Once it is determined that a sample is adulterated, or violates the tolerance limits or action level for any given chemical residue, the agency proceeds with the appropriate regulatory action. If illegal residues (above EPA tolerance or no tolerance for that particular food/pesticide combination) are found in domestic samples, the FDA can invoke various sanctions such as seizure or injunction. For imports, shipments may be stopped at the port of entry when illegal residues are found. "Detention without Physical Examination" (previously called "automatic detention") may be invoked for imports. This is based on the finding of one violative shipment if there is reason to believe that the same situation will exist in future lots, during the same shipping season, for a specific shipper, grower, geographic area, or country. Regulatory actions range from recalls to fines and even jail time for the offenders (*FDA, 1999*). The following is a list of possible regulatory actions:

- Recall and field correction
- Injunction
- Seizure
- Prosecution
- Disposition
- Indictment
- Information

SCIENTIFIC BASIS AND IMPLICATIONS

The residues monitored under in the NRP are selected with a risk assessment procedure, the Compound Evaluation System (CES), established in 1985 and revised in 1991. In the revised version, developed by the Residue Evaluation and Planning Division, USDA/FSIS, the basic approach to compound ranking involves three stages: determination of whether a compound produces a residue; if so, assessment of the toxicological hazards of the compound; and

assessment of the potential human exposure resulting from residues occurring in meat and poultry. An advisory board, the Surveillance Advisory Team, aids in the evaluation of information for compound ranking. Scientists from the EPA, the FDA, and the USDA compose this team. This advisory relationship is defined in a Memorandum of Understanding (MOU) among the three agencies (*FR, January 16, 1985*). Compounds may be rotated out of the NRP but can be added during the year if needed. Over the years, virtually all drugs, pesticides, and environmental contaminants for which suitable methods are available have been included in the NRP, except for compounds with especially low rankings, that is, low contamination potential.

Monitoring involves the sampling of specified animal populations to provide information about the occurrence of residue violations on an annual, national basis (*FDA, 1995a; FDA, 1996*). Compound selection takes into account the availability of laboratory methodology suitable for regulatory purposes. Monitoring information is obtained through a statistically based random selection of specimens of normal-appearing tissues from carcasses (of healthy animals). Generally, for a specific slaughter class-compound pair, the number of specimens chosen provides a 95% probability of detecting at least one violation when 1% of the animal population is violative. In addition to profile information, the results are used to identify producers or other entities marketing animals with violative concentrations of residues. When such producers subsequently offer animals for slaughter, these undergo enforcement testing until compliance is demonstrated.

Enforcement testing consists of the analysis of specimens obtained from individual animals or lots based on clinical signs or herd history. Testing is done to detect individual animals with violative concentrations of residues. The emphasis is on problem (high prevalence) populations, and testing is used as a tool to prevent residues from entering the food supply. Testing frequently results from decisions based on regional guidelines or direct observations. It is also used to follow up on those producers identified as marketing animals with violative concentrations of residues.

Partnership Agreements or MOUs established between the FDA and various state agencies help to increase the FDA's effectiveness in pesticide residue monitoring and maximize federal and state resources allocated for pesticide activities. These arrangements vary from data sharing, joint planning, and state collection of samples for FDA examination to FDA-State division of collection, analytical, and enforcement follow-up responsibilities for individual commodities or products of particular origin (i.e., imported vs. domestic products). The agency samples individual lots of domestically produced and imported foods and analyzes them for pesticide residues to enforce the tolerances set by the EPA. Domestic samples are collected as close as possible to the point of production in the distribution system; import samples are collected at the point of entry into U.S. commerce. Emphasis is on the raw agricultural product, which is analyzed as the unwashed, whole (unpeeled), raw commodity. Domestic and import samples collected are classified as either "surveillance" or

"compliance." Most samples are of the surveillance type, that is, there is no prior knowledge or evidence that a specific food shipment contains illegal pesticide residues. Compliance samples are collected as a follow-up to the finding of an illegal residue or when other evidence indicates that a pesticide residue problem may exist. The FDA considers several factors when planning the types and numbers of samples to collect. These include review of recently generated state and FDA residue data, regional intelligence on pesticide use, the dietary importance of the food, information on the amount of domestic food that enters interstate commerce and the amount of import foods, the chemical characteristics and toxicity of the pesticide, and production volume/pesticide usage patterns.

The FDA also samples and analyzes domestic and imported feeds for pesticide residues. The FDA's Center for Veterinary Medicine (CVM) directs this portion of the agency's monitoring via its Feed Contaminants Compliance Program. Animal feeds containing violative pesticide residues present a potential hazard to a number of different animals (e.g., laboratory animals, pets, wildlife, etc.). The major focus of CVM's monitoring is on feeds for livestock and poultry because they are foods or produce foods for human consumption.

For those contaminants identified as national problems (e.g., methyl mercury and other metals), the agency has developed Guidance Documents based on toxicity and potential exposure to the substance (*FDA, 1999a*). These Guidance Documents have no statutory authority. They merely present the relevant scientific information on each contaminant. How this information is used is entirely up to the public health officials who consult them and may be determined mostly by the particular circumstances of each case. The documents include sections on the FDA's statutory authority, sampling techniques, and trace element analysis. Estimating levels of concern for local consumption advisories are also covered. The information in these Guidance Documents indicates how tolerable levels of fish or shellfish consumption or contamination might be determined; however, it does not dictate an approach or decision regarding a particular contaminant in fish or shellfish. The first Guidance Documents (for arsenic, cadmium, chromium, lead, and nickel) address contaminants chosen because they are most likely to occur and because frequent concerns have been raised regarding their presence in fish and shellfish. Concern about these elements exists because fish tend to accumulate elemental contaminants present in the environment. These Guidance Documents have been designed for the use of public health officials (at the federal, state, and local level), members of the public, and other interested parties. These documents present the FDA's assessment of the current state of knowledge on specific contaminants, and they will be revised when important new information becomes available.

Chemical Residue Analytical Capability

The Code of Federal Regulations (21 CFR 101.9) specifies that regulatory food analysis in the U.S. must be done with the methods published in the Associa-

tion of Official Analytical Chemists (AOAC) *Official Methods of Analysis*. When there are no appropriate methods in this publication, the analyst can refer to other suitable methods published by recognized organizations like the American Association of Cereal Chemists (AACC) or the American Oil Chemist Association (AOCS). All these methods are subject to rigorous scrutiny, and each one is tested for accuracy and precision under specific review processes and collaborative studies before being approved for use (*Tanner, 1997*). In addition to these compilations of methods, most agencies have their own compendia of methods for use in the regulatory assay of samples. Some examples are the FDA *Bacteriological Analytical Manual* (BAM); the FDA *Food Additives Analytical Manual* (FAAM), vols. I & II; and the FDA *Pesticides Analytical Manual (PAM)*, vols. I & II (FDA, 1994). The AOAC plays an important role in the regulatory area publishing several of these compilations useful to laboratories performing this work.

Antimicrobials and Other Animal Drug Residues

The FSIS requires practical analytical methods for detecting, quantifying, and identifying chemical residues present in meat, poultry, and their processed products. These are used for monitoring and surveillance activities. The agency uses the available methodology to take the appropriate regulatory action against adulterated products consistent with the reliability of the analytical data. However, because of the large number of potential residues that may occur in the food chain, practical methods are not available for many compounds of interest (*Moats, 1997*). The chemistry methods used, with some few exceptions, appear in the FSIS *Analytical Chemistry Laboratory Guidebook*. The agency has defined two criteria as primary concerns for the methods defined as suitable for regulatory use: The method requires no more than 2–4 hours of analytical time per sample, and a quality assurance plan for the method is available (*Mitchell et al., 1998*).

The regulatory work of the FSIS calls for "In-Plant" tests, an essential part of the NRP. These are rapid screening methods used to detect the presence of residues at the plant level. The most widely used are:

- *SOS*, for Sulfa-On-Site, a rapid in-plant screening test implemented in April 1988 to test swine urine or serum. It provides same-day results for sulfonamide residues. SOS is used in many of the largest swine slaughtering facilities. Laboratory confirmation of violations is required.
- *CAST*, for Calf Antibiotic and Sulfonamide Test, used to test bob veal calves (less than 150 pounds and less than 3 weeks old). Before 1996 *CAST* did not require laboratory confirmation of the results, and any violation found with *CAST* resulted in immediate condemnation of the calf. After 1996, any zone of inhibition measuring more than 18 mm is sent to the laboratory for confirmation.

- *STOP*, for Swab Test on Premises, an overnight in-plant laboratory microbiological screen test implemented in 1979. It detects the presence of antibiotic residues in kidney and edible tissue. Originally developed for testing dairy cows, *STOP* is now used for a number of slaughter classes. Laboratory confirmation is required before the animal carcass is condemned. Certain *STOP*-positive samples are tested for both antibiotics and sulfonamides; the sulfonamide violations are reported with the *STOP* antibiotic violations.
- *SWAB*, a *STOP* precursor: an overnight laboratory microbiological screen test for detecting antibiotic residues in edible tissues.
- *FAST*, Fast Antimicrobials Screen Test, quickly detects both antibiotic and sulfonamide drug residues in kidneys and livers and has proved to be a suitable replacement for *CAST* and *STOP*. Although *FAST* is capable of detecting sulfonamides, this test is significantly less sensitive than the SOS test. It was implemented in pilot plants in 1995 and has been extended to approximately 50 of the largest cow and bob veal slaughtering plants since 1996.
- *CELIA, CA*, Competitive Enzyme-Labeled Immunoassay for Chloramphenicol is a laboratory test that detects and identifies chloramphenicol residues in cattle and pork muscle.

Currently, six types of detection methods are commonly used for the detection of antimicrobial residues in foods. These complement the basic, rapid "In-Plant" tests. The microbial growth inhibition assays are nonspecific qualitative tests like *Delvotest P* and *CHARM* farm tests for milk and tissues. Microbial receptor assays are more specific detection tests like *CHARM I & II*. The enzymatic colorimetric assays are qualitative enzymatic methods for rapid determinations in milk, for example, *Penzyme*. Receptor binding assays, which do not use antibodies, are qualitative enzyme-linked receptor binding assays for milk, for example, *SNAP* and *Delvo-X-Press*. Chromatographic analyses can be either qualitative like *TLC* (thin layer chromatography) or more specific and quantitative like *GC* (gas chromatography), and *HPLC* (high-pressure liquid chromatography). Immunoassays are highly specific tests that detect drug residues in milk and tissue. Examples are the *ELISA*—enzyme-linked immunosorbent assay; *Lactek*; *Cite Sulfa Trio*, and *E-Z SCREEN*—a proprietary immunoassay system for rapid detecting and identifying various antibiotics and other residues in tissue extracts. All these methods, as well as their modifications, are extensively reviewed in the literature and are used by both industry and government.

Pesticide Residue Determination

As mentioned above, the FDA is responsible for monitoring pesticide residues in the food supply by collecting and analyzing food samples from commercial

sources. The *Pesticides Analytical Manual (PAM)* is the collection of analytical methods used in FDA laboratories to examine food for pesticide residues for regulatory purposes. The manual is organized in two volumes. Volume I contains multiresidue methods used routinely because of their efficiency and broad applicability, and Volume II contains methods designed for the analysis of residues of a single compound only.

To analyze large numbers of samples, whose pesticide treatment history is usually unknown, the FDA uses analytical methods capable of simultaneously determining a number of pesticide residues. Multiresidue methods (MRMs) can determine about half of the approximately 400 pesticides with EPA tolerances and many others that have no tolerances. The most commonly used MRMs can also detect many metabolites, impurities, and alteration products of pesticides. Single-residue methods (SRMs) or selective MRMs can determine some pesticide residues in foods. An SRM usually determines one pesticide; a selective MRM measures a relatively small number of chemically related pesticides. These types of methods are usually more resource intensive per residue. Therefore, they are much less cost effective than MRMs.

The lower limit of residue measurement in the FDA's determination of a specific pesticide is usually well below tolerance levels, which generally range from 0.1 to 50 parts per million (ppm). Residues present at 0.01 ppm and above are usually measurable; however, for individual pesticides, this limit may range from 0.005 to 1 ppm. Generally, the term "trace" indicates residues detected, but at levels below the limit of quantitation (LOQ) for the method used.

Traditional sample treatment for pesticide residue determination begins with an extraction with organic solvents, followed by a cleanup step. After concentration of the extract, identification and quantitation of any residue is done by GC, with one or more element-selective detectors. This is the approach used by the FDA and by most laboratories monitoring pesticides. The detection limit (DL) for most pesticides today is in the 0.01 mg/kg (0.01 ppm or 10 ppb) range, with chromatographic methods being the most widely used for this purpose.

Pesticide residue determinations have come a long way since the early days (*Erickson et al., 1999*). In the early 1950s, the available methods allowed the determination of micrograms, of only one residue, present in the sample with rudimentary techniques like total halogen determination and nonspecific methods like visible and ultraviolet spectrophotometry. Advances in paper chromatography and introduction of gas chromatography (*GC*) eased the development of multiresidue methods late in the 1950s and in the 1960s. The introduction of the capillary GC, high-performance liquid chromatography (*HPLC*), and more selective and sensible detectors, during the 1970s was followed by the coupling of the GC with the mass spectrophotometer (*GC/MS*) in the 1980s. These techniques allowed improved residue confirmation and the analysis of pesticides with low volatility, high polarity, and even thermal instability. In the 1990s new technologies became increasingly important in this area. These

include immunochemical, capillary electrophoresis (*CE*), and automated on-line systems combining chromatographic methods for cleanup and analysis.

Over the years advances have been made in sample treatment to reduce, among other factors, the amount of chemical waste, analysis time, and cost (*Sherma, 1999*). The new techniques are more selective, requiring fewer cleanup steps and a smaller sample size because of increased instrument sensitivity. Some innovations in initial sample treatment manipulation include supercritical fluid extractions (*SCF*); on-line microextraction; pressurized liquid extraction or accelerated solvent extraction (*PLE, ASE*); microwave-assisted extraction (*MAE*); solid-phase microextraction (*SPE*) minicolumns, cartridges, and disks; and matrix solid-phase dispersion (*MSPD*) using a sorbent combined with the sample (*Sherma, 1999*). In cleanup procedures, the advances include liquid-liquid partitioning, column liquid-solid adsorption for fractionation based on polarity (with *Florisil*), and gel-permeation chromatography (*GPC*) based on molecular weight/size. Detection, screening, and quantification are done with capillary gas chromatography instead of packed columns; high-performance liquid chromatography (*HPLC*); capillary electrophoresis (*CE*); and immunoassays. These techniques cover all pesticides, from volatile to nonvolatile and thermolabile. All these methods, as well as their modifications, are extensively reviewed in the literature and are used by both industry and government (*Fong et al., 1999*).

Metal Residue Determination

Regulatory analysis of samples for trace metals follows the Guidance Documents published by the FDA (*FDA, 1999a*). The analyses require mineralization (digestion) of the samples. After digestion, there are various determinative techniques that form complete analytical methods. Digestion procedures fall into one of two general categories, dry ash or wet ash. Dry ash digestions use a long, slow ashing step, usually performed overnight in a muffle furnace. The ashing process is completed by the addition of a small quantity of inorganic acid to the residue and evaporation on a hot plate. The residue is redissolved in acid, and the solution is brought to volume with distilled or deionized water.

Wet ash digestions are characterized by short ashing times (normally 3–4 hours) and the use of acids (HCl, HNO_3, H_2SO_4, $HClO_4$). Wet ashing consists of adding acid or an acid mixture to the test portion and boiling until digestion is complete. Regardless of the digestion procedure selected, appropriate quality assurance and quality control guidelines must be followed. These include the use of contamination controls digestion blanks, spiked test portions, replicate analyses, and appropriate standard reference material.

Spectrometric techniques are usually used for the determinations. These include flame atomic absorption spectrometry (*FAAS*), graphite furnace atomic absorption spectrometry (*GFAAS*), and inductively coupled plasma-atomic emission spectrometry (*ICP-AES*). Sequential or simultaneous-mode

ICP-AES allows rapid analysis, dramatically improving throughput. Detection limits in *ICP-AES* are generally the same as those in *FAAS* except for elements that are difficult to atomize. Such elements have lower *ICP-AES* detection limits because of the higher temperature of the plasma.

Innovations to the traditional methods include the use of voltammetry for trace element determination, polarography, *ICP-MS*, *HPLC* with electrochemical and spectrophotometric detection, and neutron activation analysis (*NAA*).

Regardless of the analytical method chosen, sound scientific analytical principles must be followed. All methods used by a laboratory must be validated by the laboratory before routine sample analysis. The detection and quantitation limits and the accuracy and precision of each method must be assessed and documented for each metal, for reliable quantitation at or below the level of interest.

INTERNATIONAL IMPLICATIONS

The foods import business in the United States is flourishing. During any given week, the FDA receives products that vary from coffee from Kenya, to fresh vegetables from Mexico, to shrimp from India. The FDA has the responsibility for checking the quality of these products, and, by law, all of them must meet the same standards as domestic goods. For that reason the agency has increased its import operations staff over the past several years and has expanded surveillance. To be able to cope with the increasing demands it has established cooperative programs with state regulatory agencies for surveillance of imported products. It has also increased the use of the "blitz," short-term intensified surveillance of a specific product. These initiatives have resulted in increased civil and criminal judicial action against both importers and foreign exporters who repeatedly violate FDA regulations, as well as an increased education effort geared toward importers and their responsibilities in adhering to FDA regulations (*Long et al., 1998*; *Snyder, 1998*).

In terms of international cooperation, FDA has agreements with foreign governments, through MOUs, to expedite surveillance. In these, the governments agree to ensure that their products are manufactured under sanitary conditions, meet U.S. standards for quality, and are tested and sampled in a specific way before leaving the country. The FDA has nine MOUs with countries that export shellfish to the United States. These MOUs help ensure that the shellfish are raised, processed, packaged, and shipped properly. Sometimes the FDA inspects foreign plants to ensure that manufacturing practices meet U.S. requirements. Manufacturers of foreign goods that have been detained sometimes request an inspection, seeking advice on how to produce goods that meet FDA requirements.

The FDA is putting emphasis not only on controlling goods that contain violative residues but also on importers who continually and flagrantly violate

the law. The agency issues alerts to its district offices that contain the names and descriptions of products, shippers, or importers that have repeatedly been found to violate the laws or regulations. These "Import Alerts" help inspectors to pay special attention to a particular product when it arrives in port and automatically detain when it consistently violates FDA standards or is a known or suspected health hazard. Automatic detention alerts are used to determine which shipments should be denied entry without further examination by the agency.

For example, ceramic ware from at least eight countries is currently automatically detained because of possible lead contamination. Swordfish from all countries is automatically detained because it repeatedly has been found to contain high levels of mercury. Canned mushrooms from the People's Republic of China are automatically detained because they have caused several outbreaks of staphylococcal food poisoning.

In addition to identifying and detaining problem products, the agency identifies problem importers and foreign exporters as well. Importers who consistently bring in violative products, engage in "port shopping" (trying to enter with goods in a second port after having been refused entry elsewhere), or otherwise attempt to evade FDA regulations are warned that their products may be automatically detained. Once a product is placed on automatic detention, entry cannot resume until the shipper or importer proves that the product consistently meets FDA standards.

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CHAPTER 16

HAZARDS RESULTING FROM ENVIRONMENTAL, INDUSTRIAL, AND AGRICULTURAL CONTAMINANTS

INTRODUCTION AND DEFINITION OF ISSUES

The chemical contaminants present in food may result from their natural occurrence in soil (e.g., cadmium, lead, and mercury) or from metabolites and toxins released by contaminating microorganisms (e.g., mycotoxins), pollution arising from industrial and other human activities (e.g., lead, mercury, cadmium, and polychlorinated biphenyls, or PCBs), agricultural practices (e.g., pesticides, fertilizers, and drugs used in food animals), and food processing and packaging (e.g., nitrosamines, certain polycyclic aromatic hydrocarbons, and lead). These contaminants may present a potential hazard to human health if exposure remains uncontrolled. The United Nation's Codex Committee on Food Additives and Contaminants (CCFACs) defines a chemical contaminant as the following: any substance not intentionally added to food, which is present in such food as a result of the production (including operations carried out in crop husbandry, animal husbandry, and veterinary medicine), manufacture, processing, preparation, treatment, packing, packaging, transport or holding of such food, or as a result of environmental contamination.

For the majority of U.S. food companies, the detection of extraneous materials or foreign objects in their products is the leading source of consumer complains. Reports of chemical contamination, although less frequent than either microbiological or physical complaints, can be striking and immediate. The 1999 dioxin contamination of food in Belgium, which affected northern Europe, is an excellent and compelling example of the devastating impact of dangerous chemical residues in a food supply. The chemical contaminants in food supplies not only have immediate effects but also may lead to long-term

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chronic effects. Some contaminants, if allowed to persist in the environment, could bioaccumulate in the food chain. Environmental contaminants could potentially circulate globally and thus contaminate food supplies anywhere in the world, irrespective of the source of their origin. Thus chemical contamination of food supplies, particularly that due to environmental contaminants, is complex and may require global understanding and solutions to control.

BACKGROUND AND HISTORICAL SIGNIFICANCE

The concerns regarding hazards due to environmental, industrial, and agricultural contaminants in the middle of the nineteenth century followed the industrial developments and technological and scientific advancements in agriculture, meat, and other food production, processing, and distribution. By 1930, a variety of pesticides and other agricultural chemicals were in common use and additives were becoming common in processed foods. An increasingly urbanized, industrial society developed a greater dependence on a more sophisticated food industry to ensure an abundant and economical food supply. This followed a greater concern for food safety, particularly with respect to chemicals in foods. Congress addressed these concerns with the enactment of the Federal Food Drug and Cosmetic Act (FDCA) in 1938, which remains the basic statute governing food regulation in the United States. During the 1940s and 1950s, development in science and technology resulted in proliferation of food chemicals and new processes. Science has since made a quantum leap forward, with analytical chemistry increasing sensitivity of detection to parts per billion and, in some cases, parts per trillion. This increase in sensitivity of detection has produced evidence of trace contaminants in food that were hitherto unsuspected. Toxicology, too, has advanced with ever more exquisite searching for adverse effects with animal studies and other methods. With these advances, science has increased the inherent concern about food safety. The study of chemical contamination of food has developed as a scientific subject primarily in last 30 years or so.

The chemicals that can contaminate a food supply can arise from different types of sources or activity—for example, agricultural sources, animal production, food manufacture, packaging of food, food storage, environmental sources, industrial sources, and finally, natural sources. In recent years, this area has been intensively studied and considerable progress has been made in our knowledge of the ways these chemicals contaminate the food supply and the hazards associated with this contamination. Significant work has been done in deciding the maximum amount of a given chemical contaminant that can be consumed without risk to the consumer. Intake of some of the critical contaminants has been monitored and a considerable amount of data has been collected in various countries. Today, the majority of chemical residues that could be in foods are regulated and tolerances are set under FDCA as food additives (direct or indirect), pesticides, color additives, or animal drugs. Under

FDCA, a food is considered to be adulterated if it contains a chemical residue for which no tolerance is set or if it contains a residue at a level above a defined tolerance. A listing of prohibited chemicals in foods is maintained under Food and Drug Administration (FDA) regulations (21 CFR 189).

This chapter focuses primarily on hazards resulting from environmental, industrial, and agricultural contaminants in food. It also discusses related contaminants of natural sources and veterinary drug residues from animal sources in a food supply and tries to summarize some of the recent findings and activities in this area.

SCIENTIFIC BASIS AND IMPLICATIONS

Hazards from Environmental Contaminants in Food

Chemical contamination of the environment is a pervasive, insidious effect of human population growth, industrial growth, and technological development. We produce and consume large volumes of a wide variety of chemicals, some of which are toxic. During the production, use, and disposal of these substances, there are opportunities for losses into the environment. Contaminants may be transported long distances in air and water, be modified in form and toxicity on release into the environment, and cause ecological injury far from their original sources (Schmitt, 1998).

The environmental contaminants are a group of substances with quite diverse chemical structures that exhibit common characteristics in terms of behavior. These substances tend to be stable and thus persistent in the environment; they tend to bioaccumulate in the food chain and can be transformed with increased toxicity (Munro and Charbonneau, 1981). To control environmental pollution and protect humans and animals from the hazards of environmental contaminants, a concept of persistent organic pollutants has emerged.

The United Nations Environmental Program (UNEP) identifies the "Persistent Organic Pollutants" (POPs) with the following properties (UNEP, 1998):

1. POPs are very stable compounds and can persist in the environment for years or decades.
2. They can circulate globally through a process known as the "grasshopper effect." POPs released from one part of the world can, through a repeated (and often seasonal) process of evaporation and deposition, be transported through the atmosphere to the regions far away from the original source.
3. POP chemicals bioaccumulate through the food web and concentrate in living organisms through deposition in fatty tissues, where concentration can become magnified.

TABLE 16.1. Twelve Persistent Organic Pollutants (POPs) Targeted for Global Ban by United Nations Environmental Program (UNEP)[a]

Pesticides	Industrial toxins/by-products
Aldrin	Polychlorinated biphenyls (PCBs)
Chlordane	Furans
Endrin	Dioxins
Dichlorodiphenyltrichloroethane (DDT)	
Dieldrin	
Heptachlor	
Hexachlorobenzene	
Mirex	
Toxaphene	

[a]From UNEP (1998).

4. They are highly toxic, causing an array of adverse effects, notably death, disease, and birth defects among humans and animals. Specific effects can include cancer, allergies and hypersensitivity, damage to central and peripheral nervous systems, reproductive disorders, and disruption of the immune system. Some POPs are also considered to be endocrine disruptors and, therefore, can affect exposed individuals and their offspring.

UNEP sponsored an international agreement to phase out production, use, and release of POPs. Twelve POPs have been identified as initial phase-out targets under the new treaty (UNEP, 1998). This list includes nine organochlorine pesticides and three industrial chemicals/by-products (Table 16.1).

POPs tend to accumulate in the food chain. The requirements of chemical contaminants for accumulation in food chain are the following: (1) They have a high octanol-water partition coefficient. (2) They are stable in water and other compartments of the aquatic system. (3) They are metabolically stable in species involved in the food chain including fish and mammals. (4) Their toxicity is low in the sense that they do not eliminate the intermediate species and thereby break the food chain. Table 16.2 illustrates the above-mentioned properties of some of the well-known environmental contaminants (Clarkson, 1995).

Environmental contaminants tend to accumulate in the food supply, especially in fish, which renders them potentially hazardous to humans. Their toxicity is usually greater in higher-order mammals than in species of lower phylogenic order. For example, fish, seals, and crustaceans can tolerate much higher levels of mercury and arsenic than humans (Munro and Charbonneau, 1981).

Two major pathways—aquatic and terrestrial—depicting the accumulation of environmental contaminant in the food chain are given in Figure 16.1. These contaminants in water are accumulated by fish either directly or indirectly

TABLE 16.2. Factors Affecting Accumulation of Contaminants in Food Chains[a]

Contaminant	Log (Octanol/water)	Stability	Chain toxicity
High biomagnification			
Chlordane	High	High	Low
PCBs	High	High	Low
DDT	High	High	Low
Dioxins	High	High	Low
Low biomagnification			
PnAHs	—	Low	—
Phathalates	—	Low	—
Trichloroethylene	Low	Medium	—
Aliphatic hydrocarbon	Low	Low	—
Methoxychlor	—	Medium	High

PCBs, polychlorinated biphenyls; DDT, dichlorodiphenyltrichloroethane compounds; PnAHs, polyaromatic hydrocarbons.

[a] From Clarkson (1995).

through consumption of contaminated organisms in water. They can be accumulated directly or indirectly by humans as well. Similarly, soil contaminants can eventually get into human food through plants and animals.

Environmental contamination due to chemicals can arise in two ways including:

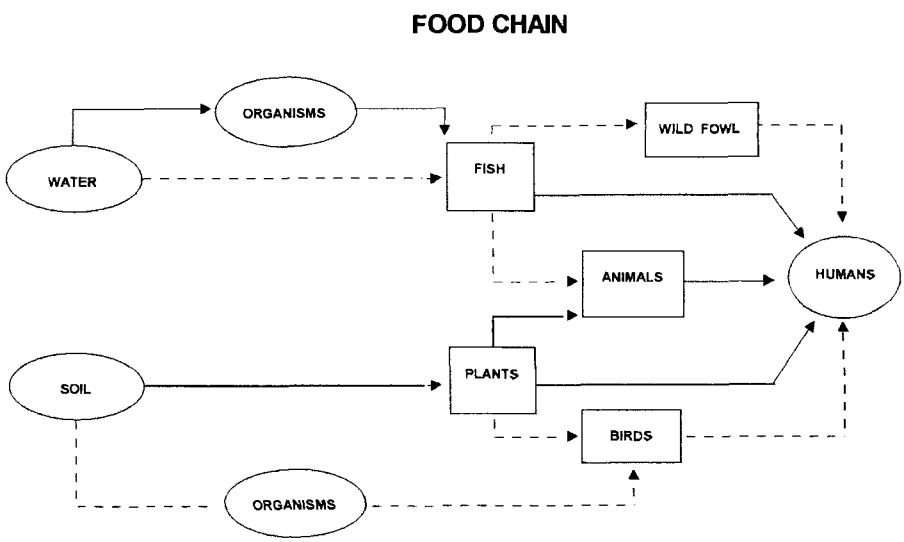

Figure 16.1. An aquatic and terrestrial food chain. Source: Clarkson (1995).

- Long-term, low-level contamination resulting from a gradual diffusion of persistent chemicals through the environment; and
- Short-term, higher-level contamination resulting from an accidental or inadvertent release of the chemical and/or its active by-product or waste product into the environment, particularly watersheds.

The Office of Technology Assessment (OTA) assembled data on food contamination due to accidental release of toxic chemicals into environment in the U.S. from 1968 to 1978. Major incidents include PCB contamination of the Hudson River, polybrominated biphenyl (PBB) contamination of animal feed in Michigan, and kepone contamination of the James River in Virginia (OTA, 1979a). Contamination of animal fats by PCB was reported in Montana which contaminated food supply in 17 states (Munro and Charbonneau, 1981). Major international incidents include methyl mercury outbreak in 1960s in Minimata Bay and in Nigata in Japan and in 1970s in Iraq (U.S. FDA, 1994). A serious mass intoxication in 1968 occurred in Japan from large-scale PCB contamination of rice-bran oil. A similar mass poisoning, called Yu-Chen, occurred in Taiwan in 1979 (World Resources Institute, 1999a). An accidental environmental release of 2,3,7,8-tetrachlorodibenzo-*para*-dioxin (TCDD) from a chemical factory in Seveso, Italy in 1976 resulted in dioxin exposure of local population. Contamination of chicken, eggs, and catfish (because of feed contamination) in the southern U.S. was reported in 1997 (WHO, 1999). A dioxin crisis was reported in Belgium in 1999 in which contaminated animal feed resulted in dangerously high levels of dioxin in chicken, beef, pork, eggs, milk, and by-products (WHO, 1999).

Industrial Contaminants

The majority of food contaminants of industrial origin are complex organic substances and sometimes organometallic or inorganic substances that are either end products or by-products of industrial processes. Table 16.3 lists some of the major chemicals of industrial origin that can contaminate foods and that are of concern because of their potential to produce adverse effects in humans. The foods that are most affected are also listed.

Industrial contaminants have been studied intensively, and considerable knowledge exists about the ways in which these contaminants make their way to the environment and eventually to human food, with resultant effects on human health. Some of the major industrial environmental contaminants are discussed in the following section.

Polychlorinated biphenyls (PCBs) Polychlorinated biphenyls (PCBs) are a group of 209 related compounds that are termed congeners of PCBs. Of these, only 20 have been reported as having toxicological effects. The congeners of concern are assigned a weighing factor based on their relative toxicities. The

TABLE 16.3. Major Food Contaminants of Industrial Origin[a]

Chemical	Source	Food Contaminated
Polychlorinated biphenyls	Electric industry[b]	Fish, human milk
Dioxins	Impurities in chlorophenols Incinerator emission	Fish, milk, beef fat
Pentachlorophenol (PCP)	Wood preservative	Various foods
Dibenzofurans	Impurities in PCP and PCB	Fish
Hexachlorobenzene	Fungicide, by-product	Animal fat Dairy products Human milk
Mirex	Pesticide	Fish Edible mammals Human milk
DDT[c] and related halogenated hydrocarbons	Pesticides	Fish Human milk
Alkyl mercury compounds	Manufacture of chlorine soda lye, acetaldehyde, seed dressing	Fish Grain
Lead	Automobile exhaust emission, coal combustion, lead industry.	Vegetables, fruits
Cadmium	Sewage sludge Smelter operations	Grains and vegetables Farmlands, meat products
Arsenic	Smelter operations	Milk, vegetables, fruits
Tin	Canning industry	Canned foods

[a] From Munro and Charbonneau (1981).

[b] Destruction of old transformers, capacitors and other devices in landfills may still be the source.

[c] DDT, dichlorodiphenyltrichloroethane compounds.

sum of the weighed concentrations form the "toxic equivalent" or TEQ (IFST, 1998). Manufacture and distribution of PCBs were discontinued in the United States in late 1970s. It has been suggested that highly contaminated bottom sediments in sewers and receiving streams may represent a reservoir for the continued release of PCBs (Munro and Charbonneau, 1981). A LOAEL (lowest observed adverse effect level) of 5 μg/kg body weight/day for Arclor 1254 has been identified for effects on the skin and on the immune system (Buckland et al., 1998).

The accidental contamination of edible rice bran oil in Japan in 1968 led to a poisoning epidemic among the Japanese families who consumed the oil. The poisoning caused chloracne, eye discharges, skin discoloration, headaches, fatigue, abdominal pain, menstrual changes, and liver disturbances. Babies born to mothers who consumed the rice oil were abnormally small and had temporary skin discoloration. At least 9–29 deaths that occurred in affected

families as of May 1975 were attributed to cancer (malignant neoplasm; National Institute of Occupational Safety and Health, 1977). Experiments in animals have demonstrated a variety of toxic effects of PCBs. Cancers have been produced in mice and rats, and reproductive disorders have been seen in monkeys. Young monkeys nursing on mothers consuming feed that contained PCBs developed toxic effects and behavioral abnormalities (OTA, 1979). Mortality studies of workers exposed to PCBs at capacitor manufacturing plants in the U.S. also suggest an increase in mortality from liver cancer (Buckland et al., 1998).

PCBs accumulate in aquatic food chains. An unusual example was presented in the cases of high blood concentrations of PCBs in an Indian community living a long distance from industrial centers in North America. The population ate fish, but PCB concentrations in the fish from the local lakes and rivers were low. However, this area is also the place where migratory loons spend their summer after wintering south in the Chesapeake Bay area, where the fish are known to have high concentrations of PCBs. It was discovered that the Indian community enjoyed in the springtime one of their favorite culinary delicacies, fresh-cooked loon eggs. The eggs were found to contain prodigious quantities of PCBs. In fact, it was calculated that one or two eggs would ensure elevated blood PCBs for the entire following year (Clarkson, 1995).

The U.S. Environmental Protection Agency (EPA) fish and wildlife advisories database of 1999 indicates that PCBs are the predominant cause of government warnings against fish caught in the wild in the U.S. (Table 16.4). Today, the main source of human exposure to PCBs is through consumption of fatty foods such as meat, fish, milk, and milk products (IFST, 1998).

The data collected by Global Environment Monitoring System–Food Contamination Monitoring and Assessment Program (GEMS/Food), provide an

TABLE 16.4. 1999 Data from U.S. Environmental Protection Agency About Fish Advisories Issued Throughout the Country[a]

	POPs-related advisories		Advisories involving PCBs	
State	Number	%	Number	%
California	69	64	32	46
Illinois	61	95	53	87
Indiana	944	58	944	100
Massachusetts	133	46	69	52
Michigan	523	73	443	85
New York	309	86	185	60
Ohio	109	74	98	90
Pennsylvania	98	99	85	87
Wisconsin	484	28	477	99

[a] From U.S. EPA (1999).

TABLE 16.5. Dietary Intake of Polychlorinated Biphenyls (PCBs) by Infants from Human Milk[a]

Country	Year	Mean daily intake (μg/kg bw/day)[b]	Remarks
Canada	1988	13.32	Inuit
	1988	3.12	Caucasian
Denmark	1982	3.32	
Finland	1982	1.92	Helsinki
Germany	1983	11.9	
Hong Kong	1985	2.19	Ethnic Chinese
India	1982	Not detected	Ahmedabad
Japan	1985	1.80	
U.K.	1980	1.86	

[a]From Baht and Moy (1997).

[b]μg/kg body weight/day; U.S. FDA suggested consumption maximum = 1 μg/kg body weight/day.

estimate of mean daily dietary intake of PCBs in adults in different countries. All the countries participating had a mean daily intake lower than the U.S. FDA's suggested consumption maximum of 1 μg/kg body weight/day. Japan and the U.S. reported intakes less than 0.05 μg/kg body weight/day during the time period of 1980–1988. The U.S. intakes were an order of magnitude lower than those in Japan, probably because of the lower amount of fish in the U.S. diet. The substantially higher daily intakes in New Zealand (0.9 μg/kg body weight/day in 1982) were due primarily to high PCB intake from dairy products. In this case, the mean daily intake approached the FDA suggested maximum, whereas the daily intake of 1.5 μg/kg body weight/day for male teens exceeds it (Baht and Moy, 1997). The estimated average U.K. dietary intake of PCBs declined from 1.0 μg/person/day in 1982 to 0.34 μg/person/day in 1992 (Buckland et al., 1998).

The dietary intake of PCBs by infants from human milk compiled by GEMS/Food is given in Table 16.5. A mean intake of about 13 μg/kg body weight/day was calculated from data reported from PCB content in the breast milk of Inuit women from the Hudson Bay Region of Northern Quebec. This high level in breast milk is ascribed to the markedly higher consumption of fish and marine mammals. However, intakes above 10 μg/kg body weight/day were also reported in Germany. High PCB levels have been reported in fish and meat of certain areas of Germany. The estimated intake of PCBs by breast-fed infants was usually far in excess of the guidance value in virtually all reporting nations (Baht and Moy, 1997). Dietary intake of PCBs in this age group is required to be monitored regularly to assess the persistence of this health hazard.

Dioxins The dioxin group of chemicals includes 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlori-

nated dibenzofurans (PCDFs) and some coplanar compounds of PCBs. The most toxic dioxin of all is TCDD. The amounts of less toxic congeners of dioxins and furans are expressed in terms of the equivalent quantity of TCDD and are indicated as "toxic equivalent" (TEQ). Residues of other congeners are multiplied by the corresponding relative toxicity weight factor (toxic equivalent factor) to calculate the TEQ of each congener. The known toxic effects of dioxin include dermal toxicity, immunotoxicity, reproductive abnormalities, teratogenicity, endocrine disruption, and carcinogenicity. Chronic exposure of animals has resulted in several types of cancer. The International Agency for Research on Cancer (IARC) categorized dioxin as a "known human carcinogen" based on human epidemiology data. The half-life in the body is, on average, 7 years (Hallikainen and Vartiainen, 1997; WHO, 1998, 1999).

Well-known examples of accidental exposures of the local population to dioxins include the incident at Seveso in 1976 and in Belgium in 1999 and other incidences as mentioned above (see the discussion of contamination of the food supply by POPs and other environmental chemicals). Most of the usual exposure to dioxins happens through the diet, with food from animal origins being the predominant source. PCDD and PCDF contamination of food is primarily caused by deposition of emissions from other sources including incinerator emission and industrial processes. This is followed by bioaccumulation up terrestrial and aquatic food chains. Other sources of exposure may include contaminated feed, improper application of sewage sludge, flooding of pastures, waste effluents, and certain types of food processing (WHO, 1998). The available information from industrialized countries indicates a daily intake of PCDDs and PCDFs on the order of 50–200 pg TEQ/person/day. Concentrations of dioxins (17 2,32,7,8-chlorine substituted dioxin/furan congeners) were estimated by the U.S. FDA in 1998–1999 in selected foods. The relatively higher amounts were found in crab (0.36 pg/g), cheese (0.38 pg/g), and cream (0.27 pg/g) and the lower amounts in scallops and eggs (0.16–0.17 pg/g) (Codex Alimentarius Commission, 2001).

The average dietary intakes of dioxins in the European Union population (after 1995) ranged between 0.4–1.5 pg TEQ/kg body weight/day. The main contributors to the average daily intake of dioxins in participating countries are milk and dairy products (contribution ranged from 16 to 39%), meat and meat products (6–32%), and fish and fish products (11–63%). Other products, mainly of plant origin (such as vegetables and cereals) contributed some 6–26% in those countries in which data were available (Codex Alimentarius Commission, 2001). Data summarized in Table 16.6 for the estimate of polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDD/F) pg TEQ/day for various countries also indicate that dairy, meat, and fish are the major contributors (Hallikainen and Vartainen, 1997). Tolerable daily intake (TDI) for dioxins has been set in the range of 1 to 4 pg/kg body weight (WHO, 1999).

Polynuclear aromatic hydrocarbons (PnAHs) This is a large group of substances with the common structural feature of two or more fused benzene rings (also known as polycyclic aromatic hydrocarbons). It is well established

TABLE 16.6. Daily Intake of Polychlorinated Dibenzo-*p*-Dioxins and Dibenzofurans (PCDD/F) pg TEQ/day

Country	Milk and dairy prod.[b]	Meat and meat prod.[b]	Fish and fish prod.[b]	Eggs	Fruit and veget.[c]	Veget[c] oil	Food industry items	Total daily intake per kg bw[d]
Canada	48.8	24.8	16	17	1.3			1.8
Finland	31.0	1.4	59.6	3				1.6
Germany	41.7	33.1	33.9	5.9	5.7	0.6		2.2
Holland	26.0	11.0	3			4.0	16	1.0
Norway	9.9	5.4	12.7	4.3		17.1		0.8
Sweden	17–53	13.1	50–55	2.8	8.6	14.3		1.8–2.5
U.K.	26.0	10.0	3.0	3.0		6.0		1.0
U.S.	8.0	18.0	6.7	0.5				0.3–3.0

[a] From Hallikainen and Vartiainen (1997).

[b] Products, [c] vegetable(s), [d] per kg body weight.

that PnAHs are environmental contaminants. They are produced during combustion and are common in diesel and gasoline exhaust where incomplete combustion of fuel occurs. The fallout of PnAHs on crops from combustion processes seems a likely cause of its contamination of food supplies; the compounds have been found in a wide range of foods in many countries (Watson, 1993). Crustaceans and shellfish from polluted waters may accumulate high levels of PnAHs. Blue crabs from a highly contaminated urban estuary in Virginia were found to contain PnAH concentrations as high as 3.1 mg/kg in muscle. Approximately 80% of the total dietary intake of PnAHs comes from cereals and the oils/fats food group. PnAH levels are high and variable in vegetable oils. Margarine was the major dietary source in one of the study. Benzo(*a*)pyrene (BP) partitions mainly into soil and then accumulates in food. In a survey of cooked foods in south India, high levels of BP (60.2 μg/g) and chrysene were observed in a sun-dried, oil-fried ribbon fish. The long-term average daily intake of BP in the U.S. is estimated to be 2.2 μg, with the food chain accounting for 97% of this (Doyle, 1993).

Some of the PnAHs are known for their long-established carcinogenicity. Not all the PnAHs are equally threatening, but the relative toxicity of different PnAHs is not known and more research is required to establish toxicity of important PnAHs (Watson, 1993). Because there is an increased lifetime risk of 3.5×10^{-4} associated with exposure to background levels of BP, ingestion of food items contaminated with BP may pose a serious health risk (Doyle et al., 1993).

Agricultural Chemicals

Various agricultural chemicals can contaminate the food supply. The organochlorine compounds used as pesticides are important in this category, and they

have been studied extensively. The following section is an attempt to review existing knowledge about the food contamination in relation to organochlorine pesticides and impact on human health.

Organochlorine pesticides DDT (dichlorodiphenyltrichloroethane compounds) was released into the civilian market in 1945, and it was used heavily over next two decades to control agricultural and forest insects as well as disease vectors. After World War II, additional organochlorine pesticides—including methoxychlor, aldrin, chlordane, and heptachlor—became available. These were followed by endosulfan, endrin, mirex, kepone, toxaphene, and others. DDT was banned in the U.S. in 1969, and toxaphene followed suit in 1983.

The ecological consequences of organochlorine pesticides were extensive. Because of their insolubility in water and resistance to complete degradation, many organochlorine compounds bioaccumulate. On accumulation by vertebrates, DDT is metabolized to DDE [1,1-dichloro-2,2-bis(*p*-chlorophenyl)-ethylene (DDE)], which is stable and toxic. In response to declining organochlorine pesticide use in North America, residue concentrations of DDT and other persistent compounds in fish and wildlife declined steadily over the last decade. Elevated levels of DDT and other organochlorine insecticides still persist in various areas, including the Great Lakes region. These insecticides also persist in soils, tending to accumulate in soil invertebrates (Schmitt, 1998).

Of all the possible health impacts from pesticide exposure, cancer has been the most frequent and most controversial focus of attention. Many pesticides show cancer-causing potential in animals, depending on the level of exposure and dose required to affect the cells. Synergistic effects of the pesticides and related chemicals in the body, the manner in which they accumulate in tissues, the length of time they remain in the system, and many other issues further complicate these observations. On the basis largely of animal studies, the U.S. EPA reports that of 321 pesticide chemicals examined, 146 are probable or possible human carcinogens. Epidemiological studies have also shown a link between exposure to organochlorine pesticides and various cancers, including lymphoma and leukemia, as well as lung, pancreatic, and breast cancer. Pesticide exposure has also been implicated in cases of immune system suppression (World Resources Institute, 1999b).

Global pesticide use is large and still climbing. In 1995, world pesticide consumption reached 2.6 million metric tons of active ingredients, with a market value of $38 billion (U.S.). Roughly 85% of this was used in agriculture. Although the volume of pesticides that developing countries use is small relative to that of developed countries (Fig. 16.2), it is nonetheless substantial and growing steadily (World Resources Institute, 1999b).

A recent survey of 60 countries found that the majority were still producing, importing, or exporting the nine POPs studied. In Africa, for instance, only two countries have banned the use of chlordane, dieldrin, or heptachlor (UNEP, 1996; World Resources Institute, 1999a). Use of chlorinated hydrocarbon pesticides is restricted or banned in most of the developed countries, but many of

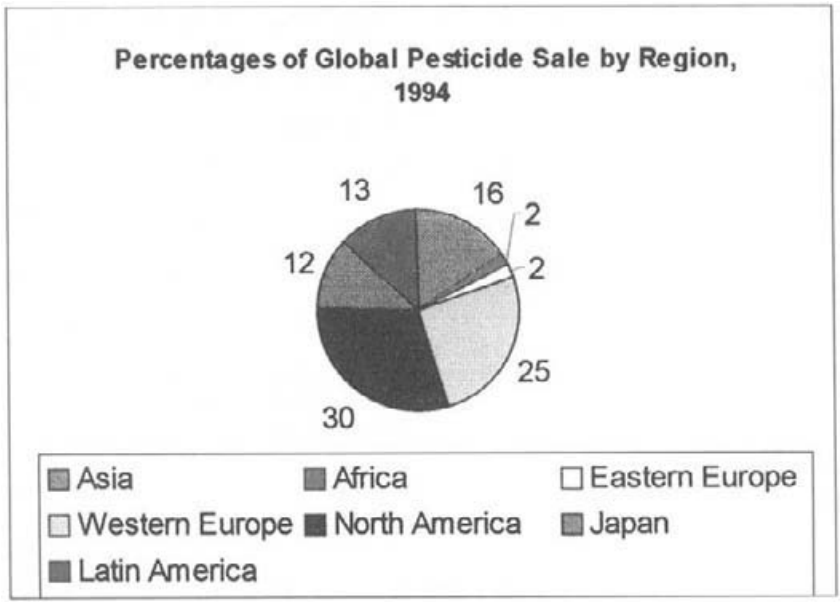

Figure 16.2. Global use of pesticides by different regions, 1994. Source: World Resources Institute (1999b).

these are still manufactured in the United States and other developed nations for export and remain widely used in developing countries. Customs records for shipments from the U.S. show that at least 108,000 metric tons of banned, restricted, or discontinued pesticides were exported from U.S. ports from 1992 to 1994 (World Resources Institute, 1999b).

The pesticides used in farmlands or other places eventually accumulate in human food; contamination will occur by the pathways discussed above and presented in Figure 16.1. The well-known patterns of food chain transfer of POP were found in a study of DDT (including metabolism of DDT to DDE) in the ecosystem of Lake Kariba, Zimbabwe, reported in 1992. Some of the DDT applied at the local farms found its way to the lake and accumulated in freshwater fish of the area known as kapenta. This fish is a staple of the central African population. As a result, the presence of DDT and other toxic chemicals in fatty tissues, including mother's milk, was noted in the population of that area (Bro-Rasmussen, 1996).

Pesticides not only can enter the food supply by direct drift onto crops, but they can ultimately contaminate animal-derived foods because of their stability in the soil and waterways. Organochlorine pesticides occur primarily in milk and dairy products, eggs, meat and animal fats, and fish (Baht and Moy, 1997). The U.S. FDA has established "action levels" for poisonous or deleterious substances in human food, including pesticides based on unavoidability by

TABLE 16.7. U.S. FDA's Action Levels for Certain Pesticide Residues in Selected Foods[a]

Residue	Commodity	Action level (ppm)
Aldrin and dieldrin	Artichokes, figs, tomatoes	0.05
	Eggs	0.03
	Fish (edible portion)	0.3
	Milk (fat basis)	0.3
Chlordane	Animal fat, rendered	0.3
	Bananas, beans, carrots	0.1
	Fish (edible portion)	0.3
Chlordecone (Kepone)	Crabmeat (edible portion)	0.4
	Fish and shellfish (edible portion)	0.3
DDT, DDE, and TDE[b]	Artichokes, celery, lettuce, mushrooms	0.5
	Cereal grains[c]	0.5
	Eggs	0.5
	Fish (edible portion)	5.0
	Grapes	0.05
	Milk (fat basis)	1.25
Heptachlor and Heptachlor epoxide	Citrus fruits, fruiting vegetables	0.01
	Cereal grains	0.01
	Eggs	0.01
	Fish (edible portion)	0.3
	Milk (fat basis)	0.1
Lindane	Barley, corn, oats, rice, wheat, rye	0.1
	Corn (fresh), beans, citrus fruits	0.5
	Eggs	0.5
	Milk (fat basis)	0.3
Mirex	Fish (edible portion)	0.1

[a] From U.S. FDA (2000).

[b] DDT, 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane; DDE, 1,1-dichloro-2,2-bis(*p*-chlorophenyl)-ethylene; TDE, 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethane.

[c] Except buckwheat, fresh sweet corn, millet, popcorn, teosinte, and wild rice.

good manufacturing practice (GMP). An action level is an informed judgment about the level of an unavoidable food contaminant to which the consumer may be safely exposed. The action levels for some of the pesticides in selected foods are given in Table 16.7. FAO–WHO have established the Acceptable Daily Intake (ADI) for various pesticides that, over a lifetime, appears to be without appreciable risk on the basis of all the facts known at the time. For example, the ADI (μg/kg body weight/day) for selected pesticides is as follows: DDT, 20; lindane, 10; aldrin, 0.1; dieldrin, 0.1; and heptachlor, 0.5 (Leoni et al., 1995).

The U.S. FDA compiles data on incidence-level and commodity-pesticide combinations and carries out its market basket survey, the Total Diet Study (TDS). The FDA recently published its 1999 data in the thirteenth report of

this program. Since 1991, the U.S. Department of Agriculture (USDA) Agriculture Marketing Service (AMS) has carried out a residual testing program directed at raw agricultural products and various processed foods in the U.S. The regulatory monitoring of the FDA in 1999 found no pesticide residue in about 60% of the domestic samples and in 65% of imported samples. Only 0.8% of domestic samples and 3.1% of imported samples had residue levels that were violative. These findings demonstrate that pesticide residues are generally well below EPA tolerances (U.S. FDA, 1999). All the pesticides studied in 1999 in the TDS were below the regulatory safety standards. DDT was detected in 22% of the samples tested, 18% showed chlopyrifos-methyl, and 14–17% of the samples showed malathion endosulfan and dieldrin. The types of pesticide residues found and the frequency of occurrence in the TDS were generally consistent with those given in previous FDA reports for the TDS of 1994 and 1995. An adjunct survey of baby foods done from 1991 to 1999 also provided evidence of only small amounts of pesticide residues in those foods (U.S. FDA, 1999).

The GEMS/Food Contamination Assessment program, based on data mostly from developed countries, observed that the dietary exposure of adult populations to potentially toxic and prevalent chlorinated pesticides in food was generally well below the Acceptable Daily Intakes (ADIs). The limited data available from developing countries indicate a higher average exposure for adults but, with a few exceptions, still within the ADIs. However, based on the levels in breast milk, a significant portion of infants in both developed and developing countries are exposed to levels of organochlorine pesticides above the respective ADIs (Baht and Moy, 1997). The excessive exposure of infants and children to pesticides is a concern that was also recognized by a National Research Council report (NRC, 1993). The Food Quality Protection Act (FQPA) of 1996 in the U.S. is defined by its explicit protection of children and requires the U.S. EPA to make more realistic assessments of the risks posed by children's exposure to pesticides. The U.S. Congress, under the provision of FQPA, directed the EPA to use an additional 10-fold factor during decision-making processes to decide tolerance levels for pesticides to account for pre- and postnatal toxicity (Goldman and Konduru, 2000).

Contaminants from Natural Sources

Heavy metals Some of our most significant environmental contamination problems are the result of mining, irrigation, and energy extraction, which result in an accumulation of naturally occurring substances in harmful concentrations. In the U.S., 557,650 abandoned mines are estimated to be the cause of contamination of 728 square kilometers of lakes and reservoirs and 19,000 kilometers of streams and rivers. Because most ores are mixtures of minerals, potentially toxic elements other than sought-after metals (including arsenic, cadmium, and mercury) may also be present and be released into the environment. Hydraulic mining and amalgamation-associated extraction of metals from sulfide ores and in other mining processes add to environmental pollution by heavy metals, including mercury (Schmitt, 1998).

TABLE 16.8. Major Heavy Metal Contaminants of Natural Origin[a]

Heavy metal	Source (origin)	Food contaminated
Elemental mercury and salts	Geological	Fish
Arsenic—various chemical forms	Geological	Soft drinks, fish, health food supplements
Selenium	Seleniferous soils	Grains
Cadmium	Geological	Fishery products
Tin	Geological	Fish

[a]From Munro and Charbonneau (1981).

Plants grown in soil with high concentrations of heavy metals can accumulate heavy metals from the soil. Leafy vegetables (e.g., lettuce) that were grown in garden soils contaminated by old silver mine dumps in Aspen, Colorado were found to accumulate very high levels of the heavy metals (Doyle et al., 1993). Major heavy metal contaminants of foods are summarized in Table 16.8.

Arsenic and cadmium are concentrated in coal ash, from which they may be leached into surface waters and accumulated to toxic concentrations by aquatic organisms. Mercury, some selenium, and other elements are released into the atmosphere from stack emissions and may be transported long distances. Mercury tends to accumulate in birds, mammals, and fish, and in even in biota of remote lakes (e.g., in Maine). Mercury was formerly a pollutant associated with gold mining and point sources such as caustic soda plants and paper mills. Coal-fired electric generating plants are the greatest source of atmospheric mercury; other important sources include municipal and hospital waste incinerators (Schmitt, 1998).

Lead Lead is contributed to food not only because of its background occurrence in soil and water but also through environmental pollution and food-processing activities (Munro and Charbonneau, 1981). The combustion of leaded gasoline, which was introduced in 1923, remains the greatest source of lead in the global atmosphere (Schmitt, 1998). The lead in airborne particulate matter settles out on plants and in water. This surface contamination may lead to higher levels of lead in fresh vegetables and fruits; subsequently, the lead can be ingested (U.S. EPA, 1977). Environmental lead concentrations in the U.S. have generally declined over the last decade, ostensibly as a result of the removal of lead from gasoline and the control of emissions from mining and point sources (Schmitt, 1998).

Lead intoxication affects the nervous system, causing peripheral neuropathy in adults and encephalopathy in children. In fetuses, levels as low as 10 μg/dl in umbilical cord blood have been reported to adversely affect neurobehavioral development. Similarly, adverse effects on intelligence are seen in children postnatally exposed to lead. Some of the important pathological findings resulting

from lead toxicity include renal dysfunction, gout, hypertension, sterility, spontaneous abortion, neonatal mortality and morbidity, suppression of immune system, cardiotoxic effects, and fatigue. Lead acetate and lead chromate have been classified as being carcinogenic in animals. Several studies have shown increased cancer mortality among lead smelter and battery plant workers (U.S. FDA, 1993a).

Lead-containing pesticides may directly increase lead levels in fruits and vegetables and, where such use has been of sufficient duration, may also contribute lead indirectly through soil. Lead in drinking water may arise from lead plumbings. The levels of lead in commercially available fruits and vegetables tend to be low and of limited toxicological significance (Munro and Charbonneau, 1981). Lead does not appear to bioconcentrate significantly in fish but does bioconcentrate in some shellfish such as mussels. The lead level in shellfish ranges from 0.1 to 0.8 ppm. Leaching of lead from ceramic ware and crystal may also contribute to lead in the diet (U.S. FDA, 1993a). Leaded paints and colored news prints can be indirect sources of lead.

Data from the FDA's TDS suggest that average dietary intake of lead for the population is around 5–10 μg/person/day. The provisional tolerable total intake level (PTTIL) of FDA is 6 μg/day for children up to the age of 6 years, 15 μg/day for children 7 years and older, 25 μg/day for pregnant women, and 75 μg/day for adults. GEMS/Food data on dietary intake of lead by adults in different countries are provided in Table 16.9.

The average intake of lead by adults in some of the countries approached or exceeded the provisional tolerable weekly intake (PTWI) of 25 μg/kg body weight established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). The relative frequency with which the mean intake of lead approached or exceeded the PTWI was even greater in the case of infants and children in both industrialized and developing countries (Baht and Moy, 1997). The hazard identification points to the most significant effect from lead being reduced cognitive development and intellectual performance in children, whereas the concern for adults is increased blood pressure and cardiovascular diseases. The Codex Committee on Food Additives and Contaminants (CCFAC) has proposed to reduce the maximum levels (MLs) in some food groups important in children's diet (Codex Committee on Food Additives and Contaminants, 1998). The U.S. Federal initiative in 1997 required all federal agencies to ensure that their policies and rules address disproportionate environmental health and safety risks to infant and children (Goldman and Koduru, 2000).

Cadmium Mining operations, as mentioned above, can result in cadmium accumulation in foods. In a well-documented incident in Japan in 1974, cadmium compounds were transported by the Kakehashi River from mines upstream to rice fields in 23 villages where river water was used for irrigation. Levels of cadmium in rice in these villages ranged from 0.19 to 0.69 ppm, whereas the concentration in rice in nonpolluted areas was less than 0.2 ppm. It

TABLE 16.9. GEMS/Food Data on Dietary Intake of Lead by Adults[a,b]

Country/Areas	Year	μg/kg bw/wk[c] Mean
Belgium	1982	20.9
Canada	1981	5.7
China	1988	5.7
Cuba	1984	63.7
Denmark	1985	7.7
Finland	1984–1988	2.3
France	1983	19.8
Germany	1987	28.6
Guatemala	1988	32.3
Hungary	1984	14.0
India	1981	56.0
Italy	1982	39.1
Japan	1988	9.8
The Netherlands	1984–1988	5.5
New Zealand	1982	24.9
Poland	1987	11.5
Republic of Korea	1985	12.3[d]
Sweden	1984–1988	1.75
Switzerland	1984–1988	3.5
Turkey	1984–1988	6.4
U.K.	1988	1.8

[a] FAO/WHO provisional tolerable weekly intake (PTWI): 25 μg/kg body weight/week.

[b] From Baht and Moy, 1997.

[c] μg/kg body weight/week.

[d] Geometric mean (Seoul families).

has been shown that the increased use of sewage sludge containing elevated levels of cadmium may result in increased cadmium levels in vegetables. Corn grown in sludge-treated farms accumulated higher concentrations of toxic substances including cadmium, which accumulated in swine tissues when they consumed the corn (Munro and Charbonneau, 1981). Most foods are known to have low levels of cadmium, with the exception of shellfish, which have been shown to accumulate cadmium with the aid of a cadmium-binding protein. Significant accumulation of cadmium has been observed in American oysters at cadmium concentrations of 5 ppb in surrounding water. Long-term chronic exposure to cadmium may result in the accumulation of toxic levels of cadmium in kidney and may lead to kidney dysfunction. Cadmium taken up by the human body is eliminated slowly, with a biological half-life estimated to be 10–30 years (Munro and Charbonneau, 1981; U.S. FDA, 1993b).

Data from the FDA's TDS suggest that mean lifetime exposure from all food (no shellfish) is 10 μg/person/day. Cereals and their products, green leafy vegetables, potatoes, liver, and milk are the major source of cadmium in the

TABLE 16.10. Dietary Intake of Cadmium by Infants and Children[a,b]

Country/Areas	Year	Age (months)	μg/kg bw/wk[c] Mean
Australia	1987	9	3.0
Canada	1987	0–12	2.4
Cuba	1984–85	3–6	9.8
Finland	1980	36	3.9
Germany	1980	1	3.2
Poland	1985	12–36	7.5
Sweden	1983	3	0.1
U.K.	1985	24	2.9
U.S.	1986–88	6–11	2.3

[a]FAO/WHO provisional tolerable weekly intake: 7 μg/kg body weight/week.

[b]From Baht and Moy, 1997.

[c]μg/kg body weight/week.

diet. Shellfish (mollusks and crustaceans), although high in cadmium (0.1–2.0 ppm), constitute much less of an average diet and thus ordinarily are not a major cadmium contributor. WHO has determined a maximum tolerable weekly intake (PTWI) of 7 μg/kg body weight/week for cadmium. A maximum tolerable daily intake of 55 μg for an adult has been suggested by the FDA. Cadmium concentration in shellfish ranged from 0.1 to 2.0 ppm in the FDA's survey (U.S. FDA, 1993b). The average weekly dietary intake of cadmium in adults from the most countries in GEMS/Food data was found to be under the FAO/WHO PTWI level. However, the 90th percentile intake in some countries exceeded the PTWI level. Table 16.10 details the GEMS/Food average weekly intakes of cadmium by infants and children reported by various countries. The average intakes of cadmium in infants and children reported from Cuba and Poland exceeded the PTWI level and in many countries it approached to a considerable percentage of PTWI. Thus the exposure to dietary cadmium in some countries seems to be a public health concern (Baht and Moy, 1997)

Arsenic Traces of arsenic are found in most foods, with the highest concentrations found in seafood, particularly shellfish, at total arsenic levels up to 30 μg/g wet weight. Nearly all the arsenic present in seafood is organic, which is considered less toxic than inorganic arsenic. Dimethylated arsenic compounds are the most abundant forms found in the environment arise by microbial conversion of arsenic. All soluble arsenic compounds are considered to be poisonous to humans. Epidemiological studies have demonstrated a causal relationship between environmental exposure of humans to inorganic arsenic and cancer of the skin and lungs. Peripheral vascular disorders have been reported in children exposed to arsenic through drinking water (U.S. FDA, 1993c).

It is estimated that in the U.S. the mean total arsenic intake from all food (except shellfish) is approximately 30 μg/day. WHO/FAO's PTWI for inorganic arsenic is 15 μg/kg body weight/week (U.S. FDA, 1993c). Certain species of marine fish and shellfish are major sources of dietary arsenic because of its tendency to accumulate in bottom-feeding species such as gray sole and shrimp. Aquatic vegetation such as seaweed has been found to contain elevated arsenic levels. Certain geological formations contain arsenopyrite, which can contaminate waters from artesian wells and can result in chronic toxicity. This has been documented in Taiwan and Nova Scotia, Canada (Munro and Charbonneau, 1981).

Mercury Large quantities of mercury are released by natural degassing from the earth's crust, as well as from combustion of fossil fuels and the operation of smelters and incinerators. Mercury vapor is transported in the atmosphere and deposited in land and aquatic ecosystems. Trace amounts of mercury are soluble in water, where bacteria can cause chemical changes to methyl mercury, a more toxic form. Fish absorb methyl mercury as they feed on aquatic organisms. In general, the methyl mercury levels for most fish range from 0.01 to 0.5 ppm. However, the levels in large predator fish (such as shark and swordfish) may reach the FDA's limit of 1 ppm (action level) for human consumption. Certain species of large tuna, typically sold as fresh steaks or sushi, can have levels over 1 ppm. The average concentration of methyl mercury for commercially important species (mostly marine in origin) is less than 0.3 ppm. The 1-ppm limit the FDA had set for commercial fish is considerably lower than levels of methyl mercury in fish known to cause illness (U.S. FDA, 1994).

In areas in which there is industrial mercury pollution, the level of methyl mercury in fish can be quite elevated. In the famous outbreak of mercury intoxication in Japan in the 1960s, first at Minimata Bay and then in Nigata, many people died (mostly from nervous damage) or became sick from eating fish from waters that were severely polluted with mercury from local industrial discharge. The average mercury content of fish samples from both areas ranged from 9 to 24 ppm. In Iraq, 459 persons died in 1971–1972 of mercury poisoning by consuming wheat treated with alkyl mercury fungicide; 6500 were hospitalized with neurological symptoms. The type of neurological disorders following methyl mercury poisoning depends on the degree of exposure (U.S. FDA, 1994).

GEMS/Food data on average weekly mercury intake by adults in different countries are presented in Table 16.11. The highest average intakes, from Poland and Denmark, are about 60% of the FAO/WHO PTWI of 3.3 μg/kg body weight/week for methyl mercury, or about 40% of the PTWI for total mercury. In a study of breast milk in Sweden, mainly among fishermen's wives who consumed relatively large amounts of fish, intake levels for breast-feeding infants were about 50% of the PTWI (Baht and Moy, 1997).

TABLE 16.11. GEMS/Food Data on Dietary Intake of Mercury by Adults[a,b]

Country/Areas	Year	μg/kg bw/wk[c] Mean
Belgium	1982	1.6
Cuba	1983	1.6
Denmark	1985	1.9
Finland	1984–88	0.23
France	1980	1.2
Germany	1981	2.6
Guatemala	1988	1.5
Italy	1982	1.3
The Netherlands	1988	1.1
New Zealand	1982	0.6
Poland	1981–83	1.0
Sweden	1988	0.23
Thailand	1987	0.8
U.K.	1985	0.3
U.S.	1986–88	0.3

[a]FAO/WHO provisional tolerable weekly intake: total mercury 5 μg/kg body weight/week; methylmercury 3.3 μg/kg body weight/week.

[b]From Baht and Moy, 1997.

[c]μg/kg body weight/week.

Radionuclides Results of radioactivity measurements, made in 1990 on foods collected in regions of Russia, Byelorussia, and the Ukraine, areas heavily contaminated by the Chernobyl accident of April 1986, suggest that mushrooms and reindeer moss accumulated very high levels of radioactive cesium. ^{90}Sr levels were high in fresh products (Doyle et al., 1993). After the Chernobyl accident, radioactive cesium levels were monitored in brown trout in a Norwegian subalpine lake situated in an area of high fallout. Average total cesium levels in 1986 rose rapidly from 300 to 7000 Bq/kg by the end of August. Mean values fell to 4700 Bq/kg during the summer of 1987 and to 3000 Bq/kg in June 1989. Half-lives of ^{137}Cs and ^{134}Cs in trout were estimated to be 3.0 and 1.3 years, respectively. After the Chernobyl incident, the reindeer and pike in southernmost Sweden contained up to 80 times higher levels of radioactivity than normal. Samples of food imported into Iraq early in 1986, before the Chernobyl accident, did not contain detectable radioactive cesium; after the accident, all lamb meat, 81% of lentils, 44% of powdered milk and chickpeas, and 17% of roast beef samples tested were contaminated with ^{134}Cs and/or ^{137}Cs (Doyle et al., 1993).

A study of radioactivity in mutton, milk, fish, and seaweed and grass in the Western Isles of Scotland indicated that a nuclear reprocessing plant located in northern England was the probable source of the excess radioactivity found in

these foods (note that measurements were made before the Chernobyl accident). A study of hypertensive patients from the islands reported a median concentration of 2.54 Bq/kg body weight of ^{137}Cs, compared with concentrations of 0.42–0.47 Bq/kg body weight from similar patients on the Scottish mainland (Doyle et al., 1993).

All of these studies suggest that radionuclides from the environment do accumulate in the food supply and in the human body. Maximum dietary intake of uranium estimated in Switzerland (40 μg or 1 Bq/person/day) was calculated to result in a fatal cancer lifetime risk of about 10^{-4} (Doyle et al., 1993).

Veterinary Drug Residues

The range of veterinary medicines used in or on food animals is extremely large. Approximately 42% of all veterinary pharmaceuticals used worldwide are used as feed additives, 19% are used as anti-infectives (e.g., antibacterials, antifungals, and antivirals), 13% as parasiticides, 11% as biologicals, and 15% in other pharmaceutical capacities (Miller, 1993).

Antimicrobials represent the largest proportion of pharmaceutical sales (Miller, 1993). First used in veterinary medicine for the treatment of mastitis and other microbial infections in dairy cows, antimicrobials were soon discovered to enhance growth and feeding efficiency of food animals. This led to their widespread use as feed supplements (Mitchell et al., 1998).

The most commonly used antimicrobials in food animals can be grouped into five major classes. These include the beta-lactams (e.g., penicillins and cephalosporins), tetracyclines (e.g., oxytetracycline, tetracycline, and chlortetracycline), aminoglycosides (e.g., streptomycin, neomycin, and gentamicin), macrolides (e.g., erythromycin), and sulfonamides (e.g., sulfamethazine). A survey of veterinarians in the U.S. revealed that antibiotics were most often prescribed or used in the treatment of lactating dairy cows, mainly for mastitis therapy. Penicillin G was most frequently used, and, except for oxytetracycline, the five most prescribed drugs were all beta-lactams approved for use in lactating dairy cattle: penicillin G, ceftiofur sodium, cloxacillin, cephapirin, and ampicillin (Sundlofs et al., 1995).

Current data estimate that 1% of animal products in the U.S. and Europe contain antibiotic residues (at very low levels). A survey of all violative carcasses in the U.S. in 1993 revealed that the drugs most frequently causing residues were penicillin (20%), streptomycin (10%), oxytetracycline (10%), sulfamethazine (9%), tetracycline (4%), gentamicin (4%), and neomycin (3%). The slaughter classes most often associated with residues were culled dairy cows, veal calves, and market hogs. Injectable drugs were responsible for 46% of the violative residues in meat, followed by oral administration at 20% (feed, water, and bolus), and intramuscular infusion at 7%. One study, based on farmer opinion, reported that 92% of antibiotic contamination of milk was likely due to the use of intramammary infusions for the treatment of mastitis. Injectible

delivery accounted for 6% of the incidences. β-lactam antibiotics are the most commonly detected residues in milk in most countries. Sulfa drugs are occasionally detected, whereas tetracyclines, aminoglycosides, macrolides, and other classes of antibiotics are rarely detected in milk. (Mitchell et al., 1998).

Although several factors—such as poorly kept treatment records or failure to identify treated animals—have contributed to the residue problem, most violations result from the use of a drug in a manner that is inconsistent with the labeling. This occurs primarily by not observing label withdrawal times, as well as "extralabel" use of the drug (e.g., different species, increased dosage, different route of administration, different frequency of treatment; Mitchell et al., 1998).

The human concerns toward residues in milk and meat, including the potential for allergic reactions in sensitized individuals (e.g., to penicillins), the emergence of resistant bacteria within animals, and the transfer of antibiotic-resistance genes to human pathogens, have strong support in the literature. Other public concerns are toxicity such as aplasia of the bone marrow (from chloramphenicol) and effects on human gut microbial populations. In addition, some compounds, such as nitrofurans, have been found to be animal carcinogens and mutagens in genotoxic tests. The validity of any public health threats posed by these concerns has been debated in the scientific community for over 40 years (Mitchell et al., 1998). Limits have been established for drug residues in foods in the form of tolerances (U.S.) or maximum residue limits (MRLs; used in Canada and the European Union), and some of those are presented in Table 16.12.

TABLE 16.12. Maximum Residue Limits (MRLs) or Tolerances of Selected Approved Veterinary Drugs for Milk[a]

	MRL or tolerance (ppb)		
Drug	Canada	European Union	U.S.
Ampicillin	10	4	10
Ceftiofur	1000* (A)	100	50** (S)
Cephapirin	20	—	20
Cloxacillin	30 (A)	30	10
Erythromycin	50	40	50 (S)
Neomycin	250 (A)	500	150
Oxytetracycline	150 (A)	100	30 (S)
Pencillin G	6	4	5 (S)
Sulfamethazine	10 (A)	100	10 (S)

[a] From Mitchell et al., (1998). A, administrative MRL (not published in Canada's Food and Drug Act but may be used for legislative enforcement); S, Safe Level (not published in U.S. Foods, Drugs and Cosmetics Act but may be used for legislative enforcement). *parent drug and metabolite; **parent drug.

REGULATORY, INDUSTRIAL, AND INTERNATIONAL IMPLICATIONS

Regulation of Chemical Contaminants in Food

Regulatory choices for dealing with food contaminants are limited. Banning of contaminated foodstuffs is usually not an acceptable alternative, because this will restrict availability of otherwise nutritious food. Completely removing the offending substance from commerce is difficult to achieve because of the persistence of chemicals in the environment. Furthermore, chemicals may not pose a significant threat if used properly. Thus the regulatory option selected in most cases has been to establish some sort of limit for acceptable levels of contaminants in food commodities and to restrict their use in commerce.

The U.S. has various laws that prevent unsafe food from reaching consumers. Most important in terms of this assessment is the FDCA. Under FDCA Section 402(a), a food is considered to be adulterated if (1) it bears or contains any poisonous or deleterious substance which may render it injurious to health, or (2) if it bears or contains any added poisonous or deleterious substance in the quantity which may ordinarily render it injurious to health. Section 406 empowers FDA to establish tolerances for "added" poisonous substances whose occurrence in food cannot be avoided or whose use is "necessary" to produce the food. Since the early 1970s, the FDA has classified environmental contaminants as "added poisonous or deleterious substances" whose occurrence cannot entirely be avoided by GMP. Tolerances for regulated food additives are set under Section 409, whereas Section 408 provides for "tolerances for pesticide chemicals in or on raw agriculture" commodities. The EPA establishes tolerance levels for pesticides in raw agricultural products (OTA, 1979b; Munro and Charbonneau, 1981; U.S. FDA, 1997).

Action levels and tolerances Relying on Section 406, the FDA prescribes the level of unavoidable contaminants that, under Section 402(a)(2)(A), will render a food adulterated. FDA relies on scientific information about acute and chronic toxicological data and other information pertaining to the contaminant to decide this level. A formal tolerance is a regulation having the force of law. An action level is an informed judgment about the level of a food contaminant to which the consumer may be safely exposed. An action level is an administrative guideline and the functional, although not legal, equivalent of a Section 406 tolerance. It is established when technological or other changes might affect the appropriateness of the tolerance in the foreseeable near future (OTA, 1979b). Action levels for unavoidable food contaminants are tabulated in the FDA publication, "Action Levels for Poisonous and Deleterious Substances in Human Food and Animal Feed" (U.S. FDA, 2000).

Monitoring the national food supply for chemical contaminants The FDA monitors the national food supply for chemical contamination. It acquires incidence/level data on particular commodity/chemical residues, includ-

ing pesticide combinations. Different chemical contaminants are targeted in different commodities. For example, agricultural products may be monitored for heavy metals and synthetic or organic chemicals in addition to pesticides. Fish samples are often analyzed for PCBs and methyl mercury in addition to pesticides. FDA also determines the total dietary intakes of some known suspected chemical contaminants in a diet, including environmental contaminants, and for that purpose carries out its market basket survey, the TDS (OTA, 1979b; U.S. FDA, 1999).

The USDA Food Safety and Inspection Service (FSIS) is responsible for regulating meats, poultry, and egg products under criteria of the Federal Meat Inspection Act (FMIA), the Poultry Products Inspection Act (PPIA), and the Egg Product Inspection Act (EPIA), respectively. These criteria include monitoring for environmental and agricultural contaminants in these products. The majority of compounds evaluated are those that are approved for use in agriculture, either administered directly to food animals or applied to agricultural crops to which food animals may eventually be exposed. Testing of meat and poultry products falls into broad monitoring and surveillance categories. The National Monitoring Program is designed to determine the frequency at which tolerance-exceeding amounts of monitored compounds are occurring in the national meat supply (OTA, 1979; Ingham and Thies, 1997).

Some of the programs of the EPA that are designed to determine the ecological impact of pollutants may include certain types of foods for analysis. This is particularly true in the case of seafood. The EPA establishes safe tolerances for pesticides residues in food ([Section 346(a)]; OTA, 1979; U.S. FDA, 1997).

In most states, the authority for regulating environmental contaminants in food rests with two or more state regulatory agencies. However, the jurisdiction and regulatory activity vary among states. Many environmental contamination incidents are initially state problems and become federal issues if they are determined to have interstate involvement (OTA, 1979).

Impact of the Food Quality Protection Act of 1996

The Food Quality Protection Act (FQPA) of 1996 requires the U.S. EPA to make more realistic assessments of the risks posed by exposures to pesticides by assessing aggregate and cumulative risks. The FQPA is defined by its explicit protection of children. The concepts for children's health components of the law came from a National Research Council report (NRC, 1993) that concluded that the toxicity of, and exposures to, pesticides are frequently different for children and adults. The committee advised the EPA to incorporate information about dietary exposures of children in risk assessments and to augment pesticide testing with new improved guidelines for neurotoxicity, developmental toxicity, endocrine effects, immunotoxicity, and developmental neurotoxicity. It recommended that the EPA include cumulative risks from pesticides that act via a common mechanism of action and aggregate risks from nonfood

exposures when developing tolerance for a pesticide. The 1996 law gives the EPA one uniform standard to use in registering all pesticides and setting tolerances. In addition to these new considerations, Congress directed the EPA to use an additional 10-fold factor during the decision-making process of tolerance level determination for pesticides to account for pre- and postnatal toxicity of these chemicals (Goldman and Koduru, 2000).

INTERNATIONAL IMPLICATIONS

Contamination of food by environmental chemicals (in particular, POPs) has received tremendous international attention. Recent efforts by the United Nations' Environmental Program to minimize emission and releases of POPs is a good example. Various international agencies are very active in the assessment and control of environmental, industrial, and agricultural contaminants in the food supply. WHO and FAO have conducted various assessments of the contamination of the food supply with pollutants in various countries. FAO-WHO have established provisional tolerable weekly intakes (PTWIs) for various chemical contaminants in food, including POPs arising from industrial, environmental, and agricultural sources.

The Global Environment Monitoring System's Food Contamination and Monitoring Assessment Program, commonly known as GEMS/Food, began as a project in cooperation with the UNEP and the FAO. The program is now implemented solely by WHO, with participating institutions located in nearly 70 countries. GEM/Food monitors 18 priority contaminants in food, and these include chemicals and metals commonly emitted during industrial processes, residues from agricultural practices, and chemical contaminants, which may arise from natural sources such as fungal contamination. Contaminants include lead, cadmium, mercury, polychlorinated biphenyls (PCBs), aflatoxins, selected pesticides such as aldrin/dieldrin, DDT, heptachlor and its epoxide, hexachlorobenzene (HCB), hexachlorocyclohexane (HCH) isomers, gamma-HCH (lindane), endosulfan, endrin, diazinon, fenitrothion, malathion, parathion, and parathion-methyl. Concentrations of these chemicals are reported in a variety of foods and total diets of adults as well as infants and children. GEM/Food maintains a database on Theoretical Maximum Daily Intakes of about 200 pesticides. Since 1976, GEMS/Food has informed governments, the Codex Alimentarius Commission and other relevant institutions, as well as the general public on levels and trends of contamination in food, their contribution to total human exposure, and significance with regard to public health and trade (GEMS/Food and WHO, 1997).

The Codex Alimentarius Commission (CAC) is a longstanding international food standards organization whose aim is to develop consensus standards to protect consumer health and ensure fair trade practices. The World Trade Organization specifically recognized the CAC as the body responsible for developing international food safety standards. The main purpose of the Codex Committee on Food Additives and Contaminants (CCFAC) is to establish

standards, maximum levels (MLs) allowed for contaminants and food additive levels, as well as other standards and codes of practice. The group sets priorities for evaluation by the Joint Expert Committee on Food Additives (JEFCA), the scientific advisory committee to CCFAC, for toxicological evaluation. The JEFCA prepares contaminant and toxicological monographs and conducts risk assessments (Troxell, 2000). A position paper on dioxins and dioxin-like PCBs is one example of the JEFCA's scientific assessment of the current situation of selected food contaminants in different countries (Codex Alimentarius Commission, 2001). Additionally, various governments have conducted detailed studies on contamination of national food supplies with pollutants, including the U.S., the U.K., Australia, New Zealand, and Japan.

CURRENT AND FUTURE IMPLICATIONS

Food safety is a priority in the U.S., with government regulations designed to maintain public confidence in the food supply. Much regulatory reform has taken place in recent years and is continuing in response to new science-based information and pressures from consumers and food-related industries. An example of this is the Food Quality Protection Act of 1996, developed in response to public and industry concern over food safety. There are specific laws to deal with food additives and pesticides that have governed the contamination aspects of food safety quite successfully.

The FDA conducts what is referred as the Total Diet Study (TDS) and monitors pesticide residues and other harmful contaminants in U.S. foods. One component of these studies involves determination of dietary intakes of pesticides. Historically, the results of these studies are consistent in that average daily intakes of pesticides and other chemicals in U.S. adults are well below acceptable tolerance levels set by the EPA (Ingham and Thies, 1997). The FDA recently published its thirteenth annual report, summarizing the results of its residue monitoring program of 1999. Results in this and earlier reports continue to demonstrate that levels of pesticide residues in the U.S. food supply are well below established safety standards. The pesticide residues in baby foods surveyed from 1991 to 1999 provided evidence of only small amounts of pesticides residue in those foods (U.S. FDA, 1999).

There are concerns about segments of populations, such as children, because they eat larger quantities of some foods relative to their body size. The FQPA mandates the collection of adequate data on food consumption patterns of infants and children to evaluate their pesticide residue intake more accurately (Ingham and Thies, 1997). A U.S. federal initiative from 1997 requires all federal agencies to ensure that their policies and rules address disproportionate environmental health and safety risks to infants and children. At the EPA, the Office of Children's Health Protection is working in a number of areas to strengthen the agency's approach to protecting children. The EPA recently moved to establish the first federal research centers dedicated solely to studying children's environmental health hazards. Grants of between $1.2 and $1.6 mil-

lion were awarded to establish eight federal research centers of this type (Goldman and Koduru, 2000).

Many of the procedures used for identifying carcinogens were developed in the 1960s and 1970s and rely on animal bioassays as well as assays that use bacterial cells or cultured mammalian cells. Questions about the applicability of the results of these assays to human beings have been asked, in particular, concerning the results of chronic toxicity tests where proportionately large doses have been used (Ingham and Thies, 1997). It is difficult to assess which of the effects observed in the initial studies play a significant role in human mutation and cancer. A combination of testing approaches, together with the biomonitoring methods, might be expected to provide an understanding of relative risk in human carcinogenesis (Ferguson, 1999).

The FQPA also requires the EPA to make more realistic assessments of the risks posed by exposures to pesticides by assessing aggregate and cumulative risks. The agency is considering making changes to decrease its reliance on animal testing when it assesses the safety of agriculture chemicals. The EPA has also proposed that developmental toxicity be assessed for all pesticides that are neurotoxic (Goldman and Konduru, 2000). The goal of these changes will be to increase confidence in testing so that substances that are most likely to endanger public health are controlled. Furthermore, decisions intended to protect people from chemicals that pose very low risks will only be made on the basis of appropriate scientific technique (Ingham and Thies, 1997).

Genetically modified foods are becoming increasingly prevalent in our modern food supply (see Chapter 36). There is considerable public concern and debate about genetic engineering of crops as a potential source of genetic hazards in the human diet. Some of the mechanisms by which new hazards could potentially appear in foods as a direct result of genetic engineering are the following. These could arise from novel expression products of inserted genes, the secondary effects of transgene expression, or random mutagenic effects occurring as a result of transgene insertion into plant genomes. It has been stressed that these risks, although real, are no greater than those occurring through traditional plant breeding. Although the possibilities of unexpected events through these controlled genetic insertions may be low, it is nevertheless recognized that there is a possibility of producing potentially hazardous new toxins or increasing the production of mutagenic compounds not previously tested through genetic engineering or traditional plant breeding. There would seem to be a strong argument for more extensive mutagenicity and/or carcinogenicity testing on genetically new products than currently required in the regulations of most countries (Ferguson, 1999).

Integrated pest management programs, development of environmentally friendly agricultural chemicals and livestock drugs, and continued vigilance on the part of regulatory agencies are needed in the decade ahead to keep our food supply safe. Research using various testing approaches combined with biomonitoring methods may provide an understanding of relative risk in human toxicity and carcinogenesis of various hazardous substances in our food. Like-

wise, new initiatives in the risk assessment of exposure of children and infants to harmful contaminants in food are urgently needed to protect them from disproportionately greater risk of these health hazards.

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PART IV

SYSTEMS FOR FOOD SAFETY SURVEILLANCE AND RISK PREVENTION

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CHAPTER 17

IMPLEMENTATION OF FSIS REGULATORY PROGRAMS FOR PATHOGEN REDUCTION

INTRODUCTION AND DEFINITION OF ISSUES

The Food Safety and Inspection Service (FSIS) of the United States Department of Agriculture (USDA) published a final rule on Pathogen Reduction and Hazard Analysis Critical Control Points (HACCP) Systems on July 25, 1996. The rule had four major components, which the Agency described:

- HACCP—Every plant must design and implement its own HACCP plan that systematically addresses the food safety hazards reasonably likely to occur in its products.
- Mandatory *E. coli* testing in slaughter plants—Every slaughter plant must regularly test carcasses for generic *E. coli* to verify the effectiveness of the plant's procedures for preventing and reducing fecal contamination, the major source of contamination with harmful bacteria like *E. coli* O157:H7 and *Salmonella*.
- Pathogen reduction performance standards for *Salmonella*—All slaughter plants and plants producing raw ground products must ensure that their *Salmonella* contamination rate is below the current national baseline prevalance.
- Sanitation standard operating procedures—As the foundation for HACCP, every plant must adopt and carry out a written plan for meeting its sanitation responsibilities.

(USDA/FSIS, Improving the Safety of Meat and Poultry, Background on a Science-based Strategy for Protecting Public Health, July 25, 1996).

These requirements of the final rule were designed to meet three objectives: (1) reduce the occurrence and numbers of pathogenic microorganisms on meat

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and poultry products; (2) reduce the incidence of foodborne illness associated with these products; and (3) provide a new framework for the modernization of the meat and poultry inspection system (July 25, 1996, 61 FR 38806).

Implementation of the new regulatory requirements meant fundamental change—on the part of the regulated industry, within the agency and its inspection force, and in the relationship between them. Thus, when the final rule was published, the agency announced a series of events designed to facilitate that change process.

As part of its plans for a continuing dialogue, the Agency committed to National and Regional HACCP Implementation Conferences, a Joint FSIS/FDA Conference on the Establishment of Food Safety Performance Standards for Temperature Controls Outside Processing Establishments, a Generic *E. coli* Testing Conference, a *Salmonella* Performance Standards Conference, a meeting with state officials, a meeting with foreign governments, a meeting on the HACCP-based Inspection Models Project, and HACCP Demonstration Projects for Small Plants (Background, July 25, 1996). In addition, the Agency had completed a top-to-bottom review, which was leading to a significant reorganization, and it had published in the Federal Register on December 29, 1995 an Advance Notice of Proposed Rulemaking outlining its intention to reform all of its regulations "... to prepare for implementation of the Agency's ... HACCP regulations and a new food safety strategy that will reduce reliance on command-and-control regulations and increase reliance on science-based preventive measures and performance standards to improve food safety" (60 FR 67469).

Whether the implementation of the pathogen reduction and HACCP requirements mandated by FSIS is judged successful depends on a wide variety of factors and cannot be fully assessed at this time. However, the experience to date can be reviewed and analyzed.

BACKGROUND AND HISTORICAL SIGNIFICANCE

The Preamble to the proposed regulations of February 3, 1995 included a multifaceted analysis to establish the need for the regulation. The first segment of the analysis addressed the origins and history of the FSIS program, providing an historical account of the purposes and operation of the inspection program from its late nineteenth-century inception through contemporary efforts at improvement. Several themes emerged. One theme is that the major public health concerns with respect to consumption of meat and poultry products have changed over time from concerns about transmission of diseases from animals to humans and the lack of sanitary conditions in slaughter and processing facilities to concerns about the invisible hazards presented by chemical residues and by pathogenic microorganisms in popular meat and poultry products. Another theme was that of an increasing demand for inspection

caused industry expansion, both in terms of the numbers of inspectors available during periods of federal budgetary constraints and of a wider variety of inspection techniques like laboratory analyses to address the invisible hazards against which consumers were not able to protect themselves. The final theme of this analytic segment was the agency's inability to realized much of the change it could plan because of concerns on the part of some consumers and some of the inspection workforce that any change would result in an inferior level of protection (60 FR 6775–6780).

The second segment of the analysis addressed the problem of foodborne illness in the United States. The discussion acknowledged the limitations of available data and presented a wide range of estimates of illnesses and deaths associated with consumption of meat and poultry products. The discussion also considered available information about the frequency with which pathogenic organisms occurred in raw, ready-to-cook meat and poultry products. It reviewed significant facts surrounding the large outbreak of foodborne illness and deaths associated with the consumption of hamburger during the winter of 1992–93 and reiterated FSIS' conclusion that no inspection failure was associated with it. Rather, the outbreak stemmed in part from an inspection system that did not require the reduction or elimination of pathogenic organisms on raw meat and poultry products (60 FR 6783).

Another segment of the preamble catalogued external studies and recommendations for change in the inspection program. External expertise embodied in the National Academy of Sciences (NAS) had urged the agency to focus on pathogenic organisms and to require that establishments adopt HACCP to control pathogens and other food safety hazards. Through multiple reports commissioned by the agency, beginning in 1985, NAS identified shortcomings of the existing system and provided a road map for making necessary improvements. Another scientific body, the National Advisory Committee on Microbiological Criteria for Foods (NACMCF), prepared a series of reports reflecting the development and implementation of HACCP principles. This work became an international standard and provided the conceptual basis from which HACCP regulatory requirements could be developed. Finally, the General Accounting Office (GAO), which is concerned with the efficiency of government programs, advocated improvements in the inspection program and endorsed HACCP as a scientific, risk-based system to better protect the public from foodborne illness (60 FR 6783–6784).

The 1993 report of the Vice-President's National Performance Review, "Creating a Government That Works Better and Costs Less," included a recommendation supporting a scientific, preventive approach to food safety (60 FR 6806).

Thus, by the mid-1990s, FSIS had a history of attempts to modernize its meat and poultry inspection program, a problem of foodborne illness associated with the consumption of meat and poultry products as reflected in the large outbreak of *E. coli* O157:H7 in the winter of 1992–93, and consider-

able external support for an approach that targeted pathogenic microorganisms that caused foodborne illness and incorporated HACCP as a scientific, preventive system of process control. Nevertheless, there remained uncertainty about whether the requirements of the July 25, 1996 final rule could be implemented and their objectives accomplished.

SCIENTIFIC AND LEGAL BASIS AND IMPLICATIONS

To be successfully implemented, regulatory requirements need a foundation that convinces constituents of the need for the requirements and of their efficacy in addressing the problem. The requirements of the PR/HACCP final rule needed both scientific and legal substance on which to base their implementation.

Support for HACCP

The centerpiece of the PR/HACCP regulation, the requirement that establishments implement HACCP systems of process control to achieve food safety objectives, had a broad basis of support. In addition to the external support mentioned above, the regulated industry had a record of supporting HACCP. The American Meat Institute (AMI) had petitioned the agency to initiate rulemaking to mandate HACCP. The International HACCP Alliance, representing significant numbers of industry associations, professional associations, universities, service groups, and foreign governments, strongly supported implementation of a mandatory HACCP program (60 FR 6806).

In addition to endorsement and support from a variety of constituents, a HACCP requirement was supportable because of the advanced state of development of this conceptual approach. The agency believed that many meat and poultry processing establishments, especially the larger ones, had already implemented HACCP systems, so that practical experience with HACCP already existed.

It also appeared to the agency that future access to international markets would increasingly depend on HACCP requirements for the regulated industry. The largest U.S. trading partner, Canada had already announced its intention to implement HACCP for meat and poultry processes. Australia and New Zealand were also implementing HACCP-based programs (60 FR 6806).

In finalizing its PR/HACCP regulation, FSIS noted that some commenters had reservations about the mandatory HACCP requirements. Small business owners affected by the rule were concerned that their ability to compete in the marketplace might be negatively impacted because larger companies were better able to bear the costs of meeting the HACCP requirements (61 FR 38809). However, representatives of small businesses did not seek an exemption from the HACCP requirements.

Support for Sanitation Standard Operating Procedures (SSOPs)

The regulatory requirement that establishments develop and implement standard operating procedures for sanitation (SSOPs) was part of both the proposed and final regulations in substantially similar form. Support for SSOPs was expressed by a wide range of commenters, largely because good sanitation in the processing facility was understood to be a necessary condition for the production of safe meat and poultry products. HACCP experts also frequently regard sanitation as a prerequisite program for HACCP (61 FR 38831, July 25, 1996).

Some commenters opposed mandatory SSOPs because they represented additional paperwork requirements, they were regarded as an additional layer of regulation, and, finally, existing regulations were considered sufficient if properly and uniformly enforced. It was certainly true that the new SSOP regulatory requirements increased the paperwork burden for inspected meat and poultry establishments: OMB approved 1,231,986 new paperwork burden hours imposed on the regulated industry because of the SSOP requirements (61 FR 38863). However, it seems unlikely that this approval would have been granted had there not been significant benefits: greater and more appropriate establishment responsibility for frontline primary sanitation controls; more flexibility for inspected establishments in determining how they would meet their basic responsibilities; and more appropriate use of federal inspection resources to verify that establishments were meeting regulatory requirements.

Support for Pathogen Reduction

As articulated in the Preambles to both its proposed and final regulations, FSIS believed that its goals of reducing foodborne illness would not be accomplished unless it combined the procedures of SSOPs and HACCP with substantive requirements for the microbial profiles of raw carcasses of livestock and birds (61 FR 38808).

The pathogen reduction features of the proposed rule received the most disparate treatment from commenters and, as a result, were the most significantly changed in the final regulation. The proposed requirements for at least one antimicrobial intervention during slaughter and strict time-temperature cooling requirements in the establishment and during transportation and distribution were not maintained in the final regulation. The proposed requirement that establishments perform testing for *Salmonella* to demonstrate compliance with a performance standard was replaced by agency testing for *Salmonella* and establishment testing for generic *E. coli* to verify process control for preventing fecal contamination of carcasses during slaughter and sanitary dressing.

The effort to accomplish pathogen reduction in raw meat and poultry products was supported by public health officials and other scientists, and lauded by consumer advocates, but generally opposed by processors of these products.

Industry viewpoints reflected key ideas of the 1974 decision by the United States Court of Appeals, District of Columbia Circuit, in denying the suit of the American Public Health Association (APHA) against the Secretary of Agriculture (*APHA v. Butz*, 511 F. 2d 331, 1974). The court held that:

> "Official inspection labels, which are placed on raw meat and poultry products by the department of Agriculture, and which contain the legend 'US Passed and Inspected' or 'US Inspected for Wholesomeness' are not false and misleading so as to constitute misbranding, notwithstanding failure to warn against food poisoning caused by *Salmonella* and other bacteria; and the Secretary does not abuse his authority by refusing to supplement inspection labels with a warning and instructions for storage and preparation of meat and poultry."

APHA had presented their request in a series of meetings and letters in 1971. In responding to these requests, the department, in a letter of July 21, 1971, acknowledged that there was a *Salmonella* problem and quoted from a report of the National Research Council:

> "... The problem of controlling salmonellosis in man is greatly complicated because of the widespread distribution of the organisms in the environment and the many ways by which they can reach the host."

The department concluded that because "there are numerous sources of contamination which might contribute to the overall problem," it would "be unjustified to single out the meat industry and require it to identify its raw products as being hazardous to health."

APHA was not satisfied with this response and reiterated its request to the Secretary "in the interest of consumers health and safety." The Department responded:

> "... you appear to disregard the fact that the American consumer knows that raw meat and poultry are not sterile and, if handled improperly, perhaps could cause illness. The Department's philosophy in this matter is that the *Salmonella* problem can be handled most effectively at the consumer level where all contributing factors converge—where the final preparation of food takes place."

In denying the APHA request the Court noted that:

> "The Wholesome Meat Act, 21 USC 604, requires that meat found to be not adulterated shall be marked 'Inspected and Passed.' Unless the presence of *Salmonella* makes meat adulterated the legend is not false or misleading and we think that the presence of *Salmonella* in meat does not constitute adulteration, within this definition. The definition is directed at poisonous or deleterious substances but not at substances such as *Salmonella* which may be inherent in the meat."

The attitude toward microbial contamination in raw meat and poultry was significantly different from that prevailing toward the other invisible hazard

with which the agency and the regulated industry had the most experience—chemical residues. With respect to these hazards, it was widely accepted that there were definite limits, sometimes expressed as tolerances established by either the Food and Drug Administration (FDA) or the Environmental Protection Agency (EPA). Of course, there were important differences in both the hazards themselves and the exposure they represented for packers: Chemical residues could sometimes be depleted by delaying the slaughter of animals, and chemical residues were usually an economic burden to the producer rather than the packing establishment. Microbial pathogens, on the other hand, grew, and their presence on carcasses appeared to be attributable primarily to the slaughter process itself.

Although there had been considerable industry-supported research on effective antimicrobial interventions, there did not seem to be a wide variety of highly effective and economically viable options among which packing plants could choose. FSIS itself maintained procedures that were not necessarily supportive of innovation in this regard. Thus it was not surprising that when, in 1994, FSIS determined that raw ground beef found to contain *Escherichia coli* O157:H7 was adulterated, the response from the regulated industry included a legal challenge to an FSIS sampling and testing program for this pathogen in raw ground beef. This unsuccessful challenge could be viewed as part of a reaction to a true paradigm shift on the part of the agency in its expectations of the slaughter industry, a shift that began, ironically, with a regulatory requirement for the same safe handling labels (59 FR 14528, March 28, 1994) that the department and the court had denied the APHA 25 years earlier.

In response to the pathogen reduction features of the February 3, 1995 proposed rule, commenters focused on three issues:

1) The proposed selection of *Salmonella* as the indicator organism;
2) The frequency of the proposed testing; and
3) The disproportionate costs to small establishments (July 25, 1996, 61 FR 38849).

Of these three, the selection of *Salmonella* as the indicator organism elicited the widest range of comments, many of the commenters opposing this choice. Some commenters opposed it because of its low incidence in beef; some considered it a poor choice because the use of a positive/negative test would not be a sensitive indicator of process control; some considered the analytic method to be difficult, time-consuming, and costly; and others opposed the choice because there was no correlation between its occurrence and that of other pathogens such as *E. coli* O157:H7, *Listeria*, or *Campylobacter*.

Commenters opposing the pathogen reduction features of the proposal because of the frequency and cost of testing tended to be concerned about the position of small establishments. Such establishments often produce multiple products, several of which could be the subject of *Salmonella* testing to determine compliance with a performance standard. The requirement for daily test-

ing without regard to volume of production also appeared to many commenters to be a disadvantage for smaller establishments (61 FR 38850 July 25, 1966). A small group of commenters supported the choice of *Salmonella* for performance standard testing because of its significance as a source of foodborne illness. Some commenters who recommended retaining *Salmonella* as the indicator organism for pathogen reduction also recommended adding a requirement for testing for generic *E. coli* because it is the best indicator of the success of process control in preventing fecal contamination of carcasses.

In its final rule, FSIS chose to follow the advice of these commenters. Thus the final regulation required that establishments producing carcasses or raw ground products meet a performance standard that would be measured by testing for *Salmonella*. The testing would be conducted by the agency; the performance standard would be based on the prevalence rate from each of the agency's baseline data collection efforts, whether focused on carcasses or ground products.

A complementary requirement was that establishments that slaughter livestock or birds would review and assess their slaughter controls to prevent fecal contamination by testing for generic *E. coli*, at rates that were proportionate to their slaughter volume. The agency convened a Scientific and Technical Conference on The Role of Microbiological Testing in Verifying Food Safety, May 1–2, 1995. The scientists concluded that "A variety of indicators exits ... but quantitative measurement of *Escherchia coli* would be more effective than qualitative *Salmonella* testing." The choice of generic *E. coli* meant that the cost and difficulty of the analysis would decline; the decision to make sampling and analysis proportionate to slaughter volume provided relief for smaller slaughterers but retained the agency objective of making microbial testing routine in inspected establishments that slaughter livestock or birds.

INDUSTRIAL AND INTERNATIONAL IMPLICATIONS

FSIS published its Final Regulatory Impact Analysis (FRIA) at the same time as it published its final rule. The FRIA discussed the costs and benefits of the final rule and attributed costs to each major component of the rule. In the FRIA, FSIS estimated that establishment compliance with the *Salmonella* performance standards will cost between $55.5 and $243.5 million over a 20-year period. The agency did not separately estimate the costs of meeting the generic *E. coli* performance criteria but rather explained that if establishments spent near the higher end of the range to ensure compliance with the *Salmonella* performance standard, spending would ensure compliance with the generic *E. coli* performance criteria; conversely, if they spent nearer the lower end of the range, they might need to incur additional expenditures to meet the generic *E. coli* performance criteria.

In the FRIA, the agency defined the public health benefits of the rule as the reduction in the cost of foodborne illness attributable to pathogens that

contaminate meat and poultry products as the manufacturing stage. Using this definition, the FRIA identified a maximum potential 20-year public health benefit of $7.13 billion to $26.59 billion that is tied to elimination of establishment-related contamination of meat and poultry by four pathogens. These estimated 20-year benefits clearly outweigh the 20-year estimated cost referenced above.

FSIS estimated benefits conservatively by assuming that they would not accrue until the fifth year after publication of the final rule, when all establishments had implemented HACCP and been subjected to the *Salmonella* compliance verification testing. Recently, the agency reported the following:

> "The results of three years of testing show that the majority of completed initial sample sets meets the *Salmonella* performance standard. *Salmonella* compliance for all sizes of establishments in all years combined is 90.7% for broilers, 80.8% for market hogs, 82.7% for cows/bulls, 94.4% for steers/heifers, 89.6% for ground beef, 100.0% for ground chicken, and 89.4% for ground turkey."

As articulated in the preamble to the final PR/HACCP rule, foreign inspection systems with establishments exporting to the United States must establish systems that are equivalent to that of the United States. As regulatory provisions of the PR/HACCP final rule were implemented in the U.S., foreign countries were evaluated to determine whether their inspection systems provide equivalent regulatory provisions with adequate levels of enforcement (61 FR 38813).

As of late August 2001, four foreign inspection systems have lost eligibility to export to the U.S. because of a failure to implement equivalent pathogen reduction regulatory requirements (Dominican Republic, Guatemala, Slovenia, and Paraguay).

CURRENT AND FUTURE IMPLICATIONS

Although it is too early to evaluate the full impact of the PR/HACCP final regulation or any of its four major features, the experience of managing the implementation of such a significant regulatory change has produced other model approaches that may be as important as the regulatory requirements themselves, especially for FSIS.

One model approach that has been used by the agency with this regulation is to hold a large number of public meetings through which agency policies have been further explained and views of the interested public have been secured. Historically, this has not been the typical approach used by FSIS, particularly in situations in which there may have been substantial disagreement about its intended course of action. However, it has proved to be a useful approach through which major differences have been reduced to manageable issues. Another model approach has been the staggered implementation schedule and

the agency's recognition that each of the groups of different-sized establishments would likely present different challenges in meeting the regulatory requirements in a timely manner. FSIS did not expect that the first group required to implement HACCP and become subject to *Salmonella* performance standards—those establishments with 500 or more employees—would have much difficulty in doing so, although they might choose to resist some of the requirements. However, it was clear that continued communication with this group would be important.

Consequently, the agency instituted weekly meetings with the large establishments and their trade association representatives focusing on implementation issues. These weekly dialogue sessions did bring numerous issues to the surface and led to new approaches to problem solving.

FSIS also believes that its Technical Services Center (TSC) and the TSC's HACCP Hotline have proven to be a major benefit in facilitating a common understanding of the regulatory requirements and how the Agency would view various approaches to meeting them; the TSC Hotline has handled over 30,000 calls since it opened.

The influence of the techniques it used during implementation of the PR/HACCP regulation is reflected in FSIS' identification of "Key Attributes for a Public Health Regulatory Agency." These attributes are:

1) A public health orientation;
2) A regulatory strategy built on science-based systems;
3) Using measures of success gauge progress in meeting public health goals;
4) An open and inclusive manner for the conduct of business;
5) Assurance that each organizational element contributes to public health goals;
6) Employment of public health professionals;
7) External relationships to mobilize other public health resources; and
8) Use of scientific data to make decisions and allocate resources

(66 FR 30684, June 7, 2001).

Small and Very Small Plants

FSIS recognized early in the HACCP implementation process that small and very small plants would need guidance that larger plants did not require. To meet these needs, a number of outreach and technical assistance programs were established. In 1999, 2373 federally inspected and 170 state-inspected small plants implemented HACCP. In 2000 over 3400 federally inspected and 2300 state-inspected plants did the same.

FSIS established a HACCP National Small and Very Small Plant Coordinator responsible for building and maintaining an infrastructure, sustaining

communication, facilitating exchange of HACCP information, and providing technical guidance and assistance for small and very small plants. All the information, materials, guidance, and outreach efforts of FSIS are provided to federally inspected and state-inspected plants at no charge.

There are contacts and coordinators in all 50 states, Puerto Rico, the District of Columbia, and the U.S. Virgin Islands that small and very small plants can contact for guidance and assistance, to find out where training is occurring, and to obtain HACCP materials or assistance in plan development or other technical assistance.

Materials have been made available through demonstration workshops, the FSIS Coordinator's office, and the contact/coordinator network. HACCP videotapes, software, HACCP workbooks, process control charting information, and other manuals related to HACCP and food safety for the meat and poultry industry have been sent to small and very small plants.

FSIS acts as a conduit to provide small and very small plants with mentors that operate similar plants; mentors in turn help to answer questions about the real-time applications, development, and validation of HACCP plans.

Implementation meetings were conducted across the country. These meetings explained the outreach programs available and the implementing FSIS Directives for HACCP, allowed Q&A exchange; and featured the HACCP Bowl (an interactive learning tool with audience participation). One meeting was videotaped and has been sent to all very small plants. It is available in English, Spanish, and Chinese.

Thirteen generic models and HACCP guidebooks are available to all requestors to assist in the development of HACCP plans for meat and poultry plants. FSIS has also sent copies of the 1997 NACMCF HACCP document and the draft Small Plant Hazard Guide to all very small plants.

Five land grant universities are working with FSIS in utilization of their meat and poultry inspected laboratories as model plants. These sites are open to the industry to view a very small plant in action under HACCP. In addition, these schools provide one-on-one assistance to very small plants. The universities are Pennsylvania State University, Iowa State University, Southern and A&M University, Ohio State University, and the University of Tennessee.

Letters about implementation from the administrator were sent to very small plants approximately every 2 months. These letters included suggested timelines for preparing a HACCP plan, a list of the contacts/coordinators, helpful hints, a checksheet for ordering materials, and useful contact numbers.

FSIS has distributed self-study packages to all very small plants. The packages contain two videos, two pamphlets, a study guide, and a poster. Completion of the material constitutes training, as required in 417.7. Individuals receive a letter of completion after notifying the contractor (HACCP WORKS and Pennsylvania State University) that all parts of the guide have been completed.

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59 FR 14528, March 28, 1994.

FSIS, Progress Report on Salmonella Testing of Raw Meat and Poultry Products, 1998–2000.

66 FR 30683, June 7, 2001.

INTERNET RESOURCES

http://www.fsis.usda.gov/OA/haccp/imphaccp.htm
Regulatory contact points website

CHAPTER 18

ADVANCES IN FOOD SANITATION: USE OF INTERVENTION STRATEGIES

JUDY W. ARNOLD

INTRODUCTION AND DEFINITION OF ISSUES

Food safety issues have begun to emerge as a result of the increased demand for fresh produce and poultry that has lead to mass market sources of production. Consumer awareness of the potential hazards has increased as a result of articles with titles such as "A Killer Strikes Again," in *Woman's Day*, stating that eating raw fruits and vegetables can be just as dangerous as eating undercooked meat. However, the American Meat Institute supported a survey in 1996 in which 43% of the respondents were aware that fruits and vegetables may contain harmful bacteria whereas 98% were aware that harmful bacteria can be present on meat and poultry products (Collins, 1997). Reduction of bacterial contamination of poultry products during processing is of major concern among processors and those concerned with food safety because of the frequent incrimination of products such as chicken, turkey, and eggs in outbreaks of foodborne illness (Franco et al., 1995; Smith and Fratamico, 1995). Mechanical equipment has vastly increased the number of carcasses processed by a single plant each day. The addition of equipment to increase automation has resulted in the presentation of new surface areas for carcasses to contact repeatedly and thus new opportunities for bacterial attachment and cross-contamination.

A need exists to determine the fundamental parameters of pathogenic microbe interactions with food processing plant surfaces to understand the outbreaks of human foodborne illnesses. When bacterial cells attach to a surface and produce extracellular fibrils that form a complex matrix conducive to growth and subsequent attachment of more bacteria, other microbes, and debris (Arnold and Shimkets, 1988), the ultimate composite is a biofilm that is resistant to cleaners and sanitizers and is extremely difficult to remove (Zottola,

Food Safety Handbook, Edited by Ronald H. Schmidt and Gary E. Rodrick
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1994). Bacterial contamination of food products in the processing environment is composed of many different species of microbes in a biofilm community.

The safety of our food supply can be immediately improved by reducing the potential for foodborne illnesses caused by bacterial contamination of food products. Food safety could be enhanced by increasing the use of materials that do not support growth and attachment of bacteria while decreasing the use of materials that enhance growth and attachment. Preventing the buildup of bacteria and food debris into biofilms during processing will also expedite the efficient use of sanitizers and disinfectants. Reducing the need for chemicals in food plant sanitation will lower consumer costs and the negative effects of agriculture on the environment. Understanding and controlling the metabolic processes of bacteria associated with food processing, finding the least amount of treatment necessary to effectively inhibit biofilms, and combining the surface material most resistant to bacterial attachment with cleaning by the most effective agent will enhance food safety and reduce the impact of sanitation practices on the environment.

BACKGROUND AND HISTORICAL SIGNIFICANCE

Microbial growth can be controlled by physical and chemical methods. Physical methods include the use of heat, low temperatures, desiccation, osmotic pressure, filtration, and radiation. Sterilization by moist or dry heat destroys all forms of microbial life on or in a material. A material is either sterile or not; there are no degrees of sterilization. Food preservation by refrigeration and desiccation decreases chemical reactions and slows bacterial growth. High osmotic strength, that is, high salt concentration, is inhibitory to most bacteria. Filtration removes bacteria from a liquid sample by passing the sample through a porous material with openings too small for bacteria, leaving the bacteria trapped on the filter material. Radiation can reduce bacterial and parasitic pathogens in certain food commodities while increasing shelf life and maintaining freshness.

Food processors may do light cleaning throughout the workday, at the end of the day, or both. Most operators conduct full-blown cleaning and sanitizing and apply longer-acting products, such as fogs and foams, after hours and on weekends. The common steps in a processing plant sanitation program begin with prerinsing with a high-pressure water spray followed by washing or scrubbing with a chemical application. Detergents may be used to wet, emulsify, lift, and suspend soil for removal. Disinfectants may be used to reduce or inhibit growth and destroy bacterial cells, but not necessarily spores or viruses. Foams and fogs give increased chemical activity because of their longer contact time and can lower levels of detergent use, penetrate hard-to-reach areas, and allow easy rinsing. Training plant personnel in application procedures is critical to achieve the necessary concentration, pH, contact time, and temperature for optimal efficacy of cleaning products. The washing steps are followed by

preoperation inspection before a final rinsing and sanitizing. Sanitizers are usually no-rinse and nonfoaming and kill a broad spectrum of microbes.

Chemical agents include several groups of substances that destroy or limit microbial growth on food surfaces or inanimate objects. The major groups, their modes of action, and current uses for reducing microbial contamination in plant sanitation are shown in Table 18.1. Disinfectants reduce or inhibit growth and destroy bacterial cells, but not necessarily spores or viruses. A bactericide kills bacteria, a fungicide kills fungi, and a virucide kills viruses. Sanitizers

TABLE 18.1. Chemicals for control of microbial growth

Chemical	Example	Antimicrobial Action	Properties
Phenol, phenolics	Carbolic acid	Disrupts membranes	Standard for disinfectants
	O-phenylphenol	Inactivates enzymes	Environmental surfaces
	Hexachlorophene		
Halogens	Iodine, chlorine	Inhibits proteins	Antiseptic wash, disinfectant, bleach
Alcohols	Ethanol, Isopropanol	Denatures proteins, Disrupts membranes	Antiseptic, tinctures Bactericide, fungicide
Heavy metals	Silver nitrate Mercuric chloride Copper sulfate, Zinc chloride	Denaturation of proteins by metal ions	Antiseptic wash Bactericide, Algicide Fungicide
Surfactants	Soaps, detergents	Emulsifies	Lifts for washing Nontoxic, noncorrosive
Quaternary ammonium compounds (quats)	Benzalkonium chloride, cetylpyridinium chloride	Inhibits enzymes	Antiseptic for skin, metals Bactericide, fungicide, virucide
Organic Acids	Sorbic acid/potassium sorbate, benzoic acid/sodium benzoate, parabens, calcium propionate, trisodium phosphate	Inhibits metabolism	Can be nontoxic Control molds and bacteria
Enzymes	Product mixtures	Inactivates substrate Inhibits metabolism	Can be nontoxic
Gases	Ethylene oxide, propylene oxide	Denaturation	Sterilizing agent for heat-sensitive objects
Oxidizing agents	Ozone, hydrogen peroxide	Oxidation	Contaminated surfaces

TABLE 18.2. Sanitation steps for processing plant surfaces

Prerinsing—high-pressure water spray
Washing, scrubbing with chemical application
Detergent—wet, emulsify, lift and suspend soil for removal
Disinfectant—can be combination of chemicals, see Table 18.1
Foams—increased chemical activity due to longer contact time, can lower levels of detergent use, easy rinsing
Fogs—penetrate hard-to-reach areas, can lower levels of detergent use, easy rinsing
Preoperation inspection
Rinsing
Sanitizing—can be no-rinse, nonfoaming; usually kills a broad spectrum of microbes

Training in application procedures is critical to achieve the necessary concentration, pH, contact time, and temperature for optimal efficacy of cleaning products.

reduce pathogens, or disease-causing microorganisms, to safe public health levels by mechanical cleansing or with chemicals that are compatible with safety and palatability of foods.

Most cleaning products on the market today contain some combination of the chemicals shown in Table 18.1 as active ingredients depending on the type of soil that is targeted for removal. The food product being processed determines the type of soil. The organic load or amount of organic matter present reduces the activity of most cleaning compounds. Table 18.2 lists the steps that might be used in a current sanitation program. Boyd et al. (2001) showed that surface cleanability and hygienic status are affected by the cleaning regime and the surface roughness.

Comparative studies between attached bacteria and planktonic (free floating) bacterial cells indicate that when bacteria become attached to surfaces, they become more resistant to both physical and chemical treatments used in plant sanitation practices. Wirtanen and Mattila-Sandholm (1992) found that the tolerance for chlorine and heat treatments of *Listeria* spp. and other microorganisms in biofilms is increased after attachment. Oh and Marshall (1995) had similar results with monolaurin and heat treatments. Dhir and Dodd (1995) found that *Salmonella enteritidis* cells that were attached were more than twice as resistant to heat treatment as planktonic cells. Somers et al. (1994) showed that attached cells of *Campylobacter jejuni*, *E. coli* O157:H7, *L. monocytogenes*, and *S. typhimurium* were all more resistant to trisodium phosphate treatment compared with planktonic cells of the same species. Iodophor, hypochlorite, anionic acid, peroxyacetic acid, fatty acid, and quaternary ammonium sanitizers were all relatively ineffective against attached bacteria during milk processing (Mosteller and Bishop, 1993).

Substantial bacterial contamination of the poultry processing environment, (e.g., carcasses and plant surfaces) involves the attachment of microbes to other microbes, debris, and inert surfaces in the formation of a biofilm. Bacteria within biofilms may be able to better survive effective food plant cleaning pro-

cedures than previously thought. Biofilm and planktonic listeriae reacted differently to the removal of microbial nutrients from surfaces. Nutrient deprivation reduced the susceptibility of planktonic cells to benzalkonium chloride but had no effect on the more resistant biofilm cells (Ren and Frank, 1993). Bacterial attachment and biofilm formation have been associated with the contamination and fouling of many different inanimate surfaces. Attachment of bacteria to solid surfaces is a contributory and critical step in bacterial pathogenesis (Lappin-Scott and Costerton, 1989). Drinking water and wastewater treatment systems must contend with the flow restriction and contamination caused by microbial colonization and biofilm development (LeChevallier et al., 1987). Attachment of bacteria to food processing equipment surfaces can lead to product contamination, spoilage, and surface destruction (Zottola, 1994).

The above-referenced studies have provided valuable knowledge about the existence of biofilms and established their importance as an industrial problem. More information is needed to design effective controls. Studying the formation and composition of biofilms on processing equipment surfaces and on food products will establish the basis for efficacious cleaning and sanitizing. Quantitative tests are needed for bacterial sampling, identification, enumeration, and testing for pathogens. Research on the structural and kinetic characteristics of bacterial attachment to surfaces presents the opportunity for reduction of pathogens and spoilage organisms by prevention of biofilm formation during food processing.

SCIENTIFIC BASIS AND IMPLICATIONS

Despite much research, there is disagreement on the causes of contamination, the role of cross-contamination in the safety of the final food product, and the effects of the presence of pathogens. Not only is there disagreement about the frequency and necessity for testing, but there is lack of uniformity in the methods used. Many disparate assays purported to detect the presence and numbers of pathogens give conflicting results and are time-consuming, expensive, or lacking in sensitivity.

Pure cultures of single organisms have been beneficial in discovering the mechanisms involved in the bacterial attachment process. Bacterial cell surfaces are covered with many complex macromolecules that can protrude, associate with each other, or be released into the environment. When a bacterial cell contacts another cell or a solid surface, complementary molecules can interact with each other or with molecules in the surrounding environment. The binding interactions may be ionic, electrostatic, bipolar, hydrophobic, or even hydrogen bonds (Marshall, 1984). Pili or fimbriae, polysaccharide polymers, and extraneous substances can interact in a biofilm for the purpose of attachment to a host or substrate (called adhesion), nutrient exchange, or protection from adverse environmental conditions (Bullitt and Makowski, 1995).

Biofilms exist in nature as a mixture of microbial species that vary with

changes in the environment. Members of the biofilm community share and compete for surface attachment, light, and nutrients for carbon and energy sources. Although traditional microbiological studies have been based on pure cultures of one species (Kim and Frank, 1994), methods are being developed to assess the biological and chemical properties of mixed populations (Arnold and Senter, 1998; Yates et al., 1998). Recently, mixed populations have been studied by attempting to isolate each of the species of bacteria into separate pure cultures or by mixing two to three organisms, often including *Pseudomonas fragi* and *E. coli* (Zottola, 1994).

Assessment of mixed cultures is difficult because the nutritional requirements and metabolic products of a combination of organisms are not cumulative. When two organisms are grown together, the nutrients utilized, intermediate compounds formed, and end products excreted during metabolism can differ from those of either organism in pure culture (Costerton et al., 1987). There is not yet sufficient evidence to substantiate that data derived from any combination of these cultures accurately depict the physiological behavior of the total mixed population.

A number of methods have been used for quantification of biofilms under specific conditions, including dry weight by filtration after solvent treatment, optical density with a biomass probe, and protein content determination. Optical density by biomass probe was shown to be the most reliable method to quantify total biofilm, and a linear relation was verified against dry weight (Joannis et al., 1998). Confocal scanning laser microscopy (CSLM) in conjunction with fluorescent stain (0.1% fluorescein) was one of the first methods that allowed optical sectioning of intact biofilms that could be analyzed by image processing techniques. The distribution of cellular and noncellular areas within the biofilm matrices was assessed (Lawrence et al., 1991). The total number of bacteria on solid surfaces can be measured with nondestructive techniques using epifluorescent microscopy with fluorochromes such as acridine orange (Holah et al., 1989; Wirtanen and Mattila, 1993; Jones and Bradshaw, 1996). Methods have also been established for the routine measurements of biofilms with automated image acquisition and semiautomated image analysis. CSLM in combination with multiple fluorescent labels with different excitation and emission spectra has been used to quantitatively separate biofilms by nutrient or substrate utilization and spatial relationships for mixed populations of bacteria (Wolfaardt et al., 1994; Lawrence et al., 1998; Bloemberg et al., 2000).

The expanding field of molecular techniques allows more and more detailed documentation not only of the spatial distribution of species in a biofilm but also of functional activities of the species (Tolker-Nielsen and Molin, 2000; Wimpenny et al., 2000). Detection and enumeration of *Desulfobacter* with an oligonucleotide DNA probe that targeted a *Desulfobacter*-specific sequence of ribosomal RNA compared favorably with conventional assays such as direct counting and serial dilution (Brink et al., 1994). Bacterial numbers from the probe assay were higher than for the commonly used serial dilution medium. It

was suggested that in situations in which these bacteria occur, they are probably not being detected. In fact, most bacterial cells from every ecosystem studied could not be cultured on standard media (Wimpenny et al., 2000). The application of molecular tools was a starting point for resolution of this problem. Species composition and community structure can be elucidated by molecular methods, and hybridization assays have revealed considerable diversity in function. Fluorescence in situ hybridization (FISH), in combination with CLSM and digital image analysis, became an important approach for the in situ identification and localization of microorganisms within complex environments (Raskin et al., 1995; Mobarry et al., 1996; Kalmbach et al., 1997).

In binary biofilms, *Vogesella indigofera*, a betadine-resistant organism, enhanced the survival of *Pseudomonas putida*, a betadine-susceptible organism. In 20-strain biofilms, where *V. indigofera* was less than 1% of the population, this protective effect for *P. putida* was not observed, suggesting that resistant organisms enhance overall biofilm disinfectant resistance (Whiteley et al., 2001). A confounding issue in reporting these data is the proposal that *Campylobacter*, *Listeria*, and other organisms can adopt a viable but nonculturable form during prolonged exposure to adverse environmental conditions (Besnard et al., 2000; Cappelier et al., 1997; Federighi et al., 1998; Leriche and Carpentier, 1995). This suggests that the reported numbers of organisms may be deceptively low.

During processing of poultry meat products, carcasses come in contact with many solid surfaces. Bacteria from the carcasses can attach to wet equipment surfaces, form biofilms, and provide a source of cross-contamination for subsequent carcasses. Results of research that compared common equipment surface materials for their susceptibility to bacterial attachment and biofilm formation showed that surfaces vary. Whole carcasses were collected from a commercial broiler processing plant and rinsed with phosphate-buffered saline to obtain relevant mixed populations of bacteria. Sample surfaces from processing equipment, including rubber picker finger, stainless steel, polyethylene link, and conveyor belt materials were tested for bacterial attachment and biofilm formation. Bacterial attachment activity and biofilm formation on the stainless steel were not significantly greater than on belt or polyethylene surfaces. Analysis by spectrophotometry and scanning electron microscopy confirmed that attachment to stainless steel, polyethylene link, and conveyor belt webbing was not significantly different from that in controls (Arnold and Silvers, 2000).

Studies to assess the kinetics of attachment of bacteria have shown that the accumulation of attached bacterial cells on test surfaces and the increase in cell density during the formation of a biofilm can occur very quickly (Arnold and Shimkets, 1988). From 0 to 2 h after exposure of the carcass rinse solutions to the stainless steel test surface, the bacterial cells were dispersed and infrequent on the surface. After 1–2 h, clumps of attached cells became larger and more frequent on the surface (Fig. 18.1). After 4 h or more, biofilm formation was evident, with most of the cells arranged in large clumps and, within the clumps,

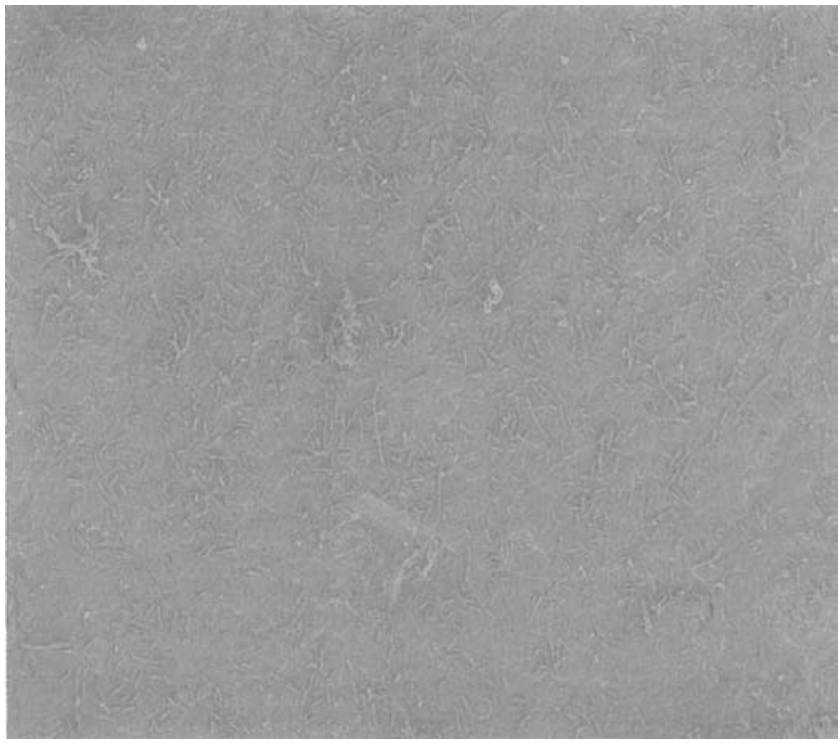

Figure 18.1. Biofilm formation after 1–2 h on stainless steel, ×1000 magnification.

most of the cells aligned side by side (Fig. 18.2). An extracellular matrix covered and obscured many individual cells.

Stainless steel is the most common material found in the processing plant, and it typifies the attachment process for most other materials. In separate experiments, samples of stainless steel were treated by physical and electrochemical methods and then tested for susceptibility to bacterial attachment, growth, and biofilm formation (Arnold and Bailey, 2001). At various times after exposure, scanning electron microscopy showed that bacterial counts on all of the treated surfaces were significantly lower than on untreated surfaces. However, stainless steel that had been electropolished showed significantly fewer bacterial cells and beginning biofilm formations than other treated surfaces. Figure 18.3 shows typical biofilm formation after 1–2 h on electropolished stainless steel (compare with Fig. 18.1). Electropolishing removes metal from the object's surface through an electrochemical process similar to, but the reverse of, electroplating.

In high-quality machine designs for components of food processing equipment today, the outward appearance and function, that is, the use and location,

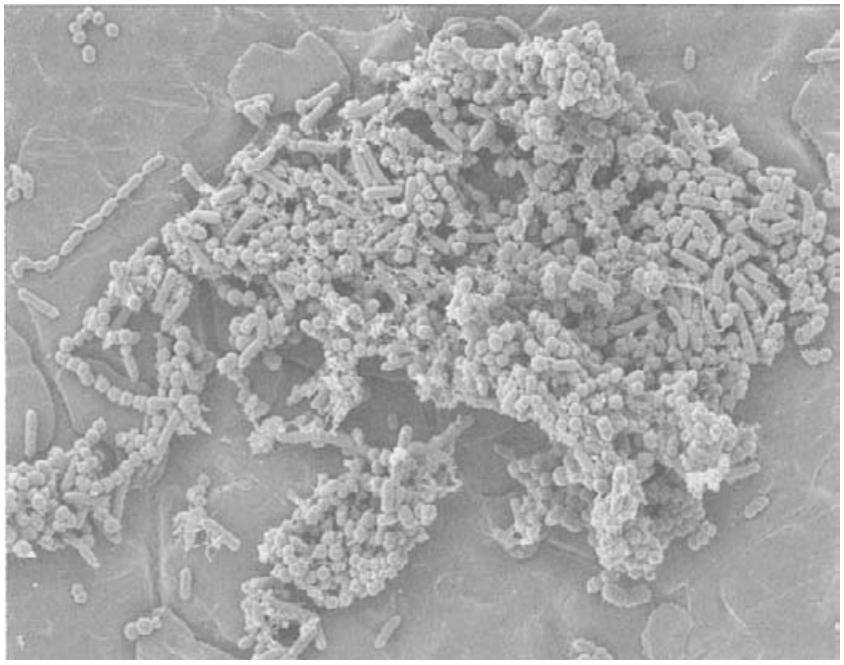

Figure 18.2. Biofilm formation after 4 h on stainless steel, ×3000.

of the equipment dictate the surface finish (Arnold and Bailey, 2001). Some covers and guards are produced from mill-polished plate and receive no further surface treatment unless welded. Sandblasting leaves a dull, uniform surface and is preferred for frames, covers, and exterior surfaces. It also removes weld discoloration and surface damage caused by the handling required in the manufacturing processes. For example, machined surfaces that do not contact the food product are usually left untreated, retaining the steel manufacturer's mill finish. Surfaces that do not normally contact the product may be sandblasted or glass beaded. Parts that normally contact the product or are very close to the product are usually steel ball burnished and acid passivated, hand polished, or electropolished. Historically, steel ball burnishing has been the most economical process of the three and has been specified unless the function requires the lower coefficient of friction provided by a form of polishing. When polishing is required, size may dictate the process. If the part is large, only the contact area may be hand polished, or, if size permits, the entire part may be electropolished.

Research on bacterial contamination of stainless steel surfaces has been conducted primarily in relation to cleanability and disinfection. The resistance or susceptibility of the surface to bacterial contamination has not been considered previously in the manufacturing of food processing equipment. Hazard

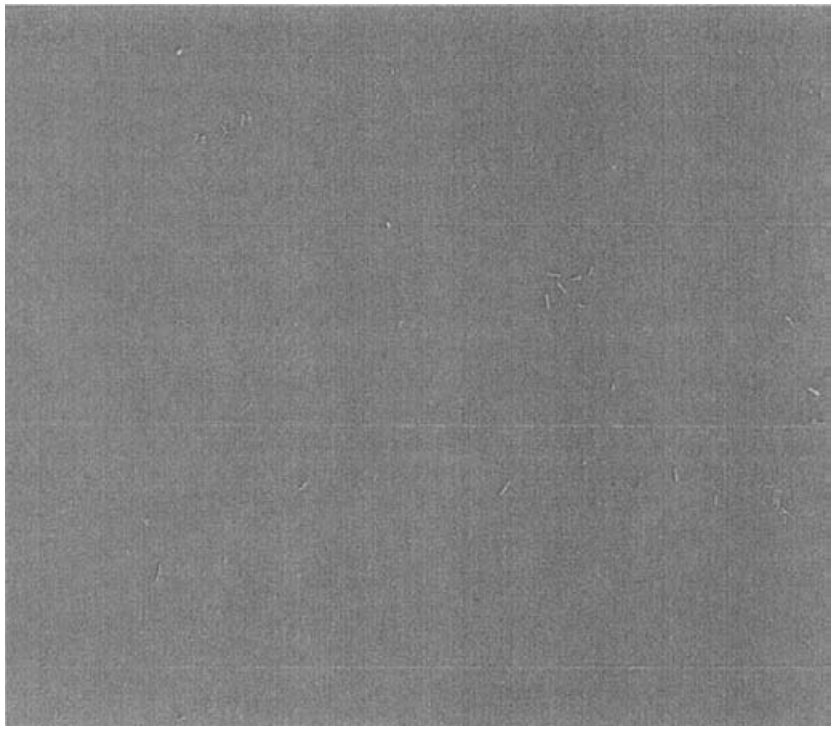

Figure 18.3. Biofilm formation after 1–2 h on electropolished stainless steel, ×1000.

Analysis Critical Control Point (HACCP) plans for poultry production and processing have given new impetus to this consideration.

For many years, the use of rubber fingers on mechanical pickers to remove feathers from broilers after scalding was considered a major contributor to cross-contamination (Dodd et al., 1988). Surprisingly, new rubber picker finger material actually resists bacterial attachment and inhibits bacterial growth and biofilm formation. Readings by spectrophotometry for a bacterial suspension with rubber picker finger material were lower than those for other surfaces. Attachment to rubber picker fingers was significantly less than attachment to stainless steel and other surfaces. Under the same conditions, at the same exposure times shown above, there was little to no accumulation of bacteria on the rubber (Fig. 18.4).

Traditional or standard test organisms used in clinical and hospital tests are not relevant for use as "indicator" organisms to test disinfectants or sanitizers against biofilms found in the food industry. Biofilms are known in general to be more resistant to disinfectants than planktonic organisms in laboratory cultures of single organisms. Bacterial numbers in biofilm samples usually decrease with chemical treatment but begin new growth when exposed to fresh medium without the chemical.

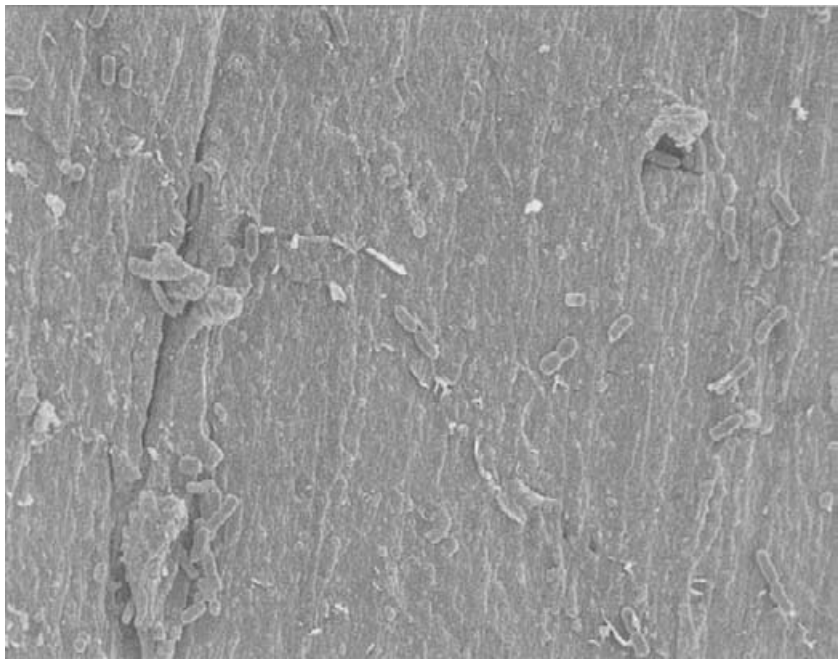

Figure 18.4. No biofilm formation after 4 h on rubber, ×3000.

Most of the microorganisms in food processing plants have not been identified by the current identification systems that are based on clinical and other environmental isolates. The unidentifiable isolates may be the most important, being specific to the food processing environment. In addition, the resistance to disinfectants of newly identified organisms of concern to food manufacture has not been documented. Initial evaluation of possible protocols for testing the resistance of a mixture of organisms found in the whole-carcass rinse to a range of disinfectants and sanitizers commonly used in the food industry has begun.

Thus, it seems obvious that the safety of our food supply can be immediately improved by reducing the potential for foodborne illnesses caused by bacterial contamination of food products. Bacterial attachment and biofilm formation have been associated with the contamination and fouling of many different surfaces (Arnold and Silvers, 2000). Attachment of bacteria to solid surfaces is a contributory and critical step in bacterial pathogenesis and biofilm formation.

The above-referenced studies have provided valuable knowledge about the existence of biofilms and established their importance as an industrial problem. More information is needed to design effective controls. An increased understanding of bacterial attachment and biofilm formation will enable us to develop interventions to counteract these processes and thereby enhance plant sanitation practices and pathogen control.

REGULATORY, INDUSTRIAL, AND INTERNATIONAL IMPLICATIONS

In early 1997, the United States Departments of Agriculture (USDA) and Health and Human Services and Environmental Protection Agency developed a program intended to coordinate a food safety initiative among federal agencies, immediately after an announcement by President Clinton to promote an initiative designed to improve the safety of the nation's food supply. The President charged the federal agencies to work with consumers, producers, and industry, among others, to identify ways to improve food safety through government and private sector action, including public-private partnerships. The interagency response is a multifaceted program designed to include surveillance, coordination of activities within the various programs and agencies, risk assessment, research, inspections, and education. The underlying premise on which this program was developed is that foodborne infections remain a major public health problem. Furthermore, sources of food contamination are said to be almost as numerous and varied as the contaminants; bacteria and other infectious organisms are pervasive in the environment.

The mission of the USDA Agricultural Research Service emphasizes the development of new knowledge and technology to ensure the consumer high-quality, safe food as well as a high-quality environment. This research also responds to the needs of the Food Safety and Inspection Service (FSIS) regulatory program, which sets a high priority for food safety concerns. Understanding the conditions conducive to formation of bacterial biofilms will provide information important for successful development of HACCP plans for poultry processing. Results of the research relative to biofilm formation will be of interest and available to other researchers in the international scientific community. Results of the research relative to surface materials will be of interest and available to conveyor, material handling, and floor and wall covering manufacturers. Methodology related to efficacious sanitation practices will be of interest and available to producers and chemical and equipment manufacturers in the food processing industry as well as FSIS personnel.

CURRENT AND FUTURE IMPLICATIONS

Physical treatments such as steam, water pressure, and heat as well as numerous chemical treatments such as chlorine, trisodium phosphate, and quaternary ammonium compounds are commonly used to reduce microbial contamination in food plants. The choice of sanitation products is often left to the plant sanitation manager. Processing control over the final microbiological quality of raw poultry products is highly variable, as evidenced by reports of contamination and foodborne illnesses. The use of chlorinated washers has not effectively reduced the incidence of contamination by enteropathogens, whose presence is detectable in small numbers per carcass. The primary goal of these plant sanitation practices has been the physical removal or killing of microbes present.

The surface resistance achieved by electropolishing produces significantly less contamination than other methods used by equipment manufacturers. In addition, the simplicity of the cleaning process and the reduction in chemical use make it very attractive for industrial applications. Unfortunately, the quality of the electropolished surface may vary considerably from manufacturer to manufacturer. There are no standards or grading system to allow the end user, the processor, to distinguish the performance of one surface from another. The sales ability of the manufacturer is more of a factor than the true quality of the material. These concerns need to be addressed and the process parameters quantitatively defined in future efforts.

The studies discussed in this chapter have provided valuable knowledge about the existence of biofilms and established their importance as an industrial problem. More information is needed to design effective controls. The question remains as to whether biofilms are effectively removed to prevent foodborne illness. A limited number of studies have suggested that removal is insufficient to balance the rates of production. The degree to which various environmental factors affect the efficiency and rate of removal has largely been ignored; seasonality and site-specific characteristics might be of paramount importance for such experiments. The use of innovative techniques to reduce bacterial contamination during poultry processing has the potential to improve product quality.

Finding the least amount of treatment necessary to effectively inhibit biofilms will be economical for the industry and for consumers as well. Methods that measure attached bacteria and biofilm formation on the surfaces of food products will identify factors that make surfaces susceptible or resistant to pathogen attachment and survival within biofilms. The immediate needs for current research are (1) development of procedures for sampling microbial biofilms on the surfaces of food products, (2) study of the role of microbial pathogens within the biofilms, and (3) development of efficacious methods of preventing or removing microbial biofilms from the surfaces. Developing a model representing such a complex phenomenon and devising quantitative tests that can predict the subsequent behavior of living organisms have been goals of scientists for many years. The ultimate goal is to use this information to reduce the possibility of foodborne transmission of pathogens to humans.

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CHAPTER 19

USE OF SURVEILLANCE NETWORKS

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INTRODUCTION AND DEFINITION OF ISSUES

Public health surveillance of foodborne disease is critical to the performance of food safety systems (Hedberg and Hirschhorn, 1996). Surveillance of human illnesses and epidemiological investigation of outbreaks can identify previously unknown hazards and provide feedback on the effectiveness of existing control measures. For example, the investigation of a multistate outbreak of *Salmonella stanley* infections in 1995 led to the first identification of alfalfa sprouts as a vehicle for *Salmonella* (Mahon et al., 1997). An outbreak of *Salmonella enteritidis* infections associated with commercially processed ice cream revealed a failure of the company's Hazard Analysis Critical Control Point (HACCP) plan to control for hazards in the transportation of ingredients (Hennessy et al., 1996).

The emergence of foodborne disease problems, such as *Escherichia coli* O157:H7, has occurred in the context of major changes in diet and industry. These include increased consumption of raw or minimally processed foods, consumption of foods out of the home, globalization of our food supply, and the mass production and distribution of ready-to-eat foods (Hedberg et al., 1994). Outbreaks of foodborne illness associated with these large distribution systems are also widely dispersed; individual cases may appear as apparently sporadic infections. The development of national and international surveillance networks, such as the National Molecular Sub-typing Network for Foodborne Pathogens (PulseNet), will be the only effective way to identify and control these widely dispersed outbreaks (Swaminathan et al., 2001).

BACKROUND AND HISTORICAL SIGNIFICANCE

In the United States, surveillance for foodborne diseases is conducted under the jurisdiction of state or local health departments. The Centers for Disease

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Control and Prevention (CDC) conducts national surveillance for diseases such as *E. coli* O157:H7 infection, salmonellosis, and shigellosis that have been made nationally reportable in collaboration with the Council of State and Territorial Epidemiologists (Roush et al., 1999). Reports of cases are submitted to the CDC through the National Electronic Telecommunications System for Surveillance (NETSS) and annually summarized in the *MMWR Summary of Notifiable Diseases*, United States (CDC, 1999d). A separate Public Health Laboratory Information System (PHLIS) system was established for electronically reporting information on isolates from State Public Health Laboratories to the CDC (Bean et al., 1992). PHLIS forms the basis of the National *Salmonella* and *Shigella* Surveillance Systems. Outbreaks of foodborne disease are reported by state and local health departments to the CDC's Foodborne-Disease Outbreak Surveillance System. The most recent 5-year surveillance summary covered outbreaks reported from 1993 to 1997 (Olsen et al., 2000).

As part of the CDC's response to concern over emerging infections (CDC, 1998b), and in conjunction with President Clinton's National Food Safety Initiative, CDC developed several new approaches to enhance foodborne disease surveillance (Table 19.1). These included developing a *Salmonella* Outbreak Detection Algorithm (SODA) to run on PHLIS (Hutwagner et al., 1997), a multisite Active Surveillance System for Foodborne Diseases (FoodNet) (CDC, 2000), and the National Molecular Sub-typing Network for Foodborne Pathogens (PulseNet), which uses standardized pulsed-field gel electrophoresis (PFGE) protocols to subtype foodborne pathogens and report PFGE patterns through an electronic database at CDC (Swaminathan et al., 2001). These surveillance networks were developed to increase the likelihood of detecting an outbreak and to increase the timeliness of its detection.

SCIENTIFIC BASIS AND IMPLICATIONS

PHLIS represented the first extension of the personal computer-based information revolution into public health surveillance (Bean et al., 1992). It allowed state public health laboratories to transmit data electronically to the CDC. It also provided a common format for data storage and analysis both at the CDC and in the states. Data reported through PHLIS represent the results of passive reporting of isolates from clinical laboratories. Although the completeness of passive reporting may vary by state, for any given state it tends to be consistent from year to year. This consistency in reporting over time allows PHLIS to be used to track trends in the reporting of *Salmonella* serotypes. To take advantage of this characteristic of data in PHLIS, the CDC modified a quality control method used in manufacturing, to construct an algorithm for detecting unusual clusters of cases (Hutwagner et al., 1997).

SODA was implemented at the CDC in 1995 and subsequently in several state health departments. The algorithm automatically compares recently reported *Salmonella* cases to a 5-year mean number of cases of the same sero-

TABLE 19.1. Characteristics of Major National Foodborne Disease Surveillance Networks in the United States

Characteristic	FoodNet	PHLIS/SODA	PulseNet
Purpose	Quantify and monitor foodborne illnesses.	Monitor trends, detect outbreaks.	Monitor trends, detect outbreaks.
Geographic scope	Nine sentinel sites encompassing 11% of U.S. population.	Nationwide.	6 area subtyping laboratories; 42 other participating public health laboratories.
Methods	Active laboratory-based surveillance with related surveys of laboratories, physicians, and population.	Electronic submission of information on isolates. Serotype-specific outbreak detection.	Molecular subtyping by PFGE, electronic transmission of PFGE patterns. Detection of PFGE pattern clusters.
Ability to detect widely dispersed outbreaks	Limited to outbreaks occurring in surveillance area.	Limited by sensitivity and specificity of serotype-specific surveillance.	Limited by incomplete participation, inadequate epidemiological resources.
Potential for future development	Cost and level of activity limit it to sentinel site applications.	Has achieved full potential.	Could be expanded nationwide to form the basis of an integrated foodborne disease surveillance system.

type and week of report. If a statistically significant increase is detected, notification is sent to the state with the elevated case counts. In May 1995, SODA confirmed that a multistate outbreak of *Salmonella stanley* was occurring in the United States. The outbreak had been recognized and was being investigated by the Michigan Department of Public Health before SODA notification, but knowledge of the widespread nature of the outbreak facilitated the epidemiological investigation and led to identification of alfalfa sprouts as the source (Mahon et al., 1997). SODA played a similar role in defining the geographic dimensions of an outbreak of *Salmonella agona* infections associated with toasted oats cereal (CDC, 1998a). Because it compares current cases to 5-year means, SODA appears to be most effective at detecting case clusters of uncommon serotypes. As in other applications of serotype-specific surveillance, there is no reason to believe that SODA is either especially sensitive or specific

for detecting outbreaks caused by common serotypes such as *Salmonella typhimurium*.

Surveillance systems based on models similar to PHLIS and SODA have been developed in Australia and Europe. Enter-net is a European Union (EU) surveillance system for *Salmonella* and shiga toxin-producing *E. coli*. An automatic cluster-detection algorithm is applied to *Salmonella* cases reported to the EU Communicable Disease Surveillance Center from member countries, based on comparison with retrospective data from the same time frame from the previous year (Pebody et al., 1999). In Australia, a *Salmonella* Potential Outbreak Targeting System (SPOT) has been developed to query the National Enteric Pathogens Surveillance Scheme for unusual case clusters by serotype and phagetype (Stern and Lightfoot, 1999). Like SODA, cases are compared with a 5-year baseline for the time of year and geographic location. However, SPOT and SODA differ in how the baseline is calculated and in the statistical algorithm to detect differences from the baseline. The inclusion of phagetype data increases the specificity of cluster identification by SPOT.

The ability to distinguish specific subtypes among relatively common organisms, such as *E. coli* O157:H7 or *Salmonella typhimurium*, is at the heart of PulseNet, the CDC's national molecular subtyping network. PulseNet takes advantage of the combined revolutions in molecular biology and information technology. PFGE is performed by cutting the bacterial DNA into pieces and comparing how far the various pieces move across a gel. Smaller pieces move farther than big pieces. The resulting pattern resembles a bar code. Under standardized conditions, PFGE patterns are highly reproducible. PFGE was chosen for use in PulseNet because it is available in many public health laboratories, is relatively simple, provides stable and epidemiologically useful discrimination between strains in outbreak settings, and the output can be digitized and transmitted electronically between participating laboratories. Thus PFGE patterns from clusters in multiple states can be rapidly compared to determine whether each may be part of a larger, widespread outbreak. This characteristic makes PulseNet the preferred platform on which to build a truly national surveillance system for all our known foodborne disease agents.

As with serotype-specific surveillance for *Salmonella*, PulseNet is designed to detect unusual clusters of cases that may represent outbreaks. However, because PulseNet identifies clusters with distinctive PFGE patterns, there is a greater likelihood that cases in the cluster may have a common source. The utility of incorporating PFGE subtyping into routine surveillance for *E. coli* O157:H7 (Bender et al., 1997) and *Salmonella typhimurium* (Bender et al., 1998) has been demonstrated in Minnesota. For both pathogens, routine subtyping by PFGE resulted in increased outbreak detection as well as ruling out spurious clusters comprised of unrelated PFGE subtypes.

PulseNet has played a major role in recent outbreak investigations of *E. coli* O157:H7 and premade hamburger patties (CDC, 1997), *Salmonella muenchen* and unpasteurized orange juice (CDC, 1999c), *Shigella sonnei* and imported parsley (CDC, 1999b), and *Listeria monocytogenes* and hot dogs and luncheon

meats (CDC, 1999a). Although standardized PFGE conditions were not available for all of these investigations, the electronic communications about the outbreaks and the ability to transmit PFGE patterns to other investigators greatly facilitated the epidemiological investigations that identified the source of each outbreak. The primary limiting factors for PulseNet's usefulness are that not all public health laboratories are connected, not all clinical laboratories routinely submit isolates to public health laboratories, and many states do not have sufficient epidemiological resources to investigate individual cases or clusters.

In contrast to the widespread availability of PulseNet, FoodNet, the Active Surveillance System for Foodborne Diseases, was established as a sentinel site surveillance system to conduct population-based active surveillance of cases of bacterial foodborne infections, initially, among 13.2 million residents of Minnesota, Oregon, and selected counties in California, Connecticut, and Georgia. The addition of sites in New York, Maryland, Tennessee, and Colorado will bring the population under surveillance to 29 million persons in 2001 (CDC, 2000). Major goals of FoodNet were to measure the burden of diarrheal disease in the United States, to develop the means to respond rapidly to emerging foodborne diseases, and to evaluate the effectiveness of prevention strategies. The recent estimates that 76 million foodborne illnesses occur each year in the United States were based largely on results of active surveillance and population surveys conducted by FoodNet (Mead et al., 1999).

REGULATORY, INDUSTRIAL, AND INTERNATIONAL IMPLICATIONS

The ease with which people, products, and foods move across international borders makes it essential that national foodborne disease surveillance systems are sensitive to the occurrence of widely dispersed outbreaks. Food safety regulations imposed on food producers in one country will have little effect on preventing illness from foods imported from another country that may not adhere to the same standards. The outbreak of shigellosis associated with parsley imported from Mexico is an example (CDC, 1999b). Although most produce-associated outbreaks in the United States have been attributed to domestic produce, documenting outbreaks associated with imported produce is a necessary step in trying to ensure the safety of all fresh fruits and vegetables.

Furthermore, contaminated foods may have an international distribution, and recognition of an outbreak in one country may facilitate outbreak detection in other countries as well. For this reason, surveillance for foodborne diseases should be standardized as much as possible. National *Salmonella* surveillance systems in the United States, Europe, and Australia all function along similar lines. This has helped coordinate the investigation of *Salmonella* associated with alfalfa sprouts and other internationally distributed foods (Mahon et al., 1997). The potential for international surveillance of *Salmonella* and other enteric pathogens will be greater when national surveillance systems

move beyond the current PHLIS/SODA model and develop along the lines of PulseNet.

From a regulatory standpoint, the improved speed of information exchange and increased sensitivity and specificity inherent in PulseNet will lead to more timely outbreak identification and implementation of control measures. In the case of the outbreak of *E. coli* O157:H7 infections associated with Hudson's beef, the availability of PulseNet allowed a very rapid assessment of the potential magnitude of the outbreak and helped to guide USDA decisions about recall and plant interventions (CDC, 1997). In the states, being able to rapidly assess whether cases were linked to the outbreak allowed very targeted responses to the outbreak and preempted much anxiety in the community. Similarly, the ability of PulseNet to link widely separated cases of *Listeria* infection to a common source has refocused the USDA's attention on an important foodborne disease problem (CDC, 1999a).

PulseNet also provides a unique opportunity to compare pathogens from human infections with animal and environmental isolates obtained during regulatory surveys, outbreak investigations, and special studies. Laboratories at the USDA and the FDA are linked to PulseNet through the CDC. However, very little information from the USDA and the FDA has been made available through PulseNet to date.

Results of microbiological testing of food and environmental sampling by industry are not available to PulseNet. Similarly, PulseNet data are not directly accessible by industry. Individual PFGE patterns may be accessible on a case-by-case basis through a Freedom of Information request to the CDC.

FoodNet has played an important role in establishing new estimates of how much foodborne disease actually occurs in the United States. It has established baseline data on the incidence of the major foodborne bacterial pathogens. Through case control studies and population surveys, FoodNet has established risk factors for several of these same pathogens and helped estimate the proportion attributable to various foods, in particular, those regulated by the USDA. These activities provide a framework for evaluating the effectiveness of regulatory changes and the introduction of new control measures.

CURRENT AND FUTURE IMPLICATIONS

Currently in the United States, three major innovations have been made in surveillance for foodborne diseases: PHLIS/SODA, PulseNet, and FoodNet. Instead of being a true foodborne disease surveillance system, FoodNet operates as a collection of special studies to assess the magnitude of foodborne disease and to monitor trends in the occurrence of foodborne diseases in defined populations. PHLIS/SODA and PulseNet both provide a national scope for surveillance activities and provide some ability to detect widely dispersed outbreaks. PHLIS has the advantage of being a "mature" surveillance system that is fully implemented in all states. The availability of extensive historical

data makes PHLIS a valuable archive to monitor long-term trends in disease reporting. However, its reliance on serotype-specific surveillance limits the sensitivity and specificity of SODA for relatively common serotypes.

Because PulseNet features an interactive electronic communication system and highly specific subtype characterization, it appears to be a strong model for future development. The choice of PFGE as the molecular subtyping standard for PulseNet was based on both convenience and the state of our science at the time PulseNet was developed. Numerous subtyping methods are currently available and being developed. At some point, a new standard will be adopted to replace PFGE. The framework of PulseNet will function regardless of the subtyping system employed. Currently, a companion to PulseNet is being established at the CDC to provide national surveillance for caliciviruses. Calicinet will base its surveillance scheme on sequencing of polymerase chain reaction (PCR) gene products. Tracking organisms by specific gene sequences may represent the next major innovation in foodborne disease surveillance, but the challenge will lie in determining how much variability can exist in a group of organisms that all came from the same source.

For PulseNet to become fully operational, it will require the participation of all public health laboratories, either directly or through submission of isolates to regional public health laboratories. It will require routine subtyping of isolates as they are received. It will also require an investment in epidemiological resources to conduct investigations of cases and clusters as they are being identified. To further improve foodborne disease surveillance in the United States, an integrated surveillance program should be built around an expanded PulseNet. This model could be readily developed in other countries and linked electronically to form a truly international foodborne disease surveillance system.

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INTERNET SOURCES WITH ANNOTATIONS

www.cdc.gov/ncidod/dbmd

Website for the CDC's Division of Bacterial and Mycotic Diseases, with links to information and data from PHLIS, PulseNet, and FoodNet.

www2.phls.co.uk

Web site for information and data from Enter-Net.

CHAPTER 20

HAZARD ANALYSIS CRITICAL CONTROL POINT (HACCP)

DEBBY NEWSLOW

INTRODUCTION AND DEFINITION OF ISSUES

At the beginning of the twentieth century, food safety issues and concerns resulted in passage of landmark food safety regulations in the United States. For example, Upton Sinclair's *The Jungle*, which detailed significant food safety issues in meat packing facilities, had a direct impact on the passage of the Federal Meat Inspection Act (FMIA) in 1906. The Pure Food and Drug Act, which later became the Federal Food, Drug and Cosmetic Act (FDCA), was also enacted in the same era in U.S. history. At the beginning of the twenty-first century, there is, once again, an emphasis on food safety in which regulatory agencies are requiring (or proposing) the Hazard Analysis Critical Control Point (HACCP) System for certain segments of the food industry (e.g., meats and poultry, seafood). HACCP, a concept that has been around for many years, was developed by the Pillsbury Company in association with the National Aeronautics and Space Administration (NASA) and the U.S. Army Laboratories in Natick, MA in response to the needs of the space program in the early 1960s. NASA needed to ensure that the food products developed for astronauts were free of pathogens. It was not until 1973 that the federal government used the concept for HACCP as a basis for the low-acid and acidified canned food regulations (21CFR113). For the subsequent 20 years or so there was varied interest in this concept from manufacturers; however, these efforts were mostly unsuccessful. Most that tried to use it made its application too complicated by applying it to quality programs rather than food safety, which tends to burden the system.

Each year seems to bring a new sense of urgency in the world of food safety. As recently as the early 1990s, many industries (e.g., apple and citrus juice) could not conceive that pathogenic microorganisms could survive in a high-

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acid product. As years pass, it has been shown that the microorganisms continue to evolve survival mechanisms for harsh environments—consequently, microbiological detection methods have also improved. Thus reports of foodborne illnesses have become more and more frequent. It is time that every food processor seriously evaluates its processing system to define a HACCP plan that will control existing and potential food safety hazards based on current scientific principles, standards, and concerns.

The current HACCP system is based on the seven principles of HACCP as defined by the United Nations Food and Agriculture Organization (FAO)/World Health Organization (WHO)/Codex Alimentarius Commission (CAC). The CAC has incorporated the seven principles of HACCP into a document to be applied worldwide as the standard for establishing and maintaining HACCP plans for all aspects of the food industry (CAC/RCP 1-1969, Rev. 3, 1997). The National Advisory Committee on Microbiological Criteria for Foods (NACMCF) was established in 1985 in the United States and held its first meeting in 1988. The committee went on to issue a similar HACCP document based on the seven principles. This document was first issued in 1989 then revised in 1992 and 1997. It is very similar to the defined Codex document, and both are referenced in this chapter.

HACCP requirements have been accepted in the United States throughout the food industry, some voluntarily and some mandatory under regulations of the U.S. Food and Drug Administration (FDA; e.g., for seafood, fruit and vegetable juices) and the Food Safety Inspection Service (FSIS; e.g., for meats and poultry). In addition, many food industry manufacturers are now requiring raw material suppliers to have a defined HACCP plan to supply ingredients and materials to their operations. The role of HACCP as it relates to regulatory agencies is discussed later in this chapter.

"HACCP is the failure mode effect analysis (FMEA) for food. It is a product safety management system that evolved and matured in the commercial food processing industry to allow food processors to take a proactive approach to prevent food borne diseases" (Certified Quality Auditor's HACCP Handbook). The process includes the development of a HACCP plan that identifies and defines the required control for potential and existing hazards that are critical to food (product) safety. This forces the operation to define what is required to ensure products are safe. The purpose of this chapter is to provide an overview of HACCP requirements and its role overall in the safe production of food products.

SCIENTIFIC BASIS AND IMPLICATIONS

HACCP is defined as a "logical system designed to identify hazards and/or critical situations and to produce a structured plan to control these situations" (Schmidt, 1996). "HACCP is an activity developed to identify and control

potential hazards that are critical to consumer safety" (Newslow, 1997a,b). The focus of HACCP is on product safety.

Developing the HACCP Plan

A HACCP plan is defined as a "document prepared in accordance with the principles of HACCP to ensure control of hazards which are significant for food safety in the segment of the food chain under consideration" (CAC/RCP 1-1969, Rev. 3, 1997). It is very important to focus on the key word "significant" and the key phrase "segment of the food chain under consideration." Requirements as they relate to a specific process are further explained in subsequent sections of this chapter. In this text, the term "safe" refers to the processing of food products without contamination from any pathogenic organism or adulteration with harmful chemical or physical material. In addition to the HACCP plan, several preliminary steps and prerequisite programs are required for implementation of the HACCP system.

Preliminary steps of the HACCP system There are seven principles of HACCP that relate to developing a HACCP plan as defined by the CAC. However, before getting started, there are five *presteps* that Codex states must first be addressed and documented:

Assemble the HACCP team The HACCP team should include representatives from many different process activities, such as receiving, blending, maintenance, management, quality assurance, and quality control. It is very important to approach this analysis in a manner to provide insight from associates who are familiar with each aspect of the process. During this step, the scope of the HACCP plan is defined. The "segment of the food chain involved" and the type of hazards to be included are identified (CAC/RCP 1-1969, Rev. 3, 1997).

Describe the product "A full description of the product" must be documented (CAC/RCP 1-1969, Rev. 3, 1997). This includes the product, its processing requirements, storage temperature, and characteristics. Characteristics include such information that will be necessary for evaluation of the hazards, such as compositional factors (e.g., pH, water activity) and processing factors (e.g., heat treatment, chemical agents).

Identify the intended use This activity is intended to identify the use of the product, such as consumption by those segments of the population at high risk for foodborne illness (e.g., children, the elderly, pregnant women, immunocompromised individuals). For example, a citrus product such as orange juice is consumed under many different types of situations by children, the elderly, and immune-deficient individuals. In a food service situation, the intended use may be defined as being for "fast food" restaurants.

Construct the flow diagram The HACCP team must create a flow diagram of the process for which the HACCP plan will be applied. The definition of a "flow diagram" is "a systematic representation of the sequence of steps or operations used in the ... manufacture ... of" the specific product (CAC/RCP 1-1969, Rev. 3, 1997).

On-site confirmation of flow diagram The HACCP team must make an on-site evaluation of the flow diagram to confirm that it is complete and that it accurately identifies all the process steps. This is important to add credibility and accuracy to the process analysis.

Once the presteps have been completed, the HACCP team will begin their system analysis in compliance with the seven principles, as detailed below.

HACCP principles

Principle 1—Conduct a hazard analysis "Assess hazards associated with growing, harvesting, raw materials and ingredients, processing, manufacturing, distribution, marketing, preparation and consumption of the food" (Pierson and Corlett, 1992). This principle requires conducting a hazard analysis of the process. A hazard is defined as "a biological, chemical or physical agent in, or condition of, food with the potential to cause an adverse health effect." (CAC/RCP 1-1969, Rev. 3, 1997). In the NACMCF-revised definition used in the FDA Juice HACCP rule (21CFR120), a hazard is defined as "any biological, chemical, or physical hazard that is *reasonably likely* to cause illness or injury in the absence of its control." A biological (also known as microbiological) hazard relates to microorganisms that either directly or indirectly cause a food safety hazard. Examples of these types of hazards include such organisms as *E. coli* O157:H7, *Salmonella*, *Clostridium botulinum*, and *Listeria monocytogenes*. In identifying a microbiological hazard, it is imperative that the specific organism be identified and the specific criteria required to control it be defined.

Pesticides, antibiotics, mycotoxins, and allergens are examples of chemical hazards. A physical hazard may be defined as any object or material that is not normally part of the product, such as bones, twigs, seeds, metal, glass, or plastic. A physical hazard such as glass could cause an injury (e.g., broken tooth) or choking if swallowed. It has been stated by many food safety experts that physical hazards are the cause of the majority of food safety occurrences. Generally, biological hazards affect the largest numbers of individuals per occurrence, thus receiving the most publicity because of the multiple individuals affected.

Hazard analysis is defined as the "process of collecting and evaluating information on hazards and conditions leading to their presence to decide which are significant for food safety and therefore should be addressed in the HACCP Plan." (CAC/RCP 1-1969, Rev. 3, 1997). The HACCP team must define the criteria for identifying each specific hazard and evaluate each hazard

for its potential risk and the significance of its occurrence. Thus hazard analysis consists of two activities: the identification of the hazard and the subsequent evaluation of each hazard. "Risk" and "significance" are two key words in the definition of the HACCP plan. Risk is the likelihood that the hazard may occur. Significance considers how serious the resulting food hazard would be, should the hazard occur. The risk-significance relationship might also be evaluated as high, medium, or low. The criterion for evaluation may be defined as a hazard that has a medium risk of occurring with a high significance for outcome.

The identification of specific hazards will be unique for each operation. What may be a hazard for one operation may not be a hazard for another operation that manufactures the same product for the same intended use. This may be because of equipment or other process considerations. It is a good idea to benchmark with other similar operations; however, the HACCP plan should be defined specific for the operation for which it is being developed.

All hazards involved with processing the specific product must be identified. This includes not only hazards within the process but also those related to the raw ingredients and packaging materials. However, only hazards that can be controlled within the process should be identified. For example, a producer of raw hamburger meat cannot control the cooking temperature of the end user. This can be identified as a potential hazard, with communication to the end-user addressed through other programs. It would not be identified as a significant hazard for the raw hamburger processor because it cannot be controlled within the scope of the HACCP plan.

Many existing or potential hazards may be addressed through prerequisite programs (discussed below). Prerequisite programs are activities defined and managed through operational-type programs that effectively eliminate or reduce the likelihood of a food safety occurrence. They are the foundation of an effective HACCP Plan. The role of the prerequisite program is to support and eliminate potential hazards. For example, an apple concentrate manufacturer might identify pesticide residues as a significant hazard, although he would not have control of pesticide application at the agricultural production level. In this case, the HACCP plan would document a defined means for assurance through raw material purchase and inspection that the apples were free of harmful pesticides. This is most often addressed through a supplier management prerequisite program. Other examples of prerequisite programs include good manufacturing practices (GMPs; see Chapter 25) that control the use of loose jewelry, hand washing, etc. and/or a sanitation program that addresses cleaning and sanitization activities. It is important during the hazard identification and evaluation process that the prerequisite programs are referenced where appropriate and that these programs are active and effective. The overall safety of the product and effectiveness of the HACCP system depend on this.

The hazard analysis results in the identification of Critical Control Points (CCPs), which are addressed in Principle 2.

Principle 2—Identify critical control points A Critical Control Point (CCP) "is any point in the chain of food production from raw materials to finished product where the loss of control could result in an unacceptable [or potentially unacceptable] food safety risk" (Pierson and Corlett, 1992). Thus the goal of Principle 2 is to "determine the Critical Control Points required to control the identified hazards" (Pierson and Corlett, 1992). The application of Principle 2 is to identify CCPs and how they must be controlled to produce a "safe" product. A Control Point (CP) is defined as "any step at which biological, chemical, or physical factors can be controlled" (Stevenson and Bernard, 1999). The difference between a CP and a CCP is that if control is lost at the CCP, it has created either a food safety hazard or the potential for a food safety hazard. Loss of control at a CP by itself does not specifically relate to a food safety hazard, or there is a succeeding step in the process that will control the hazard. Decision making will be based on the team's analysis. The CAC HACCP document recommends the use of a "Decision Tree" in the CCP analysis. Different versions of this decision tree are included in both the CAC HACCP document (1997) and the NACMCF (1998) in the HACCP documents. This decision tree, used in relationship with the hazard analysis, asks key questions related to the outcome at a specific point in the process and its relationship to the specific food safety hazard.

It is common to be overzealous in the identification of CCPs when first beginning the analysis. The identification of too many CCPs will likely overburden the process, but too few may not protect the safety of the product. It is important that the team gives every point in the process a focused evaluation on the potential outcome if not controlled, while also evaluating its function in relationship to other points in the process. Keep in mind that the HACCP plan can be revised at any time. Decisions can be revised and changed.

Principle 3—Establish critical limits at each CCP "Establish the critical limits which must be met at each identified Critical Control Point" (Pierson and Corlett, 1992). A Critical Limit (CL) is the control parameter that is required to ensure that the product is safe. An example of a CL would be the required pasteurization time/temperature criteria necessary to deliver a "safe" milk product. A CL should not be confused with an operational limit (OL). For example, a CL set for pasteurization of milk may be 165°F $\pm$ 2°F (the legal requirement is 161°F); however, the OL identified to achieve not only a safe product but also the ultimate-quality product may be 175°F. Setting appropriate OLs allows room for process adjustment without being out of control from a safety standpoint.

Principle 4—Establish monitoring procedures for critical limits "Establish procedures to monitor critical limits" (Pierson and Corlett, 1992). The procedures required to ensure that the CCPs are, in fact, controlled must be established and implemented. "Monitoring" is defined as " the act of conducting a planned sequence of observations or measurements of control parameters to

assess whether a CCP is under control." CAC further defines monitoring as a "scheduled measurement or observation of a CCP relative to its critical limits" (CAC/RCP 1-1969, Rev. 3, 1997). Monitoring of a CCP is essential to the overall control process. Information must be available in time to "control" the hazard. The term "control" has two distinct definitions and one major application as it applies to HACCP (all definitions are taken from CAC/RCP 1-1969, Rev. 3, 1997).

Control (verb). To take all necessary actions to ensure and maintain compliance with criteria established in the HACCP plan.

Control (noun). The state wherein correct procedures are being followed and criteria are being met.

Control measure. Any action and activity that can be applied and is essential to prevent or eliminate a food safety hazard or reduce it to an acceptable level.

Target limits should be defined as a goal, with any drifts away from these targets (trends in the process) adjusted before the CCP becomes out of control. Ideally, continuous monitoring that provides records (i.e., recording charts) is the means of choice. When continuous monitoring is not possible, monitoring must be a scheduled event (CAC/RCP 1-1969, Rev. 3, 1997). Sampling at 8 A.M., 2 P.M., and 6 P.M. would be a scheduled event. Sampling with a frequency defined as "once per shift" is not considered a "scheduled" event. As a general rule, a physical or a chemical measurement provides the information quicker than waiting for microbiological results. Microbiological testing is used many times for verifying that activities are in fact in compliance with the defined parameters. The requirements for verification are addressed through Principle 6.

The defined requirements for Principle 4 also state that "all records and documents associated with monitoring CCPs must be signed by the person(s) doing the monitoring and by a responsible reviewing official(s) of the company" (CAC/RCP 1-1969, Rev. 3, 1997). This applies to each identified CCP and must be done on completion of the activity.

Principle 5—Establish corrective actions "Establish corrective action to be taken when there is a deviation identified by monitoring of a Critical Control Point" (Pierson and Corlett, 1992). A "deviation" is defined as the "failure to meet a critical limit" (Ensminger et al., 1995; CAC/RCP 1-1969, Rev. 3, 1997). Actions to be performed, should a CCP become out of control, must be defined. The corrective action must be preplanned. "Preplanned" means that the required action, should a deviation occur, is clearly defined to provide immediate action to protect against a food safety hazard. Associates responsible for these activities must have the training and authority to initiate the preplanned corrective action to protect the product and to bring the CCP under

control. Actions must also include the proper disposition of the product and records to demonstrate compliance with all the stated requirements.

An example of applying both Principles 4 and 5. In the dairy industry, it is mandatory that there be a flow diversion valve on an HTST (High Temperature Short Time) that automatically diverts the product while sounding an alarm should the temperature of the HTST unit drop below the "safe" set point. It is also required that this be tested every time the unit is started or during every 24-h period. There are many checks to ensure its continual control; however, there still must be a plan should a deviation occur that allows raw milk (high risk/high significance of occurrence in relation to a food safety hazard) to pass beyond the CCP.

Principle 6—Establish procedures for verification "Establish procedures for verification" (CAC/RCP 1-1969, Rev. 3, 1997). This principle requires verification and validation of the CCPs. Verification is defined as "the application of methods, procedures, tests, and other evaluations, in addition to monitoring to determine compliance with the HACCP Plan" (CAC/RCP 1-1969, Rev. 3, 1997) or "those activities, other than monitoring, that establish the validity of the HACCP plan and that the system is operating according to the plan" (NACMC, 1998). Verification confirms that all the defined requirements of the HACCP plan are being performed. Validation is that element of verification which is defined as the act of "obtaining evidence that the elements of the HACCP plan are effective" (CAC/RCP 1-1969, Rev. 3, 1997), or as "that element of verification focused on collecting and evaluating scientific and technical information to determine whether the HACCP plan, when properly implemented, will effectively control the identified food hazards" (NACMCF, 1998). Validation confirms that the appropriate activities are being performed to provide a safe product.

Procedures must exist to verify that the established control of a CCP is functioning properly. As described above in Principle 5, confirmation that the flow diversion valve is performing as required would be an example of a verification activity. The frequency of these checks, the required record or objective evidence providing confirmation that they have been performed, identification of responsibility, defined training criteria to perform the activities, review of deviations, and product dispositions are a few examples of what must be clearly defined in the HACCP plan for each CCP.

Validation would be the confirmation that the time/temperature of the CCP meets the defined criteria for the control of the specific microorganism that must be destroyed and/or prevented to ensure a safe food product.

Verification activities are applicable to the entire HACCP system (not just CCPs). Typical verification activities include verification of preliminary steps and prerequisite programs, review of consumer complaints that relate to food safety, calibration of process control equipment and monitoring instruments, evaluation of end product or in-process testing data, and review of all HACCP records.

Principle 7—Establish documentation and record keeping "Establish documentation and record keeping" (CAC/RCP 1-1969, Rev. 3, 1997). It is necessary to have a well-defined process for identifying and maintaining those records required to demonstrate compliance with the HACCP plan. Records must be available to provide the objective evidence (proof) not only that the CCPs have been controlled according to the required procedures but also that the prerequisite programs are being maintained in an effective manner. Without the record there is no proof that the requirement was met. There must be no assumptions and no activity left to interpretation. The record control program should include the identification of the records, retention times, responsibilities, and requirements for completion. It is recommended that these records be completed in ink or by some other permanent means with changes made by an authorized associate crossing out data and initialing. A strong argument can be made that the use of pencil, erasers, and correction fluid does not provide "permanent" data. Any "blank" fields should be explained. Notations such as "down time," "change over," "waiting for lab approval," etc. could be examples of such explanations. Also, blank forms used to record data must contain current requirements, and, when revised, obsolete versions of the forms must be collected and destroyed. Examples of records are "CCP monitoring activities, deviations and associated corrective actions, and modifications to the HACCP system" (CAC/RCP 1-1969, Rev. 3, 1997).

Management commitment Management commitment is one of two essential requirements that are not specifically mentioned as part of the seven principles. The CAC HACCP document states that "Management Commitment is necessary for implementation of an effective HACCP system" (CAC/RCP 1-1969, Rev. 3, 1997). It further emphasizes that "the successful application of HACCP requires the full commitment and involvement of management and the work force" (CAC/RCP 1-1969, Rev. 3, 1997). This cannot be overstated. Management must convey a positive message of commitment throughout all levels of the operation. This commitment must be shown through words and through actions. It is strongly recommended that management conduct scheduled (i.e., quarterly) formalized meetings to evaluate the compliance status and any issues/concerns with the HACCP plan. It is also recommended that a documented procedure be written that includes agenda items to be reviewed, required meeting attendance, and a minimum frequency for conducting the meetings.

Training Training is the second of the two essential requirements mentioned in the Codex document that are not specifically stated in the seven principles. Codex makes the following statement: "Training of personnel ... in HACCP principles and applications, and increasing awareness of consumers are essential elements for the effective implementation of HACCP" (CAC/RCP 1-1969, Rev. 3, 1997). This also cannot be overstated. It is essential that associates be trained in their related responsibilities. The requirements for being quali-

fied and competent for specific responsibilities including those specific to the HACCP plan must be defined. Records must be maintained to ensure that associates have met the defined training criteria. Remember that this must also be applied to those individuals who are on a temporary assignment. This may include those filling in for breaks, vacations, or sick leave and even those acquired through a temporary employment agency. Well-defined and effective training is essential. As with all procedures, records must be maintained to confirm (prove) that defined requirements have been met.

Prerequisite programs Prerequisite programs, as introduced above in this chapter, are the foundation of an effective HACCP plan. NACMCF developed a HACCP document titled "Hazard Analysis and Critical Control Point Principles and Application," which, as stated above, is designed in relation to the CAC document. This NACMCF document (1997) states the following regarding prerequisite programs:

> "The production of safe food products requires that the HACCP system be built upon a solid foundation of prerequisite programs.... Prerequisite programs provide the basic environment and operating conditions that are necessary for the production of safe, wholesome food" (Stevenson and Bernard, 1999).

The following are some examples of possible prerequisite programs; however, please keep in mind that the identification of specific programs will be unique to each operation and that this list is not meant to be an all-inclusive listing. Again, specific prerequisite programs depend on the specific operation and its overall HACCP plan. Some examples include:

- Sanitation (defines requirements for cleaning and sanitizing activities)
- SSOP (sanitation standard operating procedures)
- SOP (standard operating procedures)
- Basic GMPs
- Foreign material control
- Quality control and microbiological testing
- Document control
- Pest control
- Calibration
- Water quality and water treatment programs
- Sensory training
- Supplier certification and on-going supplier evaluations
- Control of nonconforming product
- Receiving, storage, and control of raw ingredients and packaging materials

- Hazardous material control
- Product identification, traceability, and recall
- Handling customer complaints
- Labeling (application and control of labels)
- Preventive maintenance
- Allergen control
- Training
- Record control (includes record identification and maintenance)
- Formalized management review process
- Corrective/preventive action (includes root cause analysis and follow-up evaluations confirming effectiveness of actions taken)
- Internal auditing

The hazard analysis should reference specific prerequisite programs. As stated above, these are programs that are in place that support the operation's overall HACCP plan. In other words, the existence of a supportive activity either eliminates the hazard or reduces it to an acceptable level. The HACCP plan will reference (link) to the specific prerequisite programs as they relate to specific concerns or hazards. It is essential that these programs are both active and effective. The effectiveness of the HACCP process overall will depend on them. It is quite common to have the majority of potential hazards defined and managed through an organization's prerequisite programs. It is very important to understand the true meaning and impact of these programs. If the potential hazard is identified as a foreign material such as jewelry entering an open container, the potential for this hazard would be reduced or eliminated through an effective GMP program that prohibits jewelry and other loose items in the manufacturing areas.

Let's revisit the process for hazard analysis more closely. While determining the potential risk and severity of a hazard, the impact of this relationship may be lessened by the impact of a consistent effective prerequisite program. This is why it is essential that prerequisite programs are well defined and managed in an effective manner. If these programs are haphazardly adhered to, the reliance on them to have a positive effect on potential food safety hazards will be lessened.

It might be asked, "Why bother with the prerequisite program? Just call it a CCP and manage it through the HACCP plan." This absolutely must not be an option. A CCP has significant and specific requirements. Keep in mind that the definition of a CCP states, "If this point in the process is not controlled then it will either result in a food safety hazard or at a minimum a potential food safety hazard" (CAC/RCP 1-1969, Rev. 3, 1997). By identifying a point in the process as a CCP, it is being said that this point, if not controlled, will result in either a food safety hazard or a potential food safety hazard. Basically

it does not matter if, in reality, this is the case. In addition, it creates many requirements of the HACCP process, which may not always be practical. It must be further emphasized and clearly understood that a deviation of a CCP is critical and requires an immediate corrective action to protect the product. Every deviation must be addressed and documented and have records to show actions taken. A predetermined corrective action must define an immediate action to be taken to divert the product and to ensure that the hazardous or potentially hazardous product is not released for consumption.

"HACCP cannot be successfully applied in a vacuum. Rather, HACCP must be supported by a strong foundation of prerequisite programs. It cannot be overemphasized that sound prerequisite programs are essential to successful development and implementation of a HACCP system" (Sperber et al., 1998). An effective HACCP plan is supported wherever possible by well-defined and effective prerequisite programs.

Prerequisite programs differ from the overall HACCP focus in that most often these types of programs function across product lines managed system-wide rather than according to a product-specific focus. Generally a deviation in a prerequisite requirement will not directly result in a food safety hazard. It is the effectiveness of the overall program that has the direct impact on the HACCP system. "Deviations from compliance with a prerequisite program usually do not result in action against the product. Deviations from compliance in a HACCP system normally [do] result in action against the product" (Sperber et al., 1998).

Specific prerequisite programs are going to be unique to every process. As implied throughout this chapter, there really is no right or wrong program. A diverse cross-functional trained team performs the development of the HACCP plan. The identification of the hazards and the related prerequisite programs should be identified through the team evaluations.

Implementing the HACCP System

It is very important to follow each step in the HACCP plan implementation process, and a separate HACCP plan will be necessary for each product process. For example, an orange juice processor that manufactures and packages fresh juice, chilled juice, and frozen concentrated juice would have three separate HACCP Plans. It may be possible to define one plan for the activities that all have in common, such as receiving; however, care must be made in doing this because what may be a CCP for one process may not be for another. For example, fresh orange juice may require a CCP in fruit washing and grading to control a particular biological hazard such as *E. coli* O157:H7, whereas the pasteurization step for chilled orange juice may be the CCP to control that hazard.

As discussed above, the HACCP team must carefully evaluate the risk-severity relationship. Severity of a problem could be high but the potential for occurrence extremely low. For example, *E. coli* O157:H7 contamination in

frozen concentrated orange juice has, to the best of my knowledge and literature review at this writing, never occurred. I would challenge a system that has defined heat treatment on an orange concentrate evaporator as a CCP, because there is no scientific data to indicate that this organism could even survive in this product. As a matter of fact, all existing data indicates that it could not survive. If there is a concern, then this should be monitored as part of the quality program. There would technically be nothing wrong with calling it a CCP, but doing so creates many requirements of the system, which may not be practical. Remember, realistically, there really is not a right or wrong program. The program is what the processor defines.

It is important that management understands what is involved in identifying a CCP. By definition, a CCP states that if this point in the process is not controlled it will result in a food safety hazard or, at a minimum, a potential food safety hazard. Deviation from a CCP is critical and must be addressed. Every deviation must be dealt with; documentation and records must show actions taken. This is why it is so important to carefully consider the commitment that must be given to each CCP.

In a fluid milk operation, pasteurization would be identified as a CCP. Scientific data and food laws explicitly provide evidence that if raw milk is not heated to a specific temperature for a specific time period the likelihood and severity of a potential food safety hazard is high. In other words, it is very likely to occur. If a deviation of this CCP occurs in this process, then a preplanned corrective action would be initiated to prevent the suspect product from being consumed. Think about the relationship and the potential seriousness when comparing this with the evaporation process in a citrus operation. If heat treatment is identified as a CCP, then the same controls, sense of urgency, record keeping, etc., must be applied.

The HACCP team, supported by top management, must review the scientific and technological data available and make sound business decisions. It must be emphasized that these comments should not be misunderstood to imply that these process activities are not important—they are very important and can be addressed successfully through quality and prerequisite programs without burdening the process with the requirements of a CCP.

Managing the HACCP System

Once the HACCP Plan has been implemented, it is necessary to have a defined means of ensuring that it is continually managed in a compliant manner. An individual should be assigned the responsibility to ensure that the defined plan is monitored for compliance. This would include the verification and validation requirements defined for Principle 6.

Verification confirms that all requirements are being performed as defined. Responsibility on a daily basis should be assigned to the departments performing the functions; however, verification can be further accomplished through a well-defined internal auditing program. These internal audits should be per-

formed at defined frequencies that are sufficient to monitor the compliance of the program. Auditors trained in compliance requirements should perform audits with records maintained to confirm activities. Identified noncompliances or potential noncompliances, whether identified from the audits or just routine activities, should be well documented, including root cause analysis, timely response to findings, and follow-up for effectiveness of actions taken. It is recommended that, if the system has a Quality Management System, auditing the HACCP plan be incorporated into this process. It is very important that the auditors are trained in HACCP requirements (such as the Codex document) before initiating the audits. Audits should also include the evaluation of prerequisite programs. Records of the audits should be included as part of the HACCP record system.

Validation is confirmation that the defined requirements are the correct requirements to ensure the production of a safe product. This would most likely be done independently of the audit process; however, as stated regarding Principle 6, requirements to ensure that this is done effectively must be fulfilled at a predefined frequency.

It is also recommended that top management review the status of HACCP activities through a structured, scheduled (quarterly or semi-annually) management meeting. If this system is ISO compliant, the status of the HACCP plan would be an excellent subject to be discussed at the Management Review meeting, providing evidence of preventive action and overall system proactivity.

Integrating HACCP

Food companies that are ISO compliant or that are pursuing the implementation of a quality management system have asked about the relationship between ISO and HACCP. It should not be a choice between one and the other. "Individually they are both excellent programs. Integration of the two can bring the best of both plus much more.... HACCP focuses on product safety while the ISO standards focus on the overall quality management system.... HACCP and ISO are fundamental to a process focusing on preventing rather than detecting or correcting a problem. The integration of these valuable tools not only makes good common sense but also good business sense. Keep in mind that both ISO and HACCP have a main objective to be proactive, preventing problems rather than fixing those occurrences that have gone wrong" (Newslow, 2001).

Which one to do first? The answer to this really depends on what has already been established. From personal experience, I would argue that having the structure and discipline inherent with an established ISO-compliant quality management system can be a huge benefit in implementing HACCP. However, that said, having an established, effective HACCP plan would also provide a strong process control foundation for a quality management system's implementation process. The decision belongs to the management of the system, but [as stated by Randy Dougherty] "a food company cannot have food quality without food safety" (Newslow, 2001).

REGULATORY IMPLICATIONS

Regulatory requirements for HACCP in the food industry are being implemented by several countries throughout the world (e.g., Australia, Canada, European Union, United States, and others). In the U.S., the U.S. Department of Agriculture (USDA)/Food Safety and Inspection Service (FSIS) has implemented mandatory HACCP regulations for meats and poultry (FSIS, 1996). In addition to HACCP requirements, this regulation emphasizes SSOPs and pathogen testing requirements. The U.S. Department of Health and Human Services (DHHS)/Food and Drug Administration (FDA) has implemented mandatory HACCP regulations for seafood products (FDA, 1995) and fruit and vegetable juice products (FDA, 2001). In general, under FDA HACCP regulations, failure to have and to implement an acceptable HACCP system by an affected processor constitutes food adulteration under the FDCA. FDA HACCP regulations also emphasize prerequisite programs such as SSOPs that address the following: safety of water; condition and cleanliness of food contact surfaces; prevention of cross-contamination; maintenance of hand washing, sanitizing and toilet facilities; protection of food from process-related adulterants; proper labeling, storage, and use of toxic materials; control of employee health; and exclusion of pests. The juice HACCP final rule also requires that processors have control measures that will consistently produce, at a minimum, a 5-log (10^5) reduction of the pertinent pathogen. Mandatory HACCP regulations are also under consideration for other segments of the food industry (e.g., alfalfa sprouts). Moreover, as described in Part VI, state regulatory agencies are moving toward HACCP programs for the retail foods sector through adoption of the FDA Food Code.

Manufacturers and retailers should review updates and the current status of regulations. Whether requirements are voluntary or mandated, each and every establishment that handles our food supply has an inherent responsibility to produce "safe" products. Current requirements may be acquired through federal documents and related texts written with a total focus on this subject. It is very important to review current material because requirements and recommendations are continually updated. Internet searches may be the best source of information and may lead to current reference material.

CURRENT AND FUTURE IMPLICATIONS

It is very important that each operation evaluates its processes as related to the defined requirements for HACCP as documented in the CAC HACCP requirements (1997). Food safety is everyone's first concern.

Each processor should have an up-to-date HACCP plan that focuses on food safety. This must be unique for each operation. The HACCP plan must include each step in the process, clearly addressed, including the identification and justification for each CCP, requirements related to each CCP, and records

to confirm compliance with the defined requirements. The purpose of this chapter is to provide an overview of the requirements, and not a "generic" plan. Generic programs do not provide the most effective HACCP plans. Each operation must understand the concepts and apply these to its processes. Benchmarking can be a very useful tool in the development and ongoing validation of a HACCP plan. Keep in mind that the HACCP plan must reflect the specific operation and not be a wish list or have points addressed only because another operation has done it. It is essential, imperative, and absolute that the plan be unique to the process and that it reflect the specifics of the product for that process. In reality, there is no specific right or wrong program. It is the program that each operation develops for its specific processes that provides confidence that the product is safe while making good practical business sense.

It is not completely clear when and if HACCP will be required of all food manufacturers, but whether it is a mandated requirement or not, having a well-defined and effective HACCP plan just makes good business sense. Having a program developed with the guidelines and thought patterns discussed in this chapter and elsewhere in this book can be effective. Keep in mind that a HACCP plan must not be considered a static program. It does require periodic (recommend at least semi-annually) validation and verification. It is through these reviews that the effectiveness of the defined HACCP plan, changes in technology, scientific data, and any other practical considerations should be evaluated. Any changes in the process or other activities must also result in a special review of the HACCP plan. It is essential that the HACCP team be empowered with the knowledge and authority to establish, maintain, and evaluate a food safety program. Team efforts must be supported by management commitment. Management commitment must be communicated through all levels of the operation and must provide the resources (e.g., money, people) including training to provide the basis of an ongoing effective HACCP plan. Nothing is more important than producing a safe product—a product that each associate would feel safe to feed his or her own family. Safety comes first, and although a HACCP plan does not guarantee a safe product, applying the complete HACCP guidelines makes it possible to develop and maintain a program that provides confidence while making good business sense.

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PART V

FOOD SAFETY OPERATIONS IN FOOD PROCESSING, HANDLING, AND DISTRIBUTION

Edited by BARRY G. SWANSON

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CHAPTER 21

FOOD PLANT SANITATION

HENRY C. CARSBERG

INTRODUCTION AND DEFINITION OF ISSUES

Sanitation Technology encompasses many areas including designing and implementing a program that support a total food safety system. There are many factors which make up a total sanitation technology "package" that will effectively insure the safety of the produce not only while the product is being produced, but when it leaves the plant and reaches the consumer. In reality, the sanitation program is the final stop gap to how safe the product will be. If the surfaces are not properly cleaned and sanitized a carry over of bacteria will be present and will in fact infect the new product being processed.

The purpose of implementing a sanitation system using the latest technology is to eliminate any foodborne pathogens on all food contact surfaces. There are many factors involved, and a variety of techniques must be used to accomplish this task. Sanitation Technology encompasses many factors and a properly trained sanitation team will be proficient in the following areas:

- Cleaning Chemistry
- Sanitizing Chemistry
- Sanitation Equipment
- Microbiology (as it pertains to foodborne pathogens)
- Rapid Testing
- ATP Testing
- Labor Usage
- Sanitation Procedures
- Food Technology (as it pertains to organic challenge)
- Food Contact Surfaces
- and additional factors which will be covered in this chapter.

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BACKGROUND AND HISTORICAL SIGNIFICANCE

In the past, sanitation was not particularly considered to be of much importance. It was a low paying position, used as an entry level position. There was little or no training and generally a lack of supervision. This resulted in high turn over of personnel. Sanitation operations were primarily conducted at night, which made it more difficult to maintain a full staff. Usually sanitation operations were placed under the direction of the production staff, which often meant that sanitation took a back seat to production runs. However, in the last 3 to 4 years, a different attitude has developed, probably due to the high profile recalls and foodborne pathogen infections bombarding the media. The sanitation staff has begun moving to the forefront and has become a separate department working closely with the quality assurance department. As sanitation is gaining new importance, more attention is being paid to the selection of sanitation personnel, training, and other technical considerations that are part of a professional sanitation/food safety program.

SCIENTIFIC BASIS AND IMPLICATIONS

Contributing Factors of a Total Sanitation/Food Safety Program

Type of food contact surface The type of material used to make up the food contact surface is of great importance. These surfaces are comprised of many materials including:

- Stainless Steel
- Rubber
- Plastic
- Fiberglass
- Concrete
- Mesh Belts
- Soft Metals
- HMU
- Wood (in some rare cases)

All materials are either porous, or as in the case of metals such as stainless steel, aluminum and others, when viewed under a microscope, have jagged saw tooth ridges. The metal surface appears to be smooth, but in reality it is a very rough terrain. Organic residues become attached to these areas and provide a good source for the bacteria, and also contribute to becoming a biofilm.

Organic challenge and biofilms In 1965, Jennings described soil as "matter out of place." Soil or organic challenge is food product or residue that does

not belong on the contact surface. The most common of soils are proteins, fats, oils, grease, carbohydrates, sugars and mineral deposits such as calcium carbonates, and burned on carbonaceous material from hot oil processing.

For every type of soil there is a different chemistry and method for removal. Fats, oils and grease require a hydroxide type of chemistry, but minerals require an acid product. Burned on soil requires a boil out technique using a high pH product.

Biofilms are probably the most dangerous of soil loads because they are difficult to detect and are a harborage and food source for bacteria, Any time there is a synthetic material in contact with a bio product, such as food soil, biofilms will occur. Pasteurizers, paddles, and other equipment will support the presence of biofilm. Synthetic conveyor belts also prove to be supportive of biofilm growth. Proteins are required for the bacteria to adhere to the surface, and as the proteins unfold, they become attached to the surface, and once attached, begin to build until a thin layer is present.

Removal of these biofilms requires hydrodynamic shear, the correct chemistry, and hand detailing with brushes and scrub pads.

The type of surface is directly related to the biofilm build up. Porous or rough surfaces provide a favorable surface for attachment. Higher surface tension can cause a more rapid attachment, whereas lower surface tension tends to decrease attachment. A thorough knowledge of the type of soil, and the type of surface is paramount to determining how to prevent, and how to eliminate biofilm.

The role of water in cleaning and sanitizing Water in itself is very solvent, and is a major ingredient in cleaning systems. The chemistry that is used is diluted with water, high pressure systems using water are used in cleaning, and water is a major player in removing soil loads, and bacteria from food contact surfaces. But, water can also be a detriment. When water used for cleaning is contaminated, problems will occur. All plant water should be tested quarterly for any foodborne, or waterborne pathogens. Another potential problem is water that is above 130 degrees fahrenheit. At this temperature, proteins begin to be "cooked" onto the metal surfaces, and the pores of most all materials are opened, allowing fats, oils, grease, and protein to enter the material. After a period of time, a brown rainbow film begins to appear which is actually the development of a biofilm. Using water at too high a temperature will also increase energy costs. Fats, oils and greases can be removed at a lower temperature, and do not require such high heat. Steam cleaning is definitely a disadvantage since a 212°F product is cooked on very rapidly. Also, high water temperature will increase in precipitation of minerals left over from processing the food ingredients and additives, and now calcium carbonate and other minerals will leave a white, chalky deposit. Water is an excellent tool, but if not used properly, can cause more work than anticipated.

Methods of agitation There are various methods of agitation used to remove organic soils, which include:

- Hand Detailing
- High Pressure
- Chemical Agitation
- Steam Cleaning (which has been used, but its disadvantages far outweigh its advantages.)

High pressure cleaning has been used, but in recent studies it has been found that high pressure cleaning produces aerosols, which allow bacteria to be transported to other areas of the environment. Thus, can produce a false sense of security to the people using the system because they feel that high pressure in and of itself provides adequate cleaning. High pressure can be likened to a leaf blower in that it moves the organics from one area to another, but in fact, it can cause mechanical damage to equipment, such as electrical boxes, bearings, etc., and in general, can cause more work than is necessary.

However, there is a place for high pressure cleaning in outside areas such as loading docks, etc.

Chemical agitation is effective in the form of gel and foam cleaning products. The basic cleaning ingredients in the chemical formula are held in place by the foam or gel carrier, and allow the cleaning product to dwell or "cling" to the vertical and radial surfaces, allowing the cleaning product to digest and release the organic challenge. Foam and gels are not in themselves cleaning products, but act as a method to hold the cleaning chemistry in place. Too much foam or gel can cause a post rinsing problem in that more water must be used to rinse the foamed or gel product from the food contact surface. Hand detailing has never been and never will be, eliminated from the leaning procedures. Hand detailing has one major advantage in that it forces the cleaning staff to inspect the surfaces that have been detailed to be sure that all organic challenge has been removed. Inspection of this cleaning step is critical due to any resident organic challenge that has not been removed. Inspection of this cleaning step is critical due to any resident organic challenge that has not been removed, will not be rinsed, therefore creating a food source and a harborage for bacteria to reside and multiply. Many pre-ops have failed due to this one lack of detail.

Rinsing sequences There are two rinses in the five step sanitation cleaning cycle. First is the pre-rinse, and the second is the post-rinse, prior to application of the sanitizer.

The purpose of the pre-rinse is to remove the majority of any organic challenge. This step reduces the amount of cleaning chemical that must be used, removes the heavy particles off the surfaces, and can remove up to 20% of the resident bacterial from the surface.

The post-rinse cycle removes any and all organic soils that have been removed by hand detailing and chemical agitation. This post rinse cycle has also been shown to remove up to 20% of residual bacterial. Also, it is impor-

tant to note, that this post rinse is critical because any and all cleaning chemistry and organics that remain will greatly affect the sanitizer that is applied. Note that most cleaning chemistry is used at a pH of 12 and higher, and it is natural for most quaternary sanitizers to be on the acid side, as is the case of iodophors and acid sanitizers. If equipment is not rinsed thoroughly after cleaning, residual detergent will raise the pH which could reduce the effectiveness of the sanitizer used. Post rinsing is most critical because is prepares the surfaces for the most important step of all, the application of the sanitizer.

Time and schedules Plan your work and work your plan. There are many complexities to our process environment: the processing equipment, production run times, return on investment. Therefore the food safety/sanitation crew needs to work smart. This is accomplished by carefully developing manpower schedules, cleaning and sanitizing times, written cleaning procedures for each piece of equipment, and realistic allocation of time and labor resources.

First, cleaning procedures for each piece of equipment and the environment must be written. Each piece of equipment must be cleaned and sanitized in a step-by-step process. A plan or procedure needs to be developed to instruct how to clean and sanitize. At this point in time, a determination must be made as to how much work needs to be accomplished, how many man hours are required to complete the task, what cleaning equipment will be utilized, and how will the chemistry be applied.

Once that has been determined, cleaning zones are established and equipment and manpower is assigned. The establishment of man hours is directly determined by the complexity of the equipment, and the time allocated for the cleaning cycle. The size of the cleaning alone is predicated upon the pieces of equipment required to be cleaned in a specific time. In some cases, a zone can be the entire plant. In other cases, a zone can be just one piece of equipment.

One reason why the food safety/sanitation cycle has not been considered a good return on investment is that planning and scheduling of the labor force has not been done. Labor is approximately 70–75% of sanitation costs, so if the food safety/sanitation works efficiently, a return on investment is accomplished.

Sanitation schedules are mandatory. They identify what the pieces of equipment are, and what areas (zones) the equipment is located in. In addition, other data important to sanitation and Hazard Analysis Critical Control Point (HACCP) plans is also included, such as the date the equipment was cleaned, who cleaned it, and what chemistry was used to clean and sanitize, and other data that is important to the specific operation. The schedule is usually designed for a 30-day cycle. At the end of the cycle, the completed schedule is copied and filed for future reference as needed. Laminating the schedule in plastic allows the information to be written in felt-tip and wiped clean after being copied, so the master remains intact for the next cycle.

Having a work plan can also allow the latitude of placing staff in other areas in the event of sickness, vacation, or used for cross training. Planning the work is paramount in having a processional food safety sanitation plan.

Sanitation Equipment

In days gone by, the old bucket-and-brush method was in vogue. Processors just did not want to spend any more money than they had to on a sanitation program. However, that attitude has changed due to the fact that dilution equipment can actually save dollars in chemistry. And, foamers, central foam systems, and CIP systems can save on labor, which is the most expensive part of a sanitation program. Cutting down on chemical costs is really only about 10% of the cost equation, where labor is about 70% of sanitation costs. That leaves the final 20% of costs in waste water management. This adds up to one very important reason why food safety/sanitation personnel should be trained in all areas of food safety and the methods of sanitation.

There are several methods of applying cleaning and sanitation chemistry:

Foam tanks These are 15 or 30 gallon tanks that can be filled at a diluter and are charged with about 60 lbs. of air pressure. These units are ASTM pressure vessels and are a single use only in that only one chemical can be applied, either a cleaning compound, or a sanitizer. Because of the surfactants in quaternary products, foaming is high, and therefore allows the quaternary to maintain a longer residence on radius and overhead surfaces.

Foam carts This is a stainless steel cart that holds 2, 5 gallon pails, one of which is the sanitizer, and the other is a cleaning compound. Lafferty Equipment in Little Rock, Arkansas manufactures a quality design, foam/rinse/sanitize unit. The entire unit is of stainless steel, and is complete with hose, wands and other accessories. All chemistry is automatically diluted. The unit will cover an 80 foot radius which cuts down on labor because the unit does not have to be moved as often. I mention the Lafferty unit only because I am most familiar with it. There may be other units that are similar on the market.

Clean in Place (CIP) systems These systems are usually found in dairies, beverage plants, and other processing facilities and allow for cleaning and sanitizing without having to disassemble the equipment. One type of Clean in Place (CIP) system is engineered and designed by the Sanimatic Corporation in Wisconsin. All CIP systems have the capability to inject chemical product at the prescribed dilution rate without any hand mixing. However, care must be taken to titrate the chemistry on a bi-weekly basis to insure the dilution rates are in fact correct. One other possible trap is that the CIP system needs to be inspected on a regular basis to insure that the cleaning efficiency is at the optimum. Doing micro counts is of great importance as well, to insure that the system is operating at full efficiency. Non-foaming cleaners and sanitizers are used in CIP cleaning. A foaming product can cause cavitation of the pump impellers, and also will reduce the cleaning efficiency of the system.

COP systems COP is cleaning out of place. This means that equipment is disassembled and placed in a tank which allows the equipment to soak in the cleaning solution. A pump can be installed which will allow the water to agitate the parts, or air can be introduced to cause agitation. Time is of the essence in COP systems since dwell time and agitation is very important, and as in CIP systems so is the dilution of the cleaning chemistry. As with CIP systems a non-foaming cleaning product is used.

Central foam/sanitize systems Without a doubt, this is one of the best methods for cleaning and sanitizing food processing facilities. All of the chemistry is placed in a locked room. Also in this room are the pumps which dispense the chemistry automatically. Usually Doseatron or Doseamatic water driven pumps are used. From this locked room the chemistry is pumped to Foam/Sanitize Drop Stations throughout the plant in schedule 80 piping. The installation costs are low, chemical safety and economy is achieved, and labor costs are reduced. Maintenance is low, if any, since there are no moving parts to speak of. A central foam system is easily installed in a new plant, and can be readily installed in an existing facility.

High pressure systems High pressure systems are excellent in some areas such as cleaning outside areas, fork lifts, pallets, loading and receiving docks, and in some cases plastic and stainless steel interlock belts. The problem in food processing facilities is as follows: It tends to create a false sense of cleaning efficiency on the part of the food safety/sanitation staff. Safety becomes an issue as the high pressure spray can come into contact with other employees causing injury. It also serves to spread organics to other areas of the plant, transporting bacteria to previously cleaned areas. Proper and accurate dilution of the chemistry is really only achieved at about 6 inches from the nozzle of the high pressure tip, after that distance the pressure is substantially reduced. Also an air current, along with an atomized vapor causes a "blowing" effect which aids in transporting organics and bacteria, often to undersides of equipment or areas that are difficult to reach with regular cleaning methods; in fact creating more work.

Foam/Sanitize drop stations Foam/Sanitize drop stations are similar to the central system, but rather than transport the chemistry from a central location, the chemistry is brought to the production area after processing, in 5 gallon pails. Since chemistry is not allowed in a processing area during operation, all chemistry must be kept in a secure room or cage until ready to use. This can cause some inconvenience, but is a controlled method of dispensing the chemistry, and at the same time contributes to reduced labor costs in application.

Cleaning Chemistry

Cleaning chemistry is sometimes made into the "cure-all" for sanitation programs. Chemical suppliers put the emphasis on chemicals because that is all they usually consider when examining a sanitation program. Chemicals are really only one of the many tools used in a total sanitation program. A mechanic does not use only a wrench or screwdriver, but has many other tools at his disposal.

First to consider is the pH of the chemical product. The pH does nothing more than tell the user whether the chemical product is an alkaline, or an acid. The type of organic challenge encountered will determine what the pH of the product should be. The following illustration shows a pH scale from 0 to 14 with 7 being neutral pH.

0 ----------7----------14
ACID NEUTRAL ALKALINE

Chemical is tested using pH test strips to determine whether it is acid or alkaline, or you can use a causticity test kit or a pH meter.

Acid products are used for removing mineral deposits such as milk stone, beer stone, and calcium carbonate types of minerals, rust and so forth. The stone type of deposits and calcium carbonate products are usually a result of heating and causing the minerals to precipitate out of solution and attach themselves to the food contact surface. This action is also similar to what happens in boiler tubes. The boiler tube becomes hot causing the mineral to precipitate out of solution and deposit onto the tubes. This causes a reduction in the heating process and the minerals must be removed by chemical action. The same occurs with cooking equipment. One example is that of cooking crab. The calcium and other minerals in the crab shell are put into solution and deposited on the cooker. Another example is in the making of beer. Beer stone is a result of cooking the grains and various ingredients in the wort onto the sides of the cooking vessel.

There are many acids on the market (e.g. phosphoric, sulfamic, nitric) that can remove the mineral deposits. The best way to keep mineral deposits from forming is to have a sanitation program that addresses this problem on a scheduled basis.

Neutral pH products are not used a great deal in the food processing industry due to the type of organic challenge that is encountered. However, there are some special applications when an acid or an alkaline product can do damage to equipment, plastics, or other materials. Then a neutral product is indicated.

Alkaline products are in the pH range of 7 to 14. The higher the pH, the stronger the action of the alkaline. At one time straight caustic was used to remove carbonaceous deposits, fats, oils, greases, and the like, but that is old technology. Alkaline products are now blended to include surfactants, wetting agents and other ingredients to increase the efficacy of the product.

Alkaline products are indicated for use on organic challenge such as fats, oils, grease, protein and carbonaceous deposits as found on doughnut fryers, deep fryers, ovens, etc.

A very efficient chemistry is that of a chlorinated caustic product which when used is very effective on protein. A peptizing effect is caused when the proteins, chlorine, caustic, wetting agents, and surfactants meet together. The most efficient ratio of chlorine/caustic is to achieve chlorine levels at 600 ppm, with a pH of 13 at a 50:1 dilution, or as high as 1 ounce of product to 1 gallon of water. Anything less just does not have the same cleaning efficiency.

The Common Detergent Ingredient chart (Table 21.1) will provide the insights needed for determining the chemical product to use and the efficiency of the various chemical ingredients.

When evaluating chemical costs, examine both the purchase cost of the chemical product, and the use cost. One should keep in mind that the lower the chemical purchase cost, the probability of less solids in the product. The purchase cost is the cost to buy the product, and the use cost is the cost to use the product. Keep in mind that a higher dilution rate will in turn mean a lower use cost and may also reduce the amount of hand detailing that may be required. Some chemicals are diluted at so many ounces per gallon, while other products are diluted in percentages. i.e., 3% per gallon of water rather than so many ounces per gallon of water. Always go by the number of ounces per gallon of water, as that is how dilution equipment is designed. One product may state to use one ounce per gallon, and another product may prescribe a 3% solution. A 3% solution would equate to 3% of 128 ounces of water, so the per ounce dilution rate would actually be 3.84 ounces per gallon. Quite a difference!

As to use cost, simply divide the purchase cost by 128 ounces to obtain the cost per ounce. Then multiply the cost per ounce by the use rate to obtain the use cost per gallon. An an example: at a purchase cost of $4.95 per gallon for chemical product, and the use rate is a 3% solution per gallon of water. Divide 4.95 by 128, the result is .038 cents per ounce. For a 3% solution you need 3.84 ounces per gallon, the use cost is .038 cents per ounce multiplied by 3.84 ounces, so the use cost would be .146 cents.

On the other hand a chemical product that costs 7.95 per gallon, but has a dilution rate of 1 ounce per gallon of water, or 7.95 divided by 128 equals .062 cents per ounce, so the use cost is .062 cents per gallon.

You can see that a difference of $3.00 in the purchase cost per gallon actually results in a use cost savings of .084 per gallon use cost. The reason? The higher priced product probably has more solids and is a higher blend of chemicals therefore it is a higher concentrate requiring less product to produce more cleaning solution. (Another hidden benefit is that you will actually purchase a little less product, as it will go farther.) The point of this exercise is to show you that you're missing the point if you only consider the purchase cost of a product. Consider the solid content, quality of the product and the dilution rate as well. A chemical supplier can very easily spec out the product without giving away secrets. In other words, know what you are buying. There is no cure-all,

TABLE 21.1

Common Detergent Ingredients													
Key to Chart A..... High Value B..... Medium Value C..... Low Value D ..... Negative Value *..... Via Precipitation ▲ ..... Via Sequestration ◆ ..... Also Stable to Heat		Comparative Ability											
	Ingredients	Emulsification	Saponification	Wetting	Dispersion	Suspension	Peptizing	Water Softening	Mineral Deposit Control	Rinsability	Suds Formation	Non-Corrosive	Non-Irritating
Basic Alkalis	Caustic Soda	C	A	C	C	C	C	C	D	D	C	D	D
	Sodium Metasilicate	B	B	C	B	C	C	C	C	B	C	B	D
	Soda Ash	C	B	C	C	C	C	C	D	C	C	C	D
	Tri-Sodium Phosphate	B	B	C	B	B	B	A*	D	B	C	C+	C
Complex Phosphates	Sodium Tetra-Phosphate	A	C	C	A	A	A	B▲	B	A	C	AA	A
	Sodium Tri-Polyphosphate	A	C	C	A	A	A	A▲	B	A	C	AA	B
	Sodium Hexametaphosphate	A	C	C	A	A	A	B▲	B	A	C	AA	A
Organic Compounds	Tetrasodium Pyrophosphate	B	B	C	B	B	B	A▲	B	A	C	AA	B
	Chelating Agents	C	C	C	C	C	A	AA◆▲	A	A	C	AA	A
	Wetting Agents	AA	C	AA	A	B	B	C	C	AA	AAA	A	A
	Organic Acids	C	C	C	C	C	B	A◆	AA	B	C	A	A
	Mineral Acids	C	C	C	C	C	C	A◆	AA	C	C	D	D

or a one product-does-all. Take all claims about how good a chemical product is with a grain of salt until you determine what the quality of the product really is.

Chemical Definitions

Saponification The chemical conversion by an alkali of water insoluble fatty acid soil in more soluble substances, soaps. That is why a deep fat fryer should be rinsed with an acid product. The alkaline of the cleaner will mix with any residual oil, thereby creating a "soap," and may cause the finished product to have a "soapy taste."

Emulsification This is the action of breaking up fats and oils and dispersing them throughout the cleaning solution. The emulsion formed must be stable enough to prevent these soils from redepositing on the equipment surfaces.

Dispersion This is the action of breaking up the solid aggregate of the soil into smaller particles to colloidal size. This is accomplished through the action of the chemical media and mechanical agitation or hand detailing.

Peptization This occurs only by chemical action without agitation and can be considered as spontaneous dispersion of the solid soil throughout the cleaning solution. Peptization is usually associated with the removal of protein soils.

Solubilization This reaction happens in one of two ways—one is chemically, the other is physically. Lactose, found in milk solids, is soluble in water and therefore easily removed. Mineral salts, found in stone deposits are solubilized by acid cleaning solutions chemically altering these products into soluble substances. Some insoluble oils are easily solubilized by surface active agents by the action of the micellular structure in an aqueous media.

Suspension The holding of the removed particulate matter in the liquid phase. Suspensions can be stabilized by the use of polyelectrolytes in solution which maintains a positive or negative charge on the dispersed phase. A stable suspension of soils is particularly important in preventing redisposition of the soils.

Wetting/penetration agents The use of these agents depends upon diffusion rates, surface tension, concentration, and how rough the surface of the material is. Surface active agents are clearly much better to all other products in lowering the surface tension of the cleaning solution allowing the oils to be rinsed away, and the penetration of the agents into cracks and into the holes of the solid deposits.

Rinsability The ability of a detergent to be freely rinsed from the surface. This ability is of prime importance since not only is the chemical product rinsed away, but also any bacteria that has been destroyed in the cleaning process. There should not be any residue cleaning chemical on the surface since the residue can affect the sanitizing chemistry.

Water softening Water softening renders the hardness of water unavailable for reaction with the components of the cleaning solution. Caustic soda will form a film of calcium and magnesium carbonates in hard water. Softening will precipitate the hard water elements as insoluble salts. Chelater chemicals tie up mineral products so as not to affect the product's cleaning effectiveness.

Corrosiveness Protecting the processing equipment from harsh cleaning products is important due to the deterioration of the metal. Some cleaning products will "burn" aluminum, and will destroy galvanized coatings. Also, bronze and copper metal will be destroyed by high pH cleaning products. In this instance, a neutral buffered chemical product is indicated.

Food Plant Sanitizers

What are they? Sanitizers are chemical agents used to reduce microbial contamination in food plants to an acceptable level. They are not meant to leave a surface sterile.

Why use sanitizers? The application of sanitizers are to help reduce product contamination during process and/or to help reduce counts from raw product.

Most cleaning operations are not sufficient to destroy or remove the bacteria present in a food plant. Therefore, we must use a chemical method to reach our goal of a sanitary surface, and reduce our risk of food contamination during processing and handling.

As a general rule, an unclean surface cannot be sanitized effectively. Therefore it is critical to both clean and sanitize regularly.

Who regulates sanitizers? In 1972, the Federal Environmental Pest Control Act defined "pest" to include bacteria and other micro-organisms. These sanitizing agents are regulated as pesticides, and are subject to the strict regulation of EPA set forth to control all use and distribution of these chemicals.

U.S. Department of Agriculture also has guidelines that must be met before a chemical is approved for use in an inspected food plant. They publish a "List of Chemical Compounds Authorized for Use" in which all such approved products are listed.

When purchasing sanitizing products, be sure they met both EPA and USDA requirements. Labeling is controlled by EPA and must be followed to the letter.

Chlorine: Form: Liquid Sodium Hypochlorite

There are many forms of chlorine releasing compounds but Sodium Hypochlorite is most common.

By far the most widely used sanitizer in the food industry worldwide, it is inexpensive and readily available. It is produced by reacting chlorine gas with sodium hydroxide (liquid caustic). It is highly activated by acids and deactivated as sanitizer by alkaline. Sanitize with this product at pH below 8.5. It is approved at a maximum concentration for no-rinse at 200 ppm on food contact surfaces.

Advantages

1. Fast germicidal action, is non-selective.
2. Dissolves easily since it is liquid.
3. Easily dispensed in controlled amounts.
4. Uniform concentrations since contents of container have same strength throughout.
5. Does not form films and isn't affected much by hardness or other water constituents.
6. Economical.
7. Very available.
8. No "pinpoint burning" of use solution vats.
9. Use dilution nontoxic.
10. Use concentration easily measured by convenient field tests.

Disadvantages

1. Characteristic odor.
2. Staining or bleaching, if spilled.
3. Comparatively short shelf life. Should be kept in cool, dark, storage area to maintain stability.
4. Must be protected from freezing.
5. High rate of interaction with organic matter decreases strength as soil is absorbed into sanitizing solution.
6. Variations in product alkalinity can affect germicidal action.
7. Misuse can cause rusting, pitting, and corrosion.
8. Possibly harmful to skin.
9. Precipitation in water containing iron may render it unacceptable.
10. Hazardous when present with acids.
11. Dissipates quickly in use dilution strength.

Chlorine Dioxide—A Comparison between Chlorine and ClO_2

Chlorine Dioxide has been in existence since about 1811, and short period of years after the discovery of chlorine. Both chorine, and chlorine dioxide were discovered by Sir Humphrey Davey.

Chlorine was used during World War I as a gas, in chemical warfare. It can be lethal. A safe way to handle chlorine, however, is to use it in the form of sodium hypochlorite, aka bleach. Hypochlorous acid is formed at the correct pH when dissolved in water.

Since the 1940's, chlorine dioxide has come into it's own and is currently used in many applications as a sanitizer and disinfectant. Such as, bleaching of pulp in paper making, bleaching of flour, drinking water disinfectant, as a vegetable wash, as well as other applications.

The EPA found that trihalomethanes or chloroforms were a by-product of chlorination. "THMs" were found to be carcinogenic, and an increase in cancers was detected where there were high THM levels.

Chlorine Dioxide Chemistry—Chlorine dioxide, a gas which is 50% oxygen by weight, dissolves readily in water. Being an oxidizer, it is very efficient against bacteria.

Chlorine Dioxide is made when two chemicals are mixed together, such as sodium chlorite, and an acid such as phosphoric. The ppm concentration is determined by how much of each product is mixed and diluted in water. (Obviously this is a simplified explanation and not something to be attempted on a trial basis.) The most accurate method is to use a chlorine dioxide generator which mixes the chemical components in exact proportions at the correct dilution. This is accomplished by drawing 2 or 4 chemical components into a mixing chamber, or a generator chamber, then injecting this mixture into the water line leading to where the solution is to be dispensed.

Table 21.2 is a comparison between Chlorine Dioxide and Chlorine.

Acidified Sodium Chlorite (Chlorine Dioxide chemistry) is odorless, colorless in solution, and has a long lasting residual. Also, in diluted solution, ClO_2 is not as aggressive as Chlorine on soft metals such as aluminum, brass, galvanized, etc.

TABLE 21.2. Comparison between Chlorine Dioxide and Chlorine

Chlorine	ClO_2
Chlorinates organics	Oxidizes only
Makes toxic NCL_3	No reaction with NCL_3
Chlorinates phenols	Destroys phenols
Poor deodorizer	Oxidizes sulfides
Carcinogens (THM's)	No carcinogens
pH sensitive (>7.5)	pH insensitive
Good biocide	10× better biocide

Due to the chemical make up of the product it is very aggressive on organic challenge such as that found in poultry chill water systems.

It has been approved as a no rinse category D-2 sanitizer by the USDA, (100 ppm) as a red meat carcass spray, for use in poultry chiller water and as a carcass spray, in seafood ice and processing, refrigerated sea water chill systems, on cut and peeled vegetables, and in ice machines. The dilution rate for these applications is from 1 to 3 ppm.

As a D-2 no rinse sanitizer, it can be used on all process equipment, can be applied foamed, is excellent for use in floor drains, drip pans in cooler units, such as found in produce cooler for the elimination of Listeria. Chlorine Dioxide is also an excellent prewash for fruits, melons, and other produce to reduce the number of pathogens which can exist on the outside skin of the product.

All in all, Chlorine Dioxide is an excellent choice in most all areas of food plant sanitation.

Quaternary Ammonium Compounds: Also known as Quats

Also known as Q.A.C. or Quats, more than one form and often mixed in a sanitizing product. (Hence, dual quats combine 2 forms). Has the reputation for being the safest sanitizer for handling and on equipment surfaces. Quats are forms of cationic surfactants, thus they are thought to have detergent and penetrating properties. Normal use dilution approved for no-rinse is 200 ppm quaternary ammonia.

Advantages

1. No objectionable odor.
2. Very mild to skin, eyes, and clothing.
3. Non-corrosive. (This factor is the same as for the water in which it is used.)
4. Ease of accurate measurement and dispensing.
5. Use dilution readily measured by practical field test.
6. Dissolved solutions react instantly,
7. Very stable in changing temperatures,
8. Very stable in storage.
9. Good penetration qualities,
10. Provides highly desirable residual bacteriostatic film.
11. Outstanding elimination and prevention of odor.
12. One of the best ingredients for "germicidal detergent" formulations.
13. Can be applied as foam because of it being a highly active surfactant.
14. Very good residual bacterial kill.
15. Widely accepted as best sanitizer for plant environmental use (i.e., floors, walls, etc.)

Disadvantages

1. Germicidal efficacy varied and selective, especially against gramnegative organisms. Including coliforms, Pseudomonas, Salmonella.
2. Moderate toxicity in use dilution.
3. Incompatibility with common detergent components complicate use germicidal efficacy may be reduced; objectionable films may be formed on treated surfaces, dissipates slowly.
4. Affected by various water constituents,
5. Different quaternary ammonium compounds vary in germicidal effectiveness. Therefore, acceptance by official agencies is limited and varied.
6. Affects rubber adversely through repeated or prolonged exposure at normal use dilutions.
7. Comparatively higher in cost.
8. Foam problem in mechanical cleaning or CIP applications.
9. Residual film can interfere with desirable bacteria in cultured products, etc.

Iodophors: "Iodine Carrier" in Latin

Generally consists of Iodine (0.5% to 2.0%), acid and surfactants. Very good bacterial kill properties but is disliked because of staining properties and cost. Sanitizer of choice for hand dip because of effectiveness, mildness to skin and color indicative. Approved use dilution strength is 2.5 ppm iodine for no-rinse applications.

Advantages

1. Fast germicidal action
2. Non-selective.
3. Well-established germicidal efficacy against vegetative cells.
4. Ease of accurate measurement and dispensing.
5. Convenient field test availability.
6. Solutions go to work instantly.
7. Good penetration qualities.
8. Pale amber color of use dilution serves as visual control.
9. Acid properties help condition hard water, prevent film formation, mineral scale build-up and milkstone.
10. Wetting agent promotes fast spot-free drying.
11. Is useful as a "germicidal detergent" for selected light soil applications.
12. Stable under normal storage conditions.
13. Mild on skin in use dilution. Best for cow preparation.

Disadvantages

1. Not as effective against spores and phage as hypochlorites.
2. Should not be used at temperatures above 110°F. (Rapid loss of strength, objectionable odor, and staining properties caused by "gassing off.")
3. Germicidal action adversely affected by highly alkaline waters or "carry over" of highly alkaline detergent solutions.
4. Corrosive to several metals commonly used in food and beverage operations.
5. Current cost is comparatively high.
6. Germicidal efficacy reduced by presence of organic matter to solution.
7. Spillage may cause staining and/or corrosion.
8. Possible residue.
9. Foam problem in mechanical (CIP) applications.
10. Not effective for removal of certain milk soils, i.e., grease and fats.
11. pH must be kept below pH 7.0 to be effective.
12. Consistent use at proper dilution will cause staining.
13. Any contact with starchy foods causes bluish color change in starch.

Anionic Acids

Many forms of these sanitizers. Very effective against most bacteria, yeast and molds. Used in limited applications at this time. Generally approved at 100 ppm for no-rinse applications.

Advantages

1. Long shelf life. Very stable under normal conditions.
2. Active against wide spectrum of micro-organisms, including some thermodurics, controls bacteriophage, most yeast strains and molds.
3. Absence of objectionable odors and staining.
4. Residual anti-bacterial film.
5. Removes and controls milk-stone and water hardness films, because of acidity levels.
6. Effective in the presence of organics or hard water.
7. Non-corrosive and non-staining to stainless steel equipment.
8. Bacterial action enhanced at higher temperatures.
9. Stability of used solutions.

TABLE 21.3. Sanitizers

Specific Area or Condition	Recommended Sanitizer	Concentration
Aluminium Equipment	Iodophor	25 ppm
	Quat	200 ppm
	ClO_2	100 ppm
Bacteriostatic Film	Quat	200 ppm
	Acid-Anionic	100 ppm
Concrete Floors	Active Chlorine	1000–5000 ppm
	Quat	500–800 ppm
	ClO_2	100 ppm
Conveyor Belts	Active Chlorine	300–500 ppm
	Iodophor	25 ppm
	ClO_2	100 ppm
Cooler Walls & Ceilings	Quat	500–800 ppm
	ClO_2	50 ppm
Hand Sanitizer	Iodophor	25 ppm
Hard Water	Acid-Anionic	130 ppm
	Iodophor	25 ppm
	Active Chlorine	200 ppm
	ClO_2	100 ppm
High Iron Water	Iodophor	25 ppm
	ClO_2	100 ppm
Odor Control	Quat	200 ppm
	ClO_2	100 ppm
Plastic Crates	Iodophor	25 ppm
	ClO_2	100 ppm
Porous Surface	Active Chlorine	200 ppm
	Quat	200 ppm
	ClO_2	100 ppm
Processing Equipment (Stainless Steel)	Acid Sanitizer	130 ppm
	Active Chlorine	200 ppm
	Iodophor	25 ppm
	Quat	200 ppm
	ClO_2	100 ppm
Rinse Water Treatment	Active Chlorine	2–7 ppm
	ClO_2	1 ppm
Tile Walls	Iodophor	25 ppm
	Quat	500–800 ppm
	ClO_2	50 ppm
Walls	Active Chlorine	200 ppm
	Quat	500–800 ppm
	ClO_2	100 ppm
Water Supply Treatment	Active Chlorine	2–7 ppm

Disadvantages

1. Effective only at acid pH (1.9–2.2 optimal)
2. Corrosive to metals other than stainless steel.
3. Sow activity against spore-forming organisms.
4. Foam problem in mechanical and CIP applications.
5. Bacterial action delayed by milk in combination with water hardness.
6. Not effective in destruction of most spores.
7. 100 ppm anionic.
8. Some products do not rinse well.

Sanitation Notes

Sanitizers: Recommended use levels Specific areas or conditions in a processing plant may require different sanitizing compounds. Table 21.3 indicates specific areas or conditions where particular sanitizers are recommended.

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CHAPTER 21

FOOD PLANT SANITATION

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INTRODUCTION AND DEFINITION OF ISSUES

Sanitation Technology encompasses many areas including designing and implementing a program that support a total food safety system. There are many factors which make up a total sanitation technology "package" that will effectively insure the safety of the produce not only while the product is being produced, but when it leaves the plant and reaches the consumer. In reality, the sanitation program is the final stop gap to how safe the product will be. If the surfaces are not properly cleaned and sanitized a carry over of bacteria will be present and will in fact infect the new product being processed.

The purpose of implementing a sanitation system using the latest technology is to eliminate any foodborne pathogens on all food contact surfaces. There are many factors involved, and a variety of techniques must be used to accomplish this task. Sanitation Technology encompasses many factors and a properly trained sanitation team will be proficient in the following areas:

- Cleaning Chemistry
- Sanitizing Chemistry
- Sanitation Equipment
- Microbiology (as it pertains to foodborne pathogens)
- Rapid Testing
- ATP Testing
- Labor Usage
- Sanitation Procedures
- Food Technology (as it pertains to organic challenge)
- Food Contact Surfaces
- and additional factors which will be covered in this chapter.

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BACKGROUND AND HISTORICAL SIGNIFICANCE

In the past, sanitation was not particularly considered to be of much importance. It was a low paying position, used as an entry level position. There was little or no training and generally a lack of supervision. This resulted in high turn over of personnel. Sanitation operations were primarily conducted at night, which made it more difficult to maintain a full staff. Usually sanitation operations were placed under the direction of the production staff, which often meant that sanitation took a back seat to production runs. However, in the last 3 to 4 years, a different attitude has developed, probably due to the high profile recalls and foodborne pathogen infections bombarding the media. The sanitation staff has begun moving to the forefront and has become a separate department working closely with the quality assurance department. As sanitation is gaining new importance, more attention is being paid to the selection of sanitation personnel, training, and other technical considerations that are part of a professional sanitation/food safety program.

SCIENTIFIC BASIS AND IMPLICATIONS

Contributing Factors of a Total Sanitation/Food Safety Program

Type of food contact surface The type of material used to make up the food contact surface is of great importance. These surfaces are comprised of many materials including:

- Stainless Steel
- Rubber
- Plastic
- Fiberglass
- Concrete
- Mesh Belts
- Soft Metals
- HMU
- Wood (in some rare cases)

All materials are either porous, or as in the case of metals such as stainless steel, aluminum and others, when viewed under a microscope, have jagged saw tooth ridges. The metal surface appears to be smooth, but in reality it is a very rough terrain. Organic residues become attached to these areas and provide a good source for the bacteria, and also contribute to becoming a biofilm.

Organic challenge and biofilms In 1965, Jennings described soil as "matter out of place." Soil or organic challenge is food product or residue that does

not belong on the contact surface. The most common of soils are proteins, fats, oils, grease, carbohydrates, sugars and mineral deposits such as calcium carbonates, and burned on carbonaceous material from hot oil processing.

For every type of soil there is a different chemistry and method for removal. Fats, oils and grease require a hydroxide type of chemistry, but minerals require an acid product. Burned on soil requires a boil out technique using a high pH product.

Biofilms are probably the most dangerous of soil loads because they are difficult to detect and are a harborage and food source for bacteria, Any time there is a synthetic material in contact with a bio product, such as food soil, biofilms will occur. Pasteurizers, paddles, and other equipment will support the presence of biofilm. Synthetic conveyor belts also prove to be supportive of biofilm growth. Proteins are required for the bacteria to adhere to the surface, and as the proteins unfold, they become attached to the surface, and once attached, begin to build until a thin layer is present.

Removal of these biofilms requires hydrodynamic shear, the correct chemistry, and hand detailing with brushes and scrub pads.

The type of surface is directly related to the biofilm build up. Porous or rough surfaces provide a favorable surface for attachment. Higher surface tension can cause a more rapid attachment, whereas lower surface tension tends to decrease attachment. A thorough knowledge of the type of soil, and the type of surface is paramount to determining how to prevent, and how to eliminate biofilm.

The role of water in cleaning and sanitizing Water in itself is very solvent, and is a major ingredient in cleaning systems. The chemistry that is used is diluted with water, high pressure systems using water are used in cleaning, and water is a major player in removing soil loads, and bacteria from food contact surfaces. But, water can also be a detriment. When water used for cleaning is contaminated, problems will occur. All plant water should be tested quarterly for any foodborne, or waterborne pathogens. Another potential problem is water that is above 130 degrees fahrenheit. At this temperature, proteins begin to be "cooked" onto the metal surfaces, and the pores of most all materials are opened, allowing fats, oils, grease, and protein to enter the material. After a period of time, a brown rainbow film begins to appear which is actually the development of a biofilm. Using water at too high a temperature will also increase energy costs. Fats, oils and greases can be removed at a lower temperature, and do not require such high heat. Steam cleaning is definitely a disadvantage since a 212°F product is cooked on very rapidly. Also, high water temperature will increase in precipitation of minerals left over from processing the food ingredients and additives, and now calcium carbonate and other minerals will leave a white, chalky deposit. Water is an excellent tool, but if not used properly, can cause more work than anticipated.

Methods of agitation There are various methods of agitation used to remove organic soils, which include:

- Hand Detailing
- High Pressure
- Chemical Agitation
- Steam Cleaning (which has been used, but its disadvantages far outweigh its advantages.)

High pressure cleaning has been used, but in recent studies it has been found that high pressure cleaning produces aerosols, which allow bacteria to be transported to other areas of the environment. Thus, can produce a false sense of security to the people using the system because they feel that high pressure in and of itself provides adequate cleaning. High pressure can be likened to a leaf blower in that it moves the organics from one area to another, but in fact, it can cause mechanical damage to equipment, such as electrical boxes, bearings, etc., and in general, can cause more work than is necessary.

However, there is a place for high pressure cleaning in outside areas such as loading docks, etc.

Chemical agitation is effective in the form of gel and foam cleaning products. The basic cleaning ingredients in the chemical formula are held in place by the foam or gel carrier, and allow the cleaning product to dwell or "cling" to the vertical and radial surfaces, allowing the cleaning product to digest and release the organic challenge. Foam and gels are not in themselves cleaning products, but act as a method to hold the cleaning chemistry in place. Too much foam or gel can cause a post rinsing problem in that more water must be used to rinse the foamed or gel product from the food contact surface. Hand detailing has never been and never will be, eliminated from the leaning procedures. Hand detailing has one major advantage in that it forces the cleaning staff to inspect the surfaces that have been detailed to be sure that all organic challenge has been removed. Inspection of this cleaning step is critical due to any resident organic challenge that has not been removed. Inspection of this cleaning step is critical due to any resident organic challenge that has not been removed, will not be rinsed, therefore creating a food source and a harborage for bacteria to reside and multiply. Many pre-ops have failed due to this one lack of detail.

Rinsing sequences There are two rinses in the five step sanitation cleaning cycle. First is the pre-rinse, and the second is the post-rinse, prior to application of the sanitizer.

The purpose of the pre-rinse is to remove the majority of any organic challenge. This step reduces the amount of cleaning chemical that must be used, removes the heavy particles off the surfaces, and can remove up to 20% of the resident bacterial from the surface.

The post-rinse cycle removes any and all organic soils that have been removed by hand detailing and chemical agitation. This post rinse cycle has also been shown to remove up to 20% of residual bacterial. Also, it is impor-

tant to note, that this post rinse is critical because any and all cleaning chemistry and organics that remain will greatly affect the sanitizer that is applied. Note that most cleaning chemistry is used at a pH of 12 and higher, and it is natural for most quaternary sanitizers to be on the acid side, as is the case of iodophors and acid sanitizers. If equipment is not rinsed thoroughly after cleaning, residual detergent will raise the pH which could reduce the effectiveness of the sanitizer used. Post rinsing is most critical because is prepares the surfaces for the most important step of all, the application of the sanitizer.

Time and schedules Plan your work and work your plan. There are many complexities to our process environment: the processing equipment, production run times, return on investment. Therefore the food safety/sanitation crew needs to work smart. This is accomplished by carefully developing manpower schedules, cleaning and sanitizing times, written cleaning procedures for each piece of equipment, and realistic allocation of time and labor resources.

First, cleaning procedures for each piece of equipment and the environment must be written. Each piece of equipment must be cleaned and sanitized in a step-by-step process. A plan or procedure needs to be developed to instruct how to clean and sanitize. At this point in time, a determination must be made as to how much work needs to be accomplished, how many man hours are required to complete the task, what cleaning equipment will be utilized, and how will the chemistry be applied.

Once that has been determined, cleaning zones are established and equipment and manpower is assigned. The establishment of man hours is directly determined by the complexity of the equipment, and the time allocated for the cleaning cycle. The size of the cleaning alone is predicated upon the pieces of equipment required to be cleaned in a specific time. In some cases, a zone can be the entire plant. In other cases, a zone can be just one piece of equipment.

One reason why the food safety/sanitation cycle has not been considered a good return on investment is that planning and scheduling of the labor force has not been done. Labor is approximately 70–75% of sanitation costs, so if the food safety/sanitation works efficiently, a return on investment is accomplished.

Sanitation schedules are mandatory. They identify what the pieces of equipment are, and what areas (zones) the equipment is located in. In addition, other data important to sanitation and Hazard Analysis Critical Control Point (HACCP) plans is also included, such as the date the equipment was cleaned, who cleaned it, and what chemistry was used to clean and sanitize, and other data that is important to the specific operation. The schedule is usually designed for a 30-day cycle. At the end of the cycle, the completed schedule is copied and filed for future reference as needed. Laminating the schedule in plastic allows the information to be written in felt-tip and wiped clean after being copied, so the master remains intact for the next cycle.

Having a work plan can also allow the latitude of placing staff in other areas in the event of sickness, vacation, or used for cross training. Planning the work is paramount in having a processional food safety sanitation plan.

Sanitation Equipment

In days gone by, the old bucket-and-brush method was in vogue. Processors just did not want to spend any more money than they had to on a sanitation program. However, that attitude has changed due to the fact that dilution equipment can actually save dollars in chemistry. And, foamers, central foam systems, and CIP systems can save on labor, which is the most expensive part of a sanitation program. Cutting down on chemical costs is really only about 10% of the cost equation, where labor is about 70% of sanitation costs. That leaves the final 20% of costs in waste water management. This adds up to one very important reason why food safety/sanitation personnel should be trained in all areas of food safety and the methods of sanitation.

There are several methods of applying cleaning and sanitation chemistry:

Foam tanks These are 15 or 30 gallon tanks that can be filled at a diluter and are charged with about 60 lbs. of air pressure. These units are ASTM pressure vessels and are a single use only in that only one chemical can be applied, either a cleaning compound, or a sanitizer. Because of the surfactants in quaternary products, foaming is high, and therefore allows the quaternary to maintain a longer residence on radius and overhead surfaces.

Foam carts This is a stainless steel cart that holds 2, 5 gallon pails, one of which is the sanitizer, and the other is a cleaning compound. Lafferty Equipment in Little Rock, Arkansas manufactures a quality design, foam/rinse/sanitize unit. The entire unit is of stainless steel, and is complete with hose, wands and other accessories. All chemistry is automatically diluted. The unit will cover an 80 foot radius which cuts down on labor because the unit does not have to be moved as often. I mention the Lafferty unit only because I am most familiar with it. There may be other units that are similar on the market.

Clean in Place (CIP) systems These systems are usually found in dairies, beverage plants, and other processing facilities and allow for cleaning and sanitizing without having to disassemble the equipment. One type of Clean in Place (CIP) system is engineered and designed by the Sanimatic Corporation in Wisconsin. All CIP systems have the capability to inject chemical product at the prescribed dilution rate without any hand mixing. However, care must be taken to titrate the chemistry on a bi-weekly basis to insure the dilution rates are in fact correct. One other possible trap is that the CIP system needs to be inspected on a regular basis to insure that the cleaning efficiency is at the optimum. Doing micro counts is of great importance as well, to insure that the system is operating at full efficiency. Non-foaming cleaners and sanitizers are used in CIP cleaning. A foaming product can cause cavitation of the pump impellers, and also will reduce the cleaning efficiency of the system.

COP systems COP is cleaning out of place. This means that equipment is disassembled and placed in a tank which allows the equipment to soak in the cleaning solution. A pump can be installed which will allow the water to agitate the parts, or air can be introduced to cause agitation. Time is of the essence in COP systems since dwell time and agitation is very important, and as in CIP systems so is the dilution of the cleaning chemistry. As with CIP systems a non-foaming cleaning product is used.

Central foam/sanitize systems Without a doubt, this is one of the best methods for cleaning and sanitizing food processing facilities. All of the chemistry is placed in a locked room. Also in this room are the pumps which dispense the chemistry automatically. Usually Doseatron or Doseamatic water driven pumps are used. From this locked room the chemistry is pumped to Foam/Sanitize Drop Stations throughout the plant in schedule 80 piping. The installation costs are low, chemical safety and economy is achieved, and labor costs are reduced. Maintenance is low, if any, since there are no moving parts to speak of. A central foam system is easily installed in a new plant, and can be readily installed in an existing facility.

High pressure systems High pressure systems are excellent in some areas such as cleaning outside areas, fork lifts, pallets, loading and receiving docks, and in some cases plastic and stainless steel interlock belts. The problem in food processing facilities is as follows: It tends to create a false sense of cleaning efficiency on the part of the food safety/sanitation staff. Safety becomes an issue as the high pressure spray can come into contact with other employees causing injury. It also serves to spread organics to other areas of the plant, transporting bacteria to previously cleaned areas. Proper and accurate dilution of the chemistry is really only achieved at about 6 inches from the nozzle of the high pressure tip, after that distance the pressure is substantially reduced. Also an air current, along with an atomized vapor causes a "blowing" effect which aids in transporting organics and bacteria, often to undersides of equipment or areas that are difficult to reach with regular cleaning methods; in fact creating more work.

Foam/Sanitize drop stations Foam/Sanitize drop stations are similar to the central system, but rather than transport the chemistry from a central location, the chemistry is brought to the production area after processing, in 5 gallon pails. Since chemistry is not allowed in a processing area during operation, all chemistry must be kept in a secure room or cage until ready to use. This can cause some inconvenience, but is a controlled method of dispensing the chemistry, and at the same time contributes to reduced labor costs in application.

Cleaning Chemistry

Cleaning chemistry is sometimes made into the "cure-all" for sanitation programs. Chemical suppliers put the emphasis on chemicals because that is all they usually consider when examining a sanitation program. Chemicals are really only one of the many tools used in a total sanitation program. A mechanic does not use only a wrench or screwdriver, but has many other tools at his disposal.

First to consider is the pH of the chemical product. The pH does nothing more than tell the user whether the chemical product is an alkaline, or an acid. The type of organic challenge encountered will determine what the pH of the product should be. The following illustration shows a pH scale from 0 to 14 with 7 being neutral pH.

0 ----------7----------14
ACID NEUTRAL ALKALINE

Chemical is tested using pH test strips to determine whether it is acid or alkaline, or you can use a causticity test kit or a pH meter.

Acid products are used for removing mineral deposits such as milk stone, beer stone, and calcium carbonate types of minerals, rust and so forth. The stone type of deposits and calcium carbonate products are usually a result of heating and causing the minerals to precipitate out of solution and attach themselves to the food contact surface. This action is also similar to what happens in boiler tubes. The boiler tube becomes hot causing the mineral to precipitate out of solution and deposit onto the tubes. This causes a reduction in the heating process and the minerals must be removed by chemical action. The same occurs with cooking equipment. One example is that of cooking crab. The calcium and other minerals in the crab shell are put into solution and deposited on the cooker. Another example is in the making of beer. Beer stone is a result of cooking the grains and various ingredients in the wort onto the sides of the cooking vessel.

There are many acids on the market (e.g. phosphoric, sulfamic, nitric) that can remove the mineral deposits. The best way to keep mineral deposits from forming is to have a sanitation program that addresses this problem on a scheduled basis.

Neutral pH products are not used a great deal in the food processing industry due to the type of organic challenge that is encountered. However, there are some special applications when an acid or an alkaline product can do damage to equipment, plastics, or other materials. Then a neutral product is indicated.

Alkaline products are in the pH range of 7 to 14. The higher the pH, the stronger the action of the alkaline. At one time straight caustic was used to remove carbonaceous deposits, fats, oils, greases, and the like, but that is old technology. Alkaline products are now blended to include surfactants, wetting agents and other ingredients to increase the efficacy of the product.

Alkaline products are indicated for use on organic challenge such as fats, oils, grease, protein and carbonaceous deposits as found on doughnut fryers, deep fryers, ovens, etc.

A very efficient chemistry is that of a chlorinated caustic product which when used is very effective on protein. A peptizing effect is caused when the proteins, chlorine, caustic, wetting agents, and surfactants meet together. The most efficient ratio of chlorine/caustic is to achieve chlorine levels at 600 ppm, with a pH of 13 at a 50:1 dilution, or as high as 1 ounce of product to 1 gallon of water. Anything less just does not have the same cleaning efficiency.

The Common Detergent Ingredient chart (Table 21.1) will provide the insights needed for determining the chemical product to use and the efficiency of the various chemical ingredients.

When evaluating chemical costs, examine both the purchase cost of the chemical product, and the use cost. One should keep in mind that the lower the chemical purchase cost, the probability of less solids in the product. The purchase cost is the cost to buy the product, and the use cost is the cost to use the product. Keep in mind that a higher dilution rate will in turn mean a lower use cost and may also reduce the amount of hand detailing that may be required. Some chemicals are diluted at so many ounces per gallon, while other products are diluted in percentages. i.e., 3% per gallon of water rather than so many ounces per gallon of water. Always go by the number of ounces per gallon of water, as that is how dilution equipment is designed. One product may state to use one ounce per gallon, and another product may prescribe a 3% solution. A 3% solution would equate to 3% of 128 ounces of water, so the per ounce dilution rate would actually be 3.84 ounces per gallon. Quite a difference!

As to use cost, simply divide the purchase cost by 128 ounces to obtain the cost per ounce. Then multiply the cost per ounce by the use rate to obtain the use cost per gallon. An an example: at a purchase cost of $4.95 per gallon for chemical product, and the use rate is a 3% solution per gallon of water. Divide 4.95 by 128, the result is .038 cents per ounce. For a 3% solution you need 3.84 ounces per gallon, the use cost is .038 cents per ounce multiplied by 3.84 ounces, so the use cost would be .146 cents.

On the other hand a chemical product that costs 7.95 per gallon, but has a dilution rate of 1 ounce per gallon of water, or 7.95 divided by 128 equals .062 cents per ounce, so the use cost is .062 cents per gallon.

You can see that a difference of $3.00 in the purchase cost per gallon actually results in a use cost savings of .084 per gallon use cost. The reason? The higher priced product probably has more solids and is a higher blend of chemicals therefore it is a higher concentrate requiring less product to produce more cleaning solution. (Another hidden benefit is that you will actually purchase a little less product, as it will go farther.) The point of this exercise is to show you that you're missing the point if you only consider the purchase cost of a product. Consider the solid content, quality of the product and the dilution rate as well. A chemical supplier can very easily spec out the product without giving away secrets. In other words, know what you are buying. There is no cure-all,

TABLE 21.1

Common Detergent Ingredients													
Key to Chart A..... High Value B..... Medium Value C..... Low Value D ..... Negative Value *..... Via Precipitation ▲ ..... Via Sequestration ◆ ..... Also Stable to Heat		Comparative Ability											
	Ingredients	Emulsification	Saponification	Wetting	Dispersion	Suspension	Peptizing	Water Softening	Mineral Deposit Control	Rinsability	Suds Formation	Non-Corrosive	Non-Irritating
Basic Alkalis	Caustic Soda	C	A	C	C	C	C	C	D	D	C	D	D
	Sodium Metasilicate	B	B	C	B	C	C	C	C	B	C	B	D
	Soda Ash	C	B	C	C	C	C	C	D	C	C	C	D
	Tri-Sodium Phosphate	B	B	C	B	B	B	A*	D	B	C	C+	C
Complex Phosphates	Sodium Tetra-Phosphate	A	C	C	A	A	A	B▲	B	A	C	AA	A
	Sodium Tri-Polyphosphate	A	C	C	A	A	A	A▲	B	A	C	AA	B
	Sodium Hexametaphosphate	A	C	C	A	A	A	B▲	B	A	C	AA	A
Organic Compounds	Tetrasodium Pyrophosphate	B	B	C	B	B	B	A▲	B	A	C	AA	B
	Chelating Agents	C	C	C	C	C	A	AA◆▲	A	A	C	AA	A
	Wetting Agents	AA	C	AA	A	B	B	C	C	AA	AAA	A	A
	Organic Acids	C	C	C	C	C	B	A◆	AA	B	C	A	A
	Mineral Acids	C	C	C	C	C	C	A◆	AA	C	C	D	D

or a one product-does-all. Take all claims about how good a chemical product is with a grain of salt until you determine what the quality of the product really is.

Chemical Definitions

Saponification The chemical conversion by an alkali of water insoluble fatty acid soil in more soluble substances, soaps. That is why a deep fat fryer should be rinsed with an acid product. The alkaline of the cleaner will mix with any residual oil, thereby creating a "soap," and may cause the finished product to have a "soapy taste."

Emulsification This is the action of breaking up fats and oils and dispersing them throughout the cleaning solution. The emulsion formed must be stable enough to prevent these soils from redepositing on the equipment surfaces.

Dispersion This is the action of breaking up the solid aggregate of the soil into smaller particles to colloidal size. This is accomplished through the action of the chemical media and mechanical agitation or hand detailing.

Peptization This occurs only by chemical action without agitation and can be considered as spontaneous dispersion of the solid soil throughout the cleaning solution. Peptization is usually associated with the removal of protein soils.

Solubilization This reaction happens in one of two ways—one is chemically, the other is physically. Lactose, found in milk solids, is soluble in water and therefore easily removed. Mineral salts, found in stone deposits are solubilized by acid cleaning solutions chemically altering these products into soluble substances. Some insoluble oils are easily solubilized by surface active agents by the action of the micellular structure in an aqueous media.

Suspension The holding of the removed particulate matter in the liquid phase. Suspensions can be stabilized by the use of polyelectrolytes in solution which maintains a positive or negative charge on the dispersed phase. A stable suspension of soils is particularly important in preventing redisposition of the soils.

Wetting/penetration agents The use of these agents depends upon diffusion rates, surface tension, concentration, and how rough the surface of the material is. Surface active agents are clearly much better to all other products in lowering the surface tension of the cleaning solution allowing the oils to be rinsed away, and the penetration of the agents into cracks and into the holes of the solid deposits.

Rinsability The ability of a detergent to be freely rinsed from the surface. This ability is of prime importance since not only is the chemical product rinsed away, but also any bacteria that has been destroyed in the cleaning process. There should not be any residue cleaning chemical on the surface since the residue can affect the sanitizing chemistry.

Water softening Water softening renders the hardness of water unavailable for reaction with the components of the cleaning solution. Caustic soda will form a film of calcium and magnesium carbonates in hard water. Softening will precipitate the hard water elements as insoluble salts. Chelater chemicals tie up mineral products so as not to affect the product's cleaning effectiveness.

Corrosiveness Protecting the processing equipment from harsh cleaning products is important due to the deterioration of the metal. Some cleaning products will "burn" aluminum, and will destroy galvanized coatings. Also, bronze and copper metal will be destroyed by high pH cleaning products. In this instance, a neutral buffered chemical product is indicated.

Food Plant Sanitizers

What are they? Sanitizers are chemical agents used to reduce microbial contamination in food plants to an acceptable level. They are not meant to leave a surface sterile.

Why use sanitizers? The application of sanitizers are to help reduce product contamination during process and/or to help reduce counts from raw product.

Most cleaning operations are not sufficient to destroy or remove the bacteria present in a food plant. Therefore, we must use a chemical method to reach our goal of a sanitary surface, and reduce our risk of food contamination during processing and handling.

As a general rule, an unclean surface cannot be sanitized effectively. Therefore it is critical to both clean and sanitize regularly.

Who regulates sanitizers? In 1972, the Federal Environmental Pest Control Act defined "pest" to include bacteria and other micro-organisms. These sanitizing agents are regulated as pesticides, and are subject to the strict regulation of EPA set forth to control all use and distribution of these chemicals.

U.S. Department of Agriculture also has guidelines that must be met before a chemical is approved for use in an inspected food plant. They publish a "List of Chemical Compounds Authorized for Use" in which all such approved products are listed.

When purchasing sanitizing products, be sure they met both EPA and USDA requirements. Labeling is controlled by EPA and must be followed to the letter.

Chlorine: Form: Liquid Sodium Hypochlorite

There are many forms of chlorine releasing compounds but Sodium Hypochlorite is most common.

By far the most widely used sanitizer in the food industry worldwide, it is inexpensive and readily available. It is produced by reacting chlorine gas with sodium hydroxide (liquid caustic). It is highly activated by acids and deactivated as sanitizer by alkaline. Sanitize with this product at pH below 8.5. It is approved at a maximum concentration for no-rinse at 200 ppm on food contact surfaces.

Advantages

1. Fast germicidal action, is non-selective.
2. Dissolves easily since it is liquid.
3. Easily dispensed in controlled amounts.
4. Uniform concentrations since contents of container have same strength throughout.
5. Does not form films and isn't affected much by hardness or other water constituents.
6. Economical.
7. Very available.
8. No "pinpoint burning" of use solution vats.
9. Use dilution nontoxic.
10. Use concentration easily measured by convenient field tests.

Disadvantages

1. Characteristic odor.
2. Staining or bleaching, if spilled.
3. Comparatively short shelf life. Should be kept in cool, dark, storage area to maintain stability.
4. Must be protected from freezing.
5. High rate of interaction with organic matter decreases strength as soil is absorbed into sanitizing solution.
6. Variations in product alkalinity can affect germicidal action.
7. Misuse can cause rusting, pitting, and corrosion.
8. Possibly harmful to skin.
9. Precipitation in water containing iron may render it unacceptable.
10. Hazardous when present with acids.
11. Dissipates quickly in use dilution strength.

Chlorine Dioxide—A Comparison between Chlorine and ClO_2

Chlorine Dioxide has been in existence since about 1811, and short period of years after the discovery of chlorine. Both chorine, and chlorine dioxide were discovered by Sir Humphrey Davey.

Chlorine was used during World War I as a gas, in chemical warfare. It can be lethal. A safe way to handle chlorine, however, is to use it in the form of sodium hypochlorite, aka bleach. Hypochlorous acid is formed at the correct pH when dissolved in water.

Since the 1940's, chlorine dioxide has come into it's own and is currently used in many applications as a sanitizer and disinfectant. Such as, bleaching of pulp in paper making, bleaching of flour, drinking water disinfectant, as a vegetable wash, as well as other applications.

The EPA found that trihalomethanes or chloroforms were a by-product of chlorination. "THMs" were found to be carcinogenic, and an increase in cancers was detected where there were high THM levels.

Chlorine Dioxide Chemistry—Chlorine dioxide, a gas which is 50% oxygen by weight, dissolves readily in water. Being an oxidizer, it is very efficient against bacteria.

Chlorine Dioxide is made when two chemicals are mixed together, such as sodium chlorite, and an acid such as phosphoric. The ppm concentration is determined by how much of each product is mixed and diluted in water. (Obviously this is a simplified explanation and not something to be attempted on a trial basis.) The most accurate method is to use a chlorine dioxide generator which mixes the chemical components in exact proportions at the correct dilution. This is accomplished by drawing 2 or 4 chemical components into a mixing chamber, or a generator chamber, then injecting this mixture into the water line leading to where the solution is to be dispensed.

Table 21.2 is a comparison between Chlorine Dioxide and Chlorine.

Acidified Sodium Chlorite (Chlorine Dioxide chemistry) is odorless, colorless in solution, and has a long lasting residual. Also, in diluted solution, ClO_2 is not as aggressive as Chlorine on soft metals such as aluminum, brass, galvanized, etc.

TABLE 21.2. Comparison between Chlorine Dioxide and Chlorine

Chlorine	ClO_2
Chlorinates organics	Oxidizes only
Makes toxic NCL_3	No reaction with NCL_3
Chlorinates phenols	Destroys phenols
Poor deodorizer	Oxidizes sulfides
Carcinogens (THM's)	No carcinogens
pH sensitive (>7.5)	pH insensitive
Good biocide	10× better biocide

Due to the chemical make up of the product it is very aggressive on organic challenge such as that found in poultry chill water systems.

It has been approved as a no rinse category D-2 sanitizer by the USDA, (100 ppm) as a red meat carcass spray, for use in poultry chiller water and as a carcass spray, in seafood ice and processing, refrigerated sea water chill systems, on cut and peeled vegetables, and in ice machines. The dilution rate for these applications is from 1 to 3 ppm.

As a D-2 no rinse sanitizer, it can be used on all process equipment, can be applied foamed, is excellent for use in floor drains, drip pans in cooler units, such as found in produce cooler for the elimination of Listeria. Chlorine Dioxide is also an excellent prewash for fruits, melons, and other produce to reduce the number of pathogens which can exist on the outside skin of the product.

All in all, Chlorine Dioxide is an excellent choice in most all areas of food plant sanitation.

Quaternary Ammonium Compounds: Also known as Quats

Also known as Q.A.C. or Quats, more than one form and often mixed in a sanitizing product. (Hence, dual quats combine 2 forms). Has the reputation for being the safest sanitizer for handling and on equipment surfaces. Quats are forms of cationic surfactants, thus they are thought to have detergent and penetrating properties. Normal use dilution approved for no-rinse is 200 ppm quaternary ammonia.

Advantages

1. No objectionable odor.
2. Very mild to skin, eyes, and clothing.
3. Non-corrosive. (This factor is the same as for the water in which it is used.)
4. Ease of accurate measurement and dispensing.
5. Use dilution readily measured by practical field test.
6. Dissolved solutions react instantly,
7. Very stable in changing temperatures,
8. Very stable in storage.
9. Good penetration qualities,
10. Provides highly desirable residual bacteriostatic film.
11. Outstanding elimination and prevention of odor.
12. One of the best ingredients for "germicidal detergent" formulations.
13. Can be applied as foam because of it being a highly active surfactant.
14. Very good residual bacterial kill.
15. Widely accepted as best sanitizer for plant environmental use (i.e., floors, walls, etc.)

Disadvantages

1. Germicidal efficacy varied and selective, especially against gramnegative organisms. Including coliforms, Pseudomonas, Salmonella.
2. Moderate toxicity in use dilution.
3. Incompatibility with common detergent components complicate use germicidal efficacy may be reduced; objectionable films may be formed on treated surfaces, dissipates slowly.
4. Affected by various water constituents,
5. Different quaternary ammonium compounds vary in germicidal effectiveness. Therefore, acceptance by official agencies is limited and varied.
6. Affects rubber adversely through repeated or prolonged exposure at normal use dilutions.
7. Comparatively higher in cost.
8. Foam problem in mechanical cleaning or CIP applications.
9. Residual film can interfere with desirable bacteria in cultured products, etc.

Iodophors: "Iodine Carrier" in Latin

Generally consists of Iodine (0.5% to 2.0%), acid and surfactants. Very good bacterial kill properties but is disliked because of staining properties and cost. Sanitizer of choice for hand dip because of effectiveness, mildness to skin and color indicative. Approved use dilution strength is 2.5 ppm iodine for no-rinse applications.

Advantages

1. Fast germicidal action
2. Non-selective.
3. Well-established germicidal efficacy against vegetative cells.
4. Ease of accurate measurement and dispensing.
5. Convenient field test availability.
6. Solutions go to work instantly.
7. Good penetration qualities.
8. Pale amber color of use dilution serves as visual control.
9. Acid properties help condition hard water, prevent film formation, mineral scale build-up and milkstone.
10. Wetting agent promotes fast spot-free drying.
11. Is useful as a "germicidal detergent" for selected light soil applications.
12. Stable under normal storage conditions.
13. Mild on skin in use dilution. Best for cow preparation.

Disadvantages

1. Not as effective against spores and phage as hypochlorites.
2. Should not be used at temperatures above 110°F. (Rapid loss of strength, objectionable odor, and staining properties caused by "gassing off.")
3. Germicidal action adversely affected by highly alkaline waters or "carry over" of highly alkaline detergent solutions.
4. Corrosive to several metals commonly used in food and beverage operations.
5. Current cost is comparatively high.
6. Germicidal efficacy reduced by presence of organic matter to solution.
7. Spillage may cause staining and/or corrosion.
8. Possible residue.
9. Foam problem in mechanical (CIP) applications.
10. Not effective for removal of certain milk soils, i.e., grease and fats.
11. pH must be kept below pH 7.0 to be effective.
12. Consistent use at proper dilution will cause staining.
13. Any contact with starchy foods causes bluish color change in starch.

Anionic Acids

Many forms of these sanitizers. Very effective against most bacteria, yeast and molds. Used in limited applications at this time. Generally approved at 100 ppm for no-rinse applications.

Advantages

1. Long shelf life. Very stable under normal conditions.
2. Active against wide spectrum of micro-organisms, including some thermodurics, controls bacteriophage, most yeast strains and molds.
3. Absence of objectionable odors and staining.
4. Residual anti-bacterial film.
5. Removes and controls milk-stone and water hardness films, because of acidity levels.
6. Effective in the presence of organics or hard water.
7. Non-corrosive and non-staining to stainless steel equipment.
8. Bacterial action enhanced at higher temperatures.
9. Stability of used solutions.

TABLE 21.3. Sanitizers

Specific Area or Condition	Recommended Sanitizer	Concentration
Aluminium Equipment	Iodophor	25 ppm
	Quat	200 ppm
	ClO_2	100 ppm
Bacteriostatic Film	Quat	200 ppm
	Acid-Anionic	100 ppm
Concrete Floors	Active Chlorine	1000–5000 ppm
	Quat	500–800 ppm
	ClO_2	100 ppm
Conveyor Belts	Active Chlorine	300–500 ppm
	Iodophor	25 ppm
	ClO_2	100 ppm
Cooler Walls & Ceilings	Quat	500–800 ppm
	ClO_2	50 ppm
Hand Sanitizer	Iodophor	25 ppm
Hard Water	Acid-Anionic	130 ppm
	Iodophor	25 ppm
	Active Chlorine	200 ppm
	ClO_2	100 ppm
High Iron Water	Iodophor	25 ppm
	ClO_2	100 ppm
Odor Control	Quat	200 ppm
	ClO_2	100 ppm
Plastic Crates	Iodophor	25 ppm
	ClO_2	100 ppm
Porous Surface	Active Chlorine	200 ppm
	Quat	200 ppm
	ClO_2	100 ppm
Processing Equipment (Stainless Steel)	Acid Sanitizer	130 ppm
	Active Chlorine	200 ppm
	Iodophor	25 ppm
	Quat	200 ppm
	ClO_2	100 ppm
Rinse Water Treatment	Active Chlorine	2–7 ppm
	ClO_2	1 ppm
Tile Walls	Iodophor	25 ppm
	Quat	500–800 ppm
	ClO_2	50 ppm
Walls	Active Chlorine	200 ppm
	Quat	500–800 ppm
	ClO_2	100 ppm
Water Supply Treatment	Active Chlorine	2–7 ppm

Disadvantages

1. Effective only at acid pH (1.9–2.2 optimal)
2. Corrosive to metals other than stainless steel.
3. Sow activity against spore-forming organisms.
4. Foam problem in mechanical and CIP applications.
5. Bacterial action delayed by milk in combination with water hardness.
6. Not effective in destruction of most spores.
7. 100 ppm anionic.
8. Some products do not rinse well.

Sanitation Notes

Sanitizers: Recommended use levels Specific areas or conditions in a processing plant may require different sanitizing compounds. Table 21.3 indicates specific areas or conditions where particular sanitizers are recommended.

CHAPTER 22

FOOD SAFETY CONTROL SYSTEMS IN FOOD PROCESSING

JOELLEN M. FEIRTAG and MADELINE VELÁZQUEZ

INTRODUCTION AND DEFINITION OF ISSUES

The food supply in the U.S. is among the safest in the world, but there are still millions of Americans who become ill because of the food they have consumed. The Centers for Disease Control and Prevention (CDC) estimate that as many as 4000 deaths and 5 million illnesses result annually from the consumption of meat and poultry products contaminated with bacterial pathogens. These deaths and illness may be reduced through actions that can be taken throughout the farm-to-table food safety chain to prevent, reduce, and eliminate harmful bacteria. After a major outbreak of foodborne illness in several western states in 1993, the Clinton administration moved to mandate safe handling labels, declare *E. coli* O157:H7 an adulterant in raw ground beef, initiate a testing program for pathogens, and encourage the development and use of new technologies to reduce harmful bacteria during slaughter and processing. On July 6, 1996, it was announced that the final rule on Pathogen Reduction and HACCP (Hazard Analysis and Critical Control Points) was ready to make this new regulatory system a reality.

BACKGROUND AND HISTORICAL SIGNIFICANCE

The identification of several emerging foodborne pathogens in the past two decades including *Escherichia coli* O157:H7, *Listeria monocytogenes*, *Campylobacter jejuni*, and *Vibrio cholera* (Knabel, 1995) and the increased incidence and publicity of foodborne illness cases and other safety issues worldwide have raised the awareness of food processors, government authorities and the gen-

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eral public of the necessity of controlling and monitoring pathogen contamination in food processing facilities.

These events have led to the creation of specific agencies in the United States and United Kingdom that monitor compliance of regulations, thus ensuring food safety in processing facilities (Giese, 1996; Strugnell, 1992). The focus of these agencies is to require that food processors have in place quality systems to monitor and avoid cross-contamination as well as microbial contamination due to an inadequate processing system for the finished product.

Another development of these safety issues has been the implementation of a systematic HACCP system in food processing facilities as a more practical and effective approach to alleviate food safety issues (Chapter 20; Ehiri and Morris, 1994). A HACCP program must be tailored to each processing facility to focus on ensuring the safety of a particular product by identifying, monitoring, verifying, and controlling critical processing steps (USA National Food Processors Association, 1993). It is recognized that the success of this type of systematic approach relies on the education of all personnel, management support, and, more importantly, effective sanitation programs and monitoring (Giese, 1996).

Therefore, food processors seek competent and practical systems to evaluate and monitor the effectiveness of their sanitation programs. Traditional food safety control systems include microbiological testing of finished products and their ingredients as well as microbiological monitoring of surfaces that come in contact with the finished product through the methods of swabbing, contact plates, and dip slides. Traditional nonmicrobiological systems include visual inspections of the surfaces. These systems however, possess a number of disadvantages (Ehiri and Morris, 1994; Griffith et al., 1997). Microbiological testing, for example, is time consuming and does not anticipate or prevent the occurrence of a hazard during processing (Ehiri and Morris, 1994).

Traditional systems of controlling food safety in food processing facilities have also evolved by the implementation of automated on-line control systems to monitor their sanitation program and HACCP plans (see review by Selman, 1990). These days, cleanliness and microbial evaluation of finished product can also be assessed with rapid monitoring methods such as adenosine triphosphate (ATP) bioluminescence, electrical monitoring, antibody-linked probes, phage-based assays and DNA and RNA probes (Waites, 1997). In particular, ATP bioluminescence assays have been adopted by numerous companies as part of their sanitation and verification plan.

The high concern for acid-resistant *Escherichia coli* serotype O157:H7 and other pathogens in beef products has led to the creation and implementation of new bacterial control systems. Their potential implementation has been evaluated to both ensure food safety and increase shelf life by reducing microbial load during processing of meat products (Swientek, 1999). These methods include antimicrobial spray washes, steam pasteurization, and gamma irradiation. Their principles, uses, and implications are discussed in the following section.

SCIENTIFIC BASIS AND IMPLICATIONS

ATP Bioluminescence: Monitoring of Sanitation Effectiveness

ATP is the major source of chemical energy in all cells (Lehninger et al., 1993). ATP bioluminescence assays are based on the firefly luciferin-luciferase system, in which the emission of the bioluminescence signal is solely driven by ATP (Lehninger et al., 1993). A luminometer instrument is used to measure the light emission in 10 s; thus a corrective action can be taken immediately before further processing. This approach has been used to detect microbial contamination in food products such as milk, beverages, meat, and poultry (Bautista et al., 1992, 1994; Graumlich, 1985; Littel and LaRocco, 1985; Siragusa and Cutter, 1995). More commonly, it has been used as a rapid method for the assessment of the cleanliness of surfaces and hygienic practices in food processing facilities (Shumaker and Feirtag, 1997; Velázquez and Feirtag, 1997).

The use of ATP bioluminescence techniques has undoubtedly influenced sanitation monitoring in food processing facilities and subsequently HACCP effectiveness. They are used as a rapid indicator of surface cleanliness in terms of both microbiological load and food residues, which contribute to a potential food safety and quality risk if processing is continued on such inadequate surfaces (Griffiths, 1996; Madl, 1997; Waites, 1997).

Therefore, ATP bioluminescence, as a rapid monitoring technique, appears to be the current popular and predominant choice by more food processing facilities as their control system to avoid cross-contamination from dirty surfaces, thus reducing the food safety risk related to improper sanitation.

Antimicrobial Spray Washes: Reduction of Microbial Load

Investigators have evaluated the effectiveness of spray washes on beef carcasses to reduce natural aerobic microflora and pathogenic bacteria. Microbial control spray wash systems effective in the reduction of artificially contaminated beef carcasses are those using hot water and organic acids (Dorsa et al., 1997a,b). Hot water washes (>70°C) were reported to significantly decrease aerobic bacteria and pathogens on carcasses (Dorsa et al., 1997a). The parallel use of hot water wash and steam vacuum was found to increase the effectiveness of the treatment.

Organic acids (lactic and acetic acid) have also been shown to inhibit microbial growth on beef during storage, although they did not appear to reduce the microbial load initially compared with water (Dorsa et al., 1997b). The effectiveness of these treatments appear to increase with the parameters used such as temperature, volume, application method, and tissue type (Dorsa et al., 1997b). Postprocessing contamination of spray wash-treated carcasses is still a possibility if they are handled inappropriately.

Spray wash systems using chlorine dioxide (Cutter and Dorsa, 1995) and trisodium phosphate (Dorsa et al., 1997b) have been shown to be ineffective in

the reduction of microbial load on beef carcasses. The latter spray wash was particularly ineffective against *Listeria innocua* (Dorsa et al., 1997b).

Steam Pasteurization: Reduction of Microbial Load

Steam pasteurization, in combination with other methods such as trimming and spray washing has been reported to achieve 99.99% reduction in the level of pathogens on beef carcasses, particularly *E. coli* O157:H7 (Washington Food Chemical News, 1995). This method is a controllable critical control point performed after evisceration and carcass wash. The system is on-line, consisting of three steps carried out in less than a minute: 1) Excess surface water is removed from the carcass to enhance heat transfer from steam. 2) Pressurized steam (220°F) is used to penetrate into cavities. The carcass surface temperature is raised to 206–207°F for 10–15 s, and 3) the carcass is sprayed with chilled, chlorinated water to enhance the kill and preserve the meat color. Carcass exposure to the steam for 15 s has been reported to achieve uniform bacterial reduction of 2.3 logs on carcass and cavities (Anon., 1995) without affecting the meat color.

Other investigators have reported the effectiveness of this control system in the reduction of enteric bacteria and pathogens on artificially contaminated beef carcasses (Nutsch et al., 1997, 1998; Phebus et al., 1997). Different parameters (180°F for 6.5 s) were used by some of these investigators, with successful results (Nutsch et al., 1998).

Steam pasteurization also offers other advantages over other control systems. It is computer monitored for air and water temperature and time of steam exposure. Also, it uses approximately 3 gallons of water compared with 120–250 gallons needed for a 190°F hot water treatment. Furthermore, it is energy efficient and environmentally friendly (Washington Food Chemical News, 1995). However, this control system, like antimicrobial spray washes, reduces the microbial load and food safety risk but does not prevent post-contamination.

Gamma Irradiation: Prevention of Postprocessing Contamination

Gamma irradiation of red meat was approved in the United States in 1997 by the Food and Drug Administration (FDA). This method offers several advantages over the control methods discussed above for reduction of microbial load on red meats. It is applied to the final packaged product with little or no detectable change in sensory quality, thus ensuring both safety and quality.

Researchers have determined the D_{10} values (kGy) needed to inactivate several bacterial pathogens, which appear to depend on the fat level of the meat and the meat temperature during gamma irradiation (^{60}CO) and the pathogen evaluated (Beuchat et al., 1993). From these studies the order of sensitivity of the evaluated pathogens in ground beef to the gamma irradiation regardless of

fat level or temperature of ground beef during irradiation was *C. jejuni* as the pathogen with theoretically highest numbers to be inactivated followed by *E. coli* O157:H7, *Staphylococcus aureus*, *L. monocytogenes*, and *Salmonella*. On the basis of these results, the probabilities of bacterial inactivation on particular pathogens and the gamma irradiation dose required can be calculated.

Consumer acceptance of this novel control system has been a matter of discussion. Recent reports on consumer perception of gamma irradiation of red meat, however, indicate some interesting results. A study by Resurreccion and Galvez (1999) reported that consumers appear to be very concerned about food safety and perceive irradiation positively as a process step to ensure food safety. In a pilot program, 51.5% of participants indicated their willingness to purchase irradiated red meat. When the same group of consumers participated in an education program on gamma irradiation, 71.3% of participants actually purchased irradiated meat in a pilot setting (Resurreccion and Galvez, 1999). Other investigators have found that an effective education program has an influence on consumer acceptance (Lusk et al., 1999).

REGULATORY, INDUSTRIAL, AND INTERNATIONAL IMPLICATIONS

The Food Safety and Inspection Service (FSIS) has created a new regulatory system for meat and poultry safety within the plants it regulates. The new science-based system will improve food safety and make better use of the agency resources. The system has four major components, 1) It requires facilities to implement HACCP systems as a tool for preventing and controlling contamination. 2) FSIS has established food safety performance standards that plants must meet and is conducting testing and other activities to ensure that those standards are met. 3) FSIS is training its inspectors to provide oversight to ensure that the industry is meeting regulatory standards. 4) FSIS has reorganized to strengthen its enforcement to deal with plants that do not meet regulatory standards.

In addition to this new regulatory approach within FSIS-regulated plants, the agency is working with other government agencies (both national and international), industry, and academia to develop and implement steps to improve food safety from farm to table.

CURRENT AND FUTURE IMPLICATIONS

To establish a solid foundation for the food safety system of the future, HACCP's core concepts of prevention, clear assignment of responsibilities, and better use of resources is the first step. But to meet the public's food safety expectations in the global food economy, a new kind of effort and collaboration is required. Reducing the risk of foodborne illness is a central priority and challenge. Food safety problems and issues are persistent, and new problems

are emerging daily. New technologies, such as those described above, are an opportunity to improve the safety, economy, and convenience of the food supply. The HACCP framework encourages industry to continue to research and implement the adoption of new technologies and procedures to control pathogenic microorganisms and reduce the incidence of foodborne illness. The development of prompt government approval processes for the implementation of these technologies is needed, along with a method to inform the public of the benefits of the technologies in providing a safer food supply.

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CHAPTER 23

FOOD SAFETY AND INNOVATIVE FOOD PACKAGING

MICHAEL L. ROONEY

INTRODUCTION AND DEFINITION OF ISSUES

Packaging has been regarded traditionally as the inert barrier between the food and the outside environment. This means that the contribution made by packaging materials to food safety is normally limited to providing a barrier to chemical and microbiological ingress. Packaging materials are normally developed to avoid release into the food of any component causing any hazard to the consumer. However, over the past two decades innovations in packaging materials have made possible the interaction of the packaging with the food so that the packaging can now perform additional roles. This introduction of activity in place of inertness introduces opportunities to influence the safety of the packaged food either by an antimicrobial effect or as an unintended consequence of contributing to maintenance of food quality. This new approach means strict regulation of components used in packaging material manufacture as well as ensuring stability under the wide range of conditions of use.

BACKGROUND AND HISTORICAL SIGNIFICANCE

Packaging development has passed through several innovative stages, which have then become accepted aspects of current use. These include liquid paperboard brick packs for aseptic liquids, bag-in-box, and retortable plastic pouches and trays. Each of these has satisfied requirements for delivery of safe, commercially sterile foods without migration of contaminants from the package into the food. As a result, several beverages are available for consumption after storage at ambient temperature. Retorted foods are available in flexibles, especially as sauces, and in trays or cups, for immediate consumption. These

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innovations have been introduced for a variety of reasons, food safety being only one. Therefore, it is essential to consider implications for safety of any innovations before they appear in the market.

The process of packaging innovation is not slowing, with several concepts being developed and some reaching commercial application. Over the past two decades, active packaging and intelligent packaging stand out as innovations with a potential major impact on food safety. Other innovations involving changes to materials represent more of an evolution of existing packaging practices. The increased use of edible coatings and the likely introduction of recycled packaging, or new biodegradable materials, will have serious impacts in the future.

Active packaging is the result of the need to improve the match of packaging material properties to the needs of the foods. Packaging is defined as active when it performs some desired role other than to provide a barrier to the external environment. One of the most visible examples is the insertion of oxygen-absorbing sachets into food packs, which commenced in 1978 with Ageless™ by Mitsubishi Gas Chemical Co. in Japan. Since then, a wide variety of functional packaging systems have been developed for both fresh and processed foods. Table 23.1 indicates the scope for a positive impact on food safety of such innovations.

Intelligent packaging tells something about the package contents or its history. A variety of indicators that measure properties—such as thermal history, gas composition, existence of leakage, or the occurrence of tampering—are included. As such, this form of packaging has the potential to reveal aspects of both the safety and quality of foods.

Packaging innovation is both a driver for, and a consequence of, food research. The implications for food safety are often an enhancement, but in some cases negative effects result. Introduction of modified-atmosphere packaging has occurred in advance of development of satisfactory indicators for both seal leakage and gas composition. Accordingly, indicator development is in the catch-up phase. Repeated examples of food tampering emphasize the

TABLE 23.1 Potential Applications of Active Packaging Affecting Food Safety

Packaging innovation	Food application
Antimicrobial film	Extended-shelf life beverages
Preservative release films	Cut surfaces of meats, cheeses
Ethanol release sachets	Bakery products
Carbon dioxide release	Fresh meats
Oxygen-scavenging films	High- and intermediate-a_w foods
Oxygen-scavenging films	Beverages
Oxygen-scavenging sachets	High- and intermediate-a_w foods
Moisture control films/pads	Horticultural produce

The film was prepared by casting from a solution of the polymer-enzyme mixture. These conditions would need to be modified to meet commercial requirements for fast film formation. However, the work showed that immobilization of a Generally Recognized as Safe (GRAS) food enzyme in a plastic is possible without chemical bonding and that migration was very minor. It will be necessary to develop a fabrication method that concentrates the enzyme near the polymer surface rather than wasting enzyme (which becomes immobilized inside the polymer, where it is not accessible to the microorganism).

Because the scope for activity of enzymes is normally limited to specific substrates, substantial research will probably be necessary to expand this pioneering work to a wider range of enzyme types if commercial usage is to be achieved. It will be necessary to determine whether pathogens can be inactivated or whether the potential benefit is limited to reducing food spoilage.

Besides the incorporation of known antimicrobial agents into or onto plastic surfaces, there is ongoing research into chemical modification of packaging surfaces to generate chemical groups toxic to microorganisms. Some work has indicated that acid groups present on the natural polymer chistosan, separated from crustacean shell waste, could be used as an antimicrobial. However, the approach of using rapid conversion of chemical groups already present on the surface of existing extruded plastic packaging is more attractive from an industrial viewpoint.

Natural and synthetic polyureas, polyhydrazides, polyurethanes, and polyamide (nylon) polymers subjected to strong ultraviolet light from a laser at 193 nm resulted in conversion of surface nitrogen-containing groups to polymer-bound amines. Some of the polymer-bound amines exhibited toxic effects on microorganisms. Exposure of UV-irradiated films treated to *Staphlococcus aureus*, *Pseudomonas fluorescens*, and *Enterococcus faecalis* in phosphate buffer resulted in a decrease in microbial count by over 4, 2, and 1 logs, respectively (Paik et al., 1998).

There have been some discussions as to whether polymer surface-bound amine groups are capable of causing cell death. Paik et al. (1998) suggest that results from reinoculation experiments show that the cells adsorbed are either inactivated or unable to reproduce after adsorption. UV irradiation of polymer surfaces requires substantially more research, but the process looks attractive when viewed in terms of industrial application. Industrial use would require rapid incorporation or activation under conditions compatible with current practice. This includes extrusion of polymers at temperatures between 150°C and 300°C or coating the polymers with a lacquer and subsequently removing solvent at line speeds used in film printing.

Release of antimicrobial agents from packaging plastics has been the subject of a significant body of research (Appendini and Hotchkiss, 1997). These compounds have been incorporated into typical food-contact plastics such as polyethylene, ethylene vinyl acetate copolymer, or polyvinylchloride. Antimicrobial agents used include quaternary ammonium compounds, imazalil, various food acidulants, and benzoic anhydride. Antimicrobial silver ions chemically bound into porous zeolite particles are incorporated into coatings on glass or into

TABLE 23.2 Antimicrobial Packaging Development and Commercialization

Process	Format	Source	Status
Ethanol release	Sachets	Mitsubishi Chemical Co.	Commercial
Silver ions	Film	Mitsubishi Chemical Co.	Commercial
Horseradish extract	Sheet	Sekisu Plastics Co.	Commercial
Antifungal Agent	Film	DuPont	Development
Organic acid release	Film	Scientific publications	Research
Enzyme binding	Film	Scientific publications	Research
Water buffering	Sheet	Showa Denko	Commercial

polyethylene films. The development status of several antimicrobial plastics is summarized in Table 23.2.

A range of antimicrobial agents with potential for use in packaging plastics is listed in a review by Hotchkiss (1995). Release of permitted food acidulants was investigated, and it was demonstrated that their acidulant polarity renders them unsuitable for use in the common nonpolar sealant plastics such as polyethlyene or polypropylene. However, conversion of acidulants to anhydrides, thereby reducing polarity, overcomes this problem. An advantage of anhydrides is that they are relatively stable to the heating involved in plastics processing and can be hydrolyzed by water vapor supplied by the food. The antifungal agent imazalil has also been shown to be suitable for release from a low-density polyethylene film in quantities that are effective in cheese, fruits, or vegetables.

Headspace gas modification Packaging materials or package inserts can impact on microbial food safety by modifying headspace gas composition. This involves removal of oxygen, addition or removal of carbon dioxide, addition of ethanol vapor, and addition or removal of water vapor. Some of these modifications may enhance or suppress microbial growth, depending particularly on the oxygen and water activity requirements of the organisms concerned. Modified-atmosphere treatments are used in commercial applications as part of a multihurdle approach to food safety in which several obstacles to microbial growth are used concurrently.

Gas atmosphere-modifying materials may be in the form of sachets or internal labels or may be the materials that form the package itself (Rooney, 1995). Oxygen-scavenging sachets that are placed inside the food package with the food have been available commercially since 1978. Their properties have been discussed in detail previously (Smith et al., 1995). The oxygen-scavenging material is normally a finely divided iron powder reduced with hydrogen. The iron powder is combined with corrosion accelerators, such as inorganic salts, and the aggregate is sealed in porous plastic sachets that allow the passage of oxygen and water vapor from the package headspace.

Since the introduction of active sachets, plastics capable of scavenging oxygen from package headspaces have been the subject of rapidly expanding

research and development (Rooney and Holland, 1979; Floros et al., 1997). Although a wide range of chemistries and physical properties are available, it is only recently that commercial products have reached the retail market.

The purpose of oxygen-scavenging packaging is to reduce the concentration of oxygen in the gaseous and dissolved state below that at which aerobic organisms can grow. Generally, the aim is to reduce the headspace oxygen concentration appropriate to the circumstances of the food environment, but concentrations below 0.1% can be routinely achieved by use of sachets. Similar results can be achieved with plastics packaging films, such as ZERO2™ currently under development by Commonwealth Scientific and Industrial Research Organisation (CSIRO) and Visy Pak in Australia. Although these dilute concentrations of oxygen are sufficient for inhibition of many aerobic microorganisms, the rate at which the oxygen is removed by the packaging system is also important. This effect of rate of oxygen removal is not observed in conventional gas-flush packaging because the oxygen concentration is minimized at the point of package sealing.

The effect of the rate of oxygen removal on the growth of yeasts, molds, and bacteria in packs of cooked ham with controlled leakage was reported by Randell et al. (1995). It was shown that, although oxygen can be removed and carbon dioxide formed in a package by microbial activity, an oxygen-scavenging sachet can remove the oxygen before microbial growth can occur, as indicated by lower carbon dioxide levels.

Sachets are also used for carbon dioxide release in conjunction with oxygen scavenging, but because the maximum carbon dioxide level is normally 21%, only limited impact on microbial growth can be expected (Smith et al., 1995). Table 23.3 shows a range of innovative packaging formats that change headspace gas composition.

A variety of desiccants are commercially available in sachet form and have the potential for maintaining low water activity in packages of dried foods. The use of desiccants for microbial inhibition in food packs is used in Japan but is not common elsewhere. However, some developments in water activity control offer some future prospects for expanding the available range of antimicrobial hurdles. The Showa Denko company manufactures Pichit™ film wrap, which rapidly absorbs water vapor. The wrap consists of two outer layers of polyvinyl alcohol sandwiching a thin layer of a humectant of a proprietary blend of a glycol and a carbohydrate. The outer layers are highly permeable to water, which passes through to the humectant layer. At present, there is no flexible packaging material that is capable of buffering humidity to specific predetermined values as is achieved by saturated salt solutions in the laboratory. Research activity in this area may have some desirable outcomes.

Package inserts designed to exhibit specifically antimicrobial action are manufactured in Japan and are used largely for the inhibition of molds. The porous sachets release ethanol vapor into the package headspace. The ethanol is weakly adsorbed onto silica gel powder and desorbed by water vapor from the food. The water is bound more strongly than the ethanol, so the product performs quite efficiently, finding its use largely in bakery products.

TABLE 23.3 Oxygen Scavenging Packaging Development and Commercialization

Format	Substrate	Source (examples)	Status
Sachet	Iron	*a–d*	Commercial
Label	Iron	*a,b*	Commercial
Closure liner	Iron	*a*	Commercial
Closure liner	Ascorbate	*e,f*	Commercial
Closure liner	Polymer bound	*g*	Trials
Film	Polymer	*e*	Trials
Film	Polymer bound	*g*	Trials
Bottles	Polymer	*h*	Commercial
Bottles	Polymer bound	*g*	Development
Bottles	Polymer-bound	*h,i*	Commercial

[a] Mitsubishi Gas Chemical Co., Tokyo, Japan

[b] Toppan Printing Co., Tokyo, Japan

[c] Multisorb Technologies, Inc., Buffalo, NY, USA

[d] ATCO, Caen, France

[e] Sealed Air Corp., Duncan, NC, USA

[f] ZapatA Technologies Inc, Hazleton, PA, USA

[g] CSIRO, Canberra, Australia

[h] AMOCO Chemical Co., USA

[i] Continental PET Technologies Inc., USA

Ethanol-releasing sachets are marketed by the Freund company as Ethicap™, and a second product marketed by the same company also absorbs oxygen concurrently, offering some prospect of a dual effect on aerobic organisms. An initial study suggests a potential for inhibition of *Listeria monocytogenes* on agar at temperatures up to 15°C (Smith et al., 1995).

Intelligent Packaging

One of the most desirable packaging adjuncts currently subject to research is a class of indicators designed to show when the food is in danger of becoming microbiologically unsafe. Indicators based on column reactions of metabolites are an example of intelligent packaging that warns the consumer of a potential hazard (Summers, 1990). The potential use of biosensors in this application has been discussed by Hotchkiss (1995). Application of sensors based on antibody or metabolite reactions offers the potential for monitoring activity of enzymes in food or of microorganisms growing thereon. If microelectronics are required for amplifying the output of such sensors, it seems likely that only wholesale cartons or pallet stacks may benefit. To date, there is not a validated system available for commercial use, but several approaches involving identification of vapors—such as combinations of ethanol, sulfides, and other characteristic volatiles—are being proposed (Eilamo et al., 1998).

Indicators of single compounds or physical properties are already commer-

cially exploited and these include indicators of time-plus-temperature (TTIs), high- or low-temperature exposure, gas composition, or leakage. All of these events or properties of a package impact on food safety from either the microbiological or chemical migration viewpoint. A wide range of TTIs are available commercially, and detailed lists of commercial and developmental systems have been reported (Selman, 1995; Ahvenainen and Hurme, 1997). The key factor limiting the application of TTIs as a guide to food safety is the requirement that the kinetics of the indicator color change should match the response of microorganisms to the combined effects of time and temperature. A lesser limitation is the placement of the indicator on the outside of shipping boxes or pallets, where temperature changes may be more extreme than in the food itself. This, however, is likely to overestimate conditions deleterious to safety and may be acceptable. Such indicators already provide a guide for design of handling systems for sensitive products subject to temperature fluctuations during distribution.

Gas composition indicators have been available for some years for use with oxygen-absorbing sachets. The color changes occur at concentration changes around 0.1%. This may be impractically low, because many acceptable modified-atmosphere packs have oxygen concentrations above this level. More recently, a carbon dioxide indicator has become available from Sealed Air (UK) Ltd. under the name Tufflex GS™.

It is important that an indicator should respond to a change in either a deliberately generated atmosphere or a specific gas concentration in the atmosphere generated by microbial growth (Ahvenainen and Hurme, 1997). If the gas composition of a package with a chosen high-carbon dioxide and low-oxygen atmosphere changes because leakage or permeation, it is important for the user to know this. If, however, there is oxygen ingress and this oxygen is consumed by microbial respiration, an unsafe environment may not be detected. Indicators that warn in an unambiguous manner of an atmosphere potentially associated with microbial activity are still required.

Detection of seal leakage is important in most packs of foods and beverages but is critical in those that are intended to be shelf stable. Currently, aseptic cups are tested by means of pressure-sensitive sensors immediately after sealing, but there is still a need for an indicator system for seal leakage in flexible packs. Several systems have been reviewed, and a range of feasible concepts have been substantially developed (Ahvenainen and Hurme, 1997). The lack of introduction of such technologies so far appears to result from a lack of enthusiasm on the part of packers , despite the large benefits expected in modified-atmosphere packaging.

Migration of Chemicals

Besides the intended release of microbial inhibitors, there is a potential for unintended effects in the use of active packaging. At the present time, most forms of antimicrobial packaging do not have approval in most countries. Sources of unwanted chemicals could include impurities in additives or reaction

residues in reactive materials (e.g., oxygen scavenging systems). Excessive migration might occur if the packaged food is handled outside the range of planned conditions, as in the case of heating the food while it is still packaged. Packaging may also be used with food types different from those intended. The introduction of active packaging concepts is sometimes subject to regulatory delays so that testing under abuse conditions can be carried out.

Recognition of the potential for migration of package additives into food is important when using active systems that involve chemical reaction. This is because reaction products may differ from the starting materials in that they may consist of smaller molecules or may have less migration from the plastic matrix, more migration into the food, or higher volatility. Reaction products may also exhibit a toxicity that constitutes a hazard to the consumer, even though the starting material may meet regulatory requirements. For this reason, the European Union has sponsored a mulitnational research project entitled "Actipack." This project is expected to assist in formulating new food contact regulations for packaging.

The prospective impact of an active packaging system can be considered by potential users early in the concept development, such as at the patent disclosure stage. Initial patent applications for several of the proposed polymeric oxygen-scavenging compositions have been followed by applications for modified systems in which reaction products expected to migrate into the food are adsorbed or otherwise prevented from migrating into the food.

Proposals sometimes put forward by politicians for recycling of used packages into food packaging materials is leading research into the barrier of plastics to contaminants. The use of surrogate compounds that simulate the diffusion of toxic chemicals commonly used around the home, such as pesticides and solvents, has been adopted by the FDA. Packaging polymers provide a barrier to these compounds that is inadequate to meet food contact regulations. The possible exception is polyethylene terephthalate, PET. Postconsumer PET is included as the middle layer in three-layer soft drink bottles in several countries. DuPont's proprietary Odor and Taste Control Technology, which uses molecular sieves as adsorbents, has been reported as being capable of removing aldehydes such as hexanal and heptanal, often found in rancid fats and oils (Anonymous, 1996). The further development of such concepts will be necessary if the risks of migration of a wide variety of non-GRAS substances associated with more widespread use of recycled materials are to be addressed.

REGULATORY, INDUSTRIAL, AND INTERNATIONAL IMPLICATIONS

Packaging materials are subject to regulations because of their contact with foods. Additional regulations apply to labeling and environmental impact. Food safety is the subject of the food contact regulations, although indicators for spoilage, gas composition, or leakage can be expected to be subject to labeling requirements. Only food contact compliance is discussed here. The

basis of these regulations varies widely internationally, although the U.S. Food and Drug Administration (FDA) and European Union (EU) requirements are used commonly as a reference point when packaging innovation is involved. An introduction to regulations applied to migration of chemicals from packaging materials in the U.S., the EU, and Japan has been published (Katan et al., 1996).

Any component of innovative packaging used in the U.S. must be judged against the criterion in Section 409 of the Federal Food, Drug and Cosmetic Act, which regulates "food additives." The latter are "any substance the intended use of which results, or is reasonably expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food...." There are restrictions on this definition depending on whether the migrating substance is GRAS or has prior sanction. Components of active packaging affected by this law include not only antimicrobial agents but also reagents derived from oxygen-scavenging plastics or humidity-buffering compositions.

Components of packaging are not normally intended to migrate into the food, and so the more recently introduced concept of "Threshold of Regulation" allows a less complicated determination of whether or not a packaging innovation meets FDA requirements (FDA, 1995). This rule exempts substances from regulation if they meet certain very strict criteria, which include limitation of the expected amount migrating to be less than 0.5 parts per billion in the diet and freedom from similarity with compounds with any carcinogenic effect. There are some other provisions, all of which are based on the premise that the amounts of migrating substances concerned are so trivial as not to require regulation.

The food safety laws of EU member states are required to reflect the EU Packaging Directives, which are based on the Framework Directive (Anonymous, 1989). These packaging directives provide for an Overall Migration Limit for total migration, Specific Migration Limits for a few specific compounds, and Negative Lists for banned substances. Any component used in the manufacture of a material for food contact must appear on one of the Positive Lists, which are being compiled at this time. Applications for inclusion of a substance on one of these lists must be made to the Scientific Committee for Food, which has expertise in toxicology and the properties of packaging material.

The chemicals involved in many of the active packaging materials proposed for food contact do not appear in current lists of approved food additives. Therefore, introduction of these materials will require lengthy food additive petition processes. The European Commission began funding a European Research Project under the FAIR program in 1998 to establish whether amendment of existing legislation to accommodate intended release of desirable substances is appropriate. The research project is multinational and is coordinated by TNO Nutrition and Food Research, an institution based at Zeist in The Netherlands.

Harmonization of European and U.S. legislation related to approval of packaging materials is not complete because of differences in approach. It is therefore necessary for approvals to be obtained in both jurisdictions. Approvals in other countries are not in any way automatic, but the evidence provided to gain approvals in the two major markets is valuable elsewhere. Japan remains the fastest country in introducing active and intelligent packaging into the market. This may be a consequence of the large research effort devoted to active and intelligent packaging research in Japan. Other factors relate to the willingness of Japanese consumers to accept innovation and the need for packaging adjuncts because of specific food types and climatic conditions.

CURRENT AND FUTURE IMPLICATIONS

Packaging innovation is both a consequence of progress in food science and a driver for this progress. Although there is a continuing evolution of packaging materials and processes, active and intelligent packaging stand out as major innovative steps in improving food safety. The departure from traditional reliance on the passive barrier properties of packaging demonstrates an increased willingness of product developers to match packaging material properties to the needs of the food.

Innovations that are reaching the commercial stage are largely taken up when the users see demonstrable benefits. This is the case with oxygen absorbers in many food packages in Japan and, more selectively, in packages of foods subject to visual spoilage in several other countries. These visual effects are the subject of efforts toward prevention of oxidative fading of the color of processed meats and elimination of mold growth in bakery products. Demonstration of food safety benefits will be more difficult, because the benefit is determined in exhaustive challenge tests rather than by consumer survey. The impact of oxygen removal from foods on the growth of anaerobes must be investigated more thoroughly so that conditions for use of oxygen-scavenging plastics and equivalent sachets can be defined.

Direct antimicrobial action by packaging needs more systematic study than has been reported thus far so that the potential for selective growth of microorganisms can be ascertained. At this stage, the commercial release of currently available antimicrobial packaging may be premature, even though this packaging is being proposed primarily to enhance food quality. The justification for extensive systematic study of more acceptable antimicrobial materials may be dependent on development of manufacturing processes that are practical and economical.

Development of indicators for several safety-related properties of foods (e.g., time and temperature history, exposure to temperature spikes, exposure to food spoilage organisms and pathogens) is needed urgently, because development of several mild treatments of foods has occurred with little attention to optimum developments in packaging. Treatments such as modified-atmosphere pack-

aging of fresh-cut produce have created consumer demand because of product quality. Packaging plastics with improved gas permeability control are needed, but indicators of headspace composition and microbial growth are more critical because the opportunity for growth of pathogens is higher here than in thermally processed foods.

Innovations are taking place in fields of packaging technology outside active and intelligent packaging. Traditional thermal processing demands packaging that can withstand at least 121°C. Enhanced forms of polyester, such as PEN, are being developed and may be used substantially in the packaging of infant foods. If ultrathin coatings of gas barriers on plastics are successfully developed, it may be possible to make greater use of plastic packages in retort applications.

Regulations covering innovation in food contact plastics are keeping pace with innovation in some countries, such as the U.S.; however, EU regulations require amendments to allow safe interaction between the food and the package. Research is currently being sponsored by the European Commission to determine whether the benefits for microbiological food safety of active and intelligent packaging can be achieved without introducing problems of migration of chemicals from the packaging.

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This publication is a collaborative effort of several experts in packaging who have surveyed potential adjuncts for packaging that will enhance the overall security of the packaged products. They propose time schedules for introduction of some of the indicators not yet available.

CHAPTER 24

SAFE HANDLING OF FRESH-CUT PRODUCE AND SALADS

DAWN L. HENTGES

INTRODUCTION AND DEFINITION OF ISSUES

Several factors have led to an increased consumption of fresh produce in recent years. These include 1) concerns about health and the recognition that fruits and vegetables, as part of a low-fat diet, can lower the risk of cancer and heart disease, 2) greater diversity of products from increased importation, and 3) increased demand for high-quality produce caused by aging of the population and income distribution shifts (Beuchat, 1996; Cook, 1990).

In response to consumer demand for freshness and convenience, fresh-cut produce offers a ready-to-eat product with "fresh"-like quality. Fresh-cut produce is defined as having 1) cut surfaces, 2) minimal processing not ensuring microbiological stability, 3) active metabolism of the plant tissue, 4) protective packaging, and 5) often extended shelf life (Nguyen-the and Carlin, 1994). Fresh-cut vegetables often include cabbage, lettuce, other salad greens, onions, green and red peppers, carrots, cauliflower, and broccoli. These are washed and may be available in peeled, cubed, shredded, or grated forms. For convenience, several items may be packaged together and may include nonproduce ingredients such as dressing and croutons. For both consumers and the food service industry, fresh-cut produce requires less labor and causes less waste than fresh unprocessed produce. Between 1998 and 2003, fresh-cut produce retail sales are projected to grow 21% (Mermelstein, 1998).

Although implicated in a small number of foodborne illness outbreaks, fresh produce exhibits substantial potential to become hazardous and provide a health risk. Because it is typically consumed raw without a final heat treatment to destroy microbial pathogens or toxins, fresh-cut produce presents a potential health risk if microbial growth is not inhibited during extended shelf life. Washing the produce and following good manufacturing practices will promote

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reduction of the initial microbial load. In addition, subinhibitory preservation methods, such as modified-atmosphere packaging, refrigerated storage, increased acidity, and/or irradiation, can be used to control growth of microorganisms and extend shelf life of fresh-cut produce. Although not mandatory for fresh-cut produce, a Hazard Analysis Critical Control Point (HACCP) system can be implemented to reduce risks from potential microbial hazards (Table 24.1).

BACKGROUND AND HISTORICAL SIGNIFICANCE

Fresh-cut fruits and vegetables possess resident microflora. In a survey of retail produce, microorganisms, predominately *Pseudomonas*, were present at 10^2–10^9 colony forming units (CFU)/g (Nguyen-the and Carlin, 1994). Coliforms are a common contaminant of raw vegetables because they have contact with the soil; however, they comprise only a small portion of the microflora. Fecal coliforms are present in even fewer numbers and are not detected on most produce (Nguyen-the and Carlin, 1994). *Escherichia coli* was observed on 0.25% of fresh fruits and 1–3% of fresh vegetables (Veloudapillai et al., 1969). Yeast (*Candida*, *Cryptococcus*, *Pichia*, *Trichosporon*, and *Torulaspora*) and molds (*Cladosporium*, *Mucor*, *Penicillium*, *Phoma*, *Rhizopus*, and *Sclerotinia*) are present on fresh produce (King et al., 1991; Nguyen-the and Carlin, 1994).

The following pathogens have been isolated from retail packages of fresh-cut produce: *Listeria monocytogenes*, *Yersinia enterocolitica*, *Aeromonas hydrophila*, *Staphylococcus aureus*, *Clostridium botulinum*, *Bacillus cereus*, *Clostridium perfringens*, and *Salmonella typhimurium* (Beuchat, 1992, 1996; Lilly et al., 1996; Nguyen-the and Carlin, 1994; Park and Lee, 1995). *L. monocytogenes* has been detected on lettuce (1–2% incidence), cabbage, potatoes (25.8%), radishes (30.3%), and cucumbers (Heisick et al., 1989); however, Petran et al. (1988) did not find *Listeria* in market samples of fresh vegetables. Cytotoxic and hemolytic *Aeromonas* (10^2–10^4 CFU/g) can be isolated from parsley, spinach, celery, broccoli, lettuce, endive, escarole, and kale (Callister and Agger, 1989). *S. aureus* is detected on fresh produce and ready-to-eat salads, most likely because of contamination by food handlers (Beuchat, 1996). A low incidence (0.36%) of *C. botulinum* spores was observed on fresh-cut vegetables (Lilly et al., 1996). In September 2001 the Food and Drug Administration completed a 1000-sample survey of domestic fresh cantaloupe, celery, cilantro, green onions, loose-leaf lettuce, parsley, strawberries, and tomatoes for the presence of *Salmonella*, *E. coli* O157:H7, and *Shigella*. Contamination of pathogenic microorganisms in fruits and vegetables does not necessarily indicate the existence of a potential hazard. The presence of competitive microorganisms, adequate nutrients, and appropriate environmental conditions affect pathogen growth and/or toxin production and virulence.

Although implicated in a small number of foodborne illness outbreaks, fresh produce exhibits substantial potential to become hazardous and provide a

TABLE 24.1. International Fresh-Cut Produce Association Model HACCP Plan for Fresh-Cut Produce[a]

Firm Name: _____

Address: _____

Date: _____

Product Description: Shredded lettuce, prepared from refrigerated lettuce; trimmed, cored, and cut; washed in a solution of potable water and chlorine (or other approved antimicrobial solution); packed in food grade plastic bags, 8 oz.–10 lb. units; with an optimum shelf life if refrigerated at 34–38°F (1.1–3.3°C). Bag and/or box contains "processed on" or "use by" date.

Method of Distribution and Storage: Product distributed under refrigeration to food service operations and retail markets; stored under refrigeration.

Intended Use and Consumer: For use in salads and sandwiches for food service customers; Prepackaged units for in-home use by consumers.

Typical consumers: general public

TABLE 24.1. *(Continued)*

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
Critical Control Point (CCP)	Significant Hazard	Critical Limits for Control Measures	Monitoring				Corrective Action(s)	Record Keeping	Verification
			What	How	Frequency	Who			
Washing	*L. monocytogenes*, *E. coli* O157:H7, *Salmonella*	Potable water @ pH 7.0	pH	pH Meter	Test water before processing; 3 times per shift	QC[b] personnel, test kits/meters evaluated by QC regularly	Preprocessing batch adjustment; manually adjust water chemistry	Recording chart; records monitored every shift by QC	Random sampling; QA[b] audit; HACCP plan validated every year; review of procedures
		Potable water containing ~1 ppm free residual chlorine* for a minimum of 30 s	Free chlorine	Test kit/automated	Continuous	QC personnel, test kits/meters evaluated by QC regularly	Hold product from last correct reading for rewashing; record incident in deviation log	Continuous strip chart	

Packaging	Metal	3.5-mm stainless steel**	Metal	Known metal sample run through detector	Hourly	Line operator	Hold product from last correct calibration and rerun product; record incident and product status in deviation log; identify source of metal and investigate line; add to preventive maintenance program	Metal detector records; calibration records taken by QC every shift; records monitored by QC every shift	Random sampling for metal analysis; QA audit; HACCP plan validated every year

[a] Used with permission from the International Fresh-Cut Produce Association.

[b] QC: quality control; QA: quality assurance.

* or other appropriate concentration of approved antimicrobial solution for wash water.

** or according to manufacturer's guidelines or customer specifications.

Signature of Company Official _____ Date _____

health risk. Four cases of botulism in 1987 were attributed to consumption of coleslaw prepared with modified-atmosphere packaged shredded cabbage (Solomon et al., 1990). Cabbage, lettuce, celery, and tomatoes are linked to cases of listeriosis (Ho et al., 1986; Schlech et al., 1983). The source of *Listeria monocytogenes* contamination was sheep manure used to fertilize the cabbage. Three outbreaks of salmonellosis, which infected more than 500 people and caused two deaths, are associated with contaminated cantaloupes and watermelons (Blostein, 1991; CDC, 1979, 1991). The interior of the melons became contaminated from the unwashed rinds during cutting, and the pathogens were able to grow while the melon was displayed in a salad bar. Tomatoes contaminated with *Salmonella javiana* and *S. montevideo* were identified as the source of foodborne illness outbreaks in 1992 (Wood et al., 1991) and 1993 (Hedberg et al., 1994), respectively. Imported raspberries infected with *Cyclospora cayetanesis* were implicated in foodborne illness outbreaks occurring in 1996 and 2000. Large outbreaks of gastroenteritis were associated with modified-atmosphere packaged shredded lettuce served in salad bars (Davis et al., 1988; Martin et al., 1986). A contaminated food handler may have introduced *Shigella sonnei* during processing of the lettuce. The consumption of green salads containing lettuce (Griffin et al., 1982; Rosenblum et al., 1990), frozen raspberries (Reid and Robinson, 1987), and frozen strawberries (Niu et al., 1992), probably contaminated by an infected worker, were implicated in hepatitis A and Norwalk viral infections. Extended shelf life allowing global distribution may facilitate widespread dissemination of pathogen-contaminated produce.

SCIENTIFIC BASIS AND IMPLICATIONS

Because it is typically consumed raw without a final heat treatment to destroy microbial pathogens or toxins, fresh-cut produce presents a potential health risk if microbial growth is not inhibited during extended shelf life. Processing operations such as trimming and washing and modified-atmosphere packaging can extend shelf life by eliminating or retarding the growth of indigenous spoilage microorganisms and can promote the growth of some pathogens. Psychrotrophic bacteria, such as *Listeria*, can survive and grow during prolonged refrigeration. Because spoilage bacteria are reduced, fresh-cut produce may remain organoleptically acceptable for long periods yet exhibit pathogen populations or toxin production significant enough to be potentially hazardous during prolonged storage. Spoilage microorganisms can provide a margin of safety as the produce becomes inedible before sufficient pathogen growth or toxin production. In addition, spoilage microorganisms competitively inhibit the growth of some pathogens, such as *Clostridium botulinum*. Spoilage of *C. botulinum*-inoculated modified-atmosphere packaged lettuce, cabbage, broccoli, carrots, green beans, and tomatoes has been shown to occur before botulinum neurotoxin production (Hotchkiss et al., 1992; Larson et al., 1997;

Petran et al., 1995). Larson et al. (1997) suggest that the probability is less than 0.001% that botulism toxin will be produced in these inoculated products before spoilage.

Sources of Microbial Contamination

Pathogenic contamination of fresh-cut produce may occur at every step of minimal processing from the field to the table. Potential sources of contamination may include irrigation water, improperly composted manure, wild or domestic animals, soil, contaminated equipment and wash water, airborne dust, and human handling. Risks can be minimized by compliance with recommended good agricultural practices (GAPs) and good manufacturing practices (GMPs) and by training personnel in the importance of sanitation and personal hygiene. Proper facility design, such as keeping raw produce separated from finished produce and maintaining positive air pressure in the processing rooms, can aid in reducing contamination during processing.

Processing procedures do not significantly change the mesophilic microflora of fresh-cut fruits and vegetables; however, these processing procedures could increase pathogenic contamination (Nguyen-the and Carlin, 1994). Cutting the fruits and vegetables provides more surface area of the produce to support the growth of microorganisms. Also, any pathogens present on the surface of fresh produce and equipment or from unsanitary handling practices will contact damaged plant tissue during peeling, slicing, chopping, and shredding. Cutting processes release cellular nutrients and provide high moisture content on the cut surfaces, supporting microbial growth. Washing the cut produce will enhance removal of free cellular fluids that contribute to enzymatic browning, a major quality defect. Antimicrobials, which inactivate microorganisms, may also be present in the damaged plant tissue. For example, *Listeria monocytogenes* and *Escherichia coli* O157:H7 were inhibited or inactivated by raw carrot juice containing phytoalexin leached from shredded carrots (Beuchat and Brackett, 1990b).

Reducing Risk of Pathogenic Microorganisms

A combination of subinhibitory preservation methods may be used to control growth of microorganisms and extend the shelf life of fresh-cut produce. These methods may include modified-atmosphere packaging, refrigerated storage, increased acidity, and/or irradiation. Washing the produce and following GMPs will promote reduction of the initial microbial load.

Surface disinfection To remove soil and reduce the number and growth of surface microorganisms, fresh produce is washed in potable water and cooled as quickly as possible after harvest. To prevent pressure differentials that draw or force water along with surface pathogens into the produce, the most appropriate temperature of the wash water is greater than the temperature of the

produce for products such as apples, celery, and tomatoes. Washing with water, however, is not a very effective operation to reduce initial microbial loads on produce. Standard washing procedures for lettuce using tap water demonstrated only a 1- to 2-$\log_{10}$ CFU/g reduction of total microflora (Adams et al., 1989). Extended washing was necessary to produce microbial reduction similar to that with hypochlorite disinfection. After washing, the produce is often immersed or sprayed with a disinfectant solution at an appropriate concentration and time period to sufficiently reduce microbiological contaminants. Cantaloupe dipped in 200 ppm hypochlorite solution exhibited smaller psychrotrophic and aerobic microbial populations than unwashed and water-washed cantaloupe (Ayhan et al., 1998). Residual water remaining on the produce after washing should be removed, usually by air drying, centrifugation, or shaking, and thus unavailable for growth of microorganisms. Sanitizer in the wash, spray, and flume waters will help prevent cross-contamination of the produce during processing operations by inactivating vegetative microbial cells.

In the produce industry, chlorine is routinely used as a sanitizer because it rapidly kills a wide spectrum of microorganisms (bacteria, fungi, and viruses), completely dissociates in water, does not leave a toxic residue on food contact surfaces, is economical, and is nontoxic to humans in low concentrations (Zhang and Farber, 1996). The degree of microbial inactivation is related to the amount of free available chlorine (hypochlorous acid) in the water. For fresh produce, a concentration of 50–200 ppm free available chlorine at pH 6.0–7.5 is recommended for effective lethality of microorganisms. A 1-$\log_{10}$ reduction in total microbial count and coliforms was observed in lettuce (Adams et al., 1989; Beuchat and Brackett, 1990a) and broccoli florets (Albrecht et al., 1995) treated with 50 ppm hypochlorite. Higher concentrations of hypochlorite did not reduce the microbial populations further. Brussels sprouts dipped in 200 ppm hypochlorite exhibited a 100-fold reduction in *Listeria monocytogenes*, 10-fold more than brussels sprouts washed with water (Brackett, 1987). The bacteriocidal effect of 10-min exposure to 200 ppm hypochlorite was greater for *Listeria* when present on lettuce than on cabbage, indicating that the type of vegetable play may a role in the antimicrobial activity of the sanitizer (Zhang and Farber, 1996). Exposure of 1–2 min to hypochlorite solution to achieve maximum lethality is sufficient on most produce. Increased exposure to hypochlorite solution from 5 to 30 min did not further decrease total microbial counts of shredded lettuce (Beuchat, 1992). The hypochlorite disinfectant concentration should be monitored continuously and adjusted as needed because the presence of organic matter may decrease the efficacy of the sanitizer and contamination of the produce may occur as microbial loads build up in unchanged or recycled wash water.

Sanitizing solutions are not effective in removing all microorganisms from produce. Microorganisms located within cells or protected regions of the plant surface may survive hypochlorite treatments (Watada et al., 1996). Salad greens have a high surface area that also contributes to increased microbial

loads. Folds and crevices in the produce surface protect microbial contaminants during disinfection. The waxy cuticle on the surface of vegetables is hydrophobic and may protect bacteria from contact with aqueous hypochlorite solutions (Adams et al., 1989). Surfactants added to improve the efficacy of hypochlorite by increasing surface wetting (Adams et al., 1989) may instead combine with, and partially neutralize, the antimicrobial activity of chlorine (Zhang and Farber, 1996). The formation of a biofilm on the surface of produce could also protect microorganisms against the lethal effects of hypochlorite (Adams et al., 1989; Nguyen-the and Carlin, 1994). Dipping or spraying produce with hypochlorite cannot be relied on to completely eliminate pathogens in fresh produce. Therefore, hypochlorite must be used in conjunction with other inhibitory processing methods to prevent pathogen growth.

Organic acid washes or sprays, such as acetic, lactic, citric, propionic, sorbic, or ascorbic acids, may be used to reduce microorganisms on fresh-cut produce; however, there may be only minimal reductions in total microbial counts beyond that occurring with water washing (Adams et al., 1989; Zhang and Farber, 1996). Antimicrobial effectiveness of the acid depends primarily on the dissociation constant (pKa) (Beuchat, 1992). On cut lettuce and cabbage, lactic acid was more effective than acetic acid in reducing *L. monocytogenes*; however, only a 0.2- to 0.5-$\log_{10}$ CFU/g reduction was observed after a 10-min exposure to 1% solutions of each organic acid (Zhang and Farber, 1996). Because organoleptic quality of vegetables may be unacceptably affected by acid, low concentrations (1% or less) of acid solution are used, and vegetables are washed after treatment.

Other antimicrobials used less often than chlorine to reduce microorganisms on produce include ozone, metabisulfite, chlorine dioxide, and peroxyacetic acid. Although not currently approved for use on raw agricultural commodities, hydrogen peroxide, acidified sodium chlorite, trisodium phosphate, and electrochemically activated water also have the potential for future use as sanitizers of fresh produce.

Although in limited use, irradiation of fresh produce is approved at doses up to 1 kGy to inhibit ripening and sprouting (21 CFR 179.26). In addition to extending shelf life, this low-dose radiation treatment may reduce some of the pathogens. At doses below 2 kGy, gamma irradiation is generally more effective (3- to 4-$\log_{10}$ CFU/g reduction) than chemical disinfection methods at decreasing total microbial counts on fresh produce (Nguyen-the and Carlin, 1994). This antimicrobial effect tends to persist longer during storage in irradiation-treated produce than produce treated with chemical disinfection methods (Nguyen-the and Carlin, 1994). Shredded carrots treated with chlorinated water (0.8–2.0 ppm) and irradiation (0.5 kGy) exhibited total microbial counts of 200 CFU/g compared with 13,000 CFU/g for nonirradiated shredded carrots (Hagenmaier and Baker, 1998). Irradiation is also used to extend the shelf life of sweet corn, strawberries, other berries, grapes, papayas, and mangos (21 CFR 179.26).

Modified-atmosphere packaging In modified-atmosphere packaging (MAP), perishable products are packaged in atmospheric gas compositions different than that of air (Larson et al., 1997). MAP extends the shelf life of minimally processed fruits and vegetables by suppressing the growth of aerobic spoilage microorganisms, reducing the rate of oxidation and enzymatic degradation, and reducing the loss of water (Austin et al., 1998). Packaging fresh-cut produce in modified atmospheres provides another method for controlling pathogen growth and toxin production. Specific gas compositions of oxygen and carbon dioxide, tailored for each type of produce, are created within the package by considering produce respiration, packaging material permeability, storage temperature, storage time, and presence of desiccants and gas-producing or -absorbing packets. As the produce respires inside the package, the oxygen level decreases while the level of carbon dioxide increases. Optimal oxygen (at least 2%) and carbon dioxide (no more than 20%) concentrations are generally maintained within the package to prevent anaerobic respiration, which accelerates senescence accompanied by development of off flavors and microbial growth (Nguyen-the and Carlin, 1994; Watada et al., 1996). Typical air composition is approximately 21% oxygen and less than 0.1% carbon dioxide. Reducing oxygen concentration to 2% and increasing carbon dioxide to 5% resulted in a more than 10-fold decrease in the respiration rate of broccoli florets (Zagory and Kader, 1988). Respiration rates of fresh-cut produce are higher than for the intact product (Watada et al., 1996) and increase two- to threefold for every 10°C rise in temperature. Fresh-cut cantaloupe, Crenshaw melons, and honeydews had similar or lower respiration rates than intact fruit at 0, 5, and 10°C, but the respiration rates were much higher at 20°C, probably because of physiological deterioration and microbial growth (Watada et al., 1996). The amount of carbon dioxide and oxygen inside the fresh-cut produce package is also contingent on the gas permeability of the package materials. Gas permeability, particularly to carbon dioxide, is dependent on temperature. During storage at a specific temperature, the atmospheric composition inside the package eventually stabilizes as the respiration rate and flow of gases through the packaging film equilibrate. If during distribution and marketing MAP fresh-cut produce is stored at temperatures different from those for which the packaging system was specifically designed, the atmosphere inside the package will be suboptimal, resulting in possible microbial growth.

Because aerobic spoilage microorganisms may be inhibited in the decreased oxygen and increased carbon dioxide conditions of MAP, fresh-cut produce may remain organoleptically acceptable for longer periods yet have pathogen populations or toxin production significant enough to be potentially hazardous. *Clostridium botulinum*, an anaerobic spore-forming bacteria, produces a potent neurotoxin of particular concern. Inhibition of competitive microflora, oxygen concentrations below 2%, and increased carbon dioxide concentrations in MAP fresh-cut produce promote spore germination and toxigenesis of *C. botulinum* (Hotchkiss et al., 1992; Nguyen-the and Carlin, 1994). Botulism toxin was detected in MAP and vented packages of fresh-cut romaine lettuce and

shredded lettuce stored at 21°C for 7 and 21 days; however, no toxin was detected in either MAP or vented packages when stored at 4.4 and 12.7°C (Petran et al., 1995). MAP lettuce, cabbage, broccoli, cauliflower, and tomatoes can support *C. botulinum* growth and may serve as potential vehicles for ingestion of botulism toxin (Hotchkiss et al., 1992; Petran et al., 1995). Growth of *L. monocytogenes* on lettuce, whole and chopped tomatoes, asparagus, broccoli, and cauliflower is not influenced by modified atmospheres of 3% O_2 and 97% N_2 (Beuchat and Brackett, 1990a, 1991); however, because shelf life is extended, MAP increases the time during which *L. monocytogenes* may grow in fresh-cut produce before spoilage occurs. At high carbon dioxide concentrations, the growth of *Aeromonas hydrophila* and *Bacillus cereus* is inhibited in MAP vegetables (Nguyen-the and Carlin, 1994).

Refrigerated storage Refrigerated storage (5°C) is a primary method used to suppress microbial growth and ensure safety of fresh-cut produce. Psychrotrophic pathogens such as *Listeria monocytogenes*, *Aeromonas hydrophila*, and *Yersinia entercolitica*, however, can survive and may reproduce at temperatures below 7°C. Refrigerated temperatures are typically used during transportation and storage of fresh-cut produce. Populations of *L. monocytogenes* and *A. hydrophila* increased significantly on lettuce, asparagus, broccoli, and cauliflower when stored for more than 8 days at 5°C (Beuchat and Brackett, 1990a, 1991; Callister and Agger, 1989). When the produce was stored at 10°C, increased growth of *L. monocytogenes* was observed after only 3 days. Beuchat and Brackett (1991) observed growth of *L. monocytogenes* on the surface of MAP whole tomatoes when stored at 21°C but not when held at 10°C. This pathogen was not detected, however, on inoculated chopped tomatoes stored at either 10°C or 21°C. Although during refrigeration of fresh-cut produce mesophilic pathogens, such as *Escherichia coli*, *Staphylococcus aureus*, *Salmonella*, and *Shigella*, may not reproduce, the microorganisms can multiply rapidly if the product is temperature abused at 10°C or greater. Although more rapid at higher temperatures, nonproteolytic *C. botulinum* can grow and produce neurotoxin on MAP fresh-cut vegetables at 7°C, whereas proteolytic strains produce neurotoxin at typical abuse temperatures, 15°C and higher (Austin et al., 1998; Hotchkiss et al., 1992; Solomon et al., 1990). To control growth of *C. botulinum* and neurotoxin production, temperatures of MAP fresh-cut produce must be strictly maintained at less than 5°C (Austin et al., 1998). Rapid growth of *E. coli* O157:H7 (del Rosario and Beuchat, 1995) and *Salmonella* (Golden et al., 1993) was observed on cantaloupe and watermelon cubes stored at 23–25°C. *E. coli* O157:H7 exhibited growth at 12 and 21°C on MAP sliced cucumbers, shredded cabbage, and shredded carrots; however, the inoculated pathogen population declined when the produce was stored at 5°C (Abdul-Raouf et al., 1993). The population of *Shigella sonnei* also decreased on shredded cabbage (Satchell et al., 1990) and shredded lettuce (Davis et al., 1988) stored at 5°C for 7 days and exhibited increased growth at 22°C. After 2 days of storage at room temperature, *S. aureus* populations decreased on

shredded lettuce and sliced celery and increased on sliced green pepper (Gourama et al., 1991). When using refrigeration to control microbial risks, the temperature at which chill injury of produce occurs must also be considered.

Acidity Overall, bacteria can survive and grow in the pH range of 4.0 to 9.0; however, specific genera need a narrower pH range, with pathogenic bacteria being the most fastidious. The optimum growth pH of many pathogens is within the pH range of vegetables (pH 4.2–7.3). Fruits present few microbial risks, in part because of their relatively low pH (1.8–5.6). The interior tissue of whole fruits with intact skins, peels, cuticles, or rinds is essentially sterile; however, cross-contamination can occur when microorganisms from the surface of the produce, unsanitary equipment, or food handlers come in contact with the interior tissue during cutting. *Shigella* spp. inoculated onto the surface of papaya, jicama, and watermelon cubes, pH 5.69, 5.97, and 6.81, respectively, grew substantially within 4–6 h at 22–27°C (Escartin et al., 1989). Chopped tomatoes and tomato slices, pH 3.99–4.37, supported the growth of *Salmonella enteritidis*, *S. infantis*, *S. typhimurium* (Asplund and Nurmi, 1991), and *S. montevideo* (Zhuang et al., 1995), but the acidic juice decreased the population of inoculated *Listeria monocytogenes* (Beuchat and Brackett, 1991).

Lactic acid bacteria (LAB), including *Lactobacillus*, *Leuconostoc*, and *Pediococcus* genera, provide another method of ensuring the safety of fresh-cut produce through competitive inhibition. During prolonged storage or temperature abuse, naturally occurring or inoculated LAB on fresh-cut fruits and vegetables produce lactic and acetic acids that inhibit the growth of some pathogens by decreasing the pH below growth requirements and inhibiting metabolism. Pathogens, however, may be able to reproduce in fresh-cut produce before LAB metabolites reduce the pH of the fruits and vegetables to inhibitory concentrations. LAB on shredded cabbage decreased the pH from 5.09 to 3.70 after storage at 24°C for 4 days (Satchell et al., 1990). When coinoculated separately with LAB, *Aeromonas hydrophila*, *Listeria monocytogenes*, *Salmonella typhimurium*, and *Staphylococcus aureus* (initial inoculum $\sim 10^5$ CFU/g) were not detected in fresh-cut mixed salad after 6 days (Vescovo et al., 1996).

REGULATORY, INDUSTRIAL, AND INTERNATIONAL IMPLICATIONS

Although the HACCP program is currently voluntary for the fresh-cut produce industry, the recent occurrence of foodborne illness outbreaks implicating fresh or minimally processed fruits and vegetables indicate the need for establishing a comprehensive food safety program in the produce industry to reduce risk from potential microbial hazards. The International Fresh-Cut Produce Association (IFPA; Alexandria, VA 22201) developed a model HACCP plan for fresh-cut produce (Table 24.1) to serve as a guide for fruit and vegetable processors developing and implementing HACCP programs tailored to ensure microbial

safety of fresh-cut produce. Compliance with GMPs and HACCP is necessary at every step, from the field to the table, to control factors related to contamination, survival, and growth of microorganisms in fresh-cut produce.

In response to the National Food Safety Initiative issued by the President of the United States, the U.S. Environmental Protection Agency, U.S. Department of Health and Human Services, and U.S. Department of Agriculture (1997) submitted a report describing a plan to improve the safety of the United States' food supply and identifying produce as an area of concern. To address the safety of fresh-cut produce, the "Guide to Minimize Microbial Food Safety Hazards for Fresh Fruits and Vegetables" was prepared by these governmental agencies (USDHHS/FDA/CFSPAN, 1998). The Guide recommends GAPs and GMPs to minimize food safety hazards common to the growing, harvesting, packing, and transporting of fruits and vegetables available in an unprocessed or minimally processed state to consumers.

Extending shelf life will promote global distribution of fresh-cut fruits and vegetables; however, it may also facilitate widespread dissemination of pathogen-contaminated produce should significant pathogen growth or toxin production occur while the produce remains organoleptically acceptable. Maintenance of sanitary conditions and prevention of temperature abuse to reduce microbial risks is necessary throughout domestic or international distribution and marketing of fresh-cut produce. During a July 3, 1999 radio address, President Clinton announced new measures to prevent unsafe food from crossing U.S. borders. He recommended passage of a bill introduced in the Congress to ensure that imported fruits and vegetables meet U.S. food safety requirements or provide protection equivalent to that required for fruits and vegetables grown in the U.S.

CURRENT AND FUTURE IMPLICATIONS

Although MAP, acidity, antimicrobials, and surface disinfection practices are methods frequently used to inhibit pathogen growth, maintaining refrigeration and decreasing storage time before consumption are the most efficient ways to ensure the safety of fresh-cut produce (Nguyen-the and Carlin, 1994). Improving the effort to educate processors, distributors, retailers, and consumers on the importance of proper temperature control and sanitation and their responsibility for product safety as a member of the HACCP team is necessary to decrease microbial risk of fresh-cut produce. Because significant pathogen growth and toxin production may occur before spoilage, "use by" dates on fresh-cut produce should clearly indicate a safe time for consumption. This will provide additional safety by reducing the time for growth of psychrotrophic microorganisms such as *Listeria*. Temperature abuse, however, at any point during processing through consumption promotes pathogen growth and shortens the safe storage period, making the printed "use by" date meaningless.

Temperature-sensitive labels that change color with temperature abuse of fresh-cut produce will provide a more accurate accounting of storage history and greater assurance of product safety than reliance on "use by" dates.

Opportunities for marketing fresh-cut produce will increase as consumers continue to demand freshness and convenience. Unfortunately, pathogenic microorganisms are capable of growing on fresh-cut produce subjected to packaging and distribution practices common to the produce industry. To ensure the safety of minimally processed produce, additional research is necessary to provide greater understanding of preservation techniques, such as MAP, antimicrobials, and competitive inhibition, when used alone or in combination to control pathogen growth on specific produce and mixtures of produce packaged together. Further exploration is also needed to identify safe, effective, and affordable alternatives to chlorine for surface disinfection of fresh-cut produce. Several nonthermal physical techniques, such as oscillating magnetic fields, high-intensity pulsed light, ultrasonics, and hydrostatic pressure, are being developed that may offer alternative treatments for improving the quality and safety of minimally processed produce.

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INTERNET RESOURCES

U.S. Department of Health and Human Services/Food and Drug Administration/ Center for Food Safety and Applied Nutrition (USDHHS/FDA/CFSPAN). 1998. Guide to Minimize Microbial Food Safety Hazards for Fresh Fruits and Vegetables. USDHHS/FDA/CFSPAN, Washington, DC. [*http://vm.cfsan.fda.gov/~dms/prodguid.html*]

This guide recommends good agricultural and manufacturing practices to minimize food safety hazards common to the growing, harvesting, packing, and transport of fruits and vegetables sold to consumers in an unprocessed or minimally processed state.

CHAPTER 25

GOOD MANUFACTURING PRACTICES: PREREQUISITES FOR FOOD SAFETY

BARRY G. SWANSON

INTRODUCTION AND DEFINITION OF ISSUES

Although both the food industry and food regulatory personnel recognize that current good manufacturing practices (GMPs) in manufacturing, packing, or holding human food are prerequisite for acceptable food safety, all too often the GMPs are misunderstood, disregarded, or ignored in the heat of applying Hazard Analysis Critical Control Point (HACCP) programs or meeting production goals. GMPs are applied as criteria to determine whether a food is *adulterated* within the meaning of the Food, Drug and Cosmetic Act 402(a)(3) that the food is manufactured under such conditions that it is unfit for food; or within the meaning of the Food, Drug and Cosmetic Act 402(a)(4) that the food is prepared, packed, or held under unsanitary conditions where the food may become contaminated with filth, or where the food may be rendered injurious to human health.

HACCP and GMPs

HACCP programs are designed and implemented to produce the safest food possible on the basis of current scientific information and practical experience. HACCP programs are prevention plans to the extent that technology and ability exist to prevent the hazards. The risks posed by some hazards can be significantly reduced but seldom eliminated or prevented, in light of human involvement. HACCP programs cannot guarantee that all foods will be safe. HACCP programs must include a written document that describes how food

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safety concerns will be controlled in a specific process at a specific location. The specific process and specific location must comply with established GMPs as HACCP foundation programs before the HACCP program can be developed and implemented. GMPs describe the broad spectra of conditions required for manufacturing, packaging, or storing human foods from employee hygiene through processing facility and equipment design, construction, and maintenance. The cleanliness and acceptability of raw materials, the inappropriate and appropriate presence of natural, unavoidable, yet undesirable biological materials in foods that are not injurious to human health (Defect Action Levels), and production and process controls are also described in the GMPs. Prerequisites such as the Food and Drug Administration GMPs, food industry specifications, compliance programs, employee training, Standard Operating Procedures (SOPs), recall, traceback, and consumer complaint programs must be in place before HACCP programs can be successfully developed and implemented.

BACKGROUND AND HISTORICAL SIGNIFICANCE

The sanitation requirements of the Food, Drug and Cosmetic Act (FDCA) generally exclude raw agricultural commodities that are cleaned, prepared, treated, or otherwise processed before marketing to the public. This exclusion recognizes that potential natural contaminants affect crops and the processors' ability to eliminate or reduce contaminants. The definition of adulterated food or food prepared, packed, or held under "insanitary" [*sic.* unsanitary] conditions is not well defined, creating interpretation controversy and confusion among regulators, industry, the courts, and consumers. Before the reorganization of the United States Department of Health, Education and Welfare (DHEW) in 1969, the Food and Drug Administration (FDA) was strictly an enforcement agency charged with enforcement of the provisions of the FDCA. However, in the 1969 DHEW reorganization, the FDA became a part of the United States Public Health Service (USPHS), operating under the auspices of the Public Health Services Act (PHSA; Schmidt, 2001). The PHSA provides federal agencies the authority to promulgate recommended ordinances (e.g., Grade A Pasteurized Milk Ordinance; Food Code) and guidance documents related to protecting public health. On the basis of this authority, the FDA promulgated the initial GMPs and, more recently, HACCP regulations for certain segments of the food industry. The initial GMPs (published on April 26, 1969) established general sanitation criteria for food handling establishments and are commonly referred to as "umbrella GMPs" (Katsuyama and Strachan, 1980). The umbrella GMPs were first put out as recommendations or guidance for the food industry and were perceived as "current GMPs (sanitation) in manufacturing, processing, packing, or holding human foods." Subsequently, the GMPs became de facto regulations because the FDA interprets failure to comply with GMPs as adulteration under the FDCA, Section 402

(prepared, packed or held under insanitary conditions), and violations of the GMPs are noted on food industry inspection documents (Schmidt, 2001). While the GMPs were being developed, it was apparent that the rules would have to be generalized and that other regulations would be necessary to regulate specific food processing operations. Therefore, the umbrella GMPs address only the basic sanitary requirements for food processing, handling, and storage.

GMPs are essential for the manufacture and distribution of foods that are safe from microbiological, chemical, and physical hazards. It is imperative that the food industry manage a comprehensive program that evaluates, identifies, and controls potential hazards at every step in the production, development, and manufacturing environment.

The basic requirements designated in the umbrella GMPs are considered the "minimum" sanitation requirements currently acceptable and practiced in the food industry. As conditions change, the requirements will also be subject to change to reflect updated technologies and practices. The GMP regulations are generally principles identifying the problem areas of sanitation in the food industry. Sanitation is generally described in terms such as "adequate," "improper," "excessive," "suitable," or "sufficient" to indicate those aspects of food plant sanitation that the FDA regards as critical to the identification of adulturated food or "insanitary" conditions.

The lack of specificity in the GMP regulations is both advantageous and unfortunate. Definite, objective requirements facilitate the determination of compliance. However, definitive regulations all too often lack the flexibility required by progress and change. Nonspecific, subjective regulations, however, depend on the interpretation of the inspector, regulator, or evaluator of the inspection report. Subjective regulations permit the relation of requirements to time and conditions, which are in effect "administrative tolerances." Although the administration of regulations may be simpler and easier when choices are limited, there may be numerous acceptable alternatives to selected requirements for food processes that will produce safe and wholesome foods.

After the introduction of the umbrella GMPs, an incident involving botulism toxin in thermally processed potato soup led to the introduction of more specific GMPs directed at sanitation in the low-acid canned food industry, which became mandatory regulations initially indexed under Part 128 in the *Code of Federal Regulations* (CFR), Title 21 (FDA Regulations). Reorganization of the FDA resulted in the codification of what were initially perceived as voluntary umbrella GMPs under Part 110, Title 21, CFR.

After the promulgation of the general umbrella GMPs, the FDA met with representatives of various segments of the food industry to exchange ideas and develop improved good manufacturing practices for specific segments of the food industry. As a result, specific GMPs were developed and codified for certain segments of the food industry (e.g., thermally processed low-acid and acidified foods, cacao products, smoked fish, frozen raw shrimp, bottled drinking water). These more specific GMPs were extensions of the umbrella GMPs, emphasizing the details of processing to maintain safety and wholesomeness in

retail consumer foods. The regulations describe either a specific industry (such as smoked fish) or a closely related class of foods (such as low-acid canned foods). In each regulation, the critical steps in the processing operations are delineated in detail, including times and temperatures, use of chemical preservatives, testing procedures, cleaning and sanitizing, process recording devices, storage conditions, record keeping, and potentially important specialized employee training (Katsuyama and Strachan, 1980).

The specific GMP regulations are divided into several subparts, each containing sections detailing requirements pertaining to various unit operations or groups of unit operations in food processing facilities. Emphasis of the revised GMPs is placed on the prevention of food product contamination from direct and indirect sources (Katsuyama, 1980). In 1986, many of the provisions from specific GMPs were incorporated into the umbrella GMP" (21CFR110). Thus many of the specific GMPs were eliminated, with the exception of those for thermally processed low-acid and acidified foods (21CFR108, 21CFR113, and 21CFR114), and bottled drinking water (21CFR129), which have been retained (Sancho, 1997).

The specific GMPs refer to the criteria and definitions in the umbrella GMPs for determining whether food processing facilities and operations conform to sanitation requirements appropriate to the time and place. Therefore, it is important to be familiar with both the general and specific GMP regulations applicable to particular food processing operations. Consumer awareness of GMPs and the sanitation precautions taken by the food industry is important to establish and maintain consumer confidence in a safe and wholesome food supply.

The FDA is continually looking for ways to regulate, enforce, and improve safety standards and the sanitation of our food supply. The FDA must recognize the need to build and maintain cutting edge expertise in scientific issues, as well as the need to obtain answers to scientific questions on regulatory issues where knowledge is lacking. FDA intramural research is essential to address gaps in scientific knowledge related to food safety decision making and to facilitate timely decision-making on emerging issues. The FDA must also strengthen ties with the extramural research sector and support competitive extramural research focused on research priorities identified by the agency. The FDA must be capable of assessments that are not only accurate and science based but timely. New methods of pathogen detection and process controls, more precise delineation of pathogenic and nonpathogenic strains of microorganisms, and new technologies must be evaluated and regulations updated in a timely manner to avoid impedance of innovation and freezing of safety assessments in obsolete frameworks. In the absence of adequate data for risk and safety assessments, a variety of strategies may be necessary to facilitate timely responses. Timeliness must not come at the expense of scientific assessment and risk analysis but may be facilitated by consultation with extramural expertise. Adequate resources must be made available to promote timely science and risk-based judgments (IFT, 1998b).

REGULATORY AND INDUSTRIAL IMPLICATIONS

Elements of Good Manufacturing Practices

GMPs, sanitation, and hygiene are key to microbiological control (IFT, 1998a). The GMPs include:

- Using high-quality raw materials with small populations of microorganisms;
- Selecting food processing equipment that is easy to clean and does not harbor contaminants;
- Sanitizing equipment regularly to prevent build up of bacteria;
- Checking equipment for cleaning adequacy with microbial assays;
- Filtering the air of food processing areas to reduce airborne contaminants; and
- Training personnel to use hygienic food handling practices (IFT, 1998a).

CFR Title 21, Part 110, *Current Good Manufacturing Practices in Manufacturing, Packing or Holding Human Foods* is divided into Subparts A through G, with Subparts D and F reserved for future considerations.

Subpart A—General Provisions This includes Section 110.3 *Definitions and interpretations* of terms such as:

- "Acid foods or acidified foods means foods that have an equilibrium pH of 4.6 or below."
- "Microorganisms means yeasts, molds, bacteria and viruses and includes, but is not limited to, species having public health significance. The term "undesirable microorganisms: includes those microorganisms that are of public health significance, that subject to food decomposition, that indicate that food is contaminated with filth, or that otherwise may cause food to be adulterated within the meaning of the act."
- "Safe moisture level is a level of moisture low enough to prevent the growth of undesirable microorganisms in the finished product under the intended conditions of manufacturing, storage and distribution. The maximum safe moisture level for a food is based on its water activity (a_W). A water activity will be considered safe for a food if adequate data are available that demonstrate that the food at or below the given water activity will not support the growth of undesirable microorganisms."
- "Sanitize means to adequately treat food contact surfaces by a process that is effective in destroying vegetative cells of microorganisms of public health significance, and in substantially reducing numbers of other undesirable microorganisms, but without adversely affecting the product or its safety for the consumer."

- "Shall is used to state mandatory requirements."
- "Should is used to state recommended or advisory procedures or identify recommended equipment."

Subpart A—General Provisions also includes Section 110.5, defining *Current good manufacturing practice*, and Section 110.10, *Personnel*, describing in part the responsibilities of plant management and personnel hygiene. It begins "The plant management shall take all reasonable measures and precautions to ensure . . .":

- "Cleanliness. All persons working in direct contact with food, food contact surfaces, and food packaging materials shall conform to hygienic practices while on duty to the extent necessary to protect against contamination of food."
- "Washing hands thoroughly (and sanitizing if necessary to protect against contamination with undesirable microorganisms) in an adequate hand washing facility before starting work, after each absence from the work station, and at any other time when the hands may have become soiled or contaminated."
- "Removing all unsecured jewelry and other objects that might fall into food, equipment, or containers."
- "Wearing, where appropriate, in an effective manner, hair nets, headbands, caps, beard covers, or other effective hair restraints."
- "Education and training. Personnel responsible for identifying sanitation failures or food contamination should have a background of education or experience, or a combination thereof, to provide a level of competency necessary for production of clean and safe food. Food handlers and supervisors should receive appropriate training in proper food handling techniques and food protection principles and should be informed of the danger of poor personal hygiene and insanitary practices."

Subpart A—General Provisions, also includes Section 110.19, *Exclusions*, describing "operations not subject to this part: Establishments engaged solely in the harvesting, storage, or distribution of one or more 'raw agricultural commodities' as defined in section 201(r) of the act, which are ordinarily cleaned, prepared, treated, or otherwise processed before being marketed to the consuming public."

Subpart B—Buildings and Facilities This includes Section 110.20, describing in part the *Plant and grounds* as:

- "Properly storing equipment, removing litter and waste, and cutting weeds or grass within the immediate vicinity of the plant buildings or structures that may constitute an attractant, breeding place, or harborage for pests."

- "Provide sufficient space for such placement of equipment and storage of materials as is necessary for the maintenance of sanitary operations and the production of safe food."

Subpart B—Buildings and Facilities also includes Section 110.35, *Sanitary operations*, describing general cleaning, sanitizing and maintenance, pest control measures, and safe storage and handling of sanitizing agents. In additon, it includes Section 110.37, *Sanitary facilities and controls*, describing adequate facilities and accommodations sufficient for the intended food processing operations.

Subpart C—Equipment This includes Section 110.40, *Equipment and utensils*, describing the design, material, and workmanship to provide adequate cleaning and maintenance.

Subpart E—Production and Process Controls In Section 110.80, *Processes and controls*, adequate sanitation principles for unit operations in the receiving, inspecting, transporting, segregating, preparing, manufacturing, packaging, and storing of food are defined. "Appropriate quality control operations shall be employed to ensure that food is suitable for human consumption and that food packaging materials are safe and suitable."

- "Raw materials and other ingredients shall either not contain levels of microorganisms that may produce food poisoning or other disease in humans, or they shall be pasteurized or otherwise treated during manufacturing operations so that they no longer contain levels that would cause the product to be adulterated. . . ."
- "Maintaining frozen foods in a frozen state"
- "Maintaining hot food at 140°F (60°C) or above"
- "Monitoring the water activity of food"
- "Monitoring the pH of raw materials, food in process, and finished food"
- "Controlling the amount of acid or acidified food added to low acid food"

Subpart E—Production and Process Controls also includes Section 110.93, *Warehousing and distribution*: "Storage and transportation of finished food shall be under conditions that will protect food against physical, chemical and microbial contamination as well as against deterioration of the food and the container."

Subpart G—Defect Action Levels This is perhaps the most misunderstood, controversial, and fearful set of regulations. Section 110.110, *Natural and unavoidable defects in food for human use that present no health hazard*, states, "Some foods, even when produced under current good manufacturing practice, contain natural or unavoidable defects that at low levels are not hazardous to

health. The Food and Drug Administration establishes maximum levels for these defects in foods produced under current good manufacturing practice and uses these levels in deciding whether to recommend regulatory action." This section was incorporated into the GMPs in 1973. The defects noted herein, which present no human health hazard, occur in raw agricultural commodities and often carry through to the finished food. The current level of permitted defects is based largely on the industry's ability to reduce the levels occurring through GMPs. The "action" levels represent the limits at or above which the FDA will take legal action to remove the commodities from the consumer market. These action levels were used by the FDA for many years and were commonly referred to as "tolerances." The tolerances were used as confidential administrative guidelines for FDA officials until the tolerances were published as "unavoidable defect levels" in 1972 (Katsuyama and Strachan, 1980).

Defect action levels cannot be used as an excuse for poor manufacturing practices. The FDA clearly advises that failure to operate under good manufacturing practices will leave a firm liable to legal sanctions even though food produced may contain natural or unavoidable defects at levels lower than the currently established action levels. The blending or mixing of foods to dilute natural or unavoidable defects is unacceptable and prohibited. The final blended lot of food is unlawful regardless of the defect level in the finished food (Katsuyama and Strachan, 1980).

Because action levels for natural or unavoidable defects are subject to frequent revision as production, processing, and detection technologies improve, the defect action levels are not included in the good manufacturing practice regulations. Defect action levels are available from the FDA upon request.

Industry-Specific Good Manufacturing Practices

Various GMPs have been developed for specific industry sectors by trade associations and related groups (e.g., smoked fish, nonfat dry milk, potatoes, packaged ice, refrigerated foods). GMPs are available in print or via the Internet from the appropriate trade associations. Each of the industry-specific GMPs is based on industrial subscription in principle to the umbrella GMPs and a commitment to providing supplemental guidelines to the umbrella GMPs to acquaint management, employees, and consumers with the manufacturing procedures essential for continuing expansion and safety assurance in selected food industries. However, there is some terminology confusion between these industry-specific GMPs and the regulatory GMPs (Schmidt, 2001). Thus, general regulatory GMPs (21CFR110) are often referred to using the acronym cGMPs (for current good manufacturing practices).

Refrigerated foods provide all of the attributes desired by consumers: convenience, freshness, and quality. However, to make refrigerated foods a practical as well as a profitable venture, a reasonable shelf life is necessary. The spoilage and pathogenic microorganisms that represent potential hazards in refrigerated foods require close attention and consideration during product development,

raw material selection, processing, storage, distribution, and handling. The immediate microbiological need is to recognize the potential hazards and take the appropriate steps to eliminate or control the hazardous situation (Moberg, 1989). The appropriate steps involve the understanding and compliance with the umbrella GMPs and GMPs for refrigerated foods (NFPA, 1988).

Temperature abuse of refrigerated foods during processing, storage, distribution, retailing or in the hands of the consumer may allow rapid and progressive growth of infectious or toxigenic microorganisms or the slower growth of *Clostridium botulinum*. Partially processed, cook-chill, or *sous vide* refrigerated foods present a significant danger. Elimination of the competitive microflora in minimally processed foods may allow surviving pathogenic sporeformers to grow unimpeded. Postprocess contaminants will find no competition to restrict their growth. Refrigeration alone does not guarantee safety from pathogenic microorganisms. Several species, including nonproteolytic types of *Clostridium botulinum*, *Yersinia enterocolitica*, *Listeria monocytogenes*, and *Aeromonas hydrophila*, may grow at refrigerated temperatures as low as 38°F (NFPA, 1988). Thus, although adequate refrigeration may aid in obtaining the desired quality during the food's shelf life, refrigeration can no longer guarantee food safety. Other safety factors—also called barriers or hurdles—are recommended for refrigerated foods to inhibit or minimize the growth of pathogenic and spoilage microorganisms during refrigerated storage or as a result of temperature abuse of the food. These barriers are safety factors of a physical, biological, or chemical nature that retard or prevent the growth of microorganisms.

Examples of barriers include 1) acid pH, 2) controlled moisture (solids) or water activity, 3) competitive microflora, 4) preservatives, and 5) thermal processing. Modified atmospheres cannot serve independently as barriers but may partially help control pathogenic or spoilage microorganisms in conjunction with another barrier. There is one notable difference between published GMPs for refrigerated foods and umbrella GMPs with regard to the acceptable upper temperature limit for refrigerated foods. Whereas the umbrella GMPs require "maintaining refrigerated foods at 45°F (7.2°C) or below as appropriate for the particular food involved," the GMPs for refrigerated foods suggest 40°F or below as the upper temperature limit. Although 40°F may be impractical or unrealistic initially, refrigerated products may achieve significant shelf life extension and provide greater microbiological safety at decreased refrigeration temperatures (Moberg, 1989).

CURRENT AND FUTURE IMPLICATIONS

GMP regulation represents a successful effort to reach a reasonable solution to improve sanitation and reduce the risk of foodborne hazards in the United States. Food safety and public health must be the primary purposes for oversight and regulation of the food system (IFT, 1998). Consumers, research scientists, and the food industry recognize that sound science-based food safety

principles will transcend the politics and economics often associated with regulatory policies. Consumers are paying an estimated $138.65 per capita per year (Morris, 1994) in combined taxes and purchase prices for food safety. As a point of reference, the 1992 per capita expenditure for food was about $2000 per year. Safety assessment of foods and ingredients must be based on product characteristics, not the process by which the food was grown or produced; establishment of food processing and hygiene controls must be based on objective scientific criteria, a principle especially germane to GMP and agricultural biotechnology (IFT, 1998). Established GMPs regulate the raw materials and ingredients, the food processing environment, and the designated process to ensure safe food products. Not only is establishing successful umbrella GMPs, encouraging progressive and successful development of specific GMPs in collaboration with the food industry, and maintaining adequate oversight of food industry compliance with GMPs improving the safety and wholesomeness of our food supply, but the success of GMP establishment of acceptable standards for sanitation in the food industry is building consumer confidence in the food industry and unsurpassed availability of safe foods.

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PART VI

FOOD SAFETY IN RETAIL FOODS

Edited by RONALD H. SCHMIDT and GARY E. RODRICK

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CHAPTER 26

COMMERCIAL FOOD SERVICE ESTABLISHMENTS: THE PRINCIPLES OF MODERN FOOD HYGIENE

ROY COSTA

INTRODUCTION AND DEFINITION OF ISSUES

The food service industry is extensive and many-faceted. It includes every type of food service operation that provides meals to people when they are away from home. The industry can be divided into two major segments, commercial and institutional operations (Ninemeier, 1995). Although both types of operations have much in common, there are important differences. From a business standpoint, commercial operations seek to maximize profits whereas institutions attempt to minimize expenses while providing for the basic nutritional needs of their clients.

Commercial food service establishments have evolved over several hundred years. The first prototypes included the English inn and the coffeehouse. Today, there are a great variety of commercial food service establishments (see Table 26.1).

Commercial food service establishments differ widely, and each possesses specific requirements for space, equipment, employees, ingredients, and supplies. Hazards are often associated with specific types of foods, recipes, and production methods. The Centers for Disease Control and Prevention (CDC) has reported that there are ten leading risk factors associated with foodborne illness outbreaks at the commercial food service level. These factors tend to change in relative order of importance from reporting period to reporting period, but the factors themselves have been consistent since outbreak data were first tabulated by the CDC in 1961. The risk factors, from the period 1983–1987 (CDC, 1990), have been tabulated in Table 26.2.

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TABLE 26.1. Some Types of Commercial Food Service Establishments

• Bars and lounges	• Coffee shops
• Bed and breakfast	• Commissaries
• Boarding houses	• Concession stands
• Cafeterias	• Fraternal organizations
• Catering	• Hotel dining rooms
• Civic groups	• Mobile food vehicles
• Private clubs	• Restaurants

Sequence of Events That Lead to Foodborne Illness Outbreaks

Outbreaks of foodborne disease are caused by foods that are contaminated intrinsically or that become contaminated during harvesting, processing, or preparation (Torok et al., 1997). Commercial food service is especially prone to outbreaks of foodborne illness because contamination often occurs during preparation and subsequent storage steps may encourage the growth of bacteria.

The foodborne biological, chemical, and physical hazards are discussed in Chapters 2 and 3. For a foodborne illness to occur, the following sequence of events is necessary (Bryan, 1981):

- The hazard must be in the food, in the people who handle the food, or in the environment where the food is being processed or handled;
- The hazard must contaminate the food;
- If biological, the hazard must (usually) proliferate or grow to sufficient numbers to cause illness;
- The hazard must survive the processing and handling system; and
- The victim must ingest a sufficient level of the hazard to become ill.

TABLE 26.2. Risk Factors for Foodborne Illness from the Period 1983–1987 (CDC, *1990*)

• Improper cooling
• Lapse of 12 hours or more between preparation and service
• Infected food handler handling implicated food
• Improper reheating
• Improper hot holding
• Contaminated raw ingredient eaten raw or as an ingredient in another food
• Foods from unsafe sources
• Use of leftovers
• Cross-contamination
• Inadequate cooking

TABLE 26.3. The 10 Leading Foodborne Illness Factors as They Relate to Contamination, Growth, or Survival.

Risk Factors	Contamination	Growth	Survival
Improper Cooling		√	
Lapse of 12 hours or more between preparation and service		√	
Infected food handler handling implicated food	√		
Improper reheating		√	√
Improper hot holding		√	
Contaminated raw ingredient	√		
Foods from unsafe sources	√		
Use of leftovers	√	√	√
Cross-contamination	√		
Inadequate cooking			√

Examining the ten leading factors in foodborne illness outbreaks, it is possible to classify the factors as associated with contamination, with growth, or with survival as is summarized in Table 26.3. In reality, outbreaks are often a combination of several factors.

Preventative measures for foodborne hazards (see Chapter 2 and 3) include (among other things): safe sources of food, safe storage methods, time and temperature control, cooking procedures, clearly written personal hygiene and employee health requirements, and effective cleaning and sanitizing. General requirements such as safe water, overall cleanliness, and maintenance of the equipment and environment are basic for food safety, and production should take place in structures that are properly designed and free of pests. Successful implementation of food safety programs requires trained employees who are empowered and motivated to carry out the food safety program under the leadership of qualified managers.

BACKGROUND AND HISTORICAL SIGNIFICANCE

Commercial food service establishments are an integral part of the U.S. economy. On a typical day in 2000, the restaurant industry posted average sales in excess of $1 billion. According to the National Restaurant Association (NRA, 2000), commercial food service establishments are the single largest commercial employer of labor, employing approximately 11 million persons in 1998. Almost half of all adults (46%) were restaurant patrons on a typical day during 1998. On an average day in 1998, 21% of U.S. households used some form of takeout or delivery. Almost 50 billion meals are eaten in restaurants and school and work cafeterias each year. Clearly, the vast majority of foods served to

consumers are safe, but exposure to unsafe practices in commercial food service has far-reaching consequences for the public.

Foodborne Illness Outbreaks

Incidence Historically, the incidence of foodborne illness from food service has been increasing. In fact, commercial food service establishments have been identified by the CDC as the leading source of foodborne illness outbreaks (Bean et al., 1996). The chief reason for this may be that victims of foodborne illness are more inclined to report illnesses associated with commercially prepared foods as opposed to home-prepared foods (Scott and Moberg, 1995), but nevertheless, consumers in general believe their risks increase when they dine away from home.

General factors that influence the increased prevalence of foodborne illness include the increasing use of commercial food service, changes in diet, new methods of producing food and distribution, the growing number of people at high risk for severe or fatal foodborne disease, and new or reemerging pathogens (Institute of Medicine, 1998).

Evolution of the commercial food service industry continues in response to changes in food production, consumption, and economic trends. Consumer demands for convenience, "fresh," and "to go meals" have created new and attractive markets for commercial food service enterprises in the last 20 years. An increase in demand for commercially prepared foods has occurred, but much of the business expansion has been in the low-profit margin, quick-serve market. To capitalize on these markets and to remain profitable, the food service industry is turning to minimally processed foods that require less time and less labor to prepare. Common examples of foods assembled from minimally processed ingredients are pizza, sandwiches, salads, and tacos. The increased handling involved, coupled with the increased consumption of such foods, has resulted in increased prevalence of foodborne illness. As new market niches open, new pathways may be created for disease transmission.

Characteristics The following is a summary of some of the more recent outbreaks of foodborne illness in commercial food service and their causes:

Wisconsin, August 2000 An outbreak of *Escherichia coli* O157:H7 in the Milwaukee area that affected 65 people, including a toddler who died as a result, was traced to raw beef sirloin. A meat grinder too close to the salad making area in a Sizzlers Restaurant was identified as the most probable source of the pathogen.

Massachusetts, June 1996 Food contaminated with *Salmonella* that was served in a Wendy's restaurant in suburban Boston sickened 38 people and may have contributed to a death. Investigators determined that the outbreak was caused by employees who did not wash their hands before handling food.

Idaho, September 1995 At least 11 cases of illness due to *E. coli* O157:H7 were traced to food eaten in a Chili's restaurant in Boise. The primary source of the *E. coli* O157:H7 bacteria is beef, but in this outbreak, authorities believe raw beef carrying the bacteria probably cross-contaminated other food served in the restaurant.

Florida, August 1995 *Salmonella newport* bacteria sickened over 850 people in the largest outbreak of foodborne illness in Florida history. Health officials who investigated the outbreak believe that *Salmonella* bacteria in chicken cross-contaminated several other foods served at Margarita y Amigas restaurant in West Palm Beach, at least in part because workers used the same cutting board for raw meat as for vegetables.

Utah, January 1995 An outbreak of 95 cases of hepatitis A was traced by the local health department to an employee of a Taco Bell restaurant in Salt Lake City. The hepatitis A virus is carried in human fecal matter and is spread when food handlers do not wash their hands thoroughly.

Washington, DC, August 1994 Hollandaise sauce contaminated with *Salmonella* served at a brunch at a hotel sickened 56 people, 20 of whom were hospitalized. According to investigators, the sauce was prepared from raw eggs and heated over a hot water bath. It was then held for nine hours at a temperature at least 20 degrees lower than that recommended by the FDA Food Code.

Georgia, October 1993 A botulism poisoning outbreak killed a customer of a delicatessen in a small south Georgia town and sickened seven others. Their illnesses were traced by CDC officials to canned cheese sauce, which had been left opened and unrefrigerated for 8 days, served on baked potatoes stuffed with barbecued meat. Health officials said proper refrigeration of the sauce could have prevented the outbreak.

Illinois, June 1993 A Mexican restaurant in a Chicago suburb served *Salmonella*-tainted food that sent 25 people to the hospital and sickened 16 others. County investigators attributed the outbreak to prepared food not being held at hot enough temperatures and to poor food handler hygiene.

Oregon, March 1993 In Grant's Pass and North Bend, 48 people were sickened by *E. coli* O157:H7 bacteria in mayonnaise served at Sizzler's restaurants. According to data reported to the CDC, the mayonnaise was cross-contaminated by a food, most likely raw or insufficiently cooked ground beef, that contained *E. coli* O157:H7 bacteria. An additional 50 cases of illness caused by *E. coli* O157:H7 bacteria in food served in Sizzler's restaurants in Oregon and Washington were reported to the CDC in 1993.

The western U.S., December 1992 to January 1993 The largest *E. coli* O157:H7 outbreak in the U.S. occurred in Washington, Idaho, Nevada, and California and was linked to contaminated hamburgers served at Jack in the Box restaurants. At least 700 cases of foodborne illness were reported. Nearly 100 of the victims developed hemolytic uremic syndrome, a serious complication resulting from *E. coli* O157:H7 infection, and four children died, the oldest just six years old.

Strategies for control Traditional food hygiene techniques no longer seem to be effective, and implementation of science-based controls is urgently needed. Hazards can be effectively controlled in commercial food service if sound management practices are developed based on knowledge of the sciences of epidemiology, food science, and microbiology. These sciences provide the public health reasoning for the U.S. Public Health Service/Food and Drug Administration (FDA) Model Food Code (Food Code, 2001). The Food Code is widely recognized as the best guidance document available for food safety in the retail and commercial food service sectors. Adoption by state and local regulatory agencies and acceptance of the Food Code by the food service industry, however, has been slow to materialize. For the Food Code to be more widely accepted, an appreciation for the scientific basis of the Food Code must be fostered within the commercial food service industry. The industry must also be convinced that the requirements are effective and practical to implement.

If one recognizes the intrinsic hazards and the various steps or stages involved with growing, harvesting, and processing a food, it becomes possible to predict the types of hazards that might occur in a finished product. As thoroughly discussed in Part IV, the Hazard Analysis Critical Control Point (HACCP) system is a systematic approach to the identification, assessment, and control of hazards in a particular food operation. This chapter will aid the reader in providing foundations for developing a HACCP plan for commercial food service by describing the science-based standards that must be met and the technically correct procedures that must be followed at all typical control points. Control points are particularly useful for food safety when effective preventative measures and science-based standards are properly applied. A control point deemed to be critical to a particular food product from a food safety perspective is known as a critical control point (CCP) and should be managed within a HACCP system. The development of critical control points requires a thorough hazard analysis (see Part IV). To ensure food safety under a HACCP system, managers must differentiate between control points and critical control points and develop monitoring procedures at critical control points so that corrective actions can be taken immediately if needed to prevent hazards from developing. Although HACCP gives the greatest control over specific hazards, the implementation of preventative measures and standardized procedures at all manageable control points will achieve a high level of food safety as well.

Fortunately, there has been increased awareness that food safety is cru-

cial (Hernandez, 1998). Reliance on "common sense," or the assumption that hazards will be pointed out during routine inspections, has given way to the adoption of sanitation standard operating procedures (SSOPs) to control general sanitation issues and the HACCP system to control specific hazards. Prerequisites of HACCP include proper facility design and layout, proper equipment design and installation, sound general sanitation, standardized procedures, ongoing training, and perhaps most importantly, management commitment.

Food safety knowledge is critical, and it is reassuring that the nationwide trend toward mandatory food manager certification and employee training is continuing. The state of Florida stands out as a leader in food safety training and deserves special mention. Florida was the first state, in 1989, with full support from industry, to require manager certification for all managers. In 1999, Florida had almost 100,000 certified food managers. Florida was also one of the first states to adopt the Food Code, and the first state, in 2000, to require mandatory training for its 500,000 food employees. Other jurisdictions have recently adopted requirements for food manager certification including California (1999), Massachusetts (2000), and Pennsylvania (2000). The increased knowledge of managers and employees is expected to have a beneficial effect on food safety in the years to come.

Changes in the labor supply have caused the commercial food services to become innovative when training and managing their employees. Commercial food service is very labor intensive, with employee turnover at 300% in some operations (Dittmer and Griffin, 1994). As many entry-level food service workers come to the job with limited skills and food safety knowledge, training of employees is essential. Under these conditions, however, training can be frustrating and time consuming. Self-paced instruction utilizing video formats, computers, and the Internet is providing effective solutions to this training problem. Easily accessible, job-specific, and standardized training programs are needed by the commercial food service industry. Training programs must also be culturally sensitive and must take into account language barriers and reading skills.

Adaptations must be made by the commercial food service industry to keep pace with social and economic changes in the marketplace. Social and economic forces, along with improved foodborne illness epidemiology, will continue to drive the evolution of food safety systems for the foreseeable future.

SCIENTIFIC BASIS AND IMPLICATIONS

The food production system consists of a series of unit operations or processing steps by which ingredients are converted to finished products. For most commercial food production, at least one of these processing steps is a critical step at which food safety control can be applied (e.g., cooking, cooling rate, safe ingredients). The more elaborate the process, the greater the likelihood that

TABLE 26.4. Typical Commercial Foodservice Control Points.

• Receiving	• Cooling
• Storing (cold storage and dry storage)	• Reheating
	• Hot holding
• Preparing	• Service and display
• Cooking	• Reuse

potential risk factors will occur during production. With this in mind, specific steps in production have been identified that provide managers with a platform for developing preventative measures for safety and quality and SSOPs for effectively controlling risk factors. These steps, known as control points, are listed in Table 26.4. Although some preventative measures and recommended practices may be more critical for food safety than others, a comprehensive list of these measures and practices should be developed and evaluated for each control point.

From the list of preventative measures and recommended practices, more detailed standardized procedures, or SSOPs, can be developed at each control point to prevent unsafe conditions from occurring. If strictly followed, SSOPs will ensure safe, high-quality food while increasing compliance with regulatory requirements. The development and implementation of SSOPs is often regarded as prerequisite to HACCP because they provide the foundation for this more intensive control system. However, regardless of whether a HACCP system is in place, strictly implemented SSOPs or other sound procedures at each control point are essential to ensure the minimization or elimination of food-related hazards.

Managing the Receiving Control Point

Foods are delivered daily to most food service operations. Foods must be moved quickly to storage, but several important procedures are required on delivery. Stewards, receiving clerks, or other designated employees are usually assigned the task of examining shipments and noting the quantities and quality of the foods received. At the same time, employees must also ensure that potential hazards are identified and that the foods are in sound condition before being accepted and moved to storage and that the food or ingredients are handled in a sanitary manner.

The preventative measures and recommended practices involved in food safety assurance at the *Receiving Control Point* are discussed below.

Sensory analysis Contamination with harmful or unwanted substances at unacceptable levels may be (but is not always) apparent to the senses (Munoz et al., 1992). Off odors are a telltale sign of decomposition in many foods (especially fish and other seafood products), and to the trained eye, a food's

appearance can be a good measure of quality. For example, the bright red color of beef and the translucent eyes of fish are signs of freshness in those products. Although the sensory qualities of food may point to unwholesome conditions or spoilage, most foodborne pathogens do not cause any noticeable changes in odor, texture, color, or flavor. Therefore, with the exception of some fish products where decomposition is directly related to presence of toxic amines or scromboid poisoning (see Part II), sensory analysis alone is an unreliable method for ensuring food safety and must be reinforced by other procedures. Furthermore, tasting of some raw, potentially hazardous agricultural commodities (e.g., raw milk, raw meat or fish) is not recommended. It is important to develop very strict detailed SSOPs regarding the sensory evaluation of food products received.

Use by dates "Use by," "best if used by," and "sell by" dates are primarily quality controls. However, because the storage life of foods is also related to safety, policies regarding "use by" dates should be developed and adhered to as part of a firm's good manufacturing practices (GMPs).

Condition of frozen foods Other than the specific requirements for frozen fish to be consumed raw (e.g., sushi or related products), there are no temperature standards regarding the receiving of frozen foods in the Food Code. However, frozen foods should be received frozen solid, because any evidence of thawing may indicate interruption of the cold chain. Soft or slushy foods are obviously indicative of improper frozen storage or transport practices. Large ice crystals or freezer burn are signs that the foods have been stored under fluctuating temperature conditions and have warmed or thawed and refrozen during storage or transport. The unintentional thawing of raw foods is primarily a quality issue, but there is a significant risk if ready to eat (RTE), potentially hazardous foods (PHFs) have reached temperatures above 41°F (5°C) for significant time periods. In any case, frozen foods that have been allowed to thaw and refreeze will have substandard quality and should be rejected.

Food product temperature Checking the temperatures of in-coming PHFs with a suitable thermometer is an effective safety measure because temperature checks may reveal favorable bacterial growth conditions. Ensuring safe temperatures for modified atmosphere packaged (MAP) foods and sous vide processed foods is especially critical because these foods have an extended shelf life and anaerobic conditions favor the growth of certain pathogens (Garcia et al., 1987).

Several methods are used to take temperatures of incoming food products. Plastic bags of foods should be folded over, and the thermometer probe should be placed between the bags. Bulk foods with replaceable lids may be visually inspected, and temperatures should be taken from several spots in the food. With certain limitations, infrared thermometers are well suited to the receiving control point. Infrared thermometers measure surface temperatures quickly

without contact; if packages are found to have elevated surface temperatures, further examination is required. RTE/PHFs, if found above 45° on delivery, should be rejected.

Many simple devices are also available for temperature monitoring and detection of temperature abuse of food products during storage and transport. Time-temperature integrators (TTI) are available to detect temperature abuse of products in transport (Taoukis and Labuza, 1989a, 1989b; Taoukis et al., 1991). A color change in the TTI indicator usually denotes a time-temperature relationship. In a typical scenario, TTI tags are activated at the shipping point and then sense temperatures through the transport and storage stages. The color change is irreversible, allowing for an accurate assessment of time and temperature. There are also data loggers, electronic devices that hold thousands of temperature data points, which can be downloaded at a later time to a standard PC for analysis. Technological advances such as these have added to the tools available to manage the receiving control point.

All thermometers and temperature recording devices used must be accurate and calibrated on a regular frequency. Accuracy of food thermometers and recording devices must be $\pm 2°F$. It is also a good idea to check the accuracy of temperature recording devices on trucks.

Delivery vehicle inspection While the temperatures and thermometers on trucks are being noted, vehicles should be inspected for any evidence of contamination. Food delivered in dirty trucks should be rejected.

Chemical use and storage Although chemical use and storage will be discussed in more detail below, there are procedures that are specific to the receiving control point. Suppliers should be required to provide assurance to the receiving manager that all chemicals meet appropriate food use regulatory requirements. The receiving of chemicals (e.g., cleaning and sanitizing supplies,; pest control materials) should be done in such a way as to protect food products from contamination. The practice of shipping foods and chemical supplies together exposes foods to a potential source of contamination. Chemicals should not be in contact with either packaged or exposed foods, and chemical containers should be examined for any signs of damage or evidence of spillage. Chemicals should be moved to safe storage areas away from food products as soon as possible. Use of chemicals in the receiving room should be done according to manufacturers' recommendations and/or regulatory requirements.

Approved source of food products and ingredients Food products received at a food service facility must be from an approved, regulated commercial manufacturer or as accepted by the regulatory authority. All ingredients and additives must be considered safe according to FDA requirements.

Receipt of raw shellfish (shell stock) is of special concern because it is frequently associated with foodborne illness outbreaks (see Part II) such as shell-

fish toxins, viral hepatitis A, Norwalk viral agents, and *Vibrios*. Shell stocks are provided with certification tags indicating the harvest location and the date of harvest (FDA, 1998). The tags also contain a unique state-issued certification number specific for each certified dealer. If the firm is involved in interstate commerce, this number appears in the FDA's Interstate Certified Shellfish Shippers List (ICSSL). Shell stock should not be accepted without such tags. Tags must remain with the product until dispensed and must be kept on file for 90 days to allow trace-back of the shellfish in the event of an illness or an outbreak. Rapid identification of harvest sites implicated in foodborne illness outbreaks is necessary to identify other contaminated supplies and to prevent further cases.

Finfish of the family Scombroidae, which include tuna, jacks, mackerel, and related species (mahi-mahi or dolphin fish) are subject to the development of histamine if held for extended periods above 45°. Ciguatera toxin may be a hazard in fish such as amberjack, snapper, and grouper if harvested from tropical or subtropical marine waters (CDC, 1990). No fish should be purchased or accepted from unsafe or unapproved sources, and close monitoring of fish at delivery for unsafe temperatures and spoilage is advised. For quality purposes, the best temperature for receiving fish is below 36°, but Food Code requirements allow up to 41°.

Foreign objects Opening large crates and bulk packages often involves the use of tools. Special box knives should be used to avoid the problem of blades breaking that ordinary box knives have. Various tools are needed, such as scissors, wire cutters, and pry bars. The potential for injury of the worker is clear, as is the potential for contamination of the food by shards of wood, bits of wire, and broken tool parts.

Foreign objects may find their way into torn packages of dry goods, bottles my break, and cans may be damaged, allowing contamination to occur. Foreign objects may already be in foods as a result of harvesting and processing. Employees must be careful to inspect the integrity of incoming packages on receipt and to inspect foods such as beans or rice for small stones at later production steps.

Damaged can goods may often be observed by careful inspection, and although slight damage to cans is probably insignificant, misshapen cans or cans with dents on the rims or seams should be rejected. Cans that are swollen have been contaminated and must be rejected.

Pest management As doors are frequently open, the receiving area is a primary source of pest entry into a food service facility. Therefore, the receiving areas must be diligently monitored for pest activity. The protection of outer openings with screens or some other barrier and the use of tight-fitting, self-closing doors make it more difficult for pests to enter. Transoms should be designed to allow hand trucks to pass over them; they should not be removed. Use screen or other covering to keep birds off structures. If bird resting areas

are present, these should be screened or blocked off. Sticky repellents can be used.

Rodents are especially good climbers, and efforts must be taken to identify and seal all points of entry. Fly curtains provide a stream of high-velocity air (500 cfm) that will deter flying insects if blower vents are angled properly.

Food spills should be cleaned promptly, and solid waste should be placed in sanitary storage facilities to avoid creating an attractive nuisance for pests. All potential harborage sites on the premises must be identified, and traps should be strategically placed to identify rodent activity. Proper drainage must be provided as well.

Proper lighting is necessary, and lights that do not unduly attract flying insects should be used. Exterior lights should be located and directed so they do not attract insects. This is particularly important at entranceways. Lights should be sodium vapor or should be placed at least 30 feet away and directed toward the facility. Insect electrocutors may be installed just within the food receiving area, and cleaned weekly. If such devices are improperly located, they may, in fact, attract flying insects into the facility. As the remains of insects in catch pans are a nuisance and attract still more insects, insect electrocutors should be located as far as possible from any food production area.

Boxes and paper provide concealment and food for roaches and are a common way that roaches gain entry into commercial food service facilities. Boxes and bags should be discarded as soon as possible and examined both for eggs and adult forms if taken into the facility.

Foods and packaging should also be examined for signs of gnawing, an indication of rodent activity. Furthermore, inspection of packages using an ultraviolet light (i.e., black light) can be used to indicate the presence of rodents.

Managing the Cold Storage Control Point

PHFs are defined in the Food Code as supporting the rapid and progressive growth of infectious and toxigenic microorganisms. Foods meeting this definition require specific temperature controls. Non-PHFs such as uncooked vegetables, fruits, and tubers typically require cold storage temperatures after delivery for quality control. After perishable foods have been delivered and accepted, they should be moved to cold storage at 41°F (5°C) as quickly as possible. Cold temperatures are maintained by refrigerated units of many types and occasionally by the use of ice. Walk-in freezers and coolers hold foods during periods of extended storage, whereas reach-in prep boxes, sandwich prep boxes, "make tables," and cold top units are designed for short-term storage or for use during preparation. Ice and refrigerated units accomplish short-term holding on salad bars and in self-service areas.

The preventative measures and recommended practices involved in food safety assurance at the *Cold Storage Control Point* are discussed below.

Time and temperature controls Improper cooling and cold storage is often cited as the most prevalent factor in foodborne illness outbreaks at the commercial food service level (Olsen et al., 2000). If PHF-RTE foods are allowed to remain at sufficiently warm temperatures for extended periods, growth of infectious as well as toxigenic microorganisms can occur (see Part II). In addition, certain bacterial toxins are relatively heat stable (e.g., *Bacillus cereus, Staphylococcus aureus*) and capable of withstanding normal cooking procedures.

Storage temperatures at or below 41°F (5°C) are considered to be safe under the Food Code. Temperatures of up to 45°F (7°C) may also be considered safe by some jurisdictions. Where possible, refrigeration units should be set to achieve temperatures well below 41°F (5°C).

In typical food service operations, various-sized portions of food are often placed in coolers while still warm. Less than ideal cold storage temperatures will increase the time that these foods stay in the danger zone [41°F (5°C) to 140°F (60°C)]. Such practices should be monitored very closely, and the refrigeration of hot food in large volume containers should be avoided. Placing hot foods in coolers with the intention of "cooling them down" is a very hazardous practice. Most walk-in coolers and reach-in type prep coolers are designed to keep cold food cold; they do not typically have the Btu capacity to keep foods cold and to cool hot foods simultaneously. Small amounts of hot foods may be placed in properly functioning coolers if they are in pans no more than four inches in depth and if the volume of food is two inches or less in the pan.

Time may be used as a control measure for bacteria (time in lieu of temperature) to allow for working quantities of food during preparation. Under the Food Code, PHFs must be discarded if they have been in the danger zone for periods greater than four hours. Facilities using such methods must clearly label such foods with the time of intended discard and provide records of these food-handling practices to regulatory authorities on request.

Thermometers and temperature-sensing devices Thermometers and temperature-sensing devices in cold storage units measure the ambient air temperature within the unit. These provide a relative measure of food temperatures, but internal temperatures of foods must be taken because food temperatures may vary widely from the ambient temperatures. Thermometers must be placed in the warmest location, which is usually nearest the door, and farthest away from the fans. Air temperature may be more difficult to measure precisely; therefore, the Food Code requires ambient air temperature thermometers to be accurate only to ± 3°F.

By checking the ambient air temperature on a routine basis, it is often possible to identify a problem with the refrigeration system before it results in an unsafe condition. Many larger food service chains use remote sensing devices that monitor temperatures continually and that activate an alarm when walk-in cooler temperatures have risen above 45°F.

Sufficient equipment and cold storage space A sufficient number of coolers and adequate cooler shelving are necessary to prevent storage units from becoming overloaded. Lack of storage space results in crowding of refrigeration units, leading to impeded airflow, floor storage, and ultimately exposure of the foods to unsafe temperatures or environmental conditions. Equipment and space issues are generally addressed at the time at which the original facility design is approved by the regulatory agency, but because production volumes or methods change it is necessary for facility designs to be reevaluated.

Criteria for determining storage space requirements include an analysis of the menu and recipes used, the maximum number of persons served, inventory turnover rates, and the resupply times for ingredients and raw materials (HITM, 1997).

Date marking Bacterial growth is slowed but does not cease at refrigeration temperatures. Furthermore, psychrotrophic pathogens (e.g., *Listeria, Yersinia*) grow to a varied degree at refrigeration temperatures (see Chapter 2). The number of days between preparation and service is an important safety factor in long-term cold storage of prepared foods. According to the Food Code, PHFs prepared on premises and kept longer than 24 hours should have the date of preparation affixed to the container. Such foods should be used within four days if the holding temperature is 45° but can be used within seven days if the storage temperature is 41° or below. Labels, or some other means of identification, should be used. Systems with color-coded adhesive dots, a different color for each day, are normally used for this purpose.

Temperature fluctuation in frozen food storage Frozen foods should remain solid while being stored in freezers. Most foods freeze at approximately 28°F (−2.2°C), but, depending on their composition, foods are not generally frozen solid until a much lower temperature is reached. Growth of typical bacterial pathogens is negligible at freezer temperatures, so for the safety of these items, there is no particular length of time to store frozen foods and no particular freezer temperature is specified. For quality purposes, temperatures of <10°F (−12°C) are desirable. It should be noted that frozen foods thawing under safe refrigeration temperatures are also protected from rapid bacterial growth.

Prevention of cross-contamination Prevention of cross-contamination of prepared RTE foods by raw, damaged, or otherwise contaminated foods during storage is absolutely necessary. The practice of storing raw meats, fish, poultry, and eggs in the same cooler as RTE foods such as vegetables, prepared meat salads, leftovers, and soups increases the potential for cross-contamination. Foods must be covered and arranged so that cooked foods are stored above raw animal foods. Separate refrigeration units to hold raw items and prepared foods reduces the risk for cross-contamination during storage.

Kitchen designs that take into account storage and production requirements will have cold storage areas for prepared foods located conveniently to minimize cross-contamination. Efficient designs also decrease the potential for room-temperature storage during preparation. The most efficient placement of storage facilities is between the receiving area and the preparation area.

In facilities with limited refrigeration space, prepared and portioned foods are often stored in coolers containing raw foods. In these situations, prevention of cross-contamination can be easily accomplished by good storage techniques such as the use of containers with tight-fitting lids. Tight-fitting lids protect the contents from incidental contamination and also help to protect the quality, flavor, and freshness of foods. Containers must be constructed from food-grade materials, with stainless steel and various plastics commonly being used. After cans are opened their contents should be placed in covered containers. Unless the food product is readily identifiable, food containers should be labeled with the name of the product.

Foods found to be damaged, spoiled, or in some other way made unfit for human consumption are occasionally held in storage for accounting purposes and for credit. Foods of this nature should be stored separately from other foods and labeled to identify them as rejected.

Foods stored off the floor Food products must be stored at least 6 inches off the floor. Shelving units must provide a six-inch clearance space for cleaning. Floor storage is acceptable only if the food container is hermetically sealed and protected from floor moisture. Cans and bottles more than likely meet the "hermetically sealed" definition; however, it is common practice to see cans and bottles that were on the floor being placed directly on preparation surfaces; contamination from the cooler floor can now be transmitted to food. For this reason, storage of any item on the floor is poor practice.

Managing the Dry Storage Control Point

Foods in dry storage are generally referred to as nonperishables or staples. Although dry foods do not support rapid bacterial growth under conditions of dry storage, certain pathogens (e.g., *Salmonella*) are highly capable of survival in dried foods (see Part II). For example, cocoa products, dried milk products, and dehydrated egg products have been associated with foodborne illness from *Salmonella* contamination and certain nut products can be a source of *Listeria*. Thus assurances of the safety and quality of dry products should be obtained from suppliers. In addition, dry food products must be stored so that they are protected from other contamination. For example, chemical and physical contamination and pest infestations are significant hazards to control at the dry storage control point.

The preventative measures and recommended practices involved in food safety assurance at the *Dry Storage Control Point* are discussed below.

Protection from contamination As discussed for cold storage, dry ingredients and food items must be stored separately from sources of contamination including raw products and damaged or otherwise contaminated foods. Tight-fitting lids are important for safety and quality purposes, because foods are protected from contamination and stay fresh longer when not exposed to air and moisture. Once packages have been opened, the packaging should be discarded and the contents should be placed in covered containers until used. Rice, beans, granulated products, spices, and condiments are typically removed from packages and stored in containers. Food-grade containers include various plastics and stainless steel. Potentially toxic metal containers, such as galvanized steel, must not be used for acidic foods. Galvanized steel cans are occasionally used to store flour and grains; this practice is probably safe as long as the products remain in their original container or the container has a food-grade plastic liner. Flour, granulated products, and powdered mixes must be stored in labeled containers to avoid mistaking them for other foods and ingredients or to prevent confusing them with chemicals.

Storage locations below the first floor, or on any lower level in a multistory structure, are at risk from overhead sewer and water lines. Storage areas are especially subject to contamination in this way, because they may not be visited frequently enough for intermittent overhead leaks to be observed. No exposed overhead water or waste line may traverse an area in which foods are stored.

Temperature and humidity For quality purposes, dry storage areas should be maintained between 50° and 70° and a relative humidity of about 50% is recommended. Installation of a separate air conditioning unit is possible in many structures. Dry storage areas should be well ventilated in any case.

Safe dispensing methods and utensils There are a variety of utensils constructed from food-grade plastics and metal appropriate for dispensing dry goods. These utensils may be stored in the products with the handles out. Scoops, ladles, kitchen spoons, and tongs are typical utensils for dispensing dry goods, but even these utensils may break or have loose parts that can contaminate foods. Cups with no handles, single-service utensils, and Styrofoam containers are inappropriate for use. Glassware should never be used as a dispensing utensil and must never be stored in a food product.

Foods stored off the floor As with wet storage, dry foods must also be stored at least 6 inches off the floor. Flour and other dry goods, if stored on pallets or dollies that are easily moveable, are exempt from the six-inch separation requirement.

Chemical storage and use If stored in dry storage rooms or cabinets, all chemicals must be stored away from food items in separate locations. Separate rooms or cabinets are good control measures when adequate space has been provided, but space is often limited. When chemicals must be stored on the same set of shelves as food the chemicals should be stored on the lowest shelf.

In situations of extreme lack of space, chemicals and food supplies can be stored on the same shelf as long as a partition is established between them. In this case, precautions to prevent the possibility of cross-contamination due to leaks, splashing, or spillage must be taken.

Pest management Pests are often a problem in dry storage areas because of the favorable environmental conditions and available food supply. Once populations of pests have been established, it becomes particularly difficult to eliminate them. The key is prevention. Cleaning spills promptly and sealing areas where pests can hide are two common pest control measures.

Pest control chemicals listed as safe for commercial food service should be used and applied by licensed pest control operators only. Foods must be protected from chemicals when they are applied. SOPs should designate a person in charge of pest control, and maps of bait locations and pest control records should be maintained.

The eggs of storage pests are often present in foods, and the eggs will eventually hatch in dry goods such as flour and macaroni. Although not typically pathogenic, storage pests destroy foods by making them unfit for human consumption. Controlling their populations is done best by intact packaging and control of storage time, temperature, and humidity.

Foreign objects Hard foreign objects and other debris may cause food to be unsafe and are offensive to the consumer. Foreign matter may get into foods during harvesting and processing, but twist ties, clips, staples, string, bits of plastic, foil, and cardboard, may be introduced into a food during storage. These small items are associated with choking or lacerations. Because broken teeth are a leading cause of insurance claims against commercial food service establishments, it is advisable to have a control program to reduce these risks.

Containers eventually break, imparting plastic or pieces of metal to food. Containers should be inspected for integrity and should be discarded if they are severely damaged.

Lighting fixtures must be shielded in food production areas, and although this may not apply to dry storage areas, it is good practice to shield all fluorescent and incandescent lighting fixtures, because glass in food is extremely hazardous.

Staples should be removed from boxes in storage and disposed of promptly. There should be rules and policies governing glass usage and breakage and for cleaning up broken glass. Packaging, including all clips and fasteners (twist ties), should be discarded immediately after the food contents have been removed.

Managing the Food Preparation Control Point

Food preparation activities include thawing, portioning, chopping, cutting, trimming, grinding, mixing, washing, paring, peeling, seasoning, dipping, and basting. Preparation is treated separately from other control points, such as

cooking, because safe preparation activities normally involve prevention of contamination and growth of bacteria. Cooking, on the other hand, is a step where destruction of pathogens can be accomplished.

Foods are moved from storage into preparation areas as needed, more or less continually. Requisitions are occasionally required to account for inventory, but typically, employees remove foods without specific authorization when it appears they are needed.

Foods are often exposed to the kitchen environment for extended periods of time while being prepared and are subject to contamination from the surroundings. Foods must be protected from hazards that have a reservoir in the environment, that is, environmental contamination. Air, although frequently contaminated with dust, bacterial spores, mold spores, particulate, and gases, is not a reservoir but a pathway that must be controlled by ventilation and filtration. Water, on the other hand, is an environment conducive to the survival and propagation of microorganisms and must be safe both microbiologically and chemically. Furthermore, excessive moisture in the air results in waterborne bio-aerosols of microorganisms that facilitate airborne contamination. Waste disposal is an activity that usually occurs simultaneously with food preparation and includes disposing of wastewater, food waste, and solid wastes containing, paper, cardboard, glass, cans, etc.

Pest management measures must be effective to control the entry and propagation of insects and rodents in the food preparation area. Because foods are exposed during preparation, control of insects such as flies and roaches is especially important at this stage of production.

During preparation, foods may also be exposed to chemical hazards caused by improper storage and usage of cleaners, sanitizers, and other compounds. Foods are prepared on equipment surfaces known as food contact surfaces, and utensils are frequently used during preparation. The surfaces of equipment and utensils may impart hazardous chemicals, foreign objects, and most importantly, biological agents as a result of cross-contamination to foods. Raw animal foods contain many types of pathogenic microorganisms (Buzby and Roberts, 1997); strict precautions must be taken to prevent their spread to RTE foods during preparation.

The labor-intensive environment of the commercial food service kitchen leads to frequent contact between the employee and the food. People can contaminate foods in a vast number of ways, but the hands of employees are perhaps the most important means through which foods become contaminated in a commercial food service environment (Scott and Bloomfield, 1990). The more foods are handled, the greater the risk of contamination from employees. Risks are highest when RTE foods are handled because no further cooking takes place.

The CDC Foodborne Illness Outbreak Summaries always include contact with foods by an infected or colonized worker as a leading factor in outbreaks (Olsen, 1997). Workers who have subclinical infections or those with clinical signs of disease may easily contaminate foods through the fecal-oral route via

direct contamination (Guzewich and Ross, 1999). Cross-contamination is also significant because of poor hygienic practices such as wiping hands on aprons or on common cloths, instead of hand washing. Cross-contamination is especially likely when employees are working simultaneously with raw foods and cooked foods. Employees can be a cause of chemical and physical contamination to food as well.

Workers, the environment, equipment, and foods themselves may all contribute to contamination during preparation. To create preventative measures to limit the contamination of foods during preparation, it is first necessary to recognize the sources of contamination and the mechanisms of spread. The epidemiology of foodborne illness has uncovered four basic sources of contamination to which foods are exposed during preparation (Guzewich and Ross, 1999). Preventative measures and safety standards for each of these potentials are discussed separately below.

Prevention and control of contamination from the food itself

Prevention of cross-contamination Most raw foods can harbor both pathogenic and spoilage organisms. Pathogens may be disseminated if standards to prevent cross-contamination are not in place (Paulsen, 1994). Facilities designed with separate areas for preparing raw foods and RTE foods have an advantage over facilities in which all types of foods are prepared in the same area. Preparing raw foods at different times, in lieu of different areas, may also be advantageous. RTE foods can easily become cross-contaminated when different foods in various stages of production are being prepared in close proximity.

Washing fruits and vegetables Raw vegetables and fruit are a source of contamination and often do not receive a cooking step. Vegetables may be contaminated with a variety of vegetative bacterial pathogens as well as spores (Beuchat, 1996).

All fresh vegetables must be thoroughly washed before processing. Washing vegetables is a prudent practice, but washing alone can not be counted on as a measure to reduce populations of pathogens to safe levels (Zhuang and Beuchat, 1996). *Cyclospora* can not be completely removed by washing fruits and vegetables. Similarly, washing sprouts does not remove contamination from *E. coli* or *Salmonella*. Any chemical used to wash vegetables must meet the stringent federal requirements of a food additive.

Washing vegetables in plain water removes soil and other physical contamination, and use of a scrub brush on tubers, melons, and root vegetables facilitates cleaning. The scrubbing action may also remove some but not all pesticide residues and other chemical contamination. Washing of vegetables should be done in warm, flowing water. Washing in cold water may cause migration of contaminates into the vegetable (Buchanan et al., 1999). Although mushrooms may absorb a small amount of water when washed, this is negligible and not a sufficient reason not to wash them.

Thawing Seafood and raw meats of all types including beef ribs, steaks, chops, ground beef, chicken, turkey, and many processed foods are typically received and stored frozen. Small quantities of leftover meats, soups, stocks, and gravies are often frozen in commercial food service establishments and stored with the intention of using them later. Many other RTE foods are delivered frozen (e.g., lasagna, hotdogs and meatballs). Thawing of frozen foods is often necessary before cooking for culinary considerations such as quality and taste. Individual portions (e.g., hamburger patties, fish fillets) or small batches of frozen RTE foods (e.g., french fries), are often heated directly from the frozen state, whereas large food items (e.g., turkeys) or large quantities of raw foods (e.g., shrimp) are generally thawed before cooking.

Thawing raw foods at temperatures above 41°F (5°C) allows favorable bacterial growth conditions for pathogens on the surface of the food. However, competition from other microflora and the fact that the foods are still relatively cold reduces this risk. Therefore, improper thawing of raw foods, although not desirable, may not be a critical concern for foodborne illness. A critical concern would occur if PHFs remain at elevated temperatures for extended periods of time after thawing especially if improper cooking follows. In this case, the population of pathogenic organisms consumed may be very high and illness may result.

To avoid temperature abuse during thawing, four methods are commonly recommended:

- *Thawing under refrigeration.* Refrigerators should keep frozen foods from rising past 41°F (some jurisdictions allow 45°F), never allowing portions to reach the temperature danger zone, which is between 41°F and 140°F. Adequate time must be allowed because the thawing in a refrigerator may take several days for large roasts and turkeys.
- *Thawing under cold running water.* Water temperatures vary with geographic locations and seasons, but 70°F is common in municipal water supplies. While under cold running water, the exterior portion of the food may reach 70°F while the interior rises to thawing temperatures. For this reason, thawing under cold running water should be a technique used with small portions of foods or accomplished as quickly as possible (in less than 4 hours).
- *Thawing in a microwave oven.* It is possible to use the "low" or "defrost" settings of a microwave oven to thaw foods. Foods thawed in a microwave should be cooked immediately on removal from the microwave or cooked in the microwave itself.
- *Thawing during cooking.* When cooking frozen foods, it is vitally important to ensure that the interior portion of the food is adequately cooked. Generally, cooking frozen foods requires approximately a third more cooking time than cooking thawed or fresh foods (HITM, 1997). Failure to adjust the cooking time and failure to test the temperature of the interior portions of such foods has resulted in infectious agents being passed to consumers.

Minimizing time at unsafe temperatures Preparing foods at room temperatures over extended periods is a hazardous practice that may result in PHFs rising into the extreme temperature danger zone between 70°F and 120°F. Temperature ranges and prolonged preparation steps that allow for the germination of spores, and the elaboration of toxins, make any subsequent cooking or re-heating ineffective. When PHF are above 41°F and below 140°F for more than 4 hours the foods must be discarded under Food Code standards. Cooked PHFs must be moved quickly from the cooking process to the cooling and storage steps or must be maintained out of the danger zone during production.

Ice protection Ice is used extensively by commercial food service establishments as an ingredient in beverages, as a cooling aid for foods such as shrimp and fish, for ice baths, and for cold holding units (salad bars). If ice is made from safe water supplies it can be assumed to be safe for consumption unless it has been contaminated. Ice can become contaminated, during storage and during dispensing. Scoops for ice must be kept sanitary and in good repair; if scoops are left on soiled surfaces they may contaminate the ice when the ice is dispensed. If pieces of the scoop break off, foreign objects may enter the product. Drinking glasses and other glassware must never be used to scoop ice. Ice bins are moist environments subject to the growth of bacteria and mold. Ice bins are opened and closed frequently, allowing foreign matter to be easily introduced. Ice bins may also be located outdoors, increasing the chance for contamination; outside ice bins must be protected by an overhead structure such as a roof or overhang. Drains for ice bins must be installed so that backflow from sewage lines is precluded. Contamination of ice by virus, bacteria, and parasites may occur as the result of improper plumbing of waste lines. Backflow prevention is obtained by the maintenance of an air gap between the receiving receptacle of the plumbing fixture and the discharge end of the drainpipe. The distance between the two must be twice the diameter of the drain line but no less than 1 inch.

Prevention and control of contamination from equipment and utensils

Equipment construction, design, number, and installation. The number of various pieces of equipment and their capacity, placement, and design have a significant impact on food safety. Equipment for processing raw meats should be completely separated from the areas used to process vegetables and other RTE foods. The failure to properly place production equipment leads to the cross-contamination of foods. Alternatively, a barrier can be positioned between processing areas.

Food contact surfaces of equipment must be made of approved materials. Although stainless steel is usually recommended, other approved surfaces for food contact in certain applications include various types of hard plastic, hard rubber, and maple, oak, and other hardwoods. Non-food contact surfaces can range from sealed wood for shelving to glass for windows on beverage cooler

doors. Design criteria established by Underwriters Laboratories (UL) and the National Sanitation Foundation (NSF) greatly simplify the selection of suitable equipment. In general, food contact surfaces must be smooth, nonporous, durable, nontoxic, and suitable for cleaning and sanitizing.

For easy cleaning, sinks, for example, must have rounded corners (coving) so food particles do not become trapped in crevices; any two surfaces that meet at a 90° angle pose a cleaning problem. There must be no hard to get to places where foods can be trapped, and all mechanical equipment such as slicers and mixers must be readily disassembled with normal hand tools for inspection and cleaning.

All equipment must be supported 6 inches off the floor. Legs on coolers and freezers accomplish this. Household equipment such as freezers and refrigerators are commonly seen in commercial foodservice establishments placed directly on the floor with no legs. Pests and cleaning problems often result from this application. Table-mounted food preparation equipment such as grinders, mixers, and choppers can be bolted to the table and the crevices sealed, or they can be positioned on legs with a 4-inch clearance to allow for cleaning and inspection.

For safety and practicality during food preparation, a 3-foot-wide aisle, at minimum, should be maintained between any stationary equipment. Equipment should be located a minimum of 4 inches from walls to allow cleaning behind the unit, and shelves should have a 2-inch clearance to the wall. Prep tables, sinks, and other equipment are often placed in very close proximity. Not allowing sufficient space between them for cleaning results in food particles becoming lodged in crevices. Surfaces that abut may also be sealed or joined together to prevent the accumulation of contamination.

Preparation sinks are required for washing vegetables, obtaining water, ice baths, thawing foods, and a host of other food preparation activities. An insufficient number of prep sinks slows production but also leads to an increase in the potential for cross-contamination. Food preparation equipment, such as mixers, choppers, slicers, ovens, broilers, etc. may be in constant use, lessening the frequency of routine maintenance and cleaning.

Equipment and utensil maintenance. Maintenance of equipment is a necessary component of a safe operation. Maintenance schedules are often described in an owner's manual, which should be kept with the equipment. Owner's manuals may not always be available because these documents may not be saved and they might not transfer from operation to operation with the equipment. If a manual is available, strict attention to the necessary maintenance features reduces the possibility of breakdowns and lengthens the equipment's usable service life.

Gaskets made from rubber and similar materials need cleaning with mild dish detergent and warm water. The use of strong alkaline agents on gasket surfaces causes them to become brittle. Because they rarely come in contact with foods, sanitizers are not necessarily required. After cleaning, gaskets should be wiped with a food-grade lubricant to keep them pliable.

Hinges and latches on doors of refrigerators need lubrication with safe food-grade lubricants. Refrigeration components such as compressors and filters must be cleaned regularly; failure to do so results in increased cost and decreased performance of the unit. Refrigeration units must be checked frequently for problems in operation, and any increase in temperatures in any refrigeration unit should be investigated.

Can opener blades need frequent changing to avoid metal shavings, a physical contaminant that may be introduced to a food during preparation. Electrical cords on equipment require inspection on a regular basis. Light bulbs in walk-in coolers and under grease hoods require protective screens or shields for foreign object control. Shatterproof florescent bulbs are an alternative, and when in use, these bulbs do not require shielding. The use of high-intensity lights (quartz lamps) for heating and maintaining food temperatures requires a protective shield or other safeguards to prevent physical contamination and to protect employees from burns.

Carbonators for drink dispensing machines mix carbon dioxide (CO_2) with water. The carbonated water is then mixed with syrup to produce the beverage. Where the potable waterline connects to the carbonator, a hundred-mesh screen is installed to trap small pieces of debris and sand. Small particulate matter can foul the backflow prevention device (check valve) on the carbonator if the screen is damaged. Because CO_2 is under pressure, it is possible that under periods of loss of pressure in the waterline, CO_2 can be pumped back into the waterline. CO_2 is corrosive, and copper lines may be dissolved, releasing copper into the water. When pressure returns the copper contamination will be flushed into beverages, causing copper poisoning when ingested. Inspection and replacement of the screen is advised to prevent failure of the check valve.

If equipment and utensils used for preparing foods are in poor repair, physical contamination of the food can result. Pizza roller knives lose the washer and nut on the cutting wheel, blades and handles chip and crack, the screws that hold the lid on a sandwich prep box become loose and may fall off, and many other equipment failure issues lead to contamination.

Cleaning and sanitizing equipment and utensil surfaces Equipment and utensils routinely come in contact with raw animal foods and can be a source of cross-contamination with pathogens such as *Campylobacter* during preparation (Tauxe, 1992). Therefore, sanitizing of equipment under certain conditions is critical to food safety and must be effective. Slicers, mixers, and other electromechanical equipment must receive thorough and regular cleaning and sanitizing, but they usually cannot be submersed in water. Proper procedures must be in place to clean and sanitize these items at least every 4 hours when working with PHFs. Any time there is a change from a raw food to a cooked food there is a cross-contamination potential. Cleaning alone may not make the surface of the equipment safe; sanitizing of the surface is therefore also necessary.

Sanitizing is a process that must reduce contamination to safe levels; the U.S. Public Health Service (USPHs) has defined a sanitized surface as a surface having less than 100 CFU per 8 $in.^2$ (FDA, 1976). Reducing contamination to

this level requires at least four basic steps: wash, rinse, sanitize, and air dry. Because triple sinks are not movable and most mechanical ware washing machines are appropriate only for small pieces of equipment and utensils, three buckets for the purpose of satisfying the requirements for sanitizing must be set up and moved around the food service environment for in-place sanitizing. Because the three-bucket method is cumbersome and labor intensive, it is somewhat common to observe improper sanitizing of food preparation areas. Many commercial food service operators have the mistaken idea that the sanitized wiping cloth is sufficient to both remove visible soil and reduce harmful microorganisms to safe levels. This is not possible unless the sanitizer is used at toxic concentrations. Cross-contamination, which is frequently identified as a major factor in foodborne illness outbreaks, can occur when cleaning and sanitizing procedures are incorrectly applied.

Utensils used in the preparation of food are easily moved from one location to another, and one utensil may have a utility for a variety of functions. The greatest danger is cross-contamination, defined as the transfer of pathogens from raw animal foods to cooked or RTE foods. For example, a knife used to cut a loin of beef into steaks that is then used to cut cooked potatoes is likely to transfer bacteria such as *E. coli* O157:H7 to the potatoes. The wash-rinse-sanitize-air dry method is the only approved method for cleaning and sanitizing in-use utensils. It is therefore important to have sufficient knives, spoons, tongs, ladles, etc., to accommodate a variety of needs, lessening the frequency that utensils must be sanitized. Utensils in contact with RTE foods are not necessarily contaminated; therefore, it is probably unnecessary to sanitize a kitchen utensil between various cooked foods. For example, it is unnecessary to sanitize a spoon between stirring cooked chicken noodle soup and stirring cooked chicken gravy; it is equally unnecessary to sanitize a knife between applying mustard and applying mayonnaise to a sandwich. A clean wiping cloth stored in dilute sanitizer may be used to clean such utensils without the need for a wash step. However, use of a sanitized cloth to wipe chicken blood from a meat cleaver will not render the utensil sanitized and will contaminate the cloth.

Separate equipment/utensils for raw and ready to eat (RTE) foods Separate equipment and utensils for preparing raw foods reduces the risk for cross-contamination. Color-coded cutting boards provide a means of designating different surfaces for different foods. Green cutting boards can be used for raw vegetables, yellow for raw chicken, blue for raw fish, red for raw beef, etc. White cutting boards can be designated for RTE foods such as sandwiches or cooked foods. Once contaminated by a raw food the cutting board should not be used for a different type of raw food without first being cleaned and sanitized, in part because of the allergies and sensitivities that some consumers may have. Food allergies and sensitivities are a special concern of commercial food service, and these maladies are seemingly increasing in the population (FDA, 1994). Persons allergic to fish may be exposed to fish allergens by a steak, for example, if the steak is placed on the same cutting board as a fish.

Cross-contamination between species of foods is a growing concern to persons with food allergies and food intolerance.

In-use utensils stored in a sanitary manner It is impractical to continuously wash, rinse, and sanitize utensils while preparing and serving food; therefore, utensils are generally used continuously for several hours at a time. Pauses in preparation between orders, between preparation steps, or between customers, necessitate that the utensil be temporarily stored. Time and temperature controls can be applied to the problem of food debris and growth of bacteria on soiled, in-use utensils. Failure to control this type of contamination may lead to the introduction of spoilage organisms, harmful bacteria or toxin into products by utensils. There are four acceptable ways to store in-use utensils to control contamination and growth of bacteria on their surfaces:

- *In the product with the handle out.* This method assumes that the products themselves are being maintained at safe temperatures and that handles do not contaminate the products.
- *Clean and dry on a food contact surface.* This method implies that the utensil has been cleaned of ready to eat food debris by a sanitized wiping cloth. The utensil must be sanitized or changed every 4 hours.
- *In a running water dipper well.* This method implies that the flushing action of the water is sufficient to rinse food particles down the drain with volumes of water adequate to reduce concentrations of bacteria to safe levels.
- *In hot water at 140°F.* In this case, the temperature of the water prevents the growth of bacteria, and the water need not be running. From a practical side, the water must be changed frequently and the utensil cleaned free of food particles regularly.

In-use utensils are prohibited from being placed in standing water at room temperature, and from being left at room temperatures while soiled with potentially hazardous food remains. The use of sanitizer is also not allowed as means of storing soiled utensils.

Utensils for dispensing salt, sugar, and margarine or utensils such as rolling pins, basting brushes, and the like are simply required to be stored so as to minimize the contact that hands would have with the foods being prepared. This is easily accomplished by keeping the handles out of the products. Such utensils should be cleaned at appropriate intervals to remove food soil.

Controlled use of disposable gloves Surfaces of gloves become contaminated in the same way as hands, from the human body, from foods, and from the contaminated surfaces of equipment and utensils. In a sense gloves can be thought of as a layer of skin (Fendler et al., 1997). Changing single-use gloves at a frequency that parallels the hand washing regimen and sanitizing regimen is necessary. Observation of employees will often reveal that employees either change gloves when it is unnecessary or change gloves too infrequently.

Typical times when it is necessary to change gloves are:

Any time one would have ordinarily washed one's hands
Whenever they have been torn or have become excessively soiled
Every 4 hours at a minimum when working with PHFs
When one leaves and returns to the workstation

Because the environment of the glove may cause occlusion of the skin, the population and growth of bacteria greatly increase beneath rubber gloves. Therefore, hand washing is essential when changing gloves and at regular intervals (Larson, 1989).

Chemical contamination control Chemical contamination may be introduced into food during preparation if polishes, detergents, sanitizers, lubricants, and cleaners are not properly used and not safely applied on the working surfaces of equipment and utensils. Placing dilute sanitizer solutions near equipment is not hazardous; however, placement of concentrated sanitizers in jugs and other containers on or above food equipment is potentially hazardous.

Many types of detergents and cleaners are used to clean equipment and utensils, and, although not highly toxic, they may cause exposures if residues remain. Detergents must be used according to label directions and manufacturers' requirements. Sanitizers should be used in very low concentrations; exceeding these concentrations will possibly expose consumers to potentially toxic chemicals.

Lubricants such as grease, hydraulic oil, gear oil, and WD40 are potentially toxic and should not come in contact with any food contact surface of equipment or utensils or with any surface where there is potential for them to drip on to foods. Only food-grade lubricants should be used on slicers, rotisseries, rack conveyors, and other food processing equipment.

Handling of grease Grease-laden vapors are produced when foods are fried, grilled, or cooked in open containers. Grease on surfaces such as the stove hood or fixed fire extinguisher piping can contaminate foods when heavy accumulation occurs. Cleaning of surfaces where grease accumulates is necessary for sanctation fire safety.

Prevention and control of contamination from people

Medical certification: Health status of employees may vary on even a daily basis. A once yearly physical may reveal chronic conditions or carrier status of a few infections agents such as Salmonella. Most U.S. health authorities no longer require health screening but the practice is still common in other countries.

Exclusion and restriction Infected workers are a leading cause of foodborne illness. *E. coli*, hepatitis A virus, *Salmonella* spp., *Shigella* spp., and *Clostridium perfringens* are enteric pathogens spread by workers (Paulson, 1994; Restaino and Wind, 1990; Snyder, 1997). The Food Code requires that employees

exhibiting symptoms such as diarrhea, fever, and vomiting or with infected cuts, burns, or lesions report their condition to the manager or immediate supervisor.

Feces from an infected worker may contain from 10^6 to 10^{10} pathogens per gram (CDC, 1990b). Effective hand washing may reduce the level of pathogens significantly, but highly virulent viral agents, such as Norwalk virus and hepatitis A, may not be entirely removed (Guzewich, 1996).

The CDC now recognizes vaccination of food service employees during outbreaks of hepatitis A as an effective public health intervention and leaves this decision to states based on the cost effectiveness of such interventions (CDC, 1999b). This is because the cost of vaccinating food workers may be low compared with the cost of immunizing whole populations or the administration of postexposure prophylaxis to patrons. Many public health agencies feel that food workers should be encouraged to get vaccinated under these conditions because this is for their own protection. Vaccination greatly reduces the risk of hepatitis A transmission during outbreaks.

Under normal conditions, restriction or exclusion of ill workers should be the first line of defense for bacterial or fecal agents. But this can only be accomplished if employees are obviously ill or if they report their symptoms to management as required. Employees must report infected cuts, wounds, burns, respiratory infections, gastrointestinal symptoms, and jaundice. Once management knows that an employee has symptoms of gastroenteritis or another communicable condition, either restriction of the employee to nonfood contact duties or exclusion of the employee from the premises must follow. Employees are placed on restriction and may not handle food, clean equipment, or clean utensils when symptoms of communicable disease exist and no diagnosis from a physician is available.

Severe illnesses such as typhoid fever, hepatitis A, shigellosis and *E. coli* O157:H7 infection, when diagnosed, trigger mandatory exclusion of the worker. A physician must clear the employee to resume work in these cases.

Food service workers unable to afford health insurance are not likely to seek conventional medical attention and are unlikely to be diagnosed. Management policies may also discourage employees from calling in sick, and managers may even feel the need to pressure employees to report to work regardless of their health status. Therefore, infected workers may be expected in food service establishments. Transmission of the agent to the host may be interrupted, however, if good sanitation practices, especially effective hand washing programs, are in place (CDC, 1999b).

Personal hygiene practices During the period 1988–1992, the second most commonly reported practice that contributed to foodborne disease was poor personal hygiene of food workers, reported in 36% of outbreaks (Bean et al., 1996). Effective systems for personal hygiene are based on an understanding of the source and nature of contamination. Of the types of contamination that can be spread by people, biological agents (e.g., bacteria, viruses, and parasites) are the most serious threats to public health. Hands may become contaminated

with biological agents when handling raw foods, contaminated supplies, contaminated environmental surfaces, or waste material. But the most important source of contamination is the contamination that people carry inside their digestive tract (e.g., enteric pathogens) or on their skin (e.g., transient microorganisms, *Staphylococcus aureus*). It has long been known that food workers can transmit pathogens to food after using the bathroom if good personal hygiene is not maintained (Crisley and Foter, 1965).

Because effective hand washing reduces the level of microorganisms, hand washing has been described by the CDC as the most important means for preventing the transmission of communicable disease. Hand washing is considered by some to be a HACCP critical control point in the preparation of RTE foods, whereas others argue that it is not completely reliable (Guzewich, 1995b).

An effective hand washing program is facilitated when personal hygiene protocols are clearly described and management takes an active role in ensuring that they are always being followed. Once developed, the program must be communicated and implemented consistently and effectively. The recommended elements of a hand washing program include ongoing training, a monitoring program, corrective actions, and a reward system. The overall effectiveness of training and implementation can be enhanced by the use of visual aids such as posters or demonstrations with currently available training aids [e.g., Glow Germ™ kits, adenosine triphosphate (ATP) swabbing technology]. Additionally, sinks are available that keep track of usage and/or that turn on and off with sensors.

Surfaces in the restroom may be contaminated. Therefore, it is best to minimize hand contact with door handles, sink faucets, and hand drying devices. Automatic valves on sinks eliminate the need to touch the sink area, thus reducing the potential for recontamination of hands after washing. Continuous-feed paper towels eliminate the need to touch cranks or levers. Under the Hospitality Institute of Technology and Management (HITM) protocols, the second wash could conceivably be accomplished after returning to the kitchen area, allowing for the removal contamination picked up after the first wash. The use of a hand sanitizer and/or antibacterial detergents or soap is recommended by many health authorities and even required by some jurisdictions (e.g., Florida). The necessity and efficacy of hand sanitizers has been debated widely. Proponents argue that they reduce the microbial burden on the hands, making disease transmission less likely (Larson, 1995). Others have found that although bacteria are reduced, the spectrum of bacteria killed is broad and both resident microflora and transient populations are reduced simultaneously (Mahl, 1978). Additionally, opponents of hand sanitizers argue that there is currently no hand sanitizer accepted by the Environmental Protection Agency (EPA) as a viracide. The Food Code requires that all sanitizers be approved by the EPA for use in commercial food service establishments. Furthermore, the use of hand sanitizers as a replacement for washing the hands is deemed an unhygienic practice by most health jurisdictions and is prohibited in the 1999 Food Code.

Hand drying devices approved by the Food Code and most jurisdictions include paper towels, air blowers, and continuous-feed cloth towels. As mentioned, continuous-feed paper towels reduce the potential for recontamination of the hands, and the scrubbing action and friction of the towel further reduces microorganisms. There is some indication that blow dryers may harbor microorganisms and deposit them on hands during their use (Restiano and Wind, 1990).

There are three components of an effective hand-washing program:

- *Where to Wash.* Hand washing must take place only in an approved hand sink. These small basin sinks must be located at strategic points throughout the establishment. All food preparation areas must be provided with at least one easily accessible and conveniently located hand lavatory. All bathrooms must have at least one hand washing facility located within the bathroom or immediately adjacent to it. Remote ware washing areas should also be provided with a hand sink, and bars require a hand sink, as well. There is no definite rule as to how many sinks are required or their placement in terms of square footage or distance apart. Although each commercial food facility is different in its requirements, the flow of foods through the operation provides a good basis for determining where and when hands are likely to be contaminated and the proper location for hand washing sinks.

  The hand washing sink should be provided with an ample supply of warm water. The HITM recommends a water temperature between 110°F and 115°F (this range may be uncomfortable for some with sensitive skin; the Food Code allows 100–110°F) and a water volume of 2 gallons per minute.

  Most regulatory agencies do not list the three-compartment sink or the utility sink as acceptable for hand washing. Because three-compartment sinks are generally used for preparing foods as well as cleaning utensils, employees in the habit of washing their hands in such sinks will eventually contaminate a food item or a utensil. The utility sink is unacceptable because surfaces are liable to be contaminated and may result in recontamination of the hands.

  Posting instructive signs at all hand washing sinks is a simple method of designating the proper sink to use. Signs are available from many health authorities because many jurisdictions provide one for posting in the restroom. The practice of designating a hand washing lavatory with a sign should be extended into the food preparation area as well.
- *When to Wash.* Knowing when to wash requires not only recognizing the sources of contamination—the person, raw animal foods, supplies, and contaminated surfaces in the environment—but also recognizing when contact has been made with them.

  The key times to wash hands are before handling anything that must not be contaminated (RTE foods, clean utensils) and after handling anything that is contaminated (urine, feces, vomit, raw meat, unwashed vege-

TABLE 26.5. Specific Times When Hand Washing is Mandatory (Food Code 1999).

• Before beginning work	• After handling soiled utensils or equipment
• Before handling foods	• During food preparation often enough to remove contamination
• After touching bare human body parts other than clean hands and clean arms	• When changing tasks where there is a possibility for cross-contamination
• After using the restroom	• When switching between raw and cooked foods
• After handling support animals	• After any other activity that contaminates the hands
• After coughing, sneezing, using a tissue or handkerchief, using tobacco, eating, or drinking	

tables, mop handles, wastewater, infected skin lesions, etc.). The greatest potential exposure to pathogens probably occurs during defecation, so personal hygiene after using the toilet is the most critical time to wash hands.

The specific times when it is mandatory to wash hands according to the Food Code are listed in Table 26.5. There are other recognized times when hands become contaminated. It is also beneficial to require employees to wash whenever they return to the kitchen. Locating a hand washing station near the entrance to the kitchen makes hand washing at this point observable for the manager and convenient for the employee.

Some commercial food service establishments require their employees to wash their hands at set time intervals as a minimum measure. This ensures that employees will wash their hands at least a minimum number of times but does not ensure that employees will wash when it is necessary. Employees with contaminated hands may actually postpone hand washing until the designated time, thereby increasing the potential for the spread of contamination.

Although the Food Code and most local jurisdictions do not list "after handling money" as a necessary time to wash hands, coins and bills are noticeably soiled. Money as a substrate has recently been shown to allow survival of pathogenic organisms for several hours (Doyle). Consumers view the handling of money and subsequent contact with foods as an unacceptable hygienic practice, and for these reasons it is advisable to wash hands at regular intervals when handling money or to designate a separate person as a cashier.

- *How to Wash.* Hands must be washed thoroughly to reduce the level of contamination by an order of five logarythmns; this five log reduction (10^5 reduction) greatly lessens the likelihood of a consumer being exposed to an infectious dose of a pathogen. Hand washing in a sense is a misnomer because fecal pathogens tend to be collected on fingertips, especially in the fingernail and cuticle area (McGinley et al., 1988). Decontamination of the fingertips must be stressed.

TABLE 26.6. Hand Washing Protocol According to Hospitality Institute of Technology and Management (HITM).

▪ Wet nail brush and hands	▪ Build a good lather again under flowing water washing from the arms down
▪ Apply a teaspoon of liquid soap to nails and brush	▪ Rinse arms hands and fingertips thoroughly
▪ Brush under flowing water, building good lather	▪ Dry arms, hands, and fingers completely with a paper towel
▪ Rinse hands and brush thoroughly to remove all lather	▪ Dispose of paper towel waste without touching the receptacle
▪ Second wash without the brush for arms, hands, and fingers	

There may be up to a trillion *Rotovirus* particles per gram of feces in an infected worker (CDC, 1990). A typical fecal smear on the side of a finger may be on the order of 1/1000th of a gram; but this very small, inconspicuous amount of waste may contain millions of viral particles. A 10^5 reduction will still leave hundreds of viral particles on hands, and these will probably be spread over several portions of food; therefore an infective dose, usually set at a minimum of 10 viral particles, may be easily transmitted, even with effective hand washing.

However, with many agents, an effective hand washing program will reduce the potential for disease transmission greatly. To achieve this level of reduction it is recommended that employees follow a prescribed protocol similar to that developed by the HITM (Table 26.6).

In addition to improper hand washing, food handlers can also contaminate food through other unhygienic practices (see partial list in Table 26.7). Such practices provide a secondary route of exposure to pathogens as well as physical or chemical contamination, give the appearance of poor sanitation to both customers and other employees, and detract from the aesthetic enjoyment of the dining experience, and are they frequently cited as poor hygienic practices by regulatory agencies and in consumer complaints.

TABLE 26.7. Unhygienic Practices of Food Handlers.

· Wiping hands on cloths and aprons	· Wearing nail polish
· Chewing gum and/or smoking while working with foods	· Wearing false fingernails
· Holding toothpicks, straws, or other objects in the mouth while preparing foods	· Touching infected pimples and boils
· Wearing excessive jewelry on the hands that may trap contamination or fall into foods	· Not wearing water coverings over bandages
· Having long fingernails	· Wearing soiled clothing
	· Touching the lip of a glass or the end of a spoon
	· Handling money without washing
	· Not wearing a hair restraint

Contamination from these practices, with the exceptions of touching infected lesions and bandages, is not a primary or direct factor associated with foodborne illness outbreaks. These poor practices are nevertheless important and should be a part of the good manufacturing practices or standard operating procedures for a commercial food service establishment.

In addition to microbiological contamination, workers can easily drop foreign objects into foods. Special precautions should be taken with small objects commonly worn or carried by people. Foreign objects that originate with people include jewelry, pen tops, buttons, threads, hairpins, name tags, watch parts, false fingernails, hair, fingernail polish, matches, cigarette butts, ashes, chewing gum, and toothpicks.

Management policies governing the habits and dress of employees are needed to control contamination. Because employees may feel discriminated against when advised about rules of dress, hairstyles, and personal ornamentation, clear and uniform policies are important.

Hair nets or caps are the best hair restraints; hair may also fall out of beards and mustaches, and specialized coverings and nets are available. Simple precautions such as wearing a uniform instead of street clothes help to standardize controls; using only push button pens instead of pens with caps and prohibiting any jewelry except a simple wedding band are other common sense controls. Employees should never smoke while in the food preparation or storage areas, nor should they use toothpicks while working around foods.

Maintenance of hand washing sinks The complete hand wash station includes a hand sink with hot and cold running water under pressure (minimum of 20 lb./in.^{2}) provided with an approved hand drying device, hand soap, nail brush, and a hand washing sign or poster. Where necessary, a hand sanitizer may be placed at the sink. The sink should be unobstructed at all times, and it should be kept clean and in good repair. Employees will not take the hand washing program seriously if the necessary items are not always provided or the sink is not working.

As stated above, hand sinks with automatic valves are easily installed, there are models that count the number of washes, and there are even automatic soap and sanitizer dispensers. By utilizing the latest technology, commercial food service establishments may be able to increase compliance with hand washing programs.

No bare hand contact of ready to eat (RTE) Foods Establishing barriers between hands and RTE foods reduces the likelihood for transmission. Such barriers include utensils such as deli paper, spoons, spatulas, forks, and gloves. Gloving is preferred to hand washing as a means of interrupting the orofecal transmission pathway by some jurisdictions, most notably the state of New York. The use of gloves is also common in the food industry because it is more easily managed than the elaborate protocols involved in hand washing compliance; from a management perspective, an employee is either wearing a glove or

he is not. Gloves have fallen into disrepute because employees, once gloved, may see themselves as protected and be more prone to touching contaminated objects without changing gloves or washing hands (Fendler et al., 1997). Because of the potential "false sense of security," many restaurants are opposed to any mandatory no bare hand contact provisions and commonly but mistakenly refer to these laws as "glove rules."

Clearly, gloves and other barriers are not a panacea for preventing every possible route of transmission; if gloves are used, training must also be done to ensure that employees are taught why they are wearing gloves, to change gloves when they are contaminated, and to wash their hands when necessary.

The Food Codes since 1993 have contained prohibitions against the bare hand contact of RTE foods, but the 1997 and 1999 Food Codes allow for alternatives to the no bare hand contact provisions when acceptable to the local authorities. This means commercial food service establishments allowing bare hand contact of RTE foods must demonstrate that alternative means are being taken to ensure that no contamination of foods will occur because of bare hand contact.

The state of Florida has adopted an "Alternative Operation Procedure" for commercial food service facilities under their jurisdiction. Florida was the first state to legislate a plan to address the Food Code provision for an alternate means of compliance to the no bare hand contact provisions. The Florida plan as outlined below forms a basis for other states to establish similar programs. Under these programs, commercial food service operations must develop an effective plan to control contamination through hand washing. Alternative plans must include a description of all controls, as well as where, when, and how to wash. In addition, these alternative plans must identify all food production locations where bare hand contact will occur, the job titles of all positions authorized to directly handle RTE foods, and the types of foods being handled. The general elements required in these "alternate plans" are listed in Table 26.8.

Food handler training and management practices Foods handled by untrained staff are assumed to be contaminated, so training is essential. Leadership and motivation are required if training is going to accomplish the goal of providing safe food; this is especially true as regards personal hygiene practices. Managers who demonstrate good hygiene will be followed, and unhygienic practices by managers tend reinforce bad habits in employees.

Body fluid precautions Saliva, perspiration, and blood may carry pathogens such as *Staphylococcus aureus*, *Streptococcus pyogenes*, hepatitis A virus and hepatitis B virus. Precautions to guard against introduction of saliva into food include not eating or smoking in food areas, but the Food Code does allow the use of a closed vessel and a straw for drinking beverages.

Perspiration is unavoidable in high-heat areas of many food service kitchens, especially in the summer. Although the Food Code does not specify or recom-

TABLE 26.8. Required Components of Alternate Means of Compliance with No Bare Hand Contact Provisions (State of Florida).

1. The plan must include a description of
   - All hand washing controls; and
   - Hand washing protocols (when, where, and how to wash).
2. The plan must identify
   - All food production locations where bare hand contact occurs;
   - The job titles of all positions authorized to directly handle RTE foods; and
   - The types of foods being handled.
3. Employees must be in compliance with the Employee Health section of the Food Code.
4. Sinks designated as hand-washing sinks must always be provided with hand soap, an approved drying device, and hot (110°) and cold water under pressure.
5. There must be an adequate number of sinks available, per the Food Code.
6. Managers must train the employees in the standards of the Food Code and the facilities policies and then make sure they are following the policies.
7. Corrective actions must be taken when deviations occur; most importantly, foods contaminated by workers must be discarded.
8. All training materials and the plan itself must be at the establishment and available for inspection by regulatory staff.

mend a maximum kitchen temperature, it is advisable to keep temperatures in all work areas relatively comfortable for food handlers and to provide adequate ventilation. Wiping of perspiration should be done in a sanitary manner with a paper towel that is disposed of promptly.

If an injury takes place involving cuts, wounds, or burns, all activity in the work area should cease and the employee should be attended to. Before work resumes several precautions should be undertaken. No employee should handle any item contaminated with blood with his/her bare hands. A glove should be used. Whether visibly contaminated or not, all utensils must be removed from the affected area and taken to the ware washing area for cleaning and sanitizing. All nonmovable equipment must be cleaned and sanitized in place. Floors, walls, and ceilings must be inspected, cleaned, and sanitized. Most importantly, all exposed foods must be discarded. All containerized foods must be inspected, and if foods are suspected of being contaminated, they must be thrown out.

Although the human immunodeficiency virus (HIV) may be carried by food service employees, no documented cases of HIV transmission have occurred through food. However, the public will react very emotionally to any foods contaminated by human blood. The most stringent precautions must be taken to prevent this from occurring. Such precautions should be included in standard operating procedures.

Wounds bandaged Infected cuts and other skin lesions may harbor large numbers of bacteria, especially *Staphylococcus aureus* (Burton, 1992). Precautions must be taken to prevent the contamination of foods with this toxigenic

pathogen. Employees must be placed on restriction if they have any infections on the hands or exposed areas of the face or arms. An exception can be made if an employee has a bandage on the hand or finger, if an impervious barrier (commonly called a finger cot) protects the bandage, and if the hand is also placed inside a sanitary glove. The employee may work unrestricted with food items with these precautions. Cuts that are not infected may be bandaged and covered with a glove.

Prevention and control of contamination from environmental hazards

Potable water In addition to cooking purposes and beverages, water also serves several other culinary and sanitary functions including ice making, dilution of chemicals, hand washing and ware washing, and general cleaning. Water is an integral part of the foods served, of the food service environment, and of food preparation. The relationship between microbiological contamination of water and human illness has been well documented throughout history. Recently, a waterborne outbreak at a New York county fair resulted in nearly 100 confirmed cases of *Campylobacter* and *E. coli* O157:H7 illness and was associated with an *unapproved* water supply well (CDC, 1999a).

Any water used in a food service facility must be potable (considered safe from microbiological and chemical hazards) by existing regulations. Wells serving commercial food service establishments must have permits as public drinking water wells under most regulatory programs. Most authorities require continuous chlorination of water supplies for disinfecting.

Written SOPs should be developed and implemented with regard to testing and certification that the water supply meets, or exceeds, the regulatory requirements for hazardous chemical residues (e.g., heavy metals, pesticides, volatile organics, nitrates) as well as microbiological standards (e.g., total coliform, fecal coliform). Additional concerns regarding water quality (e.g., hardness, iron content, turbidity, etc.) should also be monitored because these components negatively affect the functionality of water in food handling operations.

Design and maintenance of plumbing Protection of the water supply system within the establishment is a matter of cross connection control. However, good cross connection control also protects the integrity of the entire municipal water system and many utilities have an ongoing cross connection control program. A cross connection results from a direct connection between a potable source of water and a nonpotable source. Cross connections are sometimes established when hoses are attached to a faucet through a threaded hose bib connection; if the pressure in the supply line drops and the discharge end of the hose is below the surface of a contaminated supply, a back siphon may occur. Contaminates may be drawn into the water system or they may even reach the city water main if the back pressure is great enough.

More frequently, short temporary drops in water pressure create situations

in which small amounts of water can be drawn back into the building plumbing. Backflow prevention devices are used to interrupt the flow of water if and when the flow reverses direction. There are two basic types, the atmospheric vacuum breaker and the check valve. Atmospheric vacuum breakers are required on the high-pressure side of a dish machine water line because dish machines create head pressure through a pump. Check valves are usually installed on all threaded hose connections to prevent back siphoning and are sufficient when there is no pressure from the discharge side.

Mop water is considered sewage and must be disposed of safely. The only two disposal methods normally approved are the use of a curbed can wash area and the use of a utility sink. Mop water should never be disposed of in the three-compartment sink or in any preparation or hand washing sink.

All plumbing, including water lines, fixtures, and sewer lines, must be kept in good repair. There should be preventative maintenance programs in place for plumbing fixtures such as sinks that receive constant use. Repairs of leaks should be prompt to prevent water damage.

Sewage disposal Wastewater is disposed of through either on-site sewage disposal and treatment systems or through a central sewerage system. The piping that carries the wastes to the sewage system must be constructed and located so as to prevent the release of wastewater into the food facility or onto the premises.

Backflow of sewage into enclosed equipment such as mechanical dish machines and icemakers is a direct contamination threat and a severe hazard. Waste piping should be indirect and should utilize an air gap twice the diameter of the drain line between the discharge end of the drainpipe and the opening of the receptacle.

Floor drain systems are designed to allow the flushing of floors as a cleaning method. When precleaning and sweeping are inadequate, waste materials including food scraps, paper, and other debris can be washed into the floor drainpiping system. The eventual clogging of the floor drain system makes frequent clean-outs of the piping necessary as a maintenance measure. Floor drains must be trapped, and the openings must covered by a grate; floors must slope to drain into the grated opening.

Floor drain systems may also provide harborage for pests such as roaches and fruit flies. Maintenance of the floor drain system should include the periodic flushing of all floor drains to ensure that traps are kept full of water. If water in floor drainage systems evaporates, the piping is exposed to infestations and sewer gases may be released into the surrounding area. The piping from the grate to the trap needs periodic cleaning with a degreaser and a properly sized brush. A small amount of cooking oil may be added to the floor drains to prevent evaporation of the water in drains not frequently exposed to flushing action.

Grease will congeal when disposed of in the sewage system. Grease may wash into the main drain that carries all waste out to the sanitary sewer. Grease

and other blockages may cause a backflow of sewage into the piping, and sewage may eventually flow back through the floor drain system. Sewage is a highly concentrated source of pathogens, and food preparation in a facility exposed to raw sewage is extremely hazardous. Sewage in the food preparation area of a commercial food service establishment should be cause enough to close the facility until the problem is abated. Efforts must be made to keep foreign matter and grease out of the sewage system piping and to keep floor drain systems clean and operational.

Grease is also an undesirable component of the wastewater stream entering a sewage treatment plant. Most utilities have a program to test wastewater and to levy impact fees against commercial food service establishments that exceed a certain level of solids in their wastewater. Grease traps and interceptors remove some, but not all, of the grease, because fat and grease are soluble in detergents and in hot water. Grease traps of various sizes are required in most commercial food service establishments as a measure to limit grease. Grease traps must be pumped out regularly to prevent grease from entering the sanitary sewer and to prevent the possibility for overflows on the premises and blockages in sewage disposal pipes.

When central sewers are not available, septic systems are used. The strength of the septage in commercial food service is much stronger than typical household waste. The biological oxygen demand (BOD) is a way of expressing the strength of the sewage, as is the chemical oxygen demand (COD). Although septic systems may work satisfactorily for a while, problems are inevitable because of high BOD and COD. Commercial food service establishments using on-site sewage disposal methods are generally forced to limit their seating and often to limit their menu and cooking procedures. It is also common for these types of facilities to be prohibited from serving food to customers on multiuse utensils, requiring them to serve food only on disposable, single-service items.

Safe usage and storage of chemicals and toxic items Chemicals are used throughout the establishment for a variety of reasons (see Table 26.9).

TABLE 26.9. Typical Chemicals used in a Commercial Food Service Establishment

- Sanitizers used on food contact surfaces
- Disinfectants used on bathroom fixtures
- Delimers
- General purpose cleaners used on non-food contact surfaces
- Soaps
- Detergents
- Degreasers
- Drying agents
- Deodorizers
- Abrasive cleansers
- Acid-based cleaners
- Insecticides
- Solvents
- Lubricants
- Waxes
- Polishes
- Air freshener

Controlling the potential for chemical contamination during preparation is accomplished through a systematic control program, which should include the following elements:

- *Identification:* All chemicals used in a commercial food service establishment should be identified. Only chemicals that are needed for the operation should be in storage.
- *Labeling:* Containers of concentrated chemicals require the manufacturers' label to be legibly displayed. Working containers of chemicals that have been safely diluted need only the common name of the chemical such as detergent, sanitizer, degreaser, etc. Reliance on the color of the product as an indicator of the contents is a common practice but one that invariably leads to mistakes.
- *Usage:* All chemicals must be used according to their label directions. Failure to follow this simple precaution can result in serious consequences. A concentrated sanitizer (10%) chlorine in the form of sodium hypochlorite designed for a dish machine, if used in a ware washing sink, will result in severe burns to employees and possible exposure to dangerous levels of chlorine gas. Sanitizers containing ammonia must never be mixed with compounds containing chlorine; the resulting chemical reaction is exothermic and also results in the release of poisonous elemental chlorine and ammonia gases.

  Certain polishes and waxes are not approved for food contact. Label instructions often reveal such information. Labels also instruct the user for the need to wash certain poisonous compounds off after using them and to sanitize the surface. Household bleach is inexpensive and often used by commercial food service establishments. All sanitizers are regulated by federal codes, and all should have an Environmental Protection Agency (EPA) registration number. For this reason, some jurisdictions prohibit the use of household bleach as a chemical sanitizer unless it is approved for institutional usage and has an EPA number. Scented bleach is never approved as a food contact surface sanitizer.
- *Dilution:* Chemicals are often concentrated for more practical storage and efficiency and must be diluted before use. The proper dilution depends on the type of sanitizer and very often on the formulation chosen by the manufacturer; many different brands of chemicals are available. There are several automatic devices for the dispensing of chemicals including peristaltic pumps, venturi types, and hand pumps. Manufacturers' instructions and label directions are important for achieving the proper concentration.

  Dilution of typical household bleach to a safe but effective concentration can be done (when allowed by the local authority) by preparing a solution at a ratio of 1000 to 1 (1000:1 dilution) water to bleach. This is the dilution factor needed to reduce a 5.25% chlorine solution (52,500 ppm) to an approximately 50 ppm solution. Dilutions of one teaspoon of 5.25%

household bleach per gallon of water yield a concentration of about 50 ppm (the minimum concentration of chlorine for effective sanitizing). Two ounces of bleach added to 5 gallons of water yields a concentration of approximately 100 ppm (the maximum concentration for application to a food contact surface).

Commercial food service establishments often use premeasured powders and liquids for making dilutions of sanitizers. Preportioned bags and tablets simplify the procedure by calling for a specific number of packets or tablets per sink. In this case it is important to note that "more is not better" and that a specific amount of water is needed in the sink. It is common to see a waterline level indication on the sink for this purpose.

Use; Concentration and Testing: Iodine concentrations (iodophores) can be gauged based on the color of the chemical in the water, but for this and all other sanitizers and especially chlorine- and ammonia-based compounds, it is required that the concentrations be tested. Inexpensive paper test strips are available that provide a color change at an end point that can be compared with a color chart to determine concentrations. It is generally recognized that concentrations above 200 ppm chlorine, in a free-active state, are potentially toxic in foods, whereas quaternary ammonia compounds that exceed the manufacturers' recommended levels are bordering on toxicity.

The use of chemical sanitizers containing quaternary ammonia should be limited to water supplies having less than 500 mg/l calcium and magnesium hardness.

With the advent of multiple chemical sensitivities (or chemically sensitized persons) as a medical reality (Ashford and Miller, 1993), exposure to concentrations above those set by law or rule is unadvisable from both a legal and an ethical standpoint.

Accurate methods for dispensing chemical compounds and measuring concentrations are needed. The well-meaning dishwashing employee who thinks an extra splash or two of sanitizer in a sink is beneficial may actually be exposing himself and guests to potentially harmful chemical substances without realizing it.

Although outside entities such as chemical sales companies can be relied on to some extent to assist with chemical control programs, it is ultimately the owner who is responsible to ensure that chemical concentrations are effective for the purpose needed and that they are safely used.

Storage: Chemicals should be stored in areas that are under the control and supervision of management. Closets are occasionally used, and store rooms where other items such as dry goods are kept are typical places to store chemicals. Large containers of sanitizers are needed in close proximity to the ware washing areas, and it is common the to several barrels of chemicals stored on the floor in these areas.

A separate rack of shelves provides a good storage method for smaller containers of chemicals as long as no food item or food-related item (paper

goods, bags, etc.) is stored or prepared beneath. Insecticides, cleansers, and sanitizers must be stored separately or in a way that precludes the possible mixing of these items on the shelf. Storage of concentrated chemicals in the food production area is not advised because foods may be easily contaminated.

After dilutions are made, solutions are generally used in plastic spray bottles; the use of old food containers to store chemicals is ill-advised and leads to many cases of poisoning.

- *Access Restriction:* The unauthorized use of chemical agents in the production environment should be a concern for commercial food service managers. There are federal guidelines enforced by the Occupational Safety and Health Administration (OSHA) covering potential exposure to employees in the workplace. It is dangerous for untrained persons to be using hazardous chemicals of any type in a commercial food service environment. Locked storage rooms are often an attempt by management to control the usage of items of many types including expensive food items and costly liquors. It is therefore reasonable to expect that chemicals can be controlled and kept under lock and key when necessary.
- *Training:* Training is fundamental to any type of management control system and especially chemical application. Employees must be trained in the chemicals commonly needed and the standards for labeling, dilution, testing, storage, usage, etc. Once trained, employees may be authorized to have access to the storage areas and to apply the chemicals.

Ware washing Foodborne illness outbreaks are not usually traced back to poor ware washing procedures, but it is easy to see how soiled utensils can contaminate foods and how customers can be exposed to pathogens on unsanitary tableware. Numerous items become soiled during food production, and clean and sanitized items are needed for safe food preparation. Multiuse utensils must be washed between customers and are the most significant burden on the ware washing process. Utensils used to prepare, cook, and store foods are also required to be cleaned between uses and at regular intervals. Finally, equipment becomes soiled during food activities, requiring ongoing cleaning.

The employee assigned the duty of dishwasher is highly important to a sanitation program because this function, if done incorrectly, adds to the contamination of food preparation and eating utensils and food processing equipment. Commercial dish machines take considerable technical expertise to operate and are also very expensive to purchase, maintain, and repair.

The appropriate sequence of events for cleaning and sanitizing of food equipment and utensils is rinse, clean, rinse, and sanitize. After the cleaning and sanitizing process, it is important to allow the utensils to drain and air dry before storage. In general, the cleaning and sanitizing process for multiuse utensils such as dishes, flatware, glassware, and food preparation utensils is either manual (using a three-compartment sink) or mechanical (using a dish

washing machine). Either spraying or manual washing with a bucket accomplishes the cleaning of large pieces of equipment.

- *The Three-Compartment Sink Method.* Three sinks are required to accomplish each step in the cleaning and sanitizing process. The sinks must be separated by partitions to prevent soiled and detergent-laden water from coming in contact with the rinse water or sanitizer.

  Washing is done with the hottest water possible (110–120°F), agitation, and the proper level of detergent. Different food soils respond differently to various chemical compounds. Thus degreasers, abrasive cleaners, presoaks, and other agents are commonly used.

  Once items are visibly free of soil they need to be rinsed in clean water (no soap film or bubbles) to remove soap film.

  Sanitizing, the final step, is done by complete immersion in hot water [at least 171°F (77°C)] for at least 30 s or in a solution of a chemical sanitizer (in accordance with the EPA-approved manufacturer's label use requirements at an effective concentration and contact time as specified in the 1999 Food Code). The most commonly used chemical sanitizers in commercial foodservice are chlorine and quaternary ammonium compounds and, to a lesser extent, iodine-based (iodophors) compounds. If hot water immersion is used as a sanitizing process, a booster heater is usually installed on the sink. Suitable protective devices (e.g., long handled tongs, insulated rubber gloves, aprons) must also be provided for handling utensils and equipment.

  Cleaned and sanitized equipment must be allowed to drain and air dry before storage. Thus the triple sink should be equipped with two drain boards, at opposite sides, to allow separation between clean and soiled items. The drain boards should be at least 36 in. long and be sloped to drain. In smaller establishments, where space constraints generally preclude large drain boards and dish tables, racks can be used as well as movable dish tables.
- *The Mechanical Dish Washing Method.* In mechanical dishwashing machines, cycles that wash and rinse are required to meet certain time and temperature requirements dependent on whether the final rinse uses hot water or a chemical sanitizer.

  In ware machines using chemical sanitization, a wash temperature of 120°F (49°C) is generally recommended. The final rinse, however, must be appropriate for the chemical sanitizer [75°F (24°C) for chlorine sanitizers]. In addition, the machine must be operated at such conditions to ensure that the utensil is subjected to the required concentration and contact time for the sanitizer used [e.g., 50 ppm chlorine for at least seven (7) seconds]. The sanitizer concentration should be monitored regularly with appropriate test kits.

  For machines that use hot water as a sanitizer, a final temperature of 160°F must be reached on the surface of the utensil. Water temperatures of

150–165°F for washing, 170°F for the first rinse, and 180°F for the final rinse are usually necessary. Some smaller machines use two cycles, and in this case both the wash and rinse cycles must maintain 165°. Properly calibrated thermometers must be installed in the machine: thermometers for water must be accurate to ±3°F. The sensor in a hot water sanitizing machine must be positioned so as to detect the water temperature in the manifold or pipe that feeds water to the spray arm.

Jets in the wash arm spray water and chemicals onto the surface of the item for a specific period of time, as governed by the timer in stationary rack systems. Jets and the pump intake screen may become clogged, and jets may also be out of adjustment and spray arm caps may dislodge. The pattern of spray water is important for achieving uniform temperatures.

Both wash arms and screens must be washed at regular intervals. Each cycle in a dish machine has a specific time that is quite important, equally important as the temperature and concentration of chemicals provided. Machines that have rack conveyors must have the rack conveyor speed properly timed to insure exposure of the item to the various cycles for the correct amount of time.

Because there is much variability in the design and function of mechanical ware washing machines, a plate affixed to the machine (operating data plate) is required to contain the specifications for the operation of the machine.

The placement of utensils in the dish baskets must orient the utensil properly to ensure that that the entire utensil is either brought to 160° or is treated with 50 ppm chlorine for the required 7 seconds. Finally, the wash and rinse water must be dumped and refilled on a regular basis to keep from depositing food soils back onto the items.

Machines using a chemical sanitizer are required to have an alarm that alerts the operator to low sanitizer levels or to the failure of the sanitizer pump.

Storage of clean utensils and equipment Clean equipment and utensils must be stored away from areas of contamination. The usual practice is to store the items in large bus tubs or other containers on shelving until used. This practice is satisfactory as long as precautions are taken to protect the items from dust and debris. Cups and glasses should be stored inverted on food contact surfaces. If utensil racks are stored in open areas, covers should be placed over them to keep foreign matter off.

Use of wiping cloths The use of wiping cloths to clean food soils and to control spillage may result in cross-contamination unless proper procedures are followed. Wiping cloths should never be used to wipe hands or surfaces that may have been contaminated by raw animal foods or body waste. If food contact surfaces are not contaminated, or if they are only soiled by RTE food debris, they may be wiped clean with a clean/sanitized cloth. In this case, the

food contact surfaces so soiled must be washed, rinsed, and sanitized at least every 4 hours to preclude the growth of harmful microorganisms. Wiping cloths should be laundered daily or as necessary to prevent contamination of food and food contact surfaces.

Cloths or rags used on non-food contact surfaces (e.g., cleaning spills on floors and walls, cleaning highly contaminated surfaces such as bathroom fixtures or grease areas) should be laundered after each use. Placement of these cloth back into the sanitizer will only dilute the sanitizer and contaminate the solution.

Pest management Although CDC data do not generally list insect or rodent vectors as one of the top causes of foodborne illness outbreaks, it is sound public health and good business to minimize entry and eradicate these pests wherever and whenever they are found. Pests have long been known to be vectors of many types of illnesses. In 1998, the FDA reported that the presence of disease-causing flies in a food-handling establishment constituted a potentially hazardous situation (Olsen, 1998). Rodents (rats and mice) are good vectors for many communicable diseases and are a primary reservoir for such food-related illnesses as *Salmonella* (Mehan, 1984; Weber, 1982). In addition, dead and decaying bodies of rodents are highly contaminated with bacteria, and bacteria and virus can also be isolated from their droppings.

Finally, there are other aesthetic factors associated with the presence of pests. Consumers are incensed when pests or their signs are noticed in a commercial food service establishment. This may result in decreased sales and mark the establishment as low quality. Insects and or the droppings of pests in foods are extremely offensive to consumers and may result in the legal consequences of civil and administrative actions regardless of whether they have caused injury or illness to a particular consumer.

Foods in storage and preparation, and the areas they are and prepared in stored in, often provide a food supply and even a harborage potential for pests. Additionally, the ware washing area provides warmth, food, water, and good harborage conditions if walls and ceilings begin to deteriorate because of water damage. The currently accepted approach to minimizing and controlling pests is to use integrated pest management (IPM). IPM is a pest management system that is accomplished by recognizing the biological needs of pests for food and water and the breeding habits of pests and by controlling harborage and points of entry into the structure, thus minimizing reliance on hazardous chemicals. Once outer openings are effectively sealed and elimination of harborage sites has been accomplished, it is necessary to eliminate, as much as possible, any source of food and water for pests. Monitoring typical places of concealment and breeding favored by pests then allows a quick response if pest activity is identified. Traps, bait, glue boards, and other insect control devices, when strategically placed, help in monitoring and controlling pests.

If signs of pests are noted, a pest control operator (PCO) should be dispatched immediately to analyze the situation and recommend immediate

action. The PCO should be seen as part of the management team in situations like this and should be provided with any assistance necessary. Such assistance should include a diagram or schematic showing the layout of the establishment and complete access to all food preparation areas and equipment.

The goal of a pest management program is elimination of pests from the facility and creation of a pest-free environment. Although these are difficult goals to reach, they are obtainable.

Facility construction and repair Sound structures provide protection for the food environment and allow effective pest control efforts. Poorly constructed and maintained structures, while being a potential food safety problem, also result in fire and life safety issues.

All roofs, walls, and floors should be in stable condition and capable of withstanding normal forces and loads. Windows and doors should be in good repair and should open and close without difficulty as needed. Floor and wall junctions are usually coved to facilitate cleaning by the use of coved baseboards. The surfaces of floors must be durable and easily cleanable. Several types of floors are approved, with the most common surfaces being quarry tile and linoleum tile floors. Bare concrete and wooden floors make poor choices and inhibit cleaning. Surfaces of walls can vary from painted surfaces to masonry, but the key is smooth and easily cleanable surfaces. Walls are often damaged by equipment and should be patched to prevent pests from gaining entrance and for fire prevention and life safety purposes.

Premises maintenance The conditions outside the structure influence the conditions inside the structure in several ways. One principal influence is in the area of pest control. High grass and weeds, standing puddles of water, and food scraps, while unsightly, also favor pests. All bushes should be trimmed back, and all conditions that influence harborage or points of entry, such overhanging tree limbs that come close to the roof, should be evaluated.

Facility design Sanitary food handling practices are more difficult to achieve in a poorly designed facility or one that is too small for the operations intended. In addition, having an insufficient number, construction, and design or inappropriate placement of equipment makes cleaning and sanitizing, as well as other cross-contamination controls, more difficult.

In most jurisdictions, new commercial food service operations must submit building plans to a local regulatory agency (e.g., health department or county and municipal building, electrical, mechanical, and zoning inspection divisions). Before a license to operate is issued, an inspection is usually conducted to determine whether the facility was constructed and equipped according to the plans approved by these various governmental agencies. Changes in menu, seating capacity, or the design of food preparation areas or relocation or installation of equipment can trigger a plan review in many regulatory programs.

TABLE 26.10. The Recommended Kitchen and Storage Ratio to Total Square Footage.

Style	Kitchen and Storage Area
Limited menu	20–30%
Family	30–40%
Gourmet	40–50%

Facility designs must take into account the number and capacity of the equipment as well as the layout of equipment placement. Not leaving sufficient space between equipment results in a safety hazard to employees as well as an increased likelihood that cross-contamination of foods will result. Placement of equipment is also vital to proper ventilation and waste disposal. Although there are no specified dimensions for commercial food service preparation areas, it is recommended that the preparation area be sized on the basis of an analysis of the menu and the anticipated number of persons served per hour. The recommended kitchen and storage ratio to total square footage is presented in Table 26.10.

A method for facility design and layout has been described (HITM, 1997). The layout should follow the flow of foods as well as processes (e.g., food preparation, employee traffic, waste disposal). The major functional areas of a commercial food service establishment include waste storage (inside/outside), receiving, kitchen, cleaning and sanitizing (ware washing), employee facilities (restrooms, locker rooms, and break areas), bakery, cold and dry storage, salad preparation area (pantry), cooking and service staging area (expediting), and customer service.

Employee facilities Employee restrooms, locker rooms, and related employee facilities as well as public restrooms can easily become contaminated. Customers are very conscious of conditions in the bathroom and often equate this with food safety even though there is no particular risk factor identified by CDC for soiled walls, floors, or fixtures. Even if soiled bathroom surfaces are not a recognized contributing factor in foodborne outbreaks, the presence of human wastes and the potential for contamination still should not be ignored.

Bathroom surfaces should be constructed of durable, smooth, nonporous surfaces. Lighter colors make it easier to see contamination, and lighting should be bright to facilitate cleaning. The recommended step-by-step cleaning method for a bathroom is presented in Table 26.11.

Ventilation A well-ventilated commercial food service establishment is not only more comfortable for employees and guests but also more easily maintained in a clean, sanitary manner. In addition, venting of food preparation-related gases, fumes, vapors, smoke, grease, and particulate matter is necessary for employee health and safety reasons.

TABLE 26.11. Recommended Step-by-Step Cleaning Method for a Restroom

- Assemble supplies
- Mix solutions of detergents and sanitizers
- Place restroom out of order
- Empty all trash and ashtrays
- Fill toilet roll and paper towel dispensers
- Wipe dispensers
- Clean mirror, frames, light fixtures
- Scour sinks and faucets
- Rinse and dry
- Clean sink pipes
- Dry urinal bowl and pipes
- Wet mop floor and damp dry
- Clean walls and door inside and out
- Wipe partitions
- Clean air vets
- Flush toilets and clear clogs
- Wash and rinse inside and outside of bowl
- Dry toilet seat, pipes, and bowl
- Wash and rinse inside urinal
- Wipe outside urinal bowl and pipes

All bathrooms require an air exchange to the outside. No specific rate of exchange is mandated in the Food Code, but bathrooms are to be maintained free of odors to the extent possible. Fans and screened windows are usually sufficient.

Carbon monoxide emissions from cooking appliances and all products of combustion must be vented to the outside. This is done through the use of a hood placed over cooking appliances. The National Fire Prevention Association's Life Safety Code requires that all hoods be designed as fire safety devices and be capable of withstanding fire conditions. Exhausting of smoke and grease-laden vapors to the outside must be through a filter installed in the hood to reduce the fire potential. Exhaust fans create the possibility of negative air pressure in the kitchen and therefore, should be designed with make-up air to replace exhaust air at 85–90%. This also creates a slight negative pressure that prevents cooking fumes from traveling into the guest areas. The make-up air must be balanced, however, to prevent contaminants from the outside being pulled into the facility whenever doors are open.

Lighting Adequate lighting is essential for safe preparation of foods and for other functions in a commercial food service establishment. The brightest lighting should be in areas in which employees are working with food and mechanical equipment such as slicers, mixers, and choppers and wherever knives are being used for cutting foods. Mistaking chemicals for food products can occur when the lighting is poor, and good lighting also enhances foreign object control.

The Food Code requires 540 lux (50 foot-candles) of light in high-hazard areas and 220 lux (20 foot-candles) where low-hazard work, utensil washing, or general cleaning is occurring. The lowest illumination allowed is 110 lux (10 foot-candles), which is only permitted in storage areas.

Overhead lighting is subject to breakage in several ways, and falling or exploding glass fragments can be dispersed over a wide area; when this occurs all foods and equipment underneath are subject to contamination. All overhead

lighting must be shielded. Tubes that completely cover exposed bulbs and fixtures with securely mounted panels are two basic measures that can be taken. Shatterproof bulbs are also available that prevent the glass fragments from becoming dislodged should the bulb be broken or explode. All incandescent lights and quartz light fixtures must have similar protection.

Garbage disposal Waste materials produced during food preparation must be stored in the facility in a way that prevents cross-contamination or attracts pests. Thus garbage and trash should be removed on a frequent basis. Sufficient garbage cans should be available, and constant surveillance of dumpster areas with prompt attention to any spilled food wastes is absolutely necessary. Once removed, food wastes should be bagged in plastic bags, tied or sealed, and placed in dumpsters. The dumpster lid should be closed or the side door closed each time wastes are deposited.

The dumpster itself should be placed on a cement pad to facilitate cleaning, and the pad should be sloped to drain into a sanitary sewer, when permitted. Unprotected connections to the sanitary sewer allowing rain to enter are prohibited by some utilities. When sanitary sewer connection is prohibited, the wastewater and swill from dumpsters often cause unsightly conditions in the dumpster area. Self-contained trash compactors only partially alleviate this problem, and many of these will leak. If the area is well drained, a hose can be used to wash down the dumpster pad into the storm sewer, if permitted.

Dumpsters that allow rainwater to collect become very heavy and are even more likely to create nuisances. To avoid this, dumpster companies often remove the drain plugs, which adds additional problems in maintaining the dumpster areas.

Dumpsters and garbage cans must be cleaned on a regular basis. Food wastes that stay on the surfaces of these containers are a perfect food source for pests and create odors. Can washing areas that are curbed and provided with hot and cold running water are often placed outside the building or in a closet area to allow garbage cans to be cleaned. When damaged or no longer cleanable, dumpsters can usually be exchanged by the supplier.

Managing the Cooking Control Point

As discussed in Part II, most microbial pathogens, including bacterial vegetative cells as well as parasites and viruses, are generally labile to the heat treatment involved with an adequate cooking process. Heat resistance, however, does vary. For example, undercooked chicken and undercooked eggs have been linked to *Salmonella* (CDC, 1996) and undercooked ground beef has been linked to *E. coli* O157:H7 infections (CDC, 1993). There is also some evidence that certain viruses may survive temperatures ordinarily lethal to bacteria. Bacterial spores are more difficult to inactivate than vegetative cells and require pressure cooking for inactivation. Thus spores will remain after cooking (Shigehisa et al., 1985) under atmospheric conditions. Sublethal cook-

ing, will, in fact, "heat shock" spores, which causes "activation," or conversion to vegetative cells. These vegetative cells have the ability to grow and multiply if conditions are suitable. Many bacterial toxins are heat stable (e.g., staphylococcal enterotoxin, *Bacillus cereus* toxin). Thus, cooking cannot be a reliable means of inactivating these toxins.

Cooking methods vary, but baking, frying, grilling, broiling, boiling, steaming, microwaving, barbecuing, and roasting are frequent techniques in commercial food service. Although primarily viewed by chefs as a culinary technique, cooking plays a vital role in the safe preparation of food. Cooking of raw animal foods such as eggs, red meat, seafood, and poultry, from a HACCP perspective, is always a critical control point because failure of the cooking process has a high probability of resulting in an unacceptable level of contamination surviving to reach the consumer.

Cooking standards based on the destruction of *Salmonella* are generally used because of the relatively high heat resistance of this microorganism. *E. coli* destruction values are used for ground beef standards. Survival of cells in the cooking process is also influenced by the amount of time they are exposed to a given temperature, with complete destruction of most pathogens occurring at 165°F (74°C) within 15 seconds.

Although 165°F (74°C) would seem the ideal temperature to cook foods, foods range widely in their flavor and texture at this temperature; eggs cooked to this temperature are leathery, and steak cooked to 165°F (74°C) would be too well done for most tastes. It is necessary, therefore, to take into consideration the culinary aspects of food, and various time-temperature relationships exist that cause the required reduction of microorganisms. The U.S. Department of Agriculture (USDA) Food Safety and Inspection Service (FSIS) generally requires at least a 5-log reduction in *Salmonella* (beef) and in some instances (poultry) a 7-log reduction. This takes into consideration the initial predicted level and the nature of the substrate. It is known that foods with excess fat require higher temperatures to inactivate *Salmonella* than very lean meats, and dry foods are protective of *Salmonella* during cooking (Jay, 1992).

All cooking temperatures take into consideration the internal temperatures of the food as a guide for the doneness and safety of the product. By reaching a sufficiently high internal temperature, one is assured of both the destruction of organisms that may be in the muscle of meat or internalized in the food as well as those pathogens that may have been deposited on the surface through processing and handling. Commercial food service cooking standards reference the internal temperatures of foods and a corresponding time to inactivate harmful agents. When required times are low, such as 15 seconds, once temperatures are reached it can be assumed that after cooking temperature heat rise occurring naturally will ensure sufficient destruction. The quality known as "doneness" is quite subjective, depending on tastes, preferences, cultural influences, and probably several other factors. There are preferences for cooking temperatures both higher and lower than the minimum temperatures referenced in the Food Code. The FDA Food Code recommands the posting of signs warning con-

sumers of the dangers of undercooked animal foods; however, there is resistance to adoption of this part of the Food Code because of fears that there will be an adverse consumer reaction and loss of confidence in restaurants. Consumer warning signs remain as one impediment to more universal enactment of the Food Code. Nevertheless, it is common for commercial food service establishments to serve undercooked animal foods when requested to do so, although many refuse to serve undercooked ground beef.

The preventative measures and recommended practices involved in food safety assurance at the *Cooking Control Point* are discussed below.

Safe internal temperatures Foods vary in composition, so no single cooking temperature is going to give the culinary quality desired and the safety needed for all foods; there are various combinations of time and temperatures needed to inactivate pathogenic vegetative bacteria.

Eggs and egg products If eggs are cooked immediately and served, they must reach an internal temperature of at least 145°F (63°C) for at least 15 seconds to inactivate *Salmonella enteritidis*. Eggs that are broken and pooled together for later use tend to be more hazardous than individual eggs cooked immediately (St. Louis et al., 1988). For this reason Food, Code standards require eggs not for immediate service to be cooked to 155°F (68°C) for 15 seconds. Foods that contain eggs as an ingredient (e.g., binders, lasagna and quiche fillings, crab cakes, scrambled eggs), if held for later service after cooking, require 155°F (68°C) for 15 seconds as well. Fried eggs served with a liquid yolk ("sunny-side up") generally have not reached the safe internal temperature and, thus, do carry a food safety risk.

It is recommended that pasteurized egg products be substituted for raw eggs in foods that are not typically cooked at 145°F (63°C) for 15 s, such as fried battered foods, Caesar salad dressing, and béarnaise sauce. The use of "in-shell pasteurized eggs" is a growing trend that will conceivably be beneficial for egg safety and has been recommended by the FDA. Although safer than raw eggs, foods formulated with these products still require proper cooking.

Seafood products All seafood (including fish) must be cooked to 145° for 15 seconds (National Fisheries Institute, 1991). Bivalve mollusks (e.g., clams, oysters, mussels, and cockles) are benthic organisms (filter feeders); thus they have an increased potential for the accumulation of virus and bacteria as well as potentially toxic algae. As discussed in Chapter 2, most vegetative cells of bacteria are destroyed by cooking temperatures of at least 145°F (63°C) for 15 seconds. However, toxins will not be destroyed under these cooking conditions, and there is some question as to whether they are sufficient to inactivate certain viruses.

Consumers who consume raw or lightly cooked seafood are at a heightened risk for infection. For parasite destruction, fish to be used for sushi and related products must be deep frozen either at −31°F (−35°C) for 15 hours in a blast

freezer or at −4°F (−20°C) for at least 7 days in a conventional freezer. However, these freezing conditions would not completely destroy bacteria and viruses or inactivate toxins. A consumer advisory warning against raw shellfish consumption is required by regulation in Florida and several other states.

Beef products Improperly cooked beef steaks and roasts are not as likely to cause disease as improperly cooked ground beef. Steaks and whole muscle cuts of beef must, however, be cooked to at least 145°F (63°C) internal temperature for 15 s to ensure destruction of the organisms on the outside of the meat as well as any internal pathogens. A special exception is made for rare roast beef, which can be cooked to a range of time and temperatures beginning with 130°F for 121 minutes to 145°F for 3 minutes.

The failure to thoroughly cook ground beef by the commercial food service industry has resulted in catastrophic consequences for consumers because of *E. coli* O157:H7 contamination (Bell et al., 1984). Therefore, food service establishments should be especially cautious with the cooking of ground beef and should monitor time and temperatures very carefully. Ground beef must be cooked under the following conditions: 145°F (63°C) for 3 minutes, 150°F (66°C) for 1 minute, or 155°F (68°C) for 15 s.

Pork products Required cooking conditions for pork have undergone several changes in various Food Code editions. Many in the commercial food service sector cook pork well beyond the minimal temperatures required to destroy harmful bacteria and parasites like *Toxoplasma gondii* and *Trichinella spiralis*. The minimum cooking temperature is 145°F (63°C) for 15 seconds, but consumers typically reject pork unless the meat is thoroughly cooked to a white color, which requires temperatures above the minimum.

Vegetables Vegetables that are to be placed on a hot holding area are required to be heated to 140°F (60°C). The purpose in this case is not necessarily just to kill pathogens but to also ensure that heating is thorough to avoid hot holding temperatures in the danger zone.

Use of thermometers Although often used, the color and appearance of cooked foods is an unreliable method for gauging the thoroughness of cooking. For example, hamburgers may appear to have some pink color even when cooked to 155°F (69°C), whereas some ground meat patties that have not reached this temperature have no pink remaining (Fein, 1998).

The proper use of thermometers and other temperature-sensing devices is critical to control the cooking control point. Thermometers used for controlling the cooking temperatures of foods in commercial food service must be adequate for the job at hand (USDA, 1997). Thin foods need to be checked with thin-probed thermometers with the probe entering from the side of the item. The use of tip-sensitive thermometers for thin foods is also critical because thin foods do not allow sufficient insertion of a thick probe.

The most commonly used temperature-measuring devices used in commercial food service are bimetallic thermometers, thermistors, and thermocouples. Whichever one is used, it must be accurate to $\pm 2°F$ and must be checked for accuracy regularly by immersing the sensing portion in ice water, boiling water, or a combination of both. If the device can be calibrated, then it should be calibrated to 212° in boiling water and 32° in 60% ice-water slurry on a routine basis and records of such calibration should be maintained. The frequency of calibration (depending on the use) should be at a minimum of once per week. Daily calibration is necessary when the thermometer is being used continually. Temperature-measuring devices must be frequently cleaned and sanitized by an approved method, especially when changing between raw and cooked or RTE foods and between different species to avoid cross-contamination.

Bimetallic thermometers The bimetallic thermometer is the standard thermometer in the commercial food service establishment and is in common use. These thermometers are easy to use and can be carried in the shirt pocket of food handlers. However, these devices are only suitable for thick foods, for taking temperatures of foods in containers, and to monitor water and air temperatures. Additional limitations concerning most bimetallic thermometers include a propensity to go out of calibration easily when dropped or roughly handled, low sensitivity at the tip (although tip-sensitive models exist), and the relatively thick (1/8 in.) stem.

Thermistors Thermistors are commonly used because of their inexpensive price and portability. They also are relatively easy to use and can be carried in a shirt pocket. Although they have thick probes, they are tip sensitive and are thus more sensitive than most bimetallic thermometers. A disadvantage of these devices is their responsiveness in that they do not reach a stable temperature for at least 15 seconds after insertion.

Thermocouples Although more expensive than bimetallic thermometers or thermistors, thermocouples are by far the most effective temperature-measuring device available. Thermocouples are tip sensitive, have probes of various thicknesses, and are generally very responsive and accurate.

Undercooked foods by customer request Customers who request undercooked animal derived foods should be made aware of the risks involved. Many establishments indicate on their menus that the customer is responsible if he/she orders undercooked foods, but this may not be enough to ward off all liability. It is best for commercial food service operations to follow the Food Code standards for cooking temperatures. The Food Code has provisions for signage warning consumers of the dangers of undercooked foods, but these signs are very controversial and not acceptable to many in the industry.

States where oyster consumption is high, have experienced hundreds of deaths due to vibriosis from consumption of raw oysters. For this reason, con-

sumer advisory warnings for at-risk customers are mandated. Where such mandates are in place, the sign must follow the exact language provided in the regulation and be prominently displayed. Failure to post the sign is both a regulatory and a liability issue.

Microwave cooking The heating rate of a microwave oven is based on the size of the magnetron tube. The power level of these tubes runs from 500 to 2200 watts. Because of these features, microwave cooking takes a little practice and some skill. Microwave ovens work best for single-portion foods, for small orders of vegetables, and for heating breads, rolls, pies, and the like. If raw animal foods such as eggs, beef, fish, or pork are cooked in a commercial microwave, certain standards must apply to ensure the safety of the foods. Foods must reach 165°F (74°C) when cooked in a microwave. Other recommended procedures include the following.

Microwave-safe container An ideal microwave cooking vessel will transmit microwaves through the container to the food and should not absorb or reflect the microwaves. The best containers are smooth, round, and able to withstand both high and low temperatures. Glass, glass ceramic, and paper are well suited for use in microwave ovens because they do not absorb heat. Plastics also transmit microwaves well and do not absorb heat. However, hot foods may cause some plastic materials to melt.

Covered container Containers with lids are ideal because the lids conform to the vessel and help keep evaporation to a minimum. As moisture evaporates from foods, the surface cools; this cooling may affect whether surface contaminants are inactivated. If the container does not have a lid, wax paper or plastic film wraps are useful substitutes. Covering the foods also increases the cooking effect created by steam released from the food.

Heat energy can be maintained by keeping the cover on the containers after heating in a microwave oven. Foods continue to cook an additional 2 minutes after the microwaves have ceased; it is best to make use of these properties to ensure more thorough cooking.

Stirring or rotating Microwave radiation tends to be dependent on a number of variables including the shape and dimensions of an object. By rotating the foods through 360°, a more even distribution of energy is obtained. Stirring foods helps to distribute heat more evenly in the product. Unless a carousel is used, foods should be rotated about halfway through the cooking process and stirred.

Managing the Cooling Control Point

The failure to adequately cool PHFs is usually listed as the most prevalent factor associated with foodborne illness outbreaks (CDC, 1990a), the reason

being that time and temperature abuse of these foods during the cooling step allows harmful bacteria to proliferate, giving rise to both intoxication and infections. Therefore, foods must be cooled to 41°F (5°C) as rapidly as possible. Because of the hazardous nature of the cooling process, cooling of PHFs is considered a CCP in most HACCP systems.

Safe cooling of large quantities of hot foods in a commercial food service establishment requires close supervision and sufficient equipment and manpower. The procedure of placing large quantities of hot foods in deep pots in coolers is a very hazardous practice that results in foods being in the danger zone for extended periods very likely exceeding 12 hours. Food Code standards require foods in the danger zone more than 4 hours to be discarded, forcing health authorities to condemn these foods, yet the practice continues because of lack of equipment, space, manpower, and knowledge about the hazards. With some planning and standardized methods, safe cooling of foods can become efficient and routine.

The preventative measures and recommended practices involved in food safety assurance at the *Cooling Control Point* are discussed below.

Time and temperature controls Foods must pass through the optimum growth temperatures for mesophilic pathogens during cooling. Therefore, it is imperative to control the amount of time foods spend at these temperatures. Hot foods must be brought through the danger zone, 140°F (60°C) to 41°F (5°C), within 6 hours if a two-stage cooling method is used. A two-stage method requires that foods pass very quickly through the extreme danger zone of 140°F (60°C) to 70°F (21°C) within 2 hours; if this is accomplished, bacterial growth is minimized and the foods can be cooled from 70°F (21°C) to 41°F (5°C) within 4 additional hours.

Foods that require cooling from room temperature include salads, such as tuna, that are normally prepared from room-temperature ingredients. Although no longer required by the Food Code, it is still good practice to prechill the mayonnaise and other ingredients to enhance the cooling process. When foods are starting at room temperature and then cooled, the Food Code requires a 4-hour time frame to reach 41°F (5°C).

To ensure that foods have met safety standards it is necessary to use a calibrated thermometer to test foods on a basis consistent with the monitoring frequencies outlined in the facility's HACCP Plan.

Factors affecting cooling of foods The cooling of foods is influenced both by the geometry of the container and the volume of the foods in the container. The nature of the foods themselves is also a factor, with thicker, starchy, and fatty foods taking longer to reach safe temperatures. The nature of the cooling environment is also critical, adequate air circulation and colder temperature increasing the cooling rate. Shelves with slats allowing air circulation and stainless steel rather than plastic containers will also enhance cooling. Several methods are commonly used in commercial food service to increase the cool-

ing rate, and many are mentioned specifically in the Food Code, but room-temperature cooling, even for relatively short periods, is considered hazardous and will result in regulatory action when found.

Portion size In general, in cooling large portions of foods, the cooling rate decreases because of an insulating effect beyond a depth of approximately 2 inches. Therefore, it is recommended that foods be cooled in small rather than large quantities to increase the cooling rate. Some recommended practices for increasing the cooling rate include using smaller quantities of foods and preparation closer to service; subdividing foods into smaller quantities and thinner portions (e.g., slicing large roasts); and cooling in shallow pans (preferably metal for better conduction) that are less than four inches in depth to allow air to circulate around products more effectively.

Agitation It is recommended that, where feasible, foods be stirred every 15 min during cooling. The mixing action that occurs during stirring tends to allow heat to be more uniformly spread throughout the product, enhancing cooling and preventing hot and cool zones. Mixing also exposes more foods to the surfaces of the container, where cooling is most rapid, and to the rapidly cooling surface of the food (due to evaporation of water).

Food location in cooler As discussed above, the use of uncovered containers for food in storage is normally viewed as poor practice. However, in coolers, the top shelf may be used to cool uncovered food products. This method is useful for thin foods such as steaks, fillets, bacon, patties, and the like. If the food is spread evenly on a sheet pan and exposed to cold circulating air currents, the cooler itself will allow the Food Code standards to be met. It should be pointed out that most coolers are designed to maintain product temperatures and are not designed to rapidly cool large masses of hot foods in commercial food service establishments.

Other cooling methods In addition to the more traditional method of cooling foods in a refrigerator box or cooler, other alternatives are used in commercial food service. Some of these are listed below:

Ice baths Ice can be used to cool foods. In this procedure, crushed ice and water is mixed at an ice-to-water ratio of 60:1 or 6:4 and containers of foods are placed in the ice bath. Where feasible, foods should be stirred every 15 minutes to accelerate the heat transfer. In this way, foods can easily be brought from 140°F (60°C) to 70°F (21°C) in the first stage of cooling. Once temperatures reach 70°F (21°C) it may be possible to place foods on the top shelf of a cooler and reduce the temperatures to the 41°F (5°C) mark within the remaining 4-hour period.

Another innovation is to place foods in sealed plastic bags and submerse them in the ice bath. This may work for meats and for soups, gravies, sauces,

and other liquid foods as well. Ice baths can be moved into a walk-in cooler for further enhancement of the cooling process.

Direct addition of ice If done in a sanitary manner, ice may be directly added to sauces and many types of liquid foods such as soups and gravies. When doing this, the formulations should be adjusted to compensate for the additional water added in the form of ice.

Blast chillers A blast chiller blows cold air (38°) at a high volume (1000 cfm) over food products while they either tumble in a stainless steel drum or lie stationary on racks. Blast chillers are becoming very popular in large catering operations, cook/chill system, and in the institutional kitchen but are not widely applied because of their high price (in excess of $15,000 at this time).

Other cooling innovations A recent innovation is the use of a plastic paddle that is filled with water and frozen. The frozen plastic paddle is placed in the food product to reduce the temperature of the food item. Increased cooling efficiency is possible if the plastic paddle is used in combination with immersion in an ice bath.

Food cooling containers are also available that contain a gel that freezes at low temperatures. This frozen container provides an effective heat sink for rapidly cooling foods.

Managing the Reheating Control Point

Foods are reheated in commercial food service establishments for several reasons. Cold foods that are normally served hot must be rethermalized for culinary reasons. These foods may have been cooked and cooled or received cold. Hot foods may have fallen into the danger zone unintentionally, and reheating may be necessary to ensure the safety of the food. Reheating may only be relied on as a safety measure if the foods have been in the hazardous temperature zone for less than 4 hours.

Foods that have cooled and will be reheated in large batches for hot holding require specific reheating standards. Foods that have been cooled and stored properly will have little risk associated with them, and if service is immediate they may be reheated to any temperature. Reheated foods pass through the danger zone, so it is important that time standards be in place to ensure that foods do not remain in the danger zone for extended periods. Because reheating implies that the foods were previously cooked and cooled, the reheating step is considered to be a repasteurization to control the vegetative cells that may have been allowed to contaminate or proliferate during preceding steps. Outgrowth of *Clostridium perfringens* can be addressed at this step because the vegetative cells are the infectious agents and they can be destroyed by heating; *Salmonella* and possibly other pathogens on products due to cross-contamination after cooking can also be destroyed. For this reason most HACCP systems will include the reheating step as a critical control point for foods that have been

previously cooked on premises, cooled, and reheated for hot holding. It must be understood that heat-stable toxins and spores will not be inactivated, however.

The preventative measures and recommended practices involved in food safety assurance at the *Reheating Control Point* are discussed below.

Time and temperature Unless received precooked in a package from an approved commercial food processing facility, all PHFs must be reheated to 165°F (74°C) within 2 hours if reheating is for hot holding purposes. RTE foods received in a package from a commercial food processing plant need only to be reheated to 140°F (60°C) if they are being held hot. Fruits and vegetables must also be heated to 140°F (60°C) before being placed on a steam table. If foods are to be served immediately, no particular reheating temperature is required.

Equipment used for reheating foods The types of equipment used for reheating are the same as the original cooking devices normally used in cooking. Preventative measures and recommended practices regarding these devices were discussed above. Although reheating in steam tables or microwave ovens is done in certain facilities, there may be potential problems associated with using these devices for this purpose. Steam tables have been designed primarily for hot holding. With the exception of higher-efficiency gas-fired models, steam tables may not have the heating capacity to reheat large masses of cold foods. Microwave ovens also have certain limitations that should be recognized. Reheating foods in a microwave oven requires that all parts of the food reach 165°, and the same precautions that apply to cooking apply to reheating.

Managing the Hot Holding Control Point

PHFs must be held at temperatures outside the danger zone at all times (other than necessary times of preparation and service). Foods are typically held for several hours in various types of hot holding equipment such as steam tables, chaffing dishes, bains marie, and hot boxes (insulated thermal containers). Heat lamps are short-term hot holding devices and are not capable of safe long-term hot holding.

Failure to control time and temperature at the hot holding step is especially dangerous because foods may be in the zone of temperatures most favorable to bacterial growth. It should be pointed out that the generation time for *Clostridium perfringens* can be as low as 8 minutes at 106°F (40°C), a typical hot holding abuse temperature (Labbe, 1989). There is usually ample moisture in foods at this point of production as well. Because cooks are generally concerned about the flavor and qualities of foods, they may set the thermostats too low on the steam tables. Steam tables are problematic because the visual aspect of the steam rising from the unit may give untrained persons a false sense that the foods themselves are steaming when this may not be the case.

Thermometers must be provided to all hot holding devices, they may be portable types that are hung inside the units or they may be fixed and designed

into the unit. Steam tables, bains marie, and chaffing dishes require that an accurate external probe thermometer be used.

The preventative measures and recommended practices involved in food safety assurance at the *Hot Holding Control Point* are discussed below.

Temperature control PHFs must remain at 140°F (60°C) during hot holding with the exception that rare roast beef may be held as low as 130°F (54°C). There is no maximum time for hot holding foods as long as temperatures stay at 140°F (60°C) or above. The quality of the foods deteriorates rapidly, however, and long periods of hot holding are undesirable from a quality standpoint.

Hot holding equipment

Steam tables In addition to setting the temperature controls properly, steam tables have several variables that must be controlled, including the level of water in the steam wells, the depth of the insert in the well, the volume of foods in the insert, the cover for the insert, and the temperatures of the foods before being placed on the hot holding unit.

Chaffing dishes Chaffing dishes frequently have Sterno or candles as a heat source. Proper operation of the chaffing dish depends on the nature and volume of the food, the distance of the flame source from the chaffing dish, the amount of water in the dish, and various other factors. Again, because of the variables involved, hot holding for extended periods with chaffing dishes may be hazardous if performed incorrectly.

Heat lamps Heat lamps are commonly used for short-term hot holding. They are, at best, temporary measures for preserving the quality and taste of foods and for when food is waiting for pickup. When heat lamps are used for roasts being held on carving stations, they are generally ineffectual for maintaining proper internal temperatures. Roast beef is often cited as a vehicle (Bryan, 1989) of foodborne illness outbreaks partially because of the nature of inadequate hot holding during extended service periods.

The preparation of gyros utilizes a form of hot holding device comprised of a heat lamp and a revolving cone of formed meat (generally lamb or beef). These lamps generally cause the outside of the meat to reach high temperatures but will sear meats if left on. Thus the heat is typically turned off and on at irregular intervals. Hot holding with these devices is typically ineffective with gyro meats for this reason. It is recommended to slice gyro meat first and keep it hot on a steam table until assembly, but this is rarely done, most cooks preparing gyros by traditional methods.

Bains marie These are hot water baths into which pots and inserts containing food are directly placed. These units, when used correctly, generally have fewer problems than many other methods, but the volume of food and starting tem-

peratures for foods are variables that must be controlled, as is the temperature of the water bath itself.

Hot boxes Hot boxes, or staging cabinets, are another type of holding device commonly used in commercial food establishments. These units either have hot water placed in them in a pan or use Sterno as a heat source. Double walls provide insulation, and the units tend to be capable of holding hot foods as long as the doors are kept closed and the foods have gone in sufficiently hot. Many of these units are provided with temperature gauges, lessening the need to open the units until service of the food begins. Overfilling these units is common, and there are several variables to control as mentioned.

Stoves, ovens, and other cooking devices Cooking devices set on "low" are often used as hot holding units. Stoves are adequate as hot holding devices when thermostats are set properly and the units are not overfilled. Steamers can also be used for hot holding, reheating, as well as cooking, and it is necessary to be aware of the multiple use of these units. Thermometers must be located in all hot holding units, or a thermometer must be readily available to check temperatures. Pizza deck ovens often reach temperatures of 500°F (260°C) and higher. Pizza cooks often use the tops of deck ovens to store cooked foods. This practice is not safe unless the foods remain at 140°F (60°C) or higher. The use of time in lieu of temperature controls is a practical consideration for pizza.

Managing the Serving and Display Control Point

Service is the final step in the production process for foods unless the foods are recycled back into production for reworking into other foods or reservice as leftovers. Service styles range from the elaborate table service of the gourmet restaurant to the counter service of the typical quick serve restaurant (QSR). Cafeteria service is also very popular, as is buffet-style service. All of these service styles have some degree of effect on the hazards that are associated with them. Service may be lengthy, as in a large catered event, or it may be rather quick as in the counter service of a family-style eatery. Increased service times and frequent hand contact with during service risk.

Many of the preventative measures and recommended practices involved in food safety assurance at the *Service and Display Control Point* are identical to those discussed for food preparation and hot or cold holding. Thus only those that are very specific to the service and display areas are discussed below.

Time and temperature The time and temperature characteristics and concerns at catered events are typically different from those involved with sit-down table service. However, regardless of the type of food service, in all food preparation and handling, PHFs must be maintained at safe temperatures outside the danger zone except during necessary times of preparation and service. When time is used as a control, the 4-hour limit should be enforced. This could

mean that the foods served to customers at a catered event must be collected from tables every 4 hours and discarded. In standard table service in a restaurant, the time from foods being plated to their arrival on the consumer's table will be very short, although there are times when orders will be delayed in getting to servers and consequently to customers. The use of heat lamps, covered trays, heated plates and platters, and heat chutes (used for holding sandwiches in QSRs) is an attempt to maintain food quality and food temperatures between the time the foods come out of hot holding areas or cooking devices and the time they are delivered to the customers.

Foods plated far ahead of service must also be maintained at temperatures outside the danger zone. When preplated foods have accidentally gone into the danger zone for periods of less than 4 hours the foods may be reheated to 165°F (74°C) or thrown out.

Buffet and cafeteria service, which involve long-term hot holding, must be carefully monitored with regard to temperature and time. Furthermore, fresh foods should never be added to (or "married" to) old food on a serving line. Care must also be taken to ensure that adequate temperature controls are in place in other self-serve settings.

Food packaging Food packaging protects the foods in take-out operations from incidental contamination that may come from the environment and also protects packaged contents from the hands of the server. In self-service areas, packaged foods have no direct contact with consumers and may be placed in areas that would otherwise require protection. As with any food packaging, packages served to customers in a food service facility must be food grade and must not impart any hazardous materials to the foods.

Personal hygiene Servers with poor personal hygiene may easily contaminate the foods they are serving, and therefore servers must follow the same hygiene and hand washing procedures discussed above for food handlers in food preparation. Presentation of food to customers should be done in a sanitary manner by only touching the handle of utensils, the bottom or outside rim of plates and bowls, and the bottom of glassware. Appropriate utensils (i.e., *not* glassware) or a sanitary ice dispenser should be used to dispense ice.

Protection from contamination Protection of self-service areas requires barriers to be in place and serving utensils and dispensers to be adequately designed to prevent contamination. In addition, frequent monitoring of the self-serve area is indicated.

The most common barrier, the sneeze guard, should be positioned properly to maintain a distance and barrier appropriate to protect the food. All exposed foods should be located under this shield. All other foods must have covers or be wrapped. Certain individually portioned foods and condiments (e.g., packets of sugar and salt, bottles of ketchup) are safe in their original packaging. Bulk ketchup, mustard, and mayonnaise dispensers that are enclosed are protected

from contamination. Drink dispensers should be designed to be activated in such a way that the activating device or lever does not touch the rims of the drinking cups. Ice dispensers should be of sanitary design, with those not exposing ice to the customer (self-contained units) being the most desirable. Soup tureens with lids in place, wrapped individual rolls and bread, and individual creamers are other types of foods that are protected and safe under most ordinary conditions.

When foods, or the handles of serving utensils, are touched by customers, it is very possible for illness-causing organisms to be transferred to them. Self-service utensils must be designed to stay out of the foods, but typically they are placed back in the food because no other methods seem possible. If handles of foods are placed in contact with foods, transmission of disease agents to the foods is likely. Long serving pans (known as inserts) in self-service areas require utensils with long handles and shorter pans require shorter ones; in any case, the dimensions of the pan dictate the length of the utensil handle used. Soiled utensils must not be brought back to self-service areas. The Food Code requires that a sign be placed advising consumers about the need to obtain a clean utensil each time they come to the area. Self-service areas are likely to be contaminated by customers and must be inspected by a trained employee at regular intervals (every 15 minutes or less).

Managing the Reuse Control Point

Because of the time periods and extra handling often involved, leftover foods tend to be more hazardous then freshly prepared foods. Virtually all of the recommended practices and preventative measures discussed above that have dealt with contamination, growth, and survival of hazards in foods apply to the Reuse Control Point. Most importantly, the food must be handled in a sanitary manner and protected from contamination, and all time and temperature requirements must be maintained. Reused PHFs must be reheated to 165°F (74°C) and held at temperatures outside the danger zone.

Donated foods deserve special mention. Most states have Good Samaritan laws that protect commercial food service establishments from liability if they, in good faith, donate wholesome foods to a food bank or food recovery program. Such foods must be handled and stored safely under proper time and temperature controls. Many firms that participate in food donation programs freeze the foods that are donated or only donate non-PHFs.

REGULATORY, INDUSTRIAL, AND INTERNATIONAL IMPLICATIONS

Regulatory Implications

The regulation of the food industry is diverse, with more than 14 Federal agencies regulating food in the U.S. The commercial food service sector is regulated primarily by local and state agencies. Because retail food service

establishments must meet local laws, and sometimes state and federal laws, the consequences of unsafe foods produced by commercial food service establishments have a very significant regulatory impact. To deal with this problem many agencies are rethinking the way that the food service industry is regulated.

Regulatory approaches and requirements for commercial food service

Traditional inspection programs Traditional inspection programs are designed to evaluate the criteria of food safety by using a checklist and visually inspecting the premises for obvious signs of contamination. In recent years, this method has been expanded to include the evaluation of typical regulatory issues related to time and temperature, sanitizing, and hand washing. However, a significant portion of the typical 44-item inspection reports is devoted to structural, equipment, and environmental sanitation elements that have no direct relationship with the safety of the food service establishment. For this reason, traditional inspection is being questioned as a valid approach to regulating the food service industry (Pennman et al., 1996).

Establishment grading and scoring systems Checklist type inspections allow a score to be calculated. The use of this score can translate into a grade, which can then be posted for consumers to evaluate. This approach is favored by many consumer groups but is not supported by industry and has received mixed reactions from regulatory agencies. The trend has been moving toward requiring establishment grading. For example, a massive exposé in the local news media has forced establishment grading regulations in Toronto, Ontario.

A potential advantage of a grading system is that grades do, in fact, make commercial food establishments more accountable. However, there are several disadvantages. The scores are often based on less than objective criteria (e.g., clean vs. dirty); with no real way to empirically delineate the criteria, grades themselves lack validity. Additionally, several factors that may not impact or only indirectly impact food safety (e.g., windows with no screens, trash exposed at the dumpster, dirty floors, or dirty filter in a grease hood) could cumulatively contribute to an unacceptable score. Conversely, a facility with an eminently unsafe condition [e.g., 50 gallons of chicken gravy at 70°F (21°C) for 24 h] may receive a high rating if this is the only violation tabulated. Thus inspection scores may or may not correlate well with the potential for outbreaks to occur, and, subsequently, grades based on those scores may not have a significant association with safe or unsafe establishments.

HACCP-based inspections As described above, regulatory inspections (or audits) based on HACCP are designed to assess critical control points in an operation. In regulatory audits based on HACCP, the food safety system is emphasized rather than the facility itself. The process by which food is produced and handled can be audited and is more in line with the concept of

HACCP than using a checklist to examine discrete functions in an operation. The use of this methodology coupled with an internal program deployed by the operator holds much promise for ensuring food safety at the commercial food service level.

The application of HACCP in commercial food service is currently voluntary in most jurisdictions but is strongly advised and embraced by many regulators. The reason for this is a belief that a monitoring program based on sound science is a way to improve the safety of foods while at the same time comply with laws. HACCP is, however, still an industry-driven concept. The regulatory use of HACCP should be seen as complementary to the use of HACCP by industry. If regulations become the driving force for HACCP, it is easy to see that compliance will be based on doing the minimum required by law. This may have the ultimate effect of making HACCP just another government program that is imposed on industry. There are several areas in which implementation of HACCP in food service may be more difficult than in a food processing facility. For example, end product testing, which is done routinely in many food processing facilities, is rarely done in a commercial food service facility. Thus implementing meaningful HACCP verification and validation in food service is more difficult. Therefore, at this point in time, voluntary compliance with HACCP principles seems more realistic than a mandatory approach.

Preventing foodborne illness in commercial food service can be best accomplished by developing and following written, detailed SSOPs. Therefore, written SSOPs may be an integral component of a HACCP-based regulatory system. Unlike HACCP criteria, which strictly relate to critical control points, SSOPs are much broader in scope and are considered to be foundation (or prerequisite) programs for HACCP. In addition, SSOPs are usually are more closely related to the detailed provisions of most regulations.

No bare hand contact provisions Because the FDA strongly believes that bare hand contact of RTE foods is an important food protection issue, most states and local authorities must address this issue in their own codes. For reasons discussed above, however, there is great variation in the regulatory approach to this matter. Many jurisdictions will eventually either require no bare hand contact or allow a waiver to be introduced into state codes.

Mandatory manager and employee training A knowledgeable workforce is critical for meeting the food hygiene objectives of regulatory programs. Therefore, mandatory manager as well as employee training and certification legislation will be increasingly enacted. As HACCP concepts become more familiar there may also be requirements to train personnel in HACCP systems.

Industrial Implications

The commercial food service industry will be moving more to self-inspection and internal quality assurance for several reasons:

- It is good business to develop sanitation protocols and to establish them as business practices because they lead to higher profits, less waste, and better working conditions.
- Liability may be reduced if successful programs are implemented, and insurance companies may offer reduced rates for those facilities with less risk.
- Loss of reputation will result from poor inspection results, which are frequently publicized, and negative publicity about outbreaks and poor sanitation scores are costly in terms of loss of consumer confidence.

International Implications

Travel is now a leading industry worldwide. Many areas seemingly too remote just a few decades ago are now feeling the influence of tourism. Food hygiene standards are increasingly viewed as essential by travelers from western countries. It will be necessary for any travel destination to provide safe food to travelers.

There is a need for a uniform set of guidelines to be used worldwide at the commercial food service level. The challenge will be to make the concepts of food sanitation and hygiene understandable and culturally acceptable to persons unfamiliar with them. Another challenge is the lack of essential sanitary facilities such as safe water supplies and sanitary sewers. Even such items as bathroom fixtures and toilet paper are lacking in many areas of the world viewed as tourist destinations. There may also be problems with electricity, basic equipment, structures, and pests.

CURRENT AND FUTURE IMPLICATIONS

Food safety is quickly becoming a worldwide concern. Commercial food service, being very readily associated with outbreaks of disease, will continue to be scrutinized closely.

Food safety professionals will be in high demand as the industry attempts to lessen the risks of illness and improve regulatory compliance. Currently, many large regional and national chain restaurants employee food safety personnel.

Low-dose pathogens, such as *E. coli* O157:H7, will drive the basic sanitation issue in the future. Soiled work surfaces up until recently were seen as more or less an aesthetic issue. Now, even a small amount of *E. coli*-infected meat in an establishment can be spread easily to other foods and cause disease. The use of rapid testing technology will come to the fore as commercial food service establishments attempt to establish baselines for sanitation on work surfaces of equipment and employee hygiene. Such rapid testing may also be required by regulatory agencies in the future.

In addition to improved pathogen testing methods, improved technology is pushing food safety into new dimensions. Some of the additional technological

breakthroughs include food contact surface hygiene testing, environmental sampling, remote temperature sensing, and use of the Internet for transmitting food safety data and for training employees. These technological breakthroughs will forever transform the food safety paradigm for the commercial food service industry.

Competition will force those firms that cannot produce consistently safe foods out of the market. Safe foods may, however, come at the expense of traditional cooking methods, and quality, as an aesthetic issue, may suffer. For example, many foods consumed at chain restaurants are prepared in commissaries or processing plants, frozen, and rethermalized in a bag at the point of service. This precludes the problem of raw meat, but these foods tend to be less nutritious and lack the originality and spontaneous nature we often get enjoyment from.

Ultimately, the answer for the food safety problem at the commercial food service level lies in cleaner raw foods coming into a better maintained and managed establishment. Thus a major challenge for the commercial food service operator of the future will be to find, train, and retain food safety-minded employees. The operation of the future will also need inovative methods to produce foods consistent with increasing consumer demands in full compliance with strict safe food handling guidelines. In addition to a well-trained workforce, the commercial food service facility of the future will require improved technology to overcome the risk of contaminated food.

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CHAPTER 27

INSTITUTIONAL FOOD SERVICE OPERATIONS

RUBY P. PUCKETT

INTRODUCTION AND DEFINITION OF ISSUES

Throughout history, because of man's need for food, there has always been some organization for growing and preparing food for consumption. Initially this was just for family units, but as the population increased, people migrated, community needs arose, industries developed, armies were formed, and the need to manage the growth, distribution, and delivery of food became more important. This early organization and management usually became the responsibility of kings, emperors, lords, and others who had responsibility for large numbers of people. For instance, during the early Middle Ages, institutional food service revolved around habits and customs of the day. In many European countries, food and food service was an important issue, for social or economic reasons as well as availability of food. Families, guests, and servants could make up a household of hundreds. Households of royal and noble families could serve 300 or more people at each meal. Religious orders fed the "brethren" as well as thousands of pilgrims through a system of abbeys and religious units. Inns and taverns were scattered along the roads and were gathering places for travelers who were seeking food and lodging as well as a place of entertainment for local communities. Because of local and religious conflicts, many soldiers had to be fed on the battlefield. This was no minor undertaking, as food had to be secured, when possible, from local peasants or else animals had to be found, killed, and cooked. Depending on the intensity of the battle, there may have been little time for preparation and sanitation was almost nonexistent.

Today, it is not uncommon for some institutional food service establishments to feed thousands in a day, whereas others may feed less than 50. As a whole, the food service industry is vast and complex. It involves the planting,

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harvesting, processing, storage, and delivery of food from the farm to the user. It employs approximately 10 million people, with sales that exceed 400 million dollars, and accounts for over a billion dollars as an industry. Most of the employees in food service are women and minorities. Labor costs, including benefits, are one of the most expensive items in the industry.

Institutional food service operations are dynamic and constantly changing because of the shortage of personnel and the increased cost of recruiting and retaining employees. Operating funds have been decreased from corporations, school systems, insurance companies, and governmental agencies. The introduction of the branding concept, increasing efforts by contract companies to operate many of the institutional foodservice establishments, and the other food service options available to consumers have made managing an institutional food service operation a challenge. All segments of institutional foodservice are devising methods to reduce cost, increase revenues, and meet regulatory agency standards while providing safe and sanitary food service to their customers. Socioeconomic conditions, food habits, demographic changes, and customers with a variety of cultural and ethnic diversities create a wide range of needs/demands.

SCIENTIFIC BASIS AND IMPLICATIONS

Classification of Institutional Food Service Establishments

Food service is defined in the broadest sense as including all establishments where food is regularly served outside of the home. On any day, approximately 50% of all Americans eat at least one meal away from home. Some people may eat two to three meals in the same facility. More men eat meals away from home than women do. Children, during school sessions, may eat between 5 and 15 meals a week away from home (i.e., school breakfast, lunch, and after-school snack).

The food service industry encompasses a wide range of establishments with an array of menu offerings and ambiance. For years, associations and publishers have struggled with a classification system for food service establishments. There is still disagreement on how to classify the industry. The National Restaurant Association classifies the food service industry as *commercial* and *noncommercial*, and these classifications are still used, because they indicate where the customer will eat. In 1993 the *Restaurant and Institutions* annual forecast no longer divided the industry into these categories. *Restaurant USA*, and a number of professional associations, organizations, and publications use the following classification, which is currently more acceptable:

- Commercial
- Institutional
- Military

Each of these three classifications has subsections. This unit will deal with institutional food service and its subsections, which include:

- Employee feeding
- Public and parochial elementary and secondary schools
- Colleges and universities
- Hospitals
- Correctional facilities
- Long-term care (all types)
- Child care
- Clubs, sporting, and recessional camps
- Community centers
- Transportation

These classifications can be further broken down to feeding "well" versus feeding "ill" customers.

Each classification of food service operations covered under *institutional food service* has some commonality with as well as differences from other classifications. In school and college, health care, and correctional facilities, the management staff may employ registered dietitians (RD), dietetic technicians registered (DTR), and/or certified dietary managers (CDM). This professional group of employees work together to ensure that customers' nutritional needs are met. In some health care facilities, chefs have been added to the staff.

All the establishments will have menus—some will be complicated, offering many choices, others will be limited, and still others will be modified to meet the health condition or age of the customer. They all face employee problems that may include the lack of affordable child care, the lack of skilled workers, and reduced monies with which to operate. The backgrounds of customers may vary, but they all want more variety, lower prices, faster service, and higher-quality food. These establishments are challenged by decreased budgets and the need to increase profits. They all are routinely surveyed and inspected by a variety of agencies that have established codes, standards, regulations, and laws that must be followed.

Employee feeding is undergoing a tremendous change because of rising labor costs, the decreased subsidies offered by corporations, and the demands of the customer for more healthy foods, reduced prices, longer hours of operation, and "grab and go" service.

The population of correctional facilities continues to increase, with approximately the same number of men as women inmates. The population of these facilities makes up about 10% of the total population, the same percentage as nursing facilities. A wide range of ages and backgrounds is found in the

correctional facilities, with a large portion of the population in the older age bracket. A number of correctional facilities are setting up centralized kitchens where the food is prepared and transported to other correctional units. Consolidation of employee and inmate dining has lowered cost.

Feeding children at all grade levels offers a challenge to the manager. Children want the same kind of food that they eat on weekends and after school. The U.S. Department of Agriculture (USDA)/Children School Foodservice has mandated that school food meals be reduced in salt, fat, and sweets and that nutritious meals be offered. Some school food service programs have contracted out the service, and some are using more branded items to increase revenue.

College food service will continue to decline unless colleges offer the same types of food as the outside competition and at a lower price. College students want the dining halls to stay open later at night. Today's students are also demanding more healthy foods—for example, many of them are choosing a vegetarian lifestyle.

Food service for child care is challenging because of the wide age range. As the costs of food and labor continue to increase, the operators must increase their prices to parents. Affordable child care from early morning to after midnight is an ongoing problem for both parents and the operators of the facilities. Some health care organizations, corporations, and colleges subsidize child care facilities for the care of employees' children.

Health care providers, including long-term facilities, are unique because they have the responsibility of feeding both well and sick customers. In the last few years this segment of the industry has been downsized and forced to reduce cost by changing menu systems, employing more part-time employees, utilizing more ready-prepared/convenience foods, and in some instances, going "kitchenless." Menus must be modified to meet the nutritional and medical requirements of the customer. The branding concept (e.g., a complete marketing package that communicates a recognized and consistent identity to the customer) is gaining widespread acceptance in health care employee feeding. This concept reduces the number of staff and hours of operation of the food service; in some instances it may increase revenues.

It is clear that all segments of institutional food service are faced with a variety of age ranges and ethnicities of the population, cultural diversity, demands of the customer, encroachment of management companies, branding concepts, longer work weeks, higher costs, and reduced profits. Each type of institutional food service establishment will also be governed by management philosophy, policies, and procedures individualized to the organization, visions, values, goals, objectives, and systems of operation. The one thing that all of the types of establishments have in common is providing safe and sanitary food to people who are away from home for one or more meals per day. In some cases the people will be ill, while others will be healthy. Out of necessity some people will eat all their meals in the same establishment.

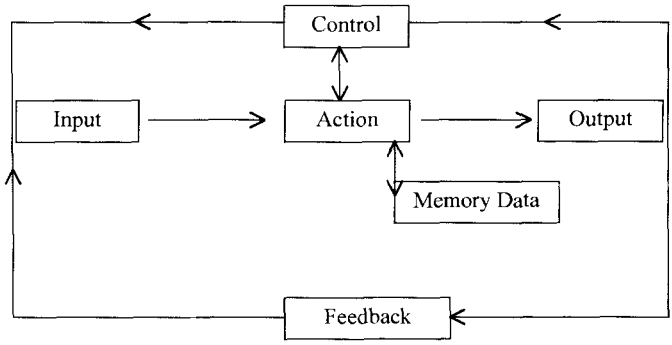


Figure 27.1. Systems model. Adapted from Dietary Manager Training Program by R.P. Puckett, Division of Continuing Education, University of Florida, Gainesville, FL, 2002. Used by permission Ruby Puckett

Application of the Systems Model and Systems Approach to Institutional Food Service

The systems model and systems approach are presented in Figures 27.1 and 27.2, respectively. A *system* is defined as an interrelation of various parts or subsystems that works in harmony to achieve a goal. *System management* is the application of systems theory to managing. Systems encompass the necessary resources needed to operate the service and are composed of *inputs (action* or *transformation)*, *outputs*, and *feedback*. System *inputs* are money, personnel, skills, time, equipment, space, utilities, materials (food/supplies), and data/information. System *outputs* transform raw materials into finished products or services. These outputs also include customer satisfaction, quality control, and financial responsibility. *Action* or *transformation* is any action taken or any activity used to change inputs to outputs. The outputs let the organization know whether the system is working as planned, or where changes or modifications need to be made. The data thus gathered are the *feedback* that allows management to make decisions, plan, and communicate. All parts of the total system are linked by the functions of management. In addition, *external forces* such as customers, regulatory agencies, suppliers, and competition exert an influence on the organization. The organization is continually trying to meet both the needs of the internal pressures as well as the needs of the outside influences (Puckett, 1999).

Institutional foodservice is a total system made up of a variety of subsystems or independent parts (Fig. 6.2.3). Each subsystem contributes to the whole while working to achieve a common goal/objective/vision, and each part receives something from the whole. Any change made in a part has an effect on the other part (Puckett, 1999).

Institutional food service establishments, in general, use a systems approach

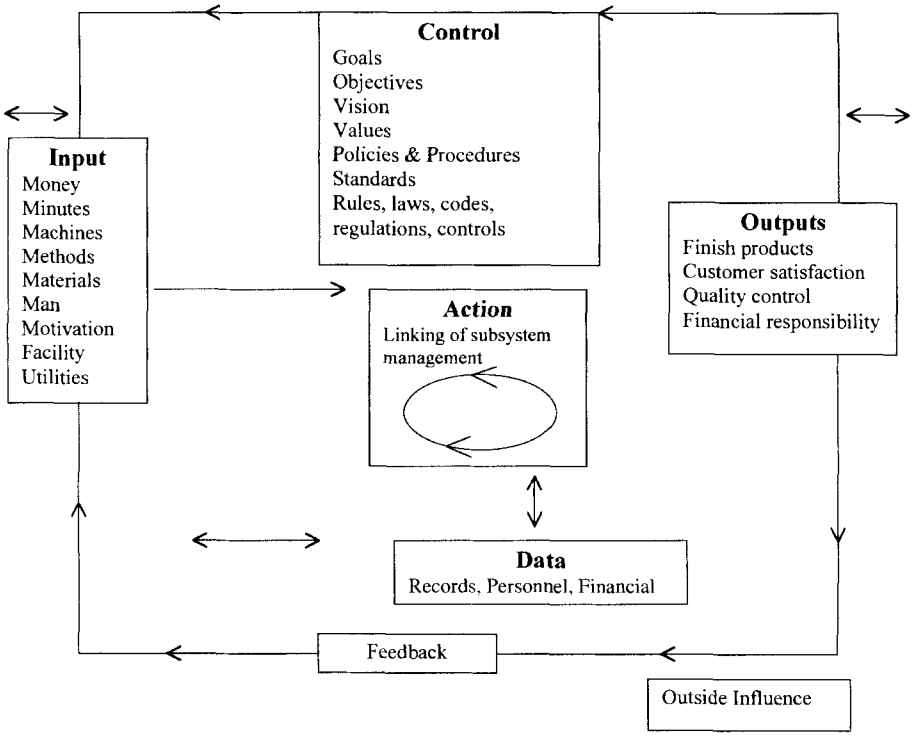


Figure 27.2. Systems approach. Adapted from Dietary Manager Training Program by R.P. Puckett, Division of Continuing Education, University of Florida, Gainesville, FL, 2002. Used by permission Ruby Puckett

to produce safe and sanitary food for the customers. The four basic types of institutional food service systems include:

- Conventional
- Ready prepared (cook-chill or cook-freeze)
- Central production
- Assembly/serve

A comparison of the subsystems for each the four basic systems is presented in Table 27.1, with specific areas of food safety concern identified in Table 27.2.

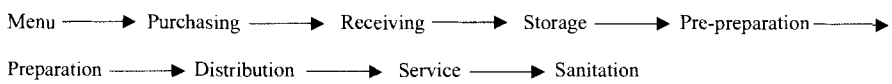


Figure 27.3. Subsystems

TABLE 27.1. Four Types of Food Service Systems.

Conventional (on-site)	Centralized Production (commissary)	Ready-Prepared Cook (chill/cook freeze)	Assembly and Serve
PURCHASE Specification Raw and prepared items to meet menu ↓	Purchase raw food items for production to meet satellite unit menu	Purchase raw food items and prepared items to meet menu needs	Purchase fully prepared foods: frozen, chilled, canned, dehydrated; prepared salad, ingredients and desserts
RECEIVE Check for thawing or damage, spoiled frozen products, dented cans ↓	→	→	→
STORE Food/supplies Store in refrigerator at 40°F or lower, store in freezer at 0°F. Store in dry storage at 65–70°F ↓	→	→	Store in freezer at 0°F or refrigerate at 32–38°F Store other items as appropriate
PRE-PREPARATION (ingredient control) Inspect, wash, peel, sort, cut, measure, weigh according to recipe ↓	→	→	None required

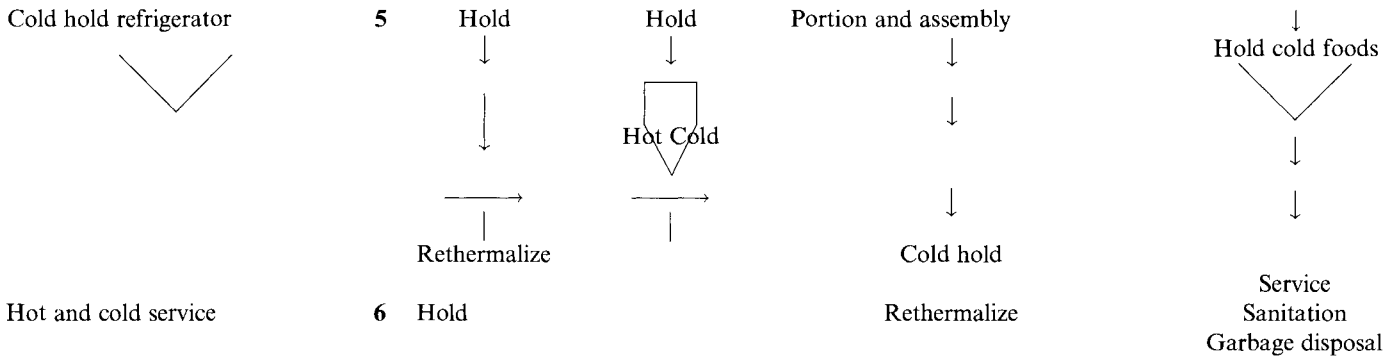
TABLE 27.1. *(Continued)*

PREPARATION → Hot/cold Small batches to large, short orders, grab and go	Prepare large batches →	Prepare large batches	None required
↓			↓
PORTION For service either individual such as salads, desserts or in steam table pans	Portion and freeze or chill and store or bulk blast freeze and chill and store OR transport to satellite in appropriate temperature control equipment	→ Store in freezer or refrigerator as appropriate for later use	
↓	↓	↓	
	Received by unit where food to be stored or served		
↓	↓		
HOLDING Short time holding in refrigerator or heated cabinets, Tray lines, bains marie OR serve at once	Hold as appropriate until serving time	→	→ Chill bulk foods, will need to be portioned
↓	↓		
	Thaw frozen foods in refrigerator at 38–40° (no more than 4 hours)	→	→
↓	↓	→	→

	Rethermalize (reheat) to internal temperature to meet Food Code 1999		
DISTRIBUTE For service at once; maintain temperature for hot/cold	↓		
↓	Assemble and Service	→	→
RETRIVAL Of supplies and clean-up (reusable flatware, service ware)	→	→	→
↓	Return usable materials (to central production area)		
	↓		
SANITIZE Appropriate sanitizing temperature	→	→	→
↓			
STORE For use at next meal	→	→	→
or			
DISCARD Disposables	→	→	→
↓			
GARBAGE Garbage in impervious bags	→	→	→
↓			
DISCARD And discard properly	→	→	→
↓			
CLEAN CANS	→	→	→

TABLE 27.2. Food Service System Area of Concern for Safe Food and Water Handling.

Conventional		Centralized Production (Commissary)	Ready-Prepared Cook (Chill/Cook Freeze)	Assembly and Serve
Receiving Store refrigerator 2°C to −0.5°C, Freezer −24°C, Dry storage 65–70°F	1	→	→	→
Pre-preparation thaw meats and poultry in refrigerator, wash, trim, clean weight, package and hold under temperature at 40°F	2	→	→	None
Preparation and Production	3	→	→	None
Cook	4	→	→	
Hot hold, steam table, hot cabinets bains Marie		**4a** Transport for cook chill/freeze **4b** Transport for conventional service	Freeze → Thaw under Refrigeration Rapid chill	None Remove from freezer Rethermalize Hold hot foods Remove from refrigerator or dry storage


Cold hold refrigerator
5
Hold
Hold
Portion and assembly
Hold cold foods
Hot Cold
Rethermalize
Cold hold
Service
Hot and cold service
6
Hold
Rethermalize
Sanitation
Garbage disposal
Service
Leftovers
7
Cool
8
Sanitation
Store
9
Garbage Disposal
Reheat
10
Service
11
Sanitation and garbage disposal
12

The establishment may use one of the systems exclusively or may use a combination of systems, depending on the skills of personnel, equipment, money available for supplies and equipment, and changes in demographics, food requests, and cultural and ethnicity characteristics of the group to be fed.

Establishing a Food Safety Program in Institutional Food Service

Providing safe and sanitary food and water to customers is vital in institutional food service establishments because the three largest groups served (e.g., children, the elderly, and the ill) are at high risk for foodborne illness. Every institutional operation must develop measures to ensure or improve food and water safety and to protect food and water from physical, chemical, and biological hazards that can cause foodborne illness to the customer (see Fig. 27.4; Puckett, 1999). It is also a goal to keep the customers coming back for their

Figure 27.4. Route of food contamination. Adapted from Puckett, R.P. and Norton, L.C. HACCP The Future Challenge, University of Florida, Gainesville, FL, 2000

food service needs. Management and employees have responsibilities to ensure this charge. Management's responsibility includes:

- Establishing goals, objectives, and policies to ensure food and water safety.
- Developing and implementing a program for safe food and water handling; developing controls and/or preventative measures to ensure food and water safety.
- Ensuring that food and water safety procedures are based on science-based information and current regulations (Puckett and Norton, 2000).
- Providing necessary tools, facilities, and resources to ensure safe handling of food and water.
- Orienting, training, continuing education, communicating, and supervising food and water safety procedures; taking corrective action as appropriate to protect the customer from foodborne illness.
- Hiring employees who present a well-groomed appearance and who pay attention to personal hygiene.
- Conducting in-house inspections and adhering to all rules, regulations, codes, and laws; staying current with all federal, state, and local codes, standards, regulations, and laws.
- Developing job assignments and procedures/methods to perform the assigned task.
- Establishing monitoring and record-keeping systems.
- Reviewing program, analyzing data, problem solving, documenting problems, monitoring outcomes.

Employees also have responsibilities for food and water safety. These include:

- Maintaining good personal hygiene—bathing and using deodorant, washing hands often, wearing gloves as approved by state or facility, wearing hair restraints (for head and beards) while working in the production area, wearing only allowed jewelry, wearing clean clothes including clean aprons, and keeping nails clean, trimmed, unpolished, and with no artificial nails.
- Smoking, dipping, or chewing tobacco/gum in specific area away from food production area; avoiding the use of drugs.
- Avoiding cross-contamination of food.
- Keeping work area and equipment clean, sanitized, and in good repair.
- Reporting any diagnosis or exposure to illness (especially *Salmonella typhi*, *Shigella* spp., *Escherichia coli* O157:H7, or hepatitis A virus) or illness symptoms (e.g., diarrhea, vomiting, fever, sore throat, jaundice, upper

respiratory disease, sneezing, coughing, runny nose, discharge from eyes) that may interfere with working in food preparation or service.

- Reporting any infected cuts, burns, open sores, lesions, or boils (non-infected cuts, abrasions, burns, and boils should be covered with a waterproof bandage, and watertight disposable gloves should be worn).
- Reporting any mishandling of food, food that may be contaminated, any temperature/time variance, and any other potentially unsafe food or water problem (Puckett and Norton, 2000).

Many institutional food service operations establish teams and give them the responsibility and authority for overseeing food and water safety. Depending on the institution, the team may be composed of members from other departments/units within the total organization. Team management works exceptionally well in health care facilities, where food safety is a number one priority. The team may be responsible for developing and implementing self-inspections, training staff, implementing a food and water safety program, and cooperating with local health officials. The team will need to be competent, possess knowledge of institutional food service operations/systems, be given the resources, time, and tools to participate in the program, and be empowered to take action. A major part of the team's time and efforts will be to perform self-inspections, monitor time and temperature controls, and train/motivate the other employees in the importance of safe handling of food and water.

Causes of Foodborne Illness in Institutional Food Service

A foodborne illness outbreak is defined as an incident in which two or more persons experience a similar illness from a common food and epidemiological analysis implicates the food as the source of the illness. Botulism outbreaks (where one illness is considered to be an outbreak) are an exception to this definition. When laboratory evidence meeting established criteria confirms the presence of a toxic agent, the outbreak is classified as being of known etiology. Otherwise, it is considered as being of unknown etiology. Outbreaks of unknown etiology are usually reported as:

<1 hour	Probable chemical poisoning
1–7 hours	Probable *Staphylococcus* food poisoning
8–14 hours	Probable *Clostridium perfringens* food poisoning
>14 hours	Other infectious or toxic agents.

In a 10-year CDC evaluation of 2434 foodborne illness outbreaks (CDC, 1999), it was determined that bacterial pathogens caused 79% of the outbreaks for which the cause was known. Of these pathogens, *Salmonella enteritidis* was the leading cause of both illness and death. In addition, 85% of the deaths caused by *Salmonella enteritidis* occurred among residents in nursing homes.

The contributing causes were identified in 1435 of the outbreaks. The frequency in which these contributing causes were identified has been summarized as follows:

- Improper holding temperature 59%
- Poor personal hygiene 36%
- Inadequate cooking 28%
- Cross-contamination 16%
- Unsafe food source 11%
- Other 11%

There are approximately 1.5 million residents living in more than 17,000 long-term facilities in the U.S. At any given time anyone may become ill from food or water that has been contaminated with microorganisms. The role of inadequate personal hygiene of the food handler has been well documented (Puckett, 1998).

Food and Water Handling Practices in Institutional Food Service Systems

Similarities can be found with regard to the precautions for safe food and water handling in the four institutional food service systems (Fig. 27.4). A food safety hazard may occur at any of the subsystems of concern (Fig. 27.5). The potential sources of these hazards that are common to all subsystems include:

- Improper personal hygiene practices (failure to wash hands, working with a communicable disease, using bare hands to handle ready-to-eat foods).
- Cross-contamination.
- Lack of proper time and temperature controls (hot and cold holding, cooking, thawing).
- Dirty equipment and utensils or other unsanitary methods/procedures.
- Lack of pest control and maintenance of equipment.
- Failure to cover, label, and date held foods.
- Improper storage of chemicals.
- No potable water.
- No documentation for validity and verification of a food safety program.
- Failure to take corrective action when a break in procedure occurs, or failure to make necessary corrections.

Additional sources of hazards associated with specific subsystems include:

Receiving/Storage: Receiving products that show signs of spoilage or pest infection and meats that are smelly, slimy, or sticky. Products show sign of thawing. Products not ordered from an approved source, and no vendor certif-

icates on file. Fresh fruits and vegetables show signs of bruising or rotting, not grade ordered. Improperly packed. Delivered in open unrefrigerated truck. Secured from local farmer. Failure to follow the temperature guide for freezing and refrigerator temperatures. Failure to store eggs at 45°F (7°C). Storing food in ice. Not using the first-in, first-out (FIFO) method for stock rotation. Accepting dented cans and going past "sell by" safe dates. Refrigerator/freezer temperature too high because of doors being left opened. Failure to control the ambient air temperature. Storing products (fresh fish and chicken) for too long a period.

Pre-preparation: Failure to remove fruits and vegetables from field boxes. Cleaning raw fresh fruits and vegetables in nonpotable water, exceeding 70°F (21°C) before storage. (If state approves, fruits and vegetable may be washed by using chemicals.) Failure to clean sinks, countertops, other work areas, equipment, and utensils after pre-preparing one item and before pre-preparing another item. Lack of adequate cutting boards or using the same cutting board or utensils to cut raw meat/poultry/fish and cooked items without sanitizing after each use. Failure to blanch celery, onions, and green peppers for 15 seconds in boiling water before adding to salad mixtures or other items that will not receive additional cooking.

Preparation: Inadequate cooking—either over- or undercooking. Lack of time and temperature monitoring of internal temperature. Placing cooked food in pan or dish which previously held raw meat, poultry, and or seafood. Improper thawing methods. Using wiping clothes that have not been rinsed in sanitizing agent. Storage of chemicals in preparation area. Failure to use proper tasting procedures.

Hot Holding: Foods held at 120°F (49°C) and 70°F (21°C) for 4 hours or longer. Hot holding equipment not operating as intended. Combining new products with old. Heating cold or lukewarm foods in steam tables or other equipment that was not designed to hold hot foods. Failure to stir food frequently to distribute heat. Food uncovered.

Transporting: Containers not covered. Food (hot or cold) not maintained at a constant temperature. Failure to use insulated food carriers during transport. Temperatures not recorded before leaving central production and not taken once received at site. Delivery vehicles not clean. Equipment not sanitized. Use of tobacco products or drugs during transport. Food left on loading dock, not immediately refrigerated or heated.

Refrigerated Storage: Refrigerator temperature not kept at 41°F (5°C) or below. Equipment not cleaned after each use before re-using. Failure to cool hot food to 41°F (5°C) within 4 hours.

Hot and Cold Service: Using dirty cutting board, utensils, equipment, and dirty hands to portion food. Failure to measure the temperature of meat and other items every 2 hours. Failure to maintain appropriate temperatures. Adding old food to new food. Failure to change serving utensils often. Using inappropriate serving utensils. Touching rims of serving dishes or eating end of utensils. Leaving serving counter dirty and littered with used/dirty utensils, serving pans, and equipment.

Cooling/Leftovers: Didn't cool hot foods from 140°F (60°C) to 70°F (21°C) within 2 hours, from 70°F (21°C) to 41°F (5°C) or below within 4 hours Food Code (FDA, 2001). Failure to divide large quantities of food into smaller portions and failure to use 2-in. pans to store. Storing hot foods in plastic. Placing large quantities of hot food in refrigerator at one time. Failure to use approved methods to cool foods before storing. Storing cooked foods next to or below raw foods. Failure to discard any contaminated product (time and temperature or other reasons).

Rethermalizing (Reheating): Didn't heat food product to an internal temperature of 165°F for 15 seconds. When microwaving, did not allow product to stand required time. Using dirty equipment or utensils for reheating. Adding various products together and failure to heat to the proper internal temperature for the new mixture. Using leftovers more than once.

Sanitation: Improper storage of cleaning products and chemicals. Chemicals and cleaning products not labeled. No Material Safety Data Sheets (MSDS) available. Temperatures in ware and dishwashing machines and sinks not recorded. Temperatures inappropriate and no documentation that problem has been solved. Failure to monitor temperature for sanitizing of dishes. Dish storage containers dirty and in poor repair, signs of pest infestation. Dish and ware washing machine not cleaned at least daily; spray arms, curtains, and traps not removed and cleaned. Improper chemicals used in ware and dishwashing machines. Incorrect amounts of detergent and chemical used in machines. Drying of dishes with cloths. No cleaning schedule. Lack of monitoring for sanitation and safety and failure to correct and document.

Garbage Disposal: Boxes not broken down. Garbage left in production area for over 6 hours. Failure to use impervious bags in garbage cans or other methods of garbage disposal. Garbage left on dock and not discarded in dumpster. Cans not sanitized after emptying.

A hazard that can lead to a foodborne illness is always present in an institutional food service operation even when the management and employees are diligent in practicing safe food handling. This is another reason for the team to perform self-inspections of the department. Self-inspection checksheets will need to be developed that identify the areas where a hazard can develop. Results of the inspections must be analyzed, and action plans for correction or improvements must be developed. The plan should have measurable outcomes and time limits for corrections and improvements.

The plan and any changes will need to be communicated to the team and staff and monitored for effectiveness. Outcomes must be documented. It may be necessary to set up training/retraining programs to ensure that all personnel understand the importance of safe food handling and their role in preventing a foodborne illness.

Control of Temperature and Time

General temperature requirements for control of bacteria are presented in Figure 27.5. Additional specific recommendations are also provided in the Food

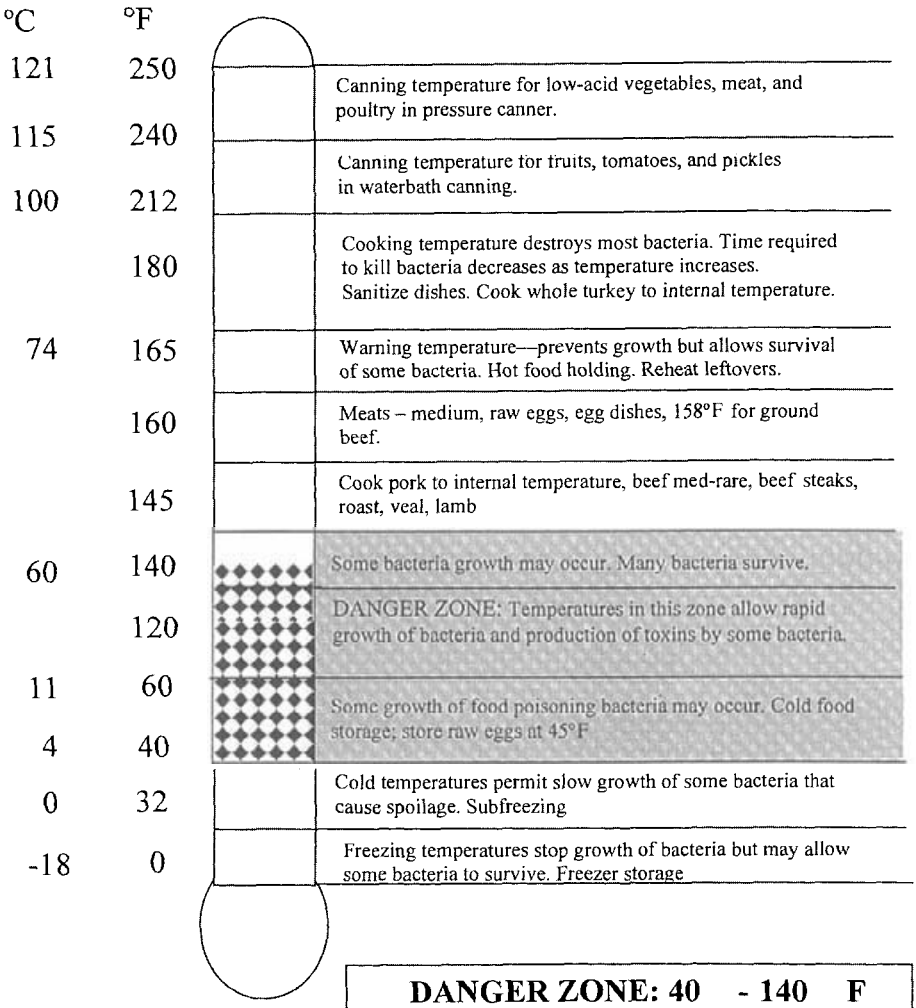


Figure 27.5. Temperature of Food for Control of Bacteria. Adapted from Dietary Manager Training Program by R.P. Puckett, Division of Continuing Education, University of Florida, Gainesville, FL, 1999. Used by permission Ruby Puckett

Code (FDA, 2001). Keeping food hot, keeping food cold, and keeping it moving are the basic food safety rules for institutional food service. Keeping food at the proper temperature—e.g., 41°F (5°C) or 140°F (60°C)—to inhibit bacteria and pathogen growth and moving it to the service area in the shortest time possible are two important keys to food safety and prevention of food-borne illness. The USDA Food Safety Inspection Service (FSIS) has outlined four safety areas in their educational program *Fight Bac*™ (FSIS, 1998). They are: CLEAN—Wash hands and surfaces often; SEPARATE—Don't cross contaminate; COOK—Cook to proper temperatures; CHILL—Refrigerate promptly. KEEP FOOD SAFE FROM BACTERIA™.

The most important temperatures that need to be monitored in institutional foodservice are summarized in the following (Puckett and Norton, 2000):

Freezer Temperature: Freeze foods quickly to 0°F (−18°C) or below to prevent the formation of large ice crystals. Maintain the freezer temperature at −10°F (−24°C). At 30°F (−4°C) some bacteria survive but growth does not occur. Do not allow freezer temperature to rise above 0°F (−18°C).

Refrigerator Temperature: Optimal temperature is 30–40°F (−1 to −4°C).

Oven Temperatures (determined where the pan of food sits in the oven): 165–212°F (74–100°C) kills most food poisoning bacteria. 250°F (132°C): very slow oven. 350°F (185°C): moderate oven (used to bake protein foods). 400–500°F (204–225°C): very hot oven. 370°F (190°C): deep fat fryers.

Machine Ware Washing Temperatures: Prewash: 100–120°F (40–49°C). Wash: 155–170°F (68–77°C). Power Rinse: 165–180°F (74–82°C). Final Rinse 180–195°F (82–91°C).

Crisis Management

When a customer complains of "food-related illness," the institutional food service establishment must have a plan in place and must take action immediately. The plan should be tailored to the institution's goals/objectives/policies and to the regulations of the public health sector of the county or state.

The following steps are suggested:

- Graciously accept the complaint.
- Follow established policy and procedure.
- Secure all pertinent data such as name, address, date, time, meal, contents of meal, when and where the food was purchased/served, if food was eaten when purchased or refrigerated, e the symptoms and when they occurred, the names of any others who ate the same food; whether medical attention was sought, and if so, the name of the physician, clinic, or health department. Fill out complaint form.
- Secure a food history of the complaint, if possible, of all meals and snacks eaten *before* and *after* the suspected meal.
- Listen carefully to the complaint. Don't admit liability or offer medical advice. Don't diagnose or suggest symptoms. Don't introduce symptoms.

Record only what the person said. Note the time the symptoms started. Remain polite and concerned.

- Try to preserve a sample of the suspected food for later microbiological testing. Label, date, and store (refrigerate, preferably freeze). Remove item from sales/service.
- Evaluate the complaint. Is it only one person, or are there multiple complaints? Is a legitimate illness described? What is the attitude of the complainant? Try to settle the complaint privately.
- Contact the appropriate people: the owner, general manager, health care administrator, school administration, prison warden, infection control coordinator, risk management, attorney, or any other person within the organization who will need the information.
- Contact the local regulatory agency responsible for investigating foodborne illness (follow the regulations for the individual county/state). Deal positively with all regulatory agencies. If CDC is to be notified, the local/state agency is usually responsible for the notification. Allow inspectors to inspect the property. Provide requested data. Be cooperative.
- Review all the information gathered (by the team as well as individually) and start an *internal* investigation that should include at least the following:
  - ✓ Check all temperature charts for correctives of temperature for hot food/cold food holding and service, refrigerator/freezer, ware washing, and any other temperature recording charts.
  - ✓ Check to determine whether all interview forms are filled out.
  - ✓ Check all employees on duty at the time of the incident—was anyone ill, did anyone have uncovered draining cuts, burns, boils, or abrasions? Did employees wash hands as per policy? Was good personal hygiene practiced and followed? Attach a list of excluded employees.
  - ✓ Check for complaints from the food service staff.
  - ✓ Check for evidence of cross-contamination.
  - ✓ Compare notes with all concerned parties.
  - ✓ What is new or different today—is there a new food item on the menu, new supplier, new employee, breakdown of equipment, improper water temperature, inappropriately stored chemicals/new chemicals, cross-contamination of raw and cooked foods, lack of sanitation/sanitizing of utensils and equipment, pest infestation?
- If only one or two customers complain, offer refunds or gift certificates. If more complaints are received, follow the established local health regulations.
- Arrange for medical service, per the policy of the establishment.
- Have food tested by an outside independent laboratory that performs epidemiological analysis of food.

- Deal with the media positively. Provide accurate information. Use language that is understandable and noninflammatory. Keep the information positive. Answer *only* the questions that are asked. Avoid jargon. Remain calm and professional. Tell the truth; don't lose credibility. Do *not* try to bluff or give out misinformation or misrepresent the situation.
- Continue the investigation both internally as well as externally.
- Take corrective action as appropriate.
- Review outcome with all managers, staff, and other concerned parties. Make changes to policies, procedures, and monitoring systems as appropriate.
- Communicate all changes to the staff and others responsible; evaluate for effective outcomes.
- As required, file for future reference (Puckett and Norton, 2000).

REGULATORY, INDUSTRIAL, AND INTERNATIONAL IMPLICATIONS

Institutional foodservice establishments feed hundreds of millions of people annually. The customers in many of these establishments are young, at high risk, elderly, and ill. Care must be taken at all times to protect this vulnerable group of people.

Foodborne illness outbreaks can cost millions of dollars, have an effect on the lives of those who were ill and the families of victims, as well as causing the closure of the establishments and loss of jobs. Increased awareness of educational efforts, through Internet websites and hot line numbers maintained by commercial organizations (e.g., food processing, retail foods, food service), consumer organizations and regulatory agencies, and news media, has resulted in a public that is better informed on food safety issues and that demands that safe food be provided. Improved programs, methods, and equipment are also being developed to assist in reducing and/or eliminating possible pathogens in food processing and handling (see Chapters 3, 4, and 5). As described in Chapter 8, hygiene standards are being developed or improved by various international organizations—for example, International Organization of Standardization (ISO standards), Food and Agriculture Organization (FAO)/World Health Organization (WHO)/Codex Alimentarius, Commission of European Communities, and others. In early 2000, the WHO announced that the Commission of the European Communities adopted the "White Paper on Food Safety" and set out a "farm-to-table" legislative action program in motion. In the U.S. and many other countries, the Hazard Analysis Critical Control Point (HACCP) system is being implemented in food processing and handling (see Part IV) to improve safety of these products. The adoption and implementation of the U.S. Public Health Service (USPHS)/FDA Food Code (FDA, 2001) by state and local regulatory agencies has also served to reduce the risk of foodborne illness in food service and retail food facilities.

Although several federal agencies share responsibility for food safety in the U.S. (GAO, 1990), the majority of the regulatory responsibility for institutional food service is at the state or local level. Through funding allocated under the President's Food Safety Initiative, these federal agencies have been working cooperatively to improve the overall safety of the food supply through improved educational programs, research, and foodborne illness reporting.

In the Department of Health and Human Services (DHHS), the FDA is responsible for protecting the nation's health against unsafe and impure foods, drugs, and cosmetics and other potential hazards, is the regulatory agency with primary responsibility for food safety of processed foods in interstate commerce, and provides oversight to cooperating states involved in regulating food service and retail foods through the Food Code (FDA, 2001). Another DHHS agency, the CDC, plays a major role in investigating and recording reports of foodborne illness, through a highly refined network of cooperation with state agencies, and is charged with protecting public health by providing leadership and direction in the control of diseases and other preventable hazards.

In the USDA, the FSIS has primary responsibility for the regulation of meat, poultry, and egg products primarily by means of inspection. In recent years, FSIS is implementing a science-based strategy to improve the safety of these products from farm to table.

Many professional and trade associations also have active programs in foodborne illness prevention and in food safety education. For example, the American Dietetic Association (ADA) has emphasized food safety for many years through continuing education programs and publications. The ADA broadened its institutional efforts when it launched a food safety campaign for 2000 to educate the public on food safety for the consumer.

The Joint Commission on the Accreditation of Healthcare Organizations (JCAHO) has established food safety standards that are used in surveying health care organizations as part of assessment of sanitary practice in accreditation standards and surveys.

The Omnibus Budget Reconciliation Act, 1987 (OBRA) has also established food safety regulations that state and federal surveys use in surveying extended care facilities. The American School Foodservice Association (ASFSA) promotes good sanitation practices, and to ensure that the practices are followed employees are required to attend training in safe food handling methods. The National Association of College and Universities Food Service (NACUFS) has established standards designed to be a self-monitoring program for improving operations and as part of a volunteer peer review program. The Division of Corrections, usually through their medical division, has developed guidelines that are used in correctional facilities. The guidelines will vary between local jails, state, and federal facilities, but they have food safety as a major goal. All states utilize local and state public health sanitarians to inspect institutional foodservices, using set guidelines that are contained in their regulatory guidelines, regulations, and codes.

As technology, industry, and customers work together to improve the food

supply, the jobs of the institutional food service establishment will be made simpler. However, there will always be the need for ongoing monitoring of all aspects of the operation for breaches in procedures and methods. Food service personnel and food handlers, from the farm to the table, need education on safe food handling procedures. Employers need to hire the right people to work in institutional food service establishments, train them to be competent, and empower them to take action in preventing foodborne illness.

CURRENT AND FUTURE IMPLICATIONS

Currently, the most effective method to use in curbing unsafe food handling procedures is to implement a HACCP process in all institutional foodservice establishments through cooperation with appropriate regulatory agencies. Ongoing monitoring and documentation of outcomes is necessary to validate that the food safety program is working and/or corrections have been made to improve the process. Policies and procedures need to be updated and communicated to staff as new products, equipment, or procedures are introduced into the system. Improved training and communication with the staff on the principles of food safety and sanitation (especially keeping food hot, keeping it cold, and keeping it moving) is a simple way to reduce problems.

The future is bright as new technologies, surveillance networks, implementation of regulatory programs for pathogen reduction, and worldwide safety issues are addressed. For example, properly implemented aquaculture technology may improve the safety of seafood. Food irradiation, where approved, has the promise of improving food safety and quality. If properly implemented, genetic modification may also have a positive impact on food safety and quality. The FDA "has concluded that the use of biotechnology in food products does not pose danger to health or safety" and more than half of the soybeans and nearly one-third of the corn planted in the U.S. are from genetically altered seeds. However, a bill has been introduced in Congress that would require extra labeling for all genetically engineered food (GEF).

Innovations within food service facilities are also being implemented including:

- Improved refrigeration and freezing equipment such as blast chillers for rapid chilling and freezing;
- Improved and more automated time and temperature-recording sensors and devices, including hand-held thermometers with software packages for data handling capabilities;
- Hand washing facilities and systems with inclusion of "fail-safe" methods;
- Improved and more efficient design and layout for institutional food service facilities using more appropriate materials;

- Improved sanitary design of food equipment that is more easily cleaned, nontoxic, and nonabsorbent.

Hopefully, in the future, HACCP data can be integrated with local and corporate information management systems to allow tracking of inventory and performance of personnel and, furthermore, communications can be developed into a wide area network (WAN) to communicate from store/plant to corporate officials to supplier to receiver. Automation is the infrastructure of the future; it will have the potential to save money, labor, and time and to be more efficient. Utilizing applied technology allows food service institutional establishment to apply the many new methods, equipment, and products available in the marketplace while achieving a higher degree of safe food and water handling procedures.

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INTERNET RESOURCES

www.cfscan.fda.gov
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CHAPTER 28

FOOD SERVICE AT TEMPORARY EVENTS AND CASUAL PUBLIC GATHERINGS

INTRODUCTION AND DEFINITION OF ISSUES

Temporary food service events or casual community gatherings where food is provided have existed since early human communities celebrated important occasions—eons before the formal governmental regulation of food processing and preparation evolved. Because food is an integral part of many community activities, temporary food service will always be part of those gatherings. Camaraderie over a shared meal is often the main reason a temporary food service event occurs, as with a supper at a club, congregation, fraternal group, or fire hall. Sometimes it is a commercial activity that takes advantage of and provides service for people at gatherings for other purposes, for instance, food vendors at summer agricultural fairs or other outdoor events. Mobile street vendors could be termed temporary food service operators because they can operate seasonally and often move from one location to another. Emergency disaster shelters often offer temporary, community-based food service, as well.

Providing a discreet definition of "temporary food service" becomes more difficult as one considers the food safety literature related to such events. Some temporary food service is overseen by food regulatory agencies, and some is not. Temporary food service at camps and mass gatherings like music festivals is usually regulated to some extent. Some temporary food service is seasonal, such as food vendors at fairs held once a year, and some, such as mobile food carts, may operate on a more regular basis, but they are unlike regular modern food service establishments because they operate under less than optimum conditions. Sometimes regulated caterers transport ready-to-eat food to a location where it is left to be held and served by persons attending a gathering at an unregulated place.

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The Food Code [United States Public Health Service (USPHS), 2001] defines "temporary food establishment" as "a food establishment that operates for a period of no more than 14 consecutive days in conjunction with a single event or celebration." However, for purposes of this discussion, "temporary food service events" will include situations that fall under this definition from the Food Code (USPHS, 2001) as well as camps, mobile food vendors, emergency disaster shelters, large social gatherings, and situations in which food prepared and delivered by a caterer is held and served by others not employed by the catering company.

Estimates of the relative size and economic value of temporary food service in the U.S. are difficult to obtain for several reasons. In 1999 the number of active temporary food service operations under permit in upstate New York was 3789, but no estimate of the economic value of these establishments is available and the number of such operations with no health department permits is unknown. The New York City Health Department does not report the number of temporary food operations as a category, but the number was estimated to vary from 1000 to 5000 annually and this does not include mobile vendors (Fogg, 2000).

BACKGROUND AND HISTORICAL SIGNIFICANCE

Foodborne illness caused by bacteria, viruses, or parasites and associated with food service at temporary events or casual public gatherings is caused by the same factors that occur in conventional food service settings. These include:

- Food preparation errors such as:
  Inadequate cooking
  Improper cooling
  Cross-contamination
  Poor personal hygiene
  Bare hand contact with ready-to-eat food
  Ill food worker preparing food
- Lack of training in or attention to safe food preparation principles.
- Food from unsafe sources.
- Contaminated water.

In addition, often the conditions under which the food is prepared at a casual event can make it very difficult to practice safe food preparation principles, and in many cases such events are not regulated in the same manner as conventional food service operations.

Some temporary food service events, whether or not such events fall under local health regulations, take place where food preparation facilities and sanitary conditions are extremely primitive or at least fail to meet modern stan-

dards. Such conditions exacerbate food handling errors that may occur [Centers for Disease Control and Prevention (CDC), 1991; Lee, et al., 1991; CDC, 1995). Other outbreaks occur at temporary events where food preparation and sanitary facilities are deemed adequate but ignorance of food safety principles and food handling errors by those in charge contribute to mishandling of food (CDC, 1994a, 1994b, 1994c; CDC 1996c). In some instances, the raw food served to patrons or guests comes from an unsafe source and when consumed raw causes illness (CDC, 1996b; CDC, 1997a). In other cases, untreated or posttreatment-contaminated water is consumed directly, in ice, or in food (CDC, 1996a; CDC, 1999).

SCIENTIFIC BASIS AND IMPLICATIONS

Foodborne Illness Outbreaks Related to Food Service at Temporary Events and Casual Public Gatherings

Bean et al. (1996) discussed the many factors related to health authorities, physicians, and consumers that influence whether or not foodborne outbreaks are reported to the CDC. It is believed that only a fraction of the estimated millions of foodborne illness cases are reported each year. Outbreaks that draw the most attention and therefore are more likely to be reported to health authorities include outbreaks that are large, interstate, and/or restaurant associated and those that cause serious illness, hospitalizations, and/or deaths. Outbreaks of mild illness in small groups or families are often not brought to the attention of either physicians or health authorities (Bean et al., 1996). These factors hold true for outbreaks traced to temporary food service events or casual public gatherings, but in recent years several such outbreaks have been reported and several are summarized below.

In 1988, raw milk consumption at a vacation religious school in Kansas caused 120 cases of *Campylobacter jejuni* infections (Bean et al., 1996). In August 1988, an estimated 3175 women who attended a 5-day outdoor music festival in Michigan became ill with gastroenteritis cause by *Shigella sonnei.* Onset of the illness peaked 2 days after the festival ended, and patients were spread throughout the United States by the time the outbreak was recognized. Investigators determined that uncooked tofu salad was the food responsible for the outbreak. During the festival over 2000 volunteers prepared the communal meals that were served, and 50 women had prepared and mixed the implicated tofu salad by hand. The larger outbreak of shigellosis was preceded by a smaller outbreak among the staff just before the festival began. The bacteria, which has a low infectious dose, was spread from the staff to attendees during the music festival. *S. sonnei* isolated from women who became ill before, during, and after the event had identical antimicrobial susceptibility patterns and plasmid profiles. Investigators compared conditions at such mass outdoor gatherings to military campaigns, where crowding of people and primitive

sanitary facilities magnify the potential for contamination of food and water. Access to soap and running water to wash hands was considered the most severe sanitary deficit at this festival, and lack of effective hand washing probably enhanced the transmission of shigellosis, both in food and from person to person. The camp was equipped with adequate potable water available in central locations; it provided an adequate number of portable toilets, and waste was removed regularly. Although attempts were made to improve personal hygiene over that of previous years, these efforts were apparently not adequate to prevent this explosive outbreak (Lee et al., 1991).

Inadequately cooked and possibly cross-contaminated round roasts that were consumed by attendees at an agricultural threshing festival in North Dakota in 1990 caused at least 70 people to become ill with gastroenteritis from *Escherichia coli* O157:H7; 16 people were hospitalized, and two children contracted hemolytic uremic syndrome (CDC, 1991). Also in 1991, 673 people who attended a festival in Connecticut became ill from *Salmonella heidelberg* infections that were caused by chicken and beef fajitas that had been improperly stored and cooked (Bean et al., 1996). After food was held at improper temperatures for several hours, *Clostridium perfringens* sickened people at casual gatherings in Wisconsin (120 cases) and in Minnesota (100 cases) in 1992 (Bean et al., 1996). *C. perfringens* infected 113 people who ate corned beef at a traditional St. Patrick's Day dinner; the corned beef had been precooked, not properly cooled, and not properly reheated before serving (CDC, 1994a). Chicken fried rice that was cooled at room temperature, and then held at ambient summer temperatures without reheating before serving, caused an outbreak of *Bacillus cereus* foodborne illness that infected 14 people, including 12 children, at a day care facility in Virginia in 1993 (CDC, 1994b). During this same year *Salmonella enteritidis* from raw eggs used to make homemade ice cream caused gastroenteritis in 12 people who attended a cookout at a psychiatric hospital and consumed the ice cream (CDC, 1994c). In 1997, Girl Scouts in Los Angeles prepared cheesecakes with minimally cooked egg yolks and raw egg whites, and 13 people at their outing became ill from gastroenteritis caused by *S. enteritidis* (CDC, 2000).

An estimated 50 people who attended a social event in Minnesota in 1995 suffered diarrheal illness associated with *Cryptosporidium parvum*. Water consumption was unrelated to the illnesses, but consumption of chicken salad at the gathering was associated with the outbreak. The hostess who prepared the chicken salad also operated a licensed day care home and prepared the salad while the children were in the home. She denied knowledge of diarrheal illness in herself or any of the children and refused to submit a stool sample. She had changed diapers before preparing the salad and reported that she had washed her hands before working in the kitchen. Investigators concluded that the food preparer in this outbreak may have contaminated the implicated salad after contact with an asymptomatically infected child in the day care home. The salad required extensive handling in preparation, was moist, and was served cold, conditions conducive to initial contamination and preservation of infec-

tious oocytes (CDC, 1996c). Outbreaks of cryptosporidiosis and asymptomatic carriage of *Cryptosporidium* have been documented in child-care settings (Tangermann, 1991; Cordell et al., 1994), as have outbreaks of shigellosis (CDC, 1992) and other enteropathogens (Van, 1991). With regard to food preparation and sanitation, licensed day care facilities in New York are required to follow regulations similar to those governing food service establishments (Caryl, 2000).

Eighteen people who attended a large retirement party in Florida in 1997 suffered symptoms of staphylococcal food poisoning after consuming ham. The salty ham, an ideal growth environment for *Staphylococcus aureus*, had been contaminated either by the preparer's hands or by a soiled slicer. In addition, the large ham was sliced hot and put into a small, tightly covered plastic container, and put first into a cooler and later into a home refrigerator, so it probably never cooled adequately. The ham was served cold at the party the following day (CDC, 1997b).

In southern Maryland in 1997, mishandling of other hams caused a tragedy. Traditional vegetable-stuffed low-salt hams, contaminated with "enormous numbers" of *Salmonella heidelberg* (and generic *Escherichia coli*), served at a large church supper caused 746 people to become ill and caused two deaths, one confirmed and one suspected. Over three dozen people were hospitalized. The stuffed hams, a local specialty, had in past years been boiled individually from the raw state to doneness in parishioners' homes. Organizers of the large supper, held yearly for 50 years, decided that this large amount of home cooking might be too risky from a food safety standpoint, so they arranged for the hams to be steamed in three crab pots at a commercial seafood distributor's facility and stored overnight piled in a cooler in a local market. Both of these services were donated by the establishments. Unfortunately, the organizers were attempting a very large quantity-cooking project—they tried to steam 38 25-pound raw hams in three steamers that were not large enough to adequately cook the meat to doneness. The hams were packed so tightly in the steamers that the ones in the center never got cooked to a high enough temperature to kill the *Salmonella*. In addition, the hams were then piled together in the cooler and probably did not cool properly, allowing the *Salmonella* to grow to large numbers. Investigators felt that the large numbers of bacteria contributed to the magnitude of the outbreak (Israel, 2000). In yet another example of good intentions gone awry, poor food handling or a contaminated ingredient in potato salad sold as part of boxed lunches during a community school fundraiser in Shubenacadie, Nova Scotia, Canada caused 39 confirmed illnesses and the death of an 80-year old woman from *Escherichia coli* O157:H7 infection (FS Net, 1998).

Consumption of rare ground beef at meals cooked over a campfire on an overnight trip near a camp in Virginia in 1994 sickened 18 campers and 2 counselors with grossly bloody diarrhea caused by *Escherichia coli* O157:H7; three people were hospitalized, including one with hemolytic uremic syndrome (CDC, 1995). Contaminated water at a day camp on the grounds of an ele-

mentary school in Florida in the summer of 1995 caused an outbreak of *Cryptosporidium parvum* that affected 72 children and 5 counselors; later 24 household members had onset of symptoms, as well. Investigators discovered that although a kitchen sink with potable water inside the school had been available for filling water coolers used at the day camp, counselors filled some of the coolers from a hose attached to an outdoor faucet. The hose and spray nozzle were also used to wash garbage pails; in addition, feces of unknown origin were observed on several occasions near the faucet and attached hose. Water samples taken from the outdoor faucet were positive for total coliforms and *C. parvum*. (CDC, 1996a).

Those who attend typical social functions sometimes unknowingly consume food from an unsafe source. In 1996, a woman ate raw oysters served at a party, became seriously ill, and died 2 days later. Earlier in her life she had suffered two serious disease conditions. *Vibrio vulnificus* was isolated from blood samples and traced to the oysters, which had been harvested in Louisiana (CDC, 1996b). In 1997, 20 persons who had attended a wedding reception in New York and who had eaten raspberries contracted cyclosporiasis. The raspberries had not been washed. Traceback data indicated that the raspberries might have come from Guatemala or Chile. Raspberries from Guatemala have been implicated in several outbreaks of cyclosporiasis in the United States and Canada (CDC, 1997a).

A highly publicized recent example of illness caused by food or water from an unsafe source or at the point of use is the outbreak that occurred late in the summer of 1999 at the Washington County Fair in eastern New York, where, despite mostly careful preparations, everything that could have gone wrong went wrong. Over 1000 people were sickened and 2 people died from *Escherichia coli* O157:H7 infection after consuming apparently unchlorinated well water that several food vendors used to make beverages and ice. Sixty-five people were hospitalized; 11 children developed hemolytic uremic syndrome (HUS), 1 of whom, a 3-year old, died. The second death was that of a 79-year old man from HUS/thrombotic thrombocytopenic purpura. Cases of diarrheal illness among fair attendees were reported from 14 New York counties and 4 states. Subsequently, some fairgoers infected with *Campylobacter jejuni* also were identified. (CDC, 1999)

New York State Health Department investigators from several jurisdictions started their Labor Day weekend investigation with a conference call on September 3, 1999 and quickly pieced together information that had been gathered from the *Escherichia coli* victims by county public health nurses. With the information that was rapidly being gathered, it soon became apparent that beverages and water consumed at the fair were the common means of exposure. Events scheduled at the fairgrounds subsequent to the county fair were cancelled. An environmental investigation determined that much of the fairgrounds was supplied with water from properly chlorinated wells. However, after a summer-long drought the water table was low and fair officials were forced to use water from an extra, usually unused well (#6) on one end of the

fairgrounds. Well #6 had been tested earlier in the summer, and there were no concerns about it at that time. This well was located near a cow barn with a manure storage pile nearby and near a septic system from an adjacent youth dormitory. It was initially conjectured that after a torrential rainstorm, surface runoff containing manure might have seeped into the underground water supply that feeds the well. Cultures of water from this well yielded high levels of coliforms and *E. coli* (New York State Department of Health, 1999). It was not known until after the outbreak that the line from well #6 to the chlorination system had for some reason been turned off sometime in the past (Fogg, 2000).

A dye tracer study conducted in the manure storage area did not show a hydraulic connection (a flow of water between two points) between that storage area and well #6 at the time of the study. A second dye study did show a hydraulic connection between the septic system of the dormitory and well #6, which is approximately 36 feet from the septic system. *Escherichia coli* O157:H7 was found in the septic system. The final report of the outbreak investigation noted that the exact environmental conditions (including drought followed by rain) present at the time of the fair could not be replicated for the later environmental studies; it also noted that because manure was removed daily, it may never be known whether manure-contaminated water percolated from the manure storage area to well #6. In addition, the source of the *E. coli* O157:H7 in the dormitory septic system is unknown and tests did not identify *Campylobacter jejuni* in samples from the dormitory septic system or well #6 (Novello, 2000).

The New York State Public Health Laboratory, the Wadsworth Center, used five different polymerase chain reaction assays to demonstrate the presence of *Escherichia coli* O157:H7 DNA in water from the implicated well and the water distribution system. Pulsed-field gel electrophoresis testing by the Wadsworth Center showed that the DNA "fingerprints" of *E. coli* O157:H7 isolates from the well, the water distribution system, the dormitory septic system, and most patients were similar (CDC, 1999). Investigators also had to track down the eight food vendors whose booths had been on the implicated water line and interview them about their activities at the fair. With the help of the state police departments in New York and Texas, one vendor was found and interviewed in Texas! Another vendor was traced to a nearby fair in New York; water he had taken from the Washington County fair to the second fair proved not to be from the contaminated source (Novello, 2000; Fogg, 2000).

New York state health officials stated that oversight and regulation of such temporary events needed to be tightened, and several immediate preventive measures were initiated by the agency. Additionally, the Health Commissioner directed her staff to review existing statutes and regulations to determine what changes to regulations or law should be made to protect the public health and safety at public events of this nature. Legislation providing the health department with explicit authority to regulate agricultural fairgrounds is being proposed (Novello, 2000). Several lawsuits against the Washington County Fair Association are pending (Fogg, 2000).

Levy et al. (1998) discussed earlier water-related outbreaks of illness not classified as waterborne disease outbreaks; these outbreaks are attributed to drinking water at its point of use rather than at the source or in the distribution system. Reported incidences included an outbreak of viral gastroenteritis contracted by 21 persons who consumed ice at a picnic in New York in 1991, the outbreak of cryptosporidiosis at the day camp in Florida in 1996 mentioned above, and an outbreak of *Escherichia coli* O157:H7-related gastroenteritis associated with ice consumption by 27 people who attended a church festival in Wisconsin. In the last outbreak, water was frozen in plastic containers that may have been contaminated by a water faucet that might have been contaminated by preparation of ground beef, or the containers themselves might have been contaminated when they were previously used to store the ground beef (Levy et al., 1998).

Mobile Food Carts

Several large cities in the United States allow vendors to sell ready-to-eat food from mobile carts on sidewalks, and this practice is prevalent in other countries, especially developing ones, as well. As populations of large cities become more diverse ethnically and culturally, the kinds of foods vended become more diverse and sometimes more hazardous than the simple hot dogs and pretzels of earlier times. The safety of foods vended at street carts is of concern because of the limited or poor facilities of the carts themselves, the possible poor food handling practices of the vendors, and the potentially hazardous foods that may be sold. New York City allows 5500 mobile food carts to be permitted, and 1000 of those are seasonal and considered temporary, in that the vendors need to buy a new permit for each season of operation. In addition to vendors with valid permits, there are an undetermined number of illegal carts with no permits. In New York City, unlike some other U.S. cities, some vendors are allowed to cook and sell a rather wide variety of potentially hazardous foods, which include most kinds of meat, poultry, ground meat, fish, tripe, and cooked vegetables, rice, and various dough products; shellfish are not allowed. These vendors are required by law to complete a certification course to operate; however, this is sometimes difficult to enforce. Fortunately, each cart sells only a limited menu of foods and the vendors typically sell food for only 4–5 hours per day, so this helps lessen the effects of any poor food handling practices that might occur (Caleb, 2000).

In a *New York Times* journalist's investigation of food safety conditions at some mobile food carts in New York City (St. George, 1998); a digital thermometer was used to test the temperatures of 51 foods immediately after purchase and commented on some poor handling practices he saw. The foods included chicken meals, rice, hamburgers, grilled sausage, beef kebabs, beef burritos/meat patties, hot dogs, gyros, and knishes. Only 12 of the 51 foods were hot enough to be considered safe if pathogens were present. Of 8

hamburgers tested, just 1 was fully cooked. Of 11 chicken dishes, 2 had reached the required temperature. None of the beef kebabs tested had reached a proper temperature. During the 2-day period not one food vendor was observed to have washed his or her hands; many of the sinks on carts were bone dry and inaccessible. Vendors were also observed to cross-contaminate ready-to-eat foods with raw meat juices; for instance, a vendor picked up a raw hamburger patty, put it on the grill, and then, without washing his hands, picked up and opened the bun in which it would be served. Other violations observed by the reporter included unrefrigerated potentially hazardous raw foods, partially cooked and fully cooked foods held for long times at ambient temperatures, and various types of cross-contamination.

Los Angeles, Santa Ana, and Orange County, California, also home to many different ethnic and immigrant groups, have some different challenges. Because geographically cities are much more spread out in California than cities like New York and Philadelphia, foods of all sorts are vended not only from typical mobile carts but also from the back of pickup trucks, old cars, and even stolen supermarket carts. Officials estimate that there are 6500 legally licensed and at least 3000 illegal vendors in Los Angeles County. Foods vended include everything from cut fruits and raw eggs and fish, to savory Mexican meat dishes, to cheese prepared at someone's home in a bathtub. Food safety violations include potentially hazardous foods stored at ambient temperatures, home-cooked foods of uncertain origin, improperly packaged items, and little or no hand washing. Health officials are burdened not only by the sheer numbers of vendors they must try to inspect but also by language and cultural perceptions and barriers that make it more difficult to explain and enforce food safety regulations. As in New York City, it is not known how many foodborne illnesses may be caused by food sold from mobile vendors (FS Net, 2000).

That pathogenic bacteria have been isolated from street-vended foods in other countries is no surprise because the same kind of mishandling of food described above has been reported wherever foods are sold from carts (Bryan et al., 1988; Bryan, et al., 1992a; 1992b; Quinones-Ramirez, 2000). Food handling errors included inadequate cooking and holding temperatures, little or no hand washing, poor ware washing facilities, and insect and vermin contamination, cross-contamination, and lengthy temperature abuse of foods. Investigators analyzed samples of purchased foods and isolated *Bacillus cereus, Clostridium perfringens*, and *Escherichia coli* (Bryan et al., 1988); *Staphylococcus aureus, Bacillus cereus*, and *Clostridium perfringens* (Bryan et al., 1992a; 1992b); *Salmonella* (Bryan et al., 1992a); and *Campylobacter jejuni* and *Campylobacter coli* (Quinones-Ramirez et al., 2000). All authors noted that such contamination represented a serious potential risk for consumers. However, in many countries where street vending is common, there is usually a lack of information about the incidence of foodborne diseases and investigations of outbreaks of these illnesses are seldom undertaken. Yet, diarrheal diseases are commonly experienced by persons of all ages in some of these countries (Bryan

et al., 1988), and epidemiological data from industrialized countries show that outbreaks of foodborne disease are frequently associated with the type of food mishandling observed (Bryan et al., 1992a).

Emergency Disaster Shelter Food Service

During January, 1998 large regions in the states of New York, Maine, and Vermont and the province of Quebec experienced devastating ice and snow storms, and later on, flooding, that caused extensive damage to properties, trees, and electrical power systems. Heavy accumulations of ice broke trees, electrical lines, and utility poles, and electrical power was lost to hundreds of thousands of households, farms, and businesses for up to four weeks. Lack of power and bitterly cold winter temperatures [0°F (−18°C) or below] forced many people to spend several days at short- and long-term emergency shelters. In New York at least nine people died, and six northern New York counties were declared federal disaster areas. Cornell University Cooperative Extension personnel who provided assistance at several shelters during the crisis made several observations that caused concern about both sanitation challenges and the safety of food handling (Moore, 1998; American Red Cross., 1998; CDC, 1998).

Hospitals and nursing homes in the affected region were overwhelmed, and many noncritical patients and residents, respectively, were taken to shelters. Some power company personnel who worked long hours to restore electrical power to the region were housed in shelters as well. The populations at many densely crowded shelters therefore consisted of all age groups from infants to the elderly, some healthy and some very sick, including persons suffering from infectious diseases. Around 9000 people were housed in 179 shelters in northern New York (Moore, 1998; American Red Cross., 1998; CDC, 1998).

The shelters were set up by the American Red Cross and other local agencies in fire halls, churches, fraternal organization buildings, schools, or whatever facility a town had that could be converted into a temporary shelter. Three of the largest Red Cross-sponsored shelters that were set up in schools housed 450, 803 and 1016 people, respectively. In many smaller shelters, overall sanitation and adequate toilet and hand washing facilities were often sorely lacking. A few shelters did not have heat or running water (Moore, 1998; American Red Cross., 1998; CDC, 1998).

Much food service during this time was provided by well-meaning but untrained volunteers in makeshift kitchen facilities that were decidedly inadequate for properly storing, preparing, and holding food in large quantities. After it was realized that in some areas electrical power would not be restored for days or weeks, shelter inhabitants were moved to regional schools where properly equipped food service kitchens were used to prepare and serve food. In addition, trailer kitchens were sent by the Southern Baptist Convention for meal preparation. The Red Cross helped to serve over 160,000 meals and provided some meal support at some of the other shelters as well. However, local

fire hall-type shelters still continued to prepare and serve food for local residents even after they ceased to sleep in the facilities (Moore, 1998; American Red Cross., 1998; CDC, 1998).

Many unsafe food receiving, handling, storage, and preparation practices were observed at short-term shelters. For example, home canned and thawed frozen foods were received, prepared food was allowed to sit at room temperature for many hours, raw meat cross-contaminated cooked food, volunteers smoked and ate while cooking, ready-to-eat food was touched with bare hands, and hand washing rules were not observed. It was interesting to note that during this period of time the third highest cause of hospital admissions in New York was gastrointestinal illness (Moore, 1998) and hospital emergency departments in Maine reported higher numbers of admissions for gastrointestinal illness as well (CDC, 1998). However, increases in the number of adverse health events reported by hospitals must be interpreted with caution because no statistics of actual foodborne illnesses related to the ice storm disaster are available (CDC, 1998).

An account of conditions at one temporary shelter provides an encouraging contrast to the more typical observations made above. A second Cornell University Cooperative Extension foods and nutrition educator in an adjacent northern New York county was actually in charge of running the emergency food service operation in the shelter in her hometown. She and a local caterer who also helped were knowledgeable about proper food handling procedures and sanitation practices; therefore, they were able to organize an effective and safe food service operation that served over 75 breakfasts, lunches, and dinners under challenging conditions for 7 days. Their group also supplied many sandwiches to the power company crews working in the area (Hess, 1998).

The safety of their food service procedures was evaluated by telephone with food safety officials at the American Red Cross and the local department of health. The evaluation revealed that the safety of food received was carefully assessed and the food was stored properly. Clean, sanitized, and appropriate equipment, thermometers, gloves, and hats were used while cooking and serving food. In addition, equipment and tables were cleaned immediately, using proper detergent and sanitizer, after each meal service was completed. Leftover food was stored properly, and temperatures were checked periodically. They also made sure that the toilet facilities were cleaned and sanitized regularly and supplied with soap and disposable towels. Even though they did not have recommended food service equipment, such as a three-compartment sink or adequate cooking stoves, in the shelter facility, they were able to set up a system that provided safe, wholesome food to the people they served because they knew the basic guidelines for safe food handling (Hess, 1998).

In addition to serving the public during disasters, temporary shelters in some towns are often activated when regular winter blizzards cause the closing of nearby interstate highways, which can strand hundreds of motorists for as long as 2 or 3 days (Moore, 1998). The American Red Cross, the Federal Emergency Management Agency, and branches of the U.S. armed forces and the

National Guard all provide emergency feeding after other natural disasters such as floods, hurricanes, and tornadoes. Many government agencies and state cooperative extension services provide guidelines for providing safe water and food during and after disasters. Disney et al. (1998) analyzed and summarized over 200 such guidelines in a USDA-CSREES-sponsored report.

REGULATORY, INDUSTRIAL, AND INTERNATIONAL IMPLICATIONS

The health codes of individual U.S. states and Canadian provinces and of local jurisdictions within states and provinces vary with regard to definitions of temporary food service and how various kinds of casual public gatherings are regulated. However, as the scientific community, the general public, and legislators learn more about the causes and prevention of foodborne illness, states and provinces and their local jurisdictions are gradually enacting more comprehensive regulations regarding safe temporary food service. In addition, the national food protection agencies in both countries have developed food codes that are meant to be adopted at state, provincial, and sometimes local levels.

The U.S. Food and Drug Administration publishes the Food Code, a reference of uniform standards that guides retail outlets such as restaurants and grocery stores and institutions such as nursing homes and child care centers on how to prevent foodborne illness. Local, state, and federal regulators use the Food Code as a model to help develop or update their own food safety rules and to be consistent with national food regulatory policy. The code is neither federal law nor federal regulation and is not preemptive, but it may be adopted and used by agencies at all levels of government that have responsibility for managing food safety risks at retail (USPHS, 2001).

At state and local levels the model Food Code may be enacted into *statute* as an act of the state legislative body, promulgated as a *regulation* by a delegated governmental administrative agency, or adopted as an *ordinance* if the local legislative body has been delegated rule-making authority. Typically, code adoption bodies publish a notice of their intent to adopt a code, make copies available for public inspection, and provide an opportunity for public input before adoption. The introductory section of the Food Code provides details on how governmental bodies can adopt the code (USPHS, 2001).

The Food Code has been adopted by some states, local municipalities, branches of the armed forces, and Native American tribal groups, as well as the National Park Service system. In addition, several other states and local jurisdictions are close to adoption of the Food Code. A majority of these entities have applied the Food Code to temporary events and other regulated food service establishments (USPHS, 1999).

The Food Code presents requirements by principle rather than by subject. For example, equipment requirements are presented under headings such as Materials, Design and Construction, Location and Installation, and Maintenance and Operation rather than organized by refrigerators, sinks, and thermometers. In this way provisions need be stated only once rather than repeated

for each piece or category of equipment. With the exception of the definitions section, a section on inspection frequency for temporary events, and small sections on construction materials and water tanks for mobile vendor facilities, there are no specific parts of the Food Code that refer to temporary events or mobile carts. The same provisions that apply to conventional facilities also apply to temporary events and mobile vendors. Annex 7 (Model Forms, Guides, and Other Aids) of the 2001 code provides a table (Chart #4) listing all the parts of the code relevant to mobile food establishments. The table facilitates finding pertinent guidelines based on the mobile unit's menu and operation. Mobile units are defined as ranging from push carts to food preparation catering vehicles (USPHS, 2001).

The Food Code is updated every two years, to coincide with the biennial meeting of the Conference for Food Protection. The conference is a group of representatives from regulatory agencies at all levels of government, the food industry, academia, and consumer organizations that works to improve food safety at the retail level. The Plan Review Development Committee of the Conference for Food Protection has developed a "Guide" for conducting plan reviews of conventional food service facilities and a second guide for temporary events. Both of these documents are available on the FDA website and will eventually be put into the Food Code as an annex. The committee expects that when the Conference for Food Protection meets in 2002, they will be asked to develop a guidance document for mobile vendors (Schrade, 2001).

Laws mandating certification of food service employees differ by state. The National Restaurant Association's Educational Foundation website provides food safety jurisdictional summaries for all the U.S. states and some municipalities. Most of the summaries do not mention temporary food service, but the summary for Monroe County in New York states that the county requires that temporary and mobile food service establishments and food carts must employ one certified manager to be present during all food preparation and service (NRA EF, 2000).

In Canada, under the Canadian Food Inspection System (CFIS) initiative, the Food Retail and Food Services Regulation and Code (FRFSRC) was approved in April 1999. This regulation serves as a model for provinces to implement in their respective legislation, and the code provides an interpretation of how the regulations can be achieved. Code 2.18.1 contains information about temporary events. Provinces are in the process of implementing the FRFSRC (St. Laurent, 2000; CFIS, 1999). Bryan et al. (1992a, b), from their work on the safety of street-vended foods in Pakistan and elsewhere, stated that health agency personnel in developing countries need to be informed about the hazards of street- and mobile-vended foods and to learn about the appropriate measures to prevent foodborne illness associated with these foods. From this one could assume that food safety regulations and education need to be enhanced in some developing countries.

In the U.S. and Canada, states and provinces with regulations in place to govern defined temporary food service events sometimes have exemptions from

certain parts of the food service code for various kinds of casual public gatherings such as religious congregations' self-catered meals, school carnivals, local fairs, and various festivals. These exemptions vary by state, province, or local municipality. In some states increasing numbers of fundraising events that involve wild game cookouts have been noted by health regulators. Wild game meats served include alligator, bear, deer, dove, elk, moose, quail, and turkey. Although there are approved sources for many of these species, many event sponsors rely on donations from hunters and hunts organized for this purpose to increase their profit margin (Reyher, 2000f). In New York, properly killed and butchered wild deer meat can be donated to charitable groups that offer food at no charge such as soup kitchens. With regard to mobile- and street-vended food, both the U.S. and Canada have well-defined regulations in place; however, it seems that in some locations political and cultural barriers, as well as health department inspection staff limitations, hamper effective enforcement of food safety regulations.

CURRENT AND FUTURE IMPLICATIONS

Many reported and unreported foodborne illnesses are caused by mishandling of food at temporary food service events and casual public gatherings. The factors that cause the illnesses are the same kinds of errors that occur in conventional food service establishments, but temporary and casual events food service may be more risky because often modern, well-equipped, sanitary food preparation facilities are lacking and those doing the cooking may have even less training in safe food preparation than regular food service workers. In addition to appropriate regulation and enforcement of food safety laws, education about how to handle food safely in temporary settings is imperative.

Knabel (1995) and Wolf (1995) summarized the demographic and lifestyle changes, as well as food system characteristics, that have influenced both food preferences and knowledge of safe food handling practices in the last two decades. Changes in family and societal structure, and in the food industry, have greatly affected food consumption and preparation habits both inside and outside the home. A survey by Williamson et al. (1992) found public knowledge to be inadequate with regard to safe food preparation. Questions about respondents' food safety knowledge and specific food handling practices indicated that many people are unaware of the dangers of improper temperature control of foods, cross-contamination, and food preparers' skin lesions. Compared with older survey participants, respondents aged 35 and younger had the least amount of knowledge about food safety concepts and practices. This indicated that perhaps children and younger adults have received little training in the basic principles of safe food preparation (Williamson et al., 1992). If this trend holds, one could make a case that foodborne illness outbreaks related to temporary food service and casual community events, as well as in the home and in

some food service establishments, will continue to occur and may even increase in the future. This possibility underscores the need for enhanced regulatory oversight of temporary food facilities and effective food safety education for those who prepare food for temporary events.

Some useful education programs and guidelines have been developed to educate temporary and casual food workers and volunteers. The Plan Review Development Committee of the Conference for Food Protection is developing a comprehensive guide for health regulators and events planners entitled, *Plan Review Guidelines for Temporary Food Establishments*, a draft of which is currently under review (Schrade, 2001). This guide spells out in detail the many factors that event organizers and regulatory personnel need to consider when food service is planned at a temporary gathering. In recent years the Food Safety and Quality National Initiative of the Cooperative State Research, Education, and Extension Service (CSREES) of the U.S. Department of Agriculture (USDA) has funded the development of many food safety education and training programs developed by food safety extension educators at several land grant universities. Table 28.1 lists some of these programs that could be useful for teaching food safety to volunteers, cooks, and food handlers who work at temporary food service events.

Other resources can be found at the website of the National Agricultural Library Food and Nutrition Information center: *http://www.nal.usda.gov/fnic*. In addition, the Food Safety and Inspection Service (FSIS) of the USDA has many fact sheets, including one entitled, *Safe handling of Complete Meals to Go*, at its website: *http://www.fsis.usda.gov/OA/pubs/meattogo.htm*. The US Food and Drug Administration (FDA) has funded two one-year education development projects. Funds were granted to the Illinois State Health Department to develop a program entitled, *Food Safety for Festivals, Fairs, and Fundraisers—An Instructional Website and Video* and to the Maricopa County, Arizona Environmental Services Department to develop a program entitled, *Risk-Based Assessment Program for Off-Site Food Service*. A USDA (CSREES) special funds grant provided support to the authors of the present chapter to develop a food safety education curriculum and food safety kit to help teach principles of safe food preparation to volunteers at emergency disaster shelters. And, as mentioned above, the report by Disney et al. (1998) provides an extensive bibliography of existing educational materials for providing safe food in emergency situations.

Education about basic food safety principles needs to be introduced in early childhood educational activities and to continue through elementary and secondary school science courses (Wolf, 1995). Widespread distribution and use of educational programs such as those described above and development of innovative food safety materials that can be incorporated into existing school science courses are essential to increase the food safety knowledge of the general public. Through effective food safety education for everyone, as well as more regulatory oversight where possible, safe food served at temporary food service events and casual community gatherings can be ensured.

TABLE 28.1. Some Food Safety Education and Training Programs for Food Workers and Volunteers at Temporary Food Service Events and Casual Public Gatherings.

Title/Resources	Developed by	University	Where to order	Cost
Safety and Food Excellence (SAFE). Slides, lesson plans, activities, references, certificates (for food service and volunteers)	Kendall, P., Gravani, R.B., Schmidt, D., Scott, D., Caldwell, K., and Weitzel, D.	Colorado State and Cornell Universities	Cornell Educational Resources Program 607/255-9252	$55.00
Food Safety Education: Community Service Learning Curriculum. Overhead masters, activities, record keeping (for youth audience)	Pivarnik, L., Smith-Patnoad, M., Steen, M.D., Swierk, M., Woods, B., and Zaletta, K.	Universities of Rhode Island and Vermont	Website: *www.uri.edu/ce/ceec/foodsafety.html*	$50.00
Safe Food Handling for the Occasional Quantity Cook, Overhead masters, brochures, magnet, activities, tips from sanitarian (for volunteers at one-time food functions)	Medeiros, L.C. and others 614/292-2699 *medeiros.1@osu.edu*	Ohio State University	Ohio State University Extension Publication Office 385 Kottman Hall, 2021 Coffey Road Columbus, OH 43210	$10.50 print materials $25.50 complete set, video
Safety Training, Resources, and Education to Combat Hunger (STRETCH). Fact sheets, cards with food safety messages; tips for using volunteers effectively.	Burgess, W. and others	Purdue University and University of Wisconsin	Purdue University Media Services Distribution Center 765/494-6794	$10.00
Food Safety from Crop to Cupboard. Food safety program for farm market vendors and shoppers. Plans to build display; fact sheets and posters.	Schneider, K.	University of Vermont	Contact Karen Schneider 802/773-3349 *karen.schneider@uvm.edu*	No cost for print materials. $10.00 Glossy posters

Safe Food for the Hungry. Food safety materials for use with emergency feeding programs	Burgess, W. and others	Purdue University	*http://www.aes.purdue.edu/ACS/sfh97/regis.html*	
Food Safety Training Program for Volunteer Foodservice Workers: Looking For a Safe Harbor. Trainer's guide, video tape, overheads, fact sheets, marketing materials, comprehensive guide book for temporary events planners.	Wright Hirsch, D., Smith-Patnoad, M., Steen, D.M., and Violette, C.	Universities of Connecticut, Rhode Island, Vermont, New Hampshire	Website: *www.uri.edu/ce/ceec/foodsafety.html*	$35.00
Soup Up Food Safety In Your Kitchen 122 color overheads or slides in 10 modules, lesson plans, activities, quizzes, references (for volunteers in soup kitchens, shelters, food banks, other quantity food situations that use volunteers)	Scott, D.L., and Gravani, R.B.	Cornell University	Cornell Educational Resources Program 607/255-9252	$350.00 complete notebook; $50.00 compact disk

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National Agricultural Library. Contains listings of helpful food safety educational resources. *http://www.nal.usda.gov/fnic*

The National Restaurant Association's Educational Foundation provides food safety jurisdictional summaries for all the US states and some municipalities within states. *http://www.edfound.org/NewASP/training/research/jurisdict/servjurisdict.asp*

The Food Safety and Inspection Service (FSIS) of the USDA has many food safety fact sheets, mostly for consumers, which would be good for volunteers; some are technical information for the food industry. *http://www.fsis.usda.gov/OA/pubs/*

PART VII

DIET, HEALTH, AND FOOD SAFETY

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CHAPTER 29

MEDICAL FOODS

MARY K. SCHMIDL and THEODORE P. LABUZA

INTRODUCTION AND DEFINITION OF ISSUES

Medical foods, also known as enteral formulas used to feed hospitalized patients or foods for those with rare diseases, have been an important achievement in science and medicine over the past 50 years. It has been estimated that there are more than 5 million patients on these types of foods in the United States and that these foods have a market value exceeding $1 billion (Frost and Sullivan, 1991; Mueller and Nestle, 1995).

Medical foods are designed to provide complete or supplemental nutritional support to individuals who are unable to ingest adequate amounts of food in a conventional form or to provide specialized nutritional support to patients who have special physiological and nutritional needs. Medical foods can be delivered in many forms, for example, sterile liquids that may be consumed directly or fed by a nasogastric or intestinal tube, rehydratable dry powders, and edible solid or semisolid forms (e.g., chewable bars). Products fed by nasogastric tube are generally considered foods under the Federal Food, Drug, and Cosmetic Act (FDCA) of 1938 and are differentiated from sterile parenteral nutrition solutions fed by vein; the latter are considered drugs and must be preapproved by the Food and Drug Administration (FDA) even though the same chemical composition may be found in the medical food and the intravenous solution.

Depending on the patient's nutritional status, a medical food may either supplement a diet for a short period of time or be the sole source of nutrition for extended periods of time. The average duration of treatment with medical foods for hospitalized patients on oral supplements has been reported to be 12 days, compared with 18.5 days for those on tube feedings (Steinberg and Anderson, 1989). Some medical foods are used for years to treat patients. For example, infants who are diagnosed at birth with phenylketonuria (PKU) are fed specialized formulas that are low in or devoid of phenylalanine and often supplemented with the amino acid tyrosine. This special formula prevents

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accumulation of phenylalanine in the blood, which causes mental retardation in these infants, who have impaired phenylalanine hydroxylase activity. This enzyme, normally found in the liver, converts phenylalanine to tyrosine. The need for these specialized diets for phenylketonurics appears to decrease with age, except during pregnancy. Such products are sometimes designated as "orphan" medical foods, a subcategory of medical foods, because their market size is extremely limited.

The key to understanding the development of nutritional products for clinical use and maintenance of individuals with metabolic disorders is the recognition that the physiological and nutritional requirements of hospitalized or compromised persons are generally different than those of average, healthy individuals. For example, many hospitalized patients:

- May have an increased need for calories (Kinney, 1976).
- Usually have an increased need for protein as a result of trauma or sepsis (Bistrian et al., 1974).
- May lack mobility, which can affect the biochemical requirements for specific nutrients (e.g., calcium).
- Exhibit malfunction of the food/nutrient-processing organs (e.g., stomach, intestine, liver, pancreas, or kidney), which can greatly alter nutrient requirements.
- Have a decreased ability to absorb and utilize nutrients if they have a disease or a resection or obstruction of the gastrointestinal tract.

Additional examples of compromised individuals include:

- Patients, such as those with cancer, thermal injury, severe trauma, dysphagia, or AIDS, who commonly are hypermetabolic and at various stages of their disease exhibit gastrointestinal dysfunction.
- Individuals with specific anaphylactic reactions to specific food components and who need special avoidance diets that are low in or devoid of the causative agents.
- Individuals with dysphagia, a swallowing impairment that results from an anatomic and physiological abnormality. Neurological illnesses, surgical procedures involving mechanical and anatomic alterations, anticancer therapy, and aging may lead to dysphagia and risk of aspiration. Diagnoses or conditions of patients who may have swallowing problems include Alzheimer disease, cerebral palsy, multiple sclerosis, Parkinson disease, and stroke.
- Individuals with inborn errors of metabolism, for example, PKU, maple syrup urine disease (MSUD), homocystinuria, galactosemia, fructosuria, hyperlipoproteinemia, who must strictly avoid specific food components/nutrients to prevent illness or death or must ingest increased amounts of certain metabolites to stimulate a specific metabolic pathway.

Advances related to medical food development have occurred in four main areas. First, our knowledge of the dietary management of acute and chronic diseases, inborn errors of metabolism, immune responses, and injury based on human physiology and biochemistry has increased. Second, advances in food process technology and the availability of certain chemical constituents have allowed the manufacturing of targeted food products containing various specialized nutrients to supply critical nutritional needs in various formats other than the original sterile liquids or rehydratable powders. Third, there has been considerable improvement in medical device, delivery and packaging systems, infusion pumps, and nonsurgical techniques that allow for convenient administration of liquid products, especially for nasogastric feeding. Finally, there is a renewed interest in enteral nutrition support dictated by hospital cost-containment measures, safety issues, and physiological benefits, including maintenance and integrity of the small intestine and pancreatic function, leading to the decrease of sepsis and infections.

BACKGROUND AND HISTORICAL SIGNIFICANCE

Early medical foods and enteral liquid feedings were developed with very primitive techniques. Evolution of these foods has enabled nutritional management of critically ill patients and has resulted in routine methods of delivery in controlled clinical settings as well as in the home, an excellent example of bringing basic research to a practical and beneficial level.

Before medical foods could be developed, a basic knowledge of metabolic pathways and the nutrients required to sustain life was necessary. It was not until the 1930s and 1940s, when the crucial roles of the essential amino acids, fatty acids, minerals, and vitamins were identified, that such development could take place. After these discoveries, coupled with the understanding of metabolic disorders and their physiology, the application to medicine was relatively rapid.

The earliest "elemental medical food products" (crystalline amino acid-glucose formulas) were spin-offs of the space program (Greenstein et al., 1957; Winitz et al., 1965). Early work, sponsored by the National Aeronautics and Space Administration, involved the use of elemental diets for in-flight space feeding to minimize the volume of human waste products. Urine presented few problems, but such was not the case for fecal material, an obvious concern because of the pilot mobility restrictions. Diets containing pure amino acids, glucose, essential vitamins, minerals, and fatty acids but devoid of residue and not requiring digestion were successfully developed and soon found other applications as medical foods. In 1960, the first clinical experience with "elemental" diets was reported by Couch et al. (1960). The diets were fed to several patients with slowly progressing neoplasms. The authors suggested that "elemental" diets could maintain positive nitrogen balance and permit nitrogen repletion in adult humans. Elemental and semi-elemental diets currently avail-

able include an array of products for the health care provider to treat patients with conditions such as compromised or nonfunctional gastrointestinal tract, pancreas, or other organs and those with the numerous diseases caused by food allergies or inborn errors of metabolism and managed by dietary means.

Increased recognition of the role of nutrition in human health and disease led to similar research in parenteral nutrition in the 1960s and 1970s. Total parenteral nutrition (TPN) products contain essential nutrients and basic building components of food systems (i.e., glucose, amino acids, and essential fatty acids). TPN products are administered intravenously (and are thus classified as drugs) to patients who cannot/will not/should not eat (enough or at all) or who cannot be fed by mouth or tube. These formulas will always be needed, primarily to provide nutritional support, when a patient is comatose, complete bowel rest is required, or the patient has little or no functional gastrointestinal tract. In most other cases, however, medical foods have become the more desirable alternative to parenteral therapy as long as there is access to and some function in the small bowel.

The importance of nutrition support in the hospital setting became very clear in the mid-1970s when research indicated that 50% of surgical patients in the U.S. suffered from moderate to severe protein-calorie malnutrition and 44% of general hospitalized patients suffered from severe caloric deficiency (Bistrian et al., 1974, 1976). Since then, many researchers have documented similar results in long-term care populations at home and in nursing homes, where eating is difficult or hard to manage (Shaver et al., 1980). Therefore, proper nutritional support of individuals in these settings can be of critical importance.

In some cases, a specially formulated medical food is not used for the purpose of a cure for the disease but instead is used to increase the patients' tolerances to disease treatment, for example, drugs, radiation, chemotherapy, and surgery. In other cases, such as treatment of infants with PKU and individuals with MSUD, the diet prevents mental retardation and death, respectively, so the effect is a direct physiological benefit. Thus "medical foods" fall in the gray area between a food that supplies nutrients and a drug that prevents, treats, cures, or mitigates a disease. A large body of research now demonstrates that appropriate nutritional support not only corrects malnutrition but also is cost effective through prevention of complications and needless deaths (Twomey and Patching, 1985; ADA, 1986; Shike, 1999).

REGULATORY, INDUSTRIAL, AND INTERNATIONAL IMPLICATIONS

Since the passage of the Pure Food and Drug Act in 1906, problems have arisen with regard to substances that are at the interface of foods and drugs. Numerous instances of FDA actions against special dietary products have occurred since that time (Merrill and Hutt, 1980). Even today, this controversy is exemplified by the current issues regarding conventional foods that have labels containing disease prevention claims (health claims) or dietary supple-

ments that now are allowed to carry "structure-function claims" (U.S. Congress, 1994). After the passage of the FDCA in 1938, medical foods were regarded as prescription drugs to ensure that their use would be supervised by physicians and to prevent misuse by healthy individuals.

In 1972, the FDA revised its classification of medical foods from "drugs" to "special dietary foods" (21 CFR 105.3) to enhance their development by and availability from the foods and drug industry. In 1973, the FDA proposed that medical foods would not be subject to the nutrition labeling regulations and defined them in 21 CFR 101.9(h)(4) as "foods represented for use solely under medical supervision to meet nutritional requirements in specific medical conditions." In 1984, a specific medical foods regulation was drafted by the FDA but was never published, because it was rejected by the Office of Management and Budget during a period of deregulation.

The FDA suggested that such foods be labeled in compliance with 21 CFR 105 (Scarbrough, 1989). Unfortunately, 21 CFR 105 provides little guidance for labeling of medical foods because it only covers products for hypoallergenic diets and weight loss and products designed as infant formulas. In 1976, the Proxmire Amendment to the FDCA (Section 411) differentiated regulation of vitamin and mineral supplements from that of medical foods, because the supplements were available over the counter and do not require use under supervision of a physician. This was further changed in 1994 with the passage of the Dietary Supplement Health and Education Act (DSHEA), which expanded the vitamin-mineral category to include herbs, botanicals, proteins, extracts, and metabolites (e.g., amino acids) and renamed them as dietary supplements. Furthermore the Act allowed for structure function claims that border on disease-drug claims, for example, "maintains healthy cholesterol" vs. "lowers cholesterol." In a way these dietary supplements are medical foods (not in the absolute legal sense) used by those who self-diagnose and self-treat.

In the early 1970s, there was considerable speculation that prepared infant foods might provide excessive salt intake for normal infants in the United States. On the basis of animal experimentation, it was hypothesized that a high sodium intake in infant diets might predispose infants to hypertension in adult life. This concern led to a recommendation that the level of salt added to strained and junior foods not exceed 0.25% and a call for a voluntary reduction in the salt added to infant foods by most manufacturers in the United States. It should be noted that there is no direct proof that a relatively large salt intake by the infant is a predisposing factor in the development of hypertension either at the time of intake or in later life. It appears that all of this attention to salt led to a technical error in manufacturing and marketing of a soy-based infant formula diet extremely low in chloride (1–2 mEq chloride per liter). By August of 1979, the Centers for Disease Control (CDC) identified 118 infants, associated with the use of this soy formula as well as a closely related special formula, as having metabolic alkalosis and failure to thrive syndrome. Because of public outrage in 1980, Congress passed the Infant Formula Act (FDCA, Section 412), which led to specific regulations (21 CFR 107.10 et seq.) containing

specific requirements for manufacture of infant formulas so as to prevent this type of problem from occurring again. Infant formulas designed for treatment of special disease conditions, such as inborn errors of metabolism, low birth weight, or unusual medical or dietary problems, and formulated without all of the nutrients normally required by 21 CFR 107.10 are allowed under 21 CFR 107.50(a). These products are classified as "Exempt Infant Formulas," and manufacturers must submit data as to composition and need for the product to FDA 90 days before commercial introduction of the product.

In 1988, Congress amended the Orphan Drug Act—which covers drugs used to treat conditions for which there are fewer than 200,000 new cases per year—to include the first legal definition of medical foods (21 U.S. Code 360ee(b)(3)). Medical foods were defined as foods formulated for consumption or administration enterally under the supervision of a physician and intended for the specific dietary management of diseases or conditions for which distinctive nutritional requirements based on recognized scientific principles are established by "medical evaluation" (U.S. Congress, 1988). This definition was intended to give credence to the concept of orphan medical foods, which were defined in the amendment as a subcategory of medical foods that includes products useful in the management of "any disease or condition that occurs so infrequently in the United States that there is no reasonable expectation that a medical food for such disease or condition will be developed without assistance" (21 U.S. Code 360ee(b)(3)). The latter definition is currently under consideration by the FDA, because many diseases such as lung cancer, breast cancer, and colon cancer have fewer than 150,000 new cases per year. As a point of reference, in the U.S., inborn errors of metabolism such as PKU, urea cycle disorder, and glycogen storage disorder are present in about 1 in 10–12,000 new births or 200–400 new cases per year (a total population of about 20,000), whereas MSUD, propionic acidemia, and methyl malonic acidemia are present in 1 in 120,000 births or 20–40 new cases per year (a total population of only about 2000).

The Codex Alimentarius Commission (CAC) is an international intergovernmental body. It is responsible for the implementation of the Joint Food and Agriculture Organization–World Health Organization (FAO/WHO) Food Standards Program, which aims to simplify and integrate food standards by developing recommended standards for food that will enhance consumer protection and fair practices in international trade (see Chapter 35). Subordinate committees of the Commission meet on a regular basis, generally every 1–3 years, to discuss and work on standards and guidelines to meet the objectives for various issues that affect international trade (e.g., contaminants, food labeling, commodity standards). One of the Codex committees is the Codex Committee on Nutrition and Food for Special Dietary Uses, which is responsible for addressing the need for standards and guidelines on nutritional quality for foods and guidelines and standards for commodities such as infant formula, cereal-based supplemental foods for infants and children, dietary supplements, and food for special dietary uses (e.g., gluten-free foods for persons with celiac

disease or very low-calorie diets for physician-supervised weight reduction). In 1991, the CAC approved standards for foods for special medical dietary uses. This was expected to foster international harmonization in this area and to lead to a larger market but has been largely ignored. These specialized dietary foods fall between the categories of normal foods and drugs, and their regulatory status is unclear.

In 1995 (60 FR 53078 and 53084), the FDA announced the agency's general policy on the development and use of standards with respect to international harmonization of regulatory requirements and guidelines and addressed, in detail, the conditions under which the FDA plans to participate with standards-setting bodies outside of the FDA in the development of standards for products regulated by the agency. Three key aspects of this policy that bear directly on the expressed concerns about the United States' participation in the development and use of international standards are that the standards must (1) ensure product safety, (2) be based on sound scientific and technical information, and (3) not be in conflict with any statue, regulation, or policy under which the FDA operates. These policies ensure that the United States' position is consistent with applicable U.S. laws. The Codex Committee on Nutrition and Foods for Special Dietary Uses continues to be extremely active. In a meeting held in Germany in 1998, it considered numerous items including provisions for "Vitamins and Mineral in Foods for Special Medical Purposes." At the meeting there was an exchange of views regarding the scientific basis of nutrient requirements for diseased people and the age groups to be considered when setting minimum and maximum levels of vitamins and minerals. A number of concerns were raised by committee members, and they agreed that the issues identified deserved additional consideration and agreed to revise the provision and to reconsider the document at the next session (Codex Alimentarius Commission, 1998).

DEFINITION OF ISSUES

The definition for medical foods in the U.S. was finally incorporated into the Nutrition Labeling and Education Act of 1990 (NLEA) (21 U.S. Code 343) and now is the current authoritative definition (U.S. Congress, 1990). The NLEA, however, exempted medical foods from the requirements of nutrition labeling to ensure that other specific regulations would be developed to control medical foods. Today in the Code of Federal Regulations [21 CFR 101.9(j)(8)] the following information is listed: "A medical food is a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation. A food is subject to this exemption only if:

(i) It is a specially formulated and processed product (as opposed to a naturally occurring foodstuff used in its natural state) for the partial or exclusive feeding of a patient by means of oral intake or enteral feeding by tube;

(ii) It is intended for the dietary management of a patient who, because of therapeutic or chronic medical needs, has limited or impaired capacity to ingest, digest, absorb, or metabolize ordinary foodstuffs or certain nutrients, or who has other special medically determined nutrient requirements, the dietary management of which cannot be achieved by the modification of the normal diet alone;

(iii) It provides nutritional support specifically modified for the management of the unique nutrient needs that result from the specific disease or condition, as determined by medical evaluation;

(iv) It is intended to be used under medical supervision; and

(v) It is intended only for a patient receiving active and ongoing medical supervision wherein the patient requires medical care on a recurring basis for, among other things, instruction on the use of the medical food."

In 1988, the FDA initiated a Compliance Program (FDA, 1989a) to enable the agency to evaluate how the medical food industry ensures proper formulation, appropriate microbiological standards, and reasonable therapeutic claims for these products. Findings to date indicate that manufacturers are meeting or exceeding current FDA regulations (Hattan and Mackey, 1989). In contrast to this, there have been problems with certain dietary supplements, for example, the tryptophan-related eosinophilia-myalgia syndrome crisis (Hertzman et al., 1991), which resulted in about 36 deaths, the proposed required warning statements for dietary supplements with ephedra (62 FR 30677; 6/4/1997) because of the high reports of adverse events, and the γ-butyrolactone (GBL) problem, in which the FDA requested that manufacturers and distributors of GBL products remove them from the marketplace after reports of some consumers lapsing into comas (Harrison, 1999).

One critical factor, related to therapeutic claims, that may inhibit research and development is the fact that many intermediary metabolites (e.g., homocysteine or hydroxycobalamine) that could be added to medical foods to help alleviate a disease condition either are drugs or might be considered drugs instead of being regulated as Generally Recognized As Safe (GRAS) substances. Because of the small market for foods designed for diseases with few cases per year, the manufacturer cannot afford to seek approval of the metabolite either as a drug through an Investigational New Drug (IND) application or as a food additive. The FDA is pursuing the possibility of instituting an Investigational New Food category for medical food ingredients under Section 409 (c) of the FDCA (FASEB, 1991). This would allow the Secretary of Health and Human Services to give exemptions for investigational use of unapproved

food additives if consistent with the public health. This is further complicated by the fact that under DSHEA a "new" metabolite can be introduced into the marketplace as a new dietary supplement without preapproval for safety or efficacy, this would apply to any biological intermediate metabolite. The manufacturer merely has to notify the FDA of its introduction 75 days before doing so (21 CFR 190.6; 62 FR 49886, 9/23/97). As such, the compound is not subject to drug, GRAS, or food additive status, and the FDA has the onus of proving it unsafe.

On November 29, 1996, the FDA released an advance notice of proposed rulemaking concerning medical foods. The notice was published in 61 FR 60661. It signaled the intention of the FDA to issue new regulations concerning medical foods sometime in the future. The purpose of the notice was to gather comments from the public about several areas of concern regarding such regulation. The notice offered several scenarios and asked a number of specific questions of interest to the FDA. For example:

- FDA invited comment with regard to the scope of the statutory definition of "medical food." Specifically, the agency queried whether it should apply a narrow, physiological definition of the term "distinctive nutritional requirement" or interpret the definition to include products that are used for patients with problems relating to ingestion or digestion but otherwise satisfy normal nutritional requirements. Additionally, they sought comment on the definition of "supervision of a physician and "specific dietary management." Note that this came right on the heels of DSHEA, which was passed in late 1994, allowed "disease/medical benefit claims" to be made indirectly, and for which little regulatory control was allowed by Congress.
- The agency asked for comments with regard to the quantity and quality of scientific evidence that should be required to support nutritional efficacy and other claims made for medical foods and
- The FDA invited comments as to whether it should develop regulations related to specific quality control standards and procedures for medical foods and the labeling of these products along with cost considerations. In DSHEA, the Congress stated that GMPs be developed for dietary supplements. The FDA has issued an advanced proposed notice of rulemaking in this area (62 FR 5699, 2/6/97), which might serve as one possible model for medical foods, although as of April 2001 no final rules have been issued by the FDA in either area. Of course, the other possible model would be the more restrictive "Infant Formula Quality Control Procedures" (21 CFR 106).

Safety

There have been serious safety problems with foods that purport to be medical foods. In 1986, four infants died as a result of being fed an oral rehydration

solution that contained lethal concentrations of potassium. The FDA identified the oral rehydration solution as the cause of these deaths (FDA, 1986). The agency inspected the manufacturing site and analyzed the product's nutrient content. It was determined that high levels of potassium occurred in the product because GMP had not been followed. It was observed that weighing scales were used improperly and that persons responsible for the formulation of the product lacked adequate training.

In 1989, problems with a nutritionally complete product containing excessive amounts of potassium and sodium were brought to the FDA's attention as a result of a complaint from the Veterans Administration Medical Center in Nashville, TN. Administration of this product to a patient resulted in hyperkalemia, or elevated blood potassium levels, which can have life-threatening consequences including fatal cardiac arrhythmias. This patient required intensive medical treatment to reduce blood potassium levels and to prevent the serious side effects of hyperkalemia. FDA inspection of the facility that had manufactured this product revealed serious flaws in their GMPs. These flaws resulted in extreme variability in product composition between lots or individual packets of product, which became evident when the product was analyzed by the FDA for nutrition composition. The product was recalled (FDA, 1989b). In 1993, in response to a complaint to the FDA from a medical center in Seattle, WA, FDA analysis of a complete nutritional product being administered enterally to patients in an intensive care unit revealed that the product contained levels of potassium that were approximately twice the amount declared on the label. The agency concluded that this product represented an acute, potentially life-threatening hazard for any person with impaired kidney function, particularly those who were not being closely monitored for serious potassium levels. As a result, a number of products were recalled (FDA, 1993a). There have also been problems with medical foods involving potential microbiological contamination. In 1993, a modular protein product and a modular carbohydrate product were recalled because they had been manufactured under conditions in which they may have become contaminated with *Salmonella* (FDA, 1993b).

Claims

Health care providers and consumers rely on the claims made for medical foods in their labeling as a significant factor in deciding whether to use a particular medical food in the clinical management of a patient with a particular disease state or condition. It is important that the claims made for such product present an accurate interpretation of the scientific evidence concerning the usefulness of the product or special formulation. It is critical for the safe and appropriate use of the medical food that the claims made for it are accurate and unbiased, and that they are based on a critical evaluation of the science available to the manufacturer. The need for health care providers and patients to have confidence in any claim that a product makes requires that a strong

standard of substantiation be in place. A strong standard of substantiation would be one that requires that data be considered in the formulation of the product and in the development of any claims about its use. The FDA has evaluated claims for a small number of medical foods on a case-by-case basis and has applied the following general principles:

- A product marketed for use as a medical food in the dietary management of a disease or condition should have characteristics that are based on scientifically validated distinctive nutritional requirements of the disease or condition.
- There should be a scientific basis for the formulation of the product and the claim made for the product.
- There should be sound, scientifically defensible evidence that the product does what it claims to do.

The agency is concerned that some of the claims made for products that purport to be medical foods are not based on sound science and that consumers who use products bearing such claims and health professionals who recommend their use are being misled regarding the value of these products. In addition to the health risks created by unsafe or ineffective medical foods, consumers and third-party payers such as insurance companies and government health care agencies suffer significant economic losses when products marketed as medical foods do not do what they claim to do (61 FR 60661 11/29/96).

SCIENTIFIC BASIS AND IMPLICATIONS

Product Classification and Manufacture

There are numerous medical food products and classification systems (Bell et al., 1989; Hatton and Mackey, 1989; Heimburger and Weinsier, 1985; Shike, 1999). The FDA's Compliance Program Guidance Manual identifies four major categories of products (FDA, 1989a): nutritionally complete products, nutritionally incomplete (modular) products, products for metabolic disorders, and rehydration products. There are also disease-specific products designed to limit or increase certain nutrients or intermediary metabolites.

Nutritionally complete products The majority of medical foods currently in use are nutritionally complete enteral formulations. These formulations supply all the required protein, fat, carbohydrates, vitamins, and minerals in sufficient quantities to maintain the nutritional status of individuals receiving no other source of nourishment and are used for nutritional sustenance of patients with a wide variety of clinical conditions. The products within this class can be further subdivided on the basis of compositional profile (i.e., amount of fiber, caloric density, milk content, absence of lactose, etc.) and range from those composed of natural and whole foods, intact protein, complex carbohydrates,

and long-chain fats in the form of triglycerides to those consisting of simple sugars, amino acids, and medium-chain triglycerides (MCTs). The latter are indicated for individuals with impaired ability to digest or absorb intact nutrients. The raw materials used in the manufacture of nutritionally complete enteral formulations are supplied in such forms as calcium and sodium caseinate, soy protein isolate, hydrolyzed proteins in the form of peptides, crystalline amino acids, hydrolyzed corn starch, sucrose, and corn, canola, soy, fish, and safflower oils.

Nutritionally incomplete products These enteral formulations supply a single nutrient or combinations of nutrients in quantities insufficient to maintain the nutritional status of normal, healthy individuals. Known as modular components, these products can be used as supplemental sources of nutrients and calories in otherwise normal diets (e.g., MCT oil for extra calories) or can be combined with other modular components to produce a nutritionally complete formula.

The number of modular components has steadily increased in the marketplace. They permit flexibility because they can be tailored to meet special individual requirements. However, the disadvantages of modular products may outweigh their advantages and limit their widespread use. Disadvantages include (1) lack of sufficient labor in most institutions to properly mix the formulations in the correct proportions; (2) need for considerable expertise during the mixing of the modular components to prevent microbial contamination; (3) expense of these individually tailored formulations; (4) increased potential for environmental or microbial contamination or both during preparation in the hospital or at home by individuals untrained in dietetics or clinical nutrition; and (5) potential for induction of metabolic disorders or deficiency states resulting from lack of or excess of specific nutrients in the blended formula.

Formulas for metabolic (genetic) disorders These formulations are manufactured specifically for individuals with inborn errors of metabolism, for example, PKU, MSUD, cystic fibrosis, urea cycle disorder, glycogen storage disease, propionic acidemia, or methylmalonic acidemia. Although not nutritionally complete in the traditional sense (e.g., PKU products have a reduced level of aromatic amino acids to which the minimum amount of phenylalanine needed to meet the growth requirement of the infant is added), these formulas are designated to provide the nutrient composition necessary for the growth and development of a person afflicted with a specific metabolic disorder. The National Organization for Rare Diseases (NORD) has been formed to help promote research into the dietary restrictions and requirements for these diseases, as well as to enable third-party insurance payments for orphan medical foods. In these metabolic disorders and others treated with special individual formulations, histopathology may change with age, affecting nutrient requirements and requiring modification of the medical food in usually unknown dimensions.

Oral rehydration solutions These medical foods consist of products indicated for replacement of water and electrolytes that have been lost through mild to severe diarrhea. Standard components of these formulations include sodium, chloride, potassium, citrate, dextrose, and sterile water.

Specialized Nutrients

Because of the specific clinical requirements for nutritional support, unique ingredients may be used to manufacture medical foods.

Protein and amino acid sources Most commercially available enteral formulas consist of whole (intact) protein as the nitrogen source and meet the minimum standard for protein quantity and quality (FAO/WHO, 1965). Formulas with nitrogen in the form of peptides or free amino acids are also available for patients with malabsorption or specific organ disease (e.g., renal or hepatic failure). Considered elemental diets, these products were developed to provide "predigested" protein to patients with impaired mucosal absorption. Because of their high osmolality, however, these diets may induce vomiting, diarrhea, and electrolyte abnormalities, which may negate much of their potential benefits (Koretz and Meyer, 1980). This intolerance appears to be overcome by initial dilution of the formula and slow continuous feeding into the gastrointestinal tract.

Because no naturally occurring protein is low in phenylalanine, there is no natural food on which to base a diet for individuals with PKU. Instead, the basis of the diet must be either (a) a mixture of synthetic amino acids that limits or excludes phenylalanine completely or (b) a protein hydrolysate from which the amino acid has been removed (e.g., by absorption onto charcoal). Because synthetic amino acids are expensive, hydrolysates are now commonly used; and casein is the usual starting material, although some amino acid supplements may be required (Bichel et al., 1954). One disadvantage of hydrolysates is the unpleasant bitter flavor of some short-chain peptides, which can lead to refusal to eat. Challenges for the future include separating out the bitter peptides and replacing those missing amino acids with nonbitter dipeptides and the possible use of the plastein reaction to recombine the peptides into larger-molecular-weight proteins with little or no flavor (Schmidl et al., 1983). For the older child, these proteins might then be texturized in some way, such as by extrusion or the "surimi gel" process, to produce a solid cheeselike product rather than a liquid solution. Finally, biotechnology may be used in the modification of milk proteins to allow the cow's mammary gland to produce a new protein without phenylalanine, that is, making the cow into a medical food manufacturing entity.

Branched-chain amino acids High levels of branched-chain amino acids (BCAA) such as leucine, isoleucine, and valine are often recommended for hepatic failure and encephalopathy, multiple-trauma, and burn patients (Fisher

et al., 1976; Brennan et al., 1986; Alexander and Gottschlish, 1990). BCAA formulas contain about 40–50% of the amino acids leucine, isoleucine and valine. Concentrations of the aromatic amino acids (AAA) (e.g. tryptophan, tyrosine, and phenylalanine) are low. The exact mechanism for the physiological function of these amino acids is not clearly understood. Patients with hepatic encephalopathy tend to have decreased levels of BCAAs and increased levels of AAAs in blood and cerebrospinal fluid. AAAs were postulated to act as false neurotransmitters in the central nervous system, contributing to hepatic encephalopathy. Thus it was hypothesized that providing a medical food containing high levels of BCAAs and low levels of AAAs may reverse or improve the hepatic encephalopathy induced by the AAA false neurotransmitters. Randomized studies examining the use of solutions high in BCAAs in patients with hepatic encephalopathy, however, have not shown a clear benefit, and today their role in these patients is controversial (Brennan et al., 1986; Alexander and Gottschlish, 1990).

Major acute illnesses with severe metabolic stress, such as sepsis, severe trauma, major operations, and burns are associated with accelerated muscle catabolism. Because BCAAs are used extensively by muscles, providing solutions high in BCAA was proposed to be beneficial for muscle preservation in severely ill and catabolic patients. Some clinical trials have shown improved nitrogen balance with enteral or parenteral solutions high in BCAAs in critically ill patients; however, other studies have not shown such a benefit or any clinically relevant benefit in decreasing morbidity or mortality.

Essential amino acids Essential amino acid (EAA) formulas are designed for feeding patients with renal failure, many of whom have trauma or sepsis. Failing kidneys have a reduced capacity for clearance of various metabolites (urea, creatinine, uric acid) and minerals (potassium, phosphate, magnesium). Serum levels of some nonessential amino acids are elevated, and levels of EAAs, such as leucine, isoleucine, and valine, are decreased. The objectives of nutritional support in patients with renal failure are to provide optimal nutrition while minimizing the load of metabolites presented for handling by the compromised kidneys. The latter objective is particularly important when an effort is being made to avoid dialysis in patients with compromised renal function. However, optimal nutrition should not be compromised because of a need for dialysis. Renal enteral feeding solutions contain EAAs, histidine, and small amounts of fat and electrolytes. They do not contain vitamins or trace elements, which must be supplemented as needed. The low content of electrolytes allows flexibility—electrolytes can be added on an individual basis as needed. Studies in which medical foods were examined in renal failure patients suggest that the administration of EAAs is associated with improved nitrogen balance and attenuation of the rise in blood urea nitrogen.

Glutamine Because most dietary proteins contain glutamine, most medical foods will contain glutamine (Lacey and Wilmore, 1990). However, the ade-

quacy of the amount of glutamine contained in protein for hospitalized patients needs further research. Low plasma glutamine levels have been correlated with diarrhea, villous atrophy, mucosal ulceration, and intestinal necrosis (Souba et al., 1985). Mucosal degeneration and atrophy are particularly undesirable in critically ill patients because these conditions predispose them to bacterial translocation (i.e., bacteria pass from the gastrointestinal tract into the bloodstream) and sepsis (Deitch et al., 1987), which can result in death. It is unclear whether glutamine must be provided to the patient in a free form, a dipeptide form (crystalline amino acid), or a bound form within whole protein to extend the beneficial effect to the gastrointestinal tract. It seems logical that glutamine in any form (free, bound in proteins, or bound in hydrolysates) would be beneficial for the gastrointestinal tract by maintaining and restoring integrity. However, further research is needed to elucidate the mechanism and verification is required to support the limited number of studies conducted thus far.

Glutamine metabolism appears to be significantly altered after injury or catabolic disease states, and recent animal studies suggest that elemental diets supplemented with this amino acid have a tropic effect on the gastrointestinal tract, with subsequent improvement in intestinal integrity (Rombeau, 1990). Conditions such as trauma and sepsis are associated with increased gastrointestinal consumption of glutamine (Alverdy et al., 1985; Alverdy, 1990).

Arginine This amino acid is considered conditionally essential during growth and in conditions that result in persistent inflammation. Arginine can stimulate the release of prolactin, insulin, growth hormone, and glucagon and is an essential component of polyamine and nucleic acid synthesis. It is a major source of nitric and nitrous oxide in vivo as well as in vitro, which are mediators of protein synthesis, vascular dilation, and electron transport. In humans, arginine administration has produced increased numbers of peripheral blood lymphocytes as well as increased response to mitogens in vitro. Arginine supplementation has also been associated with reduced hospital stays after major operations (Barbul, 1990; Daly et al., 1992). It is also interesting that a small company located in Belmont, California recently used this knowledge base to develop a new medical food bar containing high levels of arginine, focusing on easing symptoms of heart disease through improving coronary blood flow and reducing angina symptoms.

Carnitine Many novel nutrients such as carnitine, which under certain conditions may become essential, have been added to medical food products. The daily requirement of carnitine is unknown for mammalian species, including humans.

Carnitine is synthesized in the liver from the essential amino acids lysine and methionine. Individuals with a systemic carnitine deficiency have been identified (Borum, 1983). If the liver is impaired, it is very possible that synthesis of carnitine may also be impaired. Because all of the long-chain fatty acids supplied in the diet must be transported into the mitochondria via a carnitine

pathway before they can be oxidized to produce energy, adequate levels of carnitine in the tissue are essential for these individuals (Fritz, 1959). Testasecca (1987) also showed that carnitine improved the energy metabolism of patients under TPN support, whereas Bohles et al. (1984) showed improved muscle mass of hospitalized patients given supplemental carnitine. Currently there is an on-going study evaluating the efficacy of supplemental carnitine (20 mg/kg/day) in premature neonates to increase plasma total carnitine concentrations in the hope of improving their weight gain and nitrogen balance (Crill et al., 1999).

Taurine Taurine, important for normal retinal development and the synthesis of bile salts (Hayes, 1988), may be essential for infants, children, and perhaps critically ill adults. Studies on taurine supplementation and its effect on fat absorption have shown conflicting results. However, some studies with cystic fibrosis patients showed improvement in fat absorption, growth, and weight gain after taurine supplementation (Belli et al., 1987). Several medical food products are now supplemented with taurine.

Ribonucleic acid The addition of nucleotides, in the form of yeast, meat, or fish extracts, to medical foods, most of which are nucleotide free, may have therapeutic applications for those who are immunocompromised due to metabolic stress or illness and are at risk of developing infectious complications. Ribonucleic acid (RNA) may be essential for the maintenance of normal cellular immunity and for host resistance under certain conditions (Kulkarni et al., 1986). Certain rapidly growing cells, such as T lymphocytes and intestinal epithelial cells, appear to lack the ability to synthesize nucleotides under stress conditions (the salvage/dietary sources are inadequate during severe metabolic stress), thus contributing to the decrease in immune function under these conditions.

Nucleotides also may be needed in the diets of cancer and AIDS patients who, by virtue of the disease, have suppressed immune function. Diets containing nucleotides have also been reported to decrease delayed hypersensitivity responses (Kulkarni et al., 1986), increase resistance to infections (Fanslow et al., 1988), and increase interleukin-2 production (Van Buren et al., 1985).

Fatty acids Use of MCTs, which contain fatty acids composed of 6–10 linear carbon units, in medical foods is advantageous for several reasons. Medium-chain fatty acids reach the liver more quickly than longer-chain triglycerides. The majority of MCTs are retained in the liver rather than in other tissues or organs, and MCTs can be used more readily by the cell because they do not require carnitine (the synthesis of which may be compromised) for their metabolism.

MCTs may be obtained from coconut oil, which naturally contains approximately 65% medium-chain fatty acids. To isolate these fatty acids and create MCTs, the triglycerides of the coconut oil are hydrolyzed by sodium hydroxide

and fractionated by distillation and/or supercritical carbon dioxide. In the next step 6-, 8-, and 10-carbon units are reesterified onto glycerol to create the MCT.

The caloric value of MCT oil is 8.3. kcal/g, in contrast to the traditional value of 9 kcal/g for long-chain triglycerides (LCTs). The use of MCT oil is specifically indicated for the following disorders of fat absorption and lymphatic drainage from the intestine: pancreatic insufficiency, biliary atresia, chyluria, chylous fistula, celiac disease, small bowel resection, and cystic fibrosis.

MCTs are most often used in combination with LCT oils in formulas today. This combination provides essential fatty acids via the LCTs yet retains the advantage of the easy digestibility, absorption, and metabolism of the MCTs. Although MCTs and LCTs compete for absorption, the administration of MCTs in conjunction with LCTs actually increases the total intestinal absorption of both compared with that of either alone (Bach and Babayan, 1982).

Structured lipids are synthesized by hydrolyzing MCT and LCTs to form a specific mixed-triglyceride molecule that is chemically distinct from physical mixtures of MCTs and LCTs and that may be more beneficial from a digestive and metabolic standpoint. Long-chain fatty acids, preferably linoleic, can be used to meet the essential fatty acid requirement (Babayan, 1987), and fish oils may be used to provide new triglycerides containing eicosapentaenoic acid or docosahexaenoic acid for patients who may benefit from omega-3 fatty acids (Campos et al., 1999). Although cost is a barrier to widespread use of structured lipids in foods, a number of nutritional products are available for nonclinical uses such as maintaining health or body building in addition to the medical applications such as impaired gastrointestinal function or infants with food allergies (Haumann, 1997). In the area of development of specialized lipids for infant formulas that imitate mother's milk, not only do the new oils imitate the fatty acid profile found in mother's milk but also the imitation is extended to the location of the fatty acid on the glycerol molecule. This may lead to improve fat absorption, but studies are under investigation (Carnielli et al., 1996). It is also interesting that structured lipids have found a role in the fat replacement market, namely, for reducing calories. For example, triacylglycerides comprised of selected short- and long-chain fatty acids can provide the sensory characteristics of typical fat with reduced energy content because they are not efficiently absorbed and contribute only about 5 kcal/g instead of 9 kcal/g. Salatrim, which stands for short and long acyl triglyceride molecules, is representative of this class of replacers. Salatrim's functional characteristics can be tailored depending on the selection and arrangement of fatty acids used, so it has a wide array of food applications. It can replace fat in chocolate and confections, cookies, crackers, and dairy products such as sour cream, frozen desserts, and cheese. FDA accepted a GRAS affirmation petition for salatrim, which is sold under the brand name Benefat™ by Cultor Food Science. Caprocaprylobehenic triacylglyceride, commonly known as caprenin, is manufactured from glycerol by esterification with caprylic (C8:0), capric (C10:0) and behenic (C22:0) fatty acids by Procter and Gamble (P & G).

Because behenic acid is only partially absorbed and capric and caprylic acids are more readily metabolized than other longer-chain fatty acids, caprenin provides only 5 kcal/g. Caprenin's functional properties are similar to those of cocoa butter. As a result, caprenin is suitable for use in soft candy and confectionery coating. Unfortunately, in clinical studies caprenin appeared to increase blood cholesterol levels and the product has been removed from the market (P & G, personal communication, 1997).

MCTs, often the basis for structured lipids, are a source of readily available energy because they are easily absorbed without the need for pancreatic lipase and transported directly to the liver, where they are metabolized like carbohydrates. Food applications include use as a carrier for flavors, colors, and vitamins, an oil coating for dried fruits, an ingredient of reduced-calories foods, and an energy source in special nutritional foods (Megremis, 1991). Cheeses made with MCTs as well as margarines and other spreads have been suggested as food items for patients with malabsorption problems (Babayan, 1991). Specialty fats include zero-*trans* soybean margarines prepared from an interesterified soybean oil-soybean trisaturate blend (80:20) or a blend of 80:20 feedstock with additional 20% liquid soybean oil to produce a softer product (List et al., 1995). Recent developments in the production of nutritionally functional fats and oils have been reviewed by Willis et al. (1998).

Short-chain fatty acids such as acetate, butyrate, and propionate produced by bacterial fermentation in the colon and cecum can contribute up to 30% of the energy requirement for humans on high-fiber diets. Short-chain fatty acids are readily absorbed by the colonic mucosa, and those that are not metabolized there are transported to the liver for conversion to ketone bodies and other lipids. It has been suggested that under stress the body may prefer to use ketone bodies (Birkhahn and Border, 1981). Medical food products containing fermentable fibers as precursors of short-chain fatty acids are a distinct possibility for the future.

Fiber Medical foods initially were fiber free, except for those prepared by blenderizing natural foods. There has been increasing recognition that dietary fiber offers numerous physiological and metabolic benefits. Most Americans ingest 8–12 g of dietary fiber daily. The recommended amount for healthy Americans is 10–13 g of fiber per 1000 calories. Since the mid-1980s, fiber has been added to medical foods to improve gastrointestinal function by regulating transit time and facilitating absorption of fluid and electrolytes from the gut lumen (Anderson, 1989). Two of the most common fibers used in medical foods are soy polysaccharide fiber and hydrolyzed guar fiber, because of their intrinsic low viscosity and their ability to flow through feeding tubes for oral tube-feeding products. However, other fibers such as oat, pea, pectin, and natural gums, could be used if solid products, which could be produced by extrusion or gelation techniques, were manufactured. Soy polysaccharides contain about 6% water-soluble fiber. The amounts of soy polysaccharide added to enteral feeding solutions varies between 2.5 and 5.9 g/250 ml. Fiber derived from oats or

psyllium may have a cholesterol-lowering effect, whereas most insoluble fibers, such as cellulose and hemicellulose, act mostly as laxatives. Despite the physiological considerations pointing to gastrointestinal and metabolic functions of dietary fiber, results of investigations on its role in medical foods have been inconsistent (Levine, 1994).

Phytosterols Cholesterol, an amphipathic molecule, has a steroid nucleus and a branched hydrocarbon tail. Cholesterol is found in the diet both in the free form and esterified to fatty acids, particularly linoleic acid. Cholesterol is found only in foods of animal origin; plant oils are cholesterol free. Although free of cholesterol, plant materials do contain phytosterols, compounds chemically related to cholesterol. Phytosterols differ in their chemical side chain configuration and steroid ring-bonding pattern. The most common dietary phytosterols are β-sitosterol, campesterol, and stigmasterol. The 5-α-hydrogenation of phytosterols forms saturated phytosterols, including campestanol and sitostanol. Increasing evidence suggests that saturated phytosterols, such as sitostanol, inhibit cholesterol absorption better than more hydrophilic plant sterols, such as β-sitosterol. These saturated phytosterols are found in very small amounts in normal diets. Since 1995 a cholesterol-lowering margarine, Benecol®, has been sold in Finland, targeting patients with cardiovascular disease. Studies showed that regular use of the product in place of butter or other margarines will reduce LDL cholesterol by about 14% (Miettinen et al., 1995). Benecol® is a canola oil-based margarine that includes sitostanol ester (1.5 g per serving), an esterified alcohol derived from pine oil, a by-product of the wood pulp industry. It was allowed for introduction into the U.S. market as a food after some objections by FDA were satisfied in which the company self-declared the stanol ester as GRAS. Additionally, another margarine-product containing plant sterols called "Take Control" was allowed to be marketed as a conventional food as of May 1999 in the U.S. In this case, Unilever (through T.J. Lipton) also used the self-declaration allowance to designate a soy lipid sterol as a GRAS substance so it could be added to foods. Both of these products carry the structure-function claims "Benefits cholesterol" or "Helps maintains healthy cholesterol levels."

Cholestin is a product currently marketed as a dietary supplement in the U.S. The FDA issued a notice to Pharmanex. Inc. (Siam Valley, CA) that their product, Cholestin, was a drug and therefore both adulterated and misbranded because no New Drug Application (NDA) had been filed. At that time, the product label stated that it could reduce both total cholesterol and LDL cholesterol. Cholestin is a red yeast-fermented rice product that was imported from China, where it was used both to color foods and in traditional Chinese medicine (TCM). The yeast fermentation produces a compound, mevinolin, which is exactly the same compound as a drug called Mevacor® (lovastatin) manufactured by Merck and approved in 1987 to inhibit cholesterol synthesis in the liver and thereby reduce cholesterol levels in the blood. In 1998, the FDA asked the Bureau of Customs to stop (blocklist) the product at all ports of entry

into the US, that is, preventing Pharmanex from getting the raw material they used to manufacture Cholestin as a dietary supplement in the form of tablets. Subsequently, Pharmanex sued the United States (*Pharmanex v. Shalala*, Case 2:97 CV 0262K, DC Utah) to overturn that decision. On February 16, 1999 the U.S. District Court agreed and overturned the FDA decision, declaring that Cholestin is a dietary supplement on the basis that DSHEA, 21 USC Section 321(ff)(3)(B)(I) declares that a dietary supplement does not include "... an article that is approved as a new drug under Section 355 ... which was not before such approval ... marketed as a dietary supplement or as a food." Thus the court ruled that this section only applies to new drugs and that Cholestin is a dietary supplement that was used as such in China before passage of DSHEA. What this means is that a dietary supplement may contain a substance with druglike activity, but if that substance was being used or marketed as a supplement by a company before DSHEA, the fact that it was also marketed as a drug by another party before that time does not make the supplement a drug. This case followed the standard set by *Fmali Herb, Inc. v. Heckler* (715 F. 2d 1383; D.C.N.C. 9/15/83). Before *Fmali*, the FDA held that foods, herbs, and botanicals not consumed in the U.S. before passage of the 1958 Food Additives Amendment were unapproved food additives or, if not, then the company introducing them had to either get a GRAS declaration or go through the food additive process. In 1973, the FDA thus prevented a sassafras herb tea from being marketed because it contained safrole, an unapproved food additive that was a carcinogen (*US v. Select Natural Herb Tea* Civ #73-1370 RF; D.C. Cal; 7/15/73). The Fmali case essentially overturned the block list the FDA instituted on a Korean herb (renshren-fenwang-jiang) on the basis that the Food Additives Amendment did not apply only to consumption in the U.S., that is, if a product was consumed safely somewhere in the world before 1958, it can be imported into the U.S. It should also be noted that the FDA instituted a new self-affirmation process for GRAS declaration (62 FR 18938; 4/17/97), which has not been finalized. However any new, never before used herb would either have to be declared GRAS before its use in food or it could be more easily introduced as a new dietary ingredient under DSHEA. Whether FDA will appeal the Pharmanex decision to the Circuit Court is unknown. This certainly makes the decision of what is a drug versus a dietary supplement in the U.S. market very confusing and certainly will eventually impact the medical foods market as a source of new ingredients and technologies becomes available.

Reduced lactose products Lactase, an intestinal oligosaccharidase normally present in the gastrointestinal tract of young persons of all racial groups, may be lost during aging or during periods of critical illness, causing adverse reactions to lactose-containing foods. Much of the world's adult population has some degree of lactase deficiency (Paige and Bayless, 1981) and must limit intake of some dairy products.

Medical foods free of lactose are prepared by four primary techniques: (1) exclusion of lactose from the formulation, (2) addition of lactase to products that are stored at reduced temperatures to enable hydrolysis of the lactose to glucose and galactose, (3) removal of lactose from milk by ultrafiltration or ion exchange, and (4), for liquid foods, binding of the enzyme on the inner packaging surface (Labuza and Breene, 1989), where the enzyme can then cleave the lactose in the solution while in transportation.

Product Form and Packaging

Medical food products are currently manufactured and packaged in two basic forms: (1) dry powders that may be reconstituted or rehydrated into liquids and (2) sterile liquid solutions packaged in steel cans, glass containers, or multilaminated (plastic/foil/paperboard) containers. Both forms tend to produce a monotonous diet, because the product is either drunk as a liquid or fed through a tube. In contrast, many dietary supplements, with medical food-like properties are now being made with conventional food technology, for example, the margarine-like products that contain natural plant sterols, which can reduce cholesterol absorption.

Reconstitution of dry powders and use of enteral delivery sets to administer formulas can result in problems because of the risk of microbial contamination (Krey et al., 1989; Kohn-Keeth et al., 1996). However, these products are generally less expensive than equivalent ready-to-feed liquids and require less storage space. They also enable feeding in a highly concentrated form (partially hydrated)—a useful option for fluid-restricted patients. Additionally, if the product is properly dehydrated and mixed under conditions that keep the moisture content low enough (generally at the monolayer value), the chemical reactions that can occur in liquids and result in nutrient deterioration during storage/distribution are minimized (Labuza, 1980).

Because all of the components of liquid products are heat sterilized together, the potential exists for significant initial losses and adverse chemical reactions. Other reactions during storage can result in loss of essential nutrients and/or production of undesirable end products such as off-flavors, bitterness, and development of toxic substances. Labuza and Massaro (1990) and Schmidl et al. (1988) studied and reviewed some of the storage problems of parenteral and enteral liquid medical food systems.

Glass bottles used to package liquid products are transparent and inert, but they are also heavy and breakable, and the intake of air that is required to empty the container (if the product is tube fed) is sometimes thought to increase the risk of contamination. Alternatively, multilayer films composed of laminated polyethylene and/or polyvinyl chloride are impact resistant, easy to transport and handle, and flexible enough to allow easy administration without air intake. A flexible bag can be squeezed with pressure cuffs for rapid administration of large quantities of liquids for bolus feeding. However, from a

manufacturing point of view, the slower production line speeds than those for the traditional glass-packaged product and the seal integrity of the pouches remain of concern.

Semirigid multilaminate polypropylene/ethylene vinyl alcohol containers are also impact resistant at room temperature, but because they are not fully collapsible they generally require air priming in the same way that glass bottles do. Prefilled one-liter containers for enteral liquids are easier to handle than a flexible bag, save preparation time (no mixing of powders), reduce risk of formula contamination (Anderton, 1985), and generally are less expensive than other systems. Because of their convenience, these types of systems are particularly desirable for long-term, stable patients receiving care at home, generally without the need for frequent modification of formulas.

More recently, aseptically sterilized product/package systems have become more widely used in the medical foods market. These containers are laminations of aluminum foil, polyethylene, polypropylene, and paperboard—namely, the traditional "juice box" brick-shaped containers. The rectangular shape occupies less space than round containers, reducing the amount of storage space needed in nursing homes and hospitals, although one issue not resolved is the recycling of these containers.

CURRENT AND FUTURE IMPLICATIONS

Processing Opportunities

It is apparent that little thought has been given to improving medical food product forms and application of technologies other than those used for production of powders and liquids (FASEB, 1991). Levine et al. (1985) noted a lack of understanding of food technology by medical professionals, which has perhaps contributed to the more druglike approach in medical food development.

The food and dietary supplement industry has made significant progress in designing lower-salt, lower-calorie, lower-cholesterol, higher-fiber, and calcium-containing foods using new food or dietary ingredients (e.g., sugar substitutes and protein- or carbohydrate-based fat substitutes), new methods of separation (e.g., supercritical carbon dioxide extraction), and newer methods of processing (e.g., aseptic processing, hot and cold extrusion, high-pressure processing, ohmic heating, filter sterilization techniques) (Schmidl and Labuza, 1985, 1990, 1992; Schmidl et al., 1988; Labuza, 1985, 1986). Labuza (1977, 1986) explored approaches that the food industry could pursue to create foods specially designed for the renal-deficient patient, but few companies have entered this field, probably because of the very small market. Thus, those who need specialty products to manage their medical condition are faced with few product options, and, because of diet monotony, they often break their diets, leading to medical problems. In addition, with the new category of "dietary supplement" created by DSHEA and the trend to reject traditional medicine

and search for alternative treatment, they may also resort to self-diagnosis and treatment with a product or unproven intervention method touting some closely related benefit.

A variety of opportunities exist for applying food technology to the product line of medical foods. One possibility is the use of intermediate-moisture food technology derived from research on space foods. This technology enables production of a soft, moist, chewable product that provides oral gratification (because of to its texture and sweet taste) and all the necessary nutrients, except the offending one, in the form of a food bar (Labuza, 1980). Confectionery technology might also be used to produce a drier, chewable product with a moisture content sufficiently low to inhibit adverse chemical reactions. This is the technology used to make the imitation fruit leathers that are well accepted by young children. Kokx (1988) applied this technology in the exploration of a "gummy worm" designed as a food for PKU children.

Another approach is mixing of the medical food components with a non-reactive texturizer (starch, gum, protein, water, etc.), followed by extrusion at high pressure and temperature to produce a dry expanded product with a crisp texture (Dziezak, 1989). The low moisture content achieved would minimize chemical reactions during storage. Alternatively, components could be mixed with a structuring agent and water, frozen into bars, freeze dried, and then compressed, as currently done by the U.S. Army Research, Development, and Engineering Center in Natick, Massachusetts for both the military and space feeding programs.

Also, a processing technology similar to that used to produce surimi could be used to produce the medical food in the form of a textured, high-moisture gellike substance. A disadvantage of this process is the potential for microbial growth due to the high moisture content, which requires refrigeration or freezing of the product. Given the current distribution channel used for medical foods, this approach may be precluded in some areas of the world. Possibly, controlled-atmosphere-active packaging technology could be used to increase the shelf life of these refrigerated or frozen products (Labuza and Breene, 1989). Natick developed a controlled-atmosphere bread product with a 9-month shelf life that was used in Operation Desert Storm and that could be used as a delivery system for medical food products.

With respect to sterilization, the classic methods have been batch retort heating of containers and high-temperature/short-time (HTST) heating to reduce quality loss. HTST processing of liquids followed by aseptic filling of the liquid medical food products into multilaminate juice boxes may increase the interest in consumption of these products by children who have metabolic errors. Other possibilities include use of (1) ohmic heating (direct discharge of electrical currents in a liquid food slurry) for particulate-containing products such as soups; (2) ultra-high-pressure technology (Farr, 1990) to pasteurize whole fresh foods; (3) high-energy pulsed white light for pasteurization, a technique pioneered by a division of Maxwell Labs, San Diego, CA. (Dunn et al., 1989); and (4) microwave sterilization (IFT, 1989; Decareau, 1986).

The FDA has, by letter, allowed the use of gamma irradiation to sterilize fresh food products for feeding those who lack the ability to fend off bacteria and who must live in an enclosed sterile environment (Vanderveen, 1991). Although other uses of irradiation, such as the destruction of *E. coli* O157:H7 in fresh meat, have been approved and it is quite clear that these treatments are safe, consumer wariness has precluded the U.S. food industry from fully utilizing this technique (Blumenthal, 1990). Given the small volume of product needed and the potential benefit to the person because of his or her disease condition, it is likely that the FDA will continue to allow irradiation as well as other new sterilization techniques for medical foods before these techniques are approved under 21 CFR 113.

There are techniques that can improve the palatability of medical food products. Anecdotal evidence suggests that bitter off-flavors can result in poor acceptance and are the primary reason individuals do not adhere to their feeding regimens. Applicable techniques include development of biologically available, flavorless amino acid derivatives or dipeptides; microencapsulation of amino acids in slowly dissolving encapsulating agents (as is done with drugs); and addition of aroma agents to stimulate a desire to consume or to turn off the rejection syndrome—a new area of "aroma therapy" or mood foods (Labuza, 1984; Schiffman and Coney, 1984; Levine and Labuza, 1990).

Biotechnology is likely to have a major impact on the development of medical food products in the future. Harlander and Labuza (1986) have reviewed the general potential applications of biotechnology to the food industry. These include (1) use of genetic manipulation to delete undesirable components (e.g., the gene for gluten in flour) during growth of the plant or animal (Sharp et al., 1984) or to add genes for synthesis of specific therapeutic compounds (thus converting normal foods into specialized medical foods) and (2) use of enzyme bioreactor systems to convert normal food products into needed medical foods (e.g., conversion of soybean oil into MCT oil).

Needs of the Aging Population

In recent years, food scientists and nutritionists have increased their efforts to expand their knowledge and to focus on products that will help to reduce or control diet-related chronic diseases such as heart disease, atherosclerosis, hypertension, cancer, and osteoporosis, as well as to create specialty products for weight control. Beginning in the 1970s, the efforts of the food industry were directed toward reduction of fat, cholesterol, and sodium. The availability of new technologies and ingredients has fostered this continually since that time.

In the 1980s, research evolved with respect to the development of health and chronic disease foods. For example, as data became available showing the high incidence of osteoporosis in elderly women, food technologists looked for ways to add calcium to the diet (Garn, 1990). The elderly tend to avoid milk and may shun other dairy products such as cheese that are high in calories from fat and contain saturated fatty acids. For this reason, orange juice was chosen

for fortification with calcium—a difficult step because many calcium sources are insoluble in acidic solutions. At this time, not enough data are available to assess whether this product will reduce the incidence of osteoporosis. Aside from gross calcium content, potential calcium sources should be evaluated for bioavailability. Although calcium absorption efficiency varies inversely with load, fractional calcium absorption from various dairy products is similar, at approximately 30%. The calcium from most supplements is absorbed as well as that from milk, because solubility of the salts at neutral pH has little impact on calcium absorption. Absorption of one very soluble salt, calcium-citrate-malate (CAM), is better than that of other salts, and this form is commonly used in the fortified orange juice (Levenson et al., 1994)

Currently 25 million Americans are over the age of 65, and by the year 2030 there will be 57 million who are 65 or older. The increasing numbers of elderly and aged, especially in the U.S., present challenges to those concerned with their physical and emotional well-being. An understanding of the role of both early and later nutrition in slowing or modulating the aging process and in proving adequate nutritive for the elderly is important. Furthermore, nutrient needs may change with aging and the interaction of drugs and nutrients may play a major role in the nutrient needs of some elderly persons. In the past, the elderly have received very little attention as a target population for specialized nutritional food products. This is expected to change in the next few decades as the elderly continue to increase as a percentage of the total population (Dychtwald, 1990). Many physiological functions, including basal metabolic rate, heart output, lung capacity, and nerve conduction, slow down with age (Shock, 1962). Despite these changes, eating habits and often the amount of food eaten may not change significantly, contributing to obesity and/or chronic diseases. Social and psychological factors (e.g., increased economic pressure resulting from lower income during retirement) can also alter lifestyles and, ultimately, dietary habits.

Because many of the elderly live alone, eating habits may change and there may be a lack of motivation in meal preparation. Many elderly individuals also suffer from anxiety and depression, which may detrimentally affect dietary intake (Roe, 1983). However, the elderly are becoming more motivated to maintain good health, in part because of the debilitating aspects of aging and the associated medical costs. Thus consideration of the diet/disease relationship is essential. Additionally, the elderly typically exhibit increased taste and odor thresholds, which must be taken into account in producing appealing and tasteful foods for this group—an arena in which aroma therapy might be applicable (Schiffman and Coney, 1984). Recent work on the consequences of the consumption of Maillard reaction products as well as oxidized lipids on aging also suggests that significant work on controlling these deteriorative reactions in any food during distribution is also critical (Baynes, 1989).

Many of the elderly apparently have concluded that dietary supplements are beneficial. The use of micronutrient supplements by seniors, whether as single nutrients or in combination, is not unusual. Depending on the study, 33–72%

took nonprescription supplements (Schlenker, 1993; Ausman and Russell, 1993). Multivitamin-mineral supplements specifically developed for the senior market are available from several manufacturers. Some of these preparations, as well as preparations not as specifically aimed at this population, provide many of the nutrients in amounts that research has suggested are beneficial or not harmful. For example, inadequate intake of folate and vitamins B_6 and B_{12} decreases the metabolism of homocysteine, which in turn appears to increase the risk of cardiovascular disease (Selhub et al., 1993). Research about nutrient intake in the elderly is not limited to the possible beneficial effects; some studies have also led to concerns about toxicity in those persons who take supplements. For example, the possibility exists that excess stores of iron may be implicated in increased risk of mortality from cancer and ischemic heart disease in the elderly (Van Asperen et al., 1995). Writers in the popular press have either endorsed or reported the comments of experts in the field who have endorsed the use of a daily multivitamin-mineral providing approximately 100% of the Daily Value (DV) as a reasonable measure to meet micronutrient needs.

Use of complete liquid supplements (medical foods) is on the rise for the active, free-living senior (McCarthy, 1996). Print and broadcast media commercials for these products are quite common, with suggestions of extra energy and good health aimed at healthy, active seniors and baby boomers. Complete supplement drinks also are being suggested as healthy alternatives to fast-food meals and high-fat snacks in popular publications targeting readers in the 20- to 50-year-old age group. Convenience seems to be a major factor in the growing popularity of these beverages.

Beyond Medical Foods

The National Academy of Sciences' report, "Designing Foods" (1989), discussed future trends and developments in the creation of nutritionally based products for the normal population. Specific items of interest are the breeding of animals with less fat and more unsaturated fats; development of genetically engineered dairy starter cultures that will digest the cholesterol from butterfat during fermentation of cheese, resulting in a no-cholesterol product; and use of microorganisms to remove offending amino acids from proteins for those with inborn errors of metabolism.

In light of the projected trend of an ever-increasing older population coupled with an increasing awareness of the needs of the maturing American and the recent changes in the regulatory environment in the U.S., the food industry has a role in meeting the needs of this population group. A new paradigm for "optimal nutrition" may be evolving that would emphasize the positive aspects of diet and dietary supplements and the identification of physiologically active components that contribute to disease prevention or treatment. Understanding how individual nutrients and nonnutrient constituents function physiologically should allow scientists to design food products for a healthy diet. Thus, even though genetic predisposition increases susceptible people's risk for some of

these chronic diseases (especially with advancing age), optimal nutrition should enable people to achieve their maximum genetic potential and decrease their susceptibility to disease. The new diet-health paradigm acknowledges the nutrition and health aspects of food and food components and goes beyond the role of food constituents as dietary essentials for sustaining life and growth to a role in preventing or delaying the premature onset of chronic disease later in life. The promise of functional foods, nutraceuticals (although today no legal definition exists for these terms in the U.S.) and dietary supplements has emerged at a time in the twenty-first century when consumer interest in diet and health appears to be at an all-time high.

An excellent example of a functional food product was test-marketed by a major food company in 1997. The "clinically proven" mail-delivered meals were designed for people with cardiovascular problems, diabetes, and other health concerns. This project had been under development for 5 years and involved over 560 men and women in the multicenter, randomized, parallel intervention trial (McCarron et al., 1997). These products attempted to fill the need of consumers who were interested in eating healthy meals but were often confused about how to turn a "suggested diet guideline" into reality within their regular meal habits and diets. Ideally, in this program, the consumer had to commit to a 4- or 10-week meal plan that included three meals and one snack for each day. Consumers had a choice of 41 specially formulated varieties of meals including an egg sandwich for breakfast, chili or stew for lunch, pasta or chicken for dinner, and snacks such as pretzels and cookies. The products were designed to reduce the intake of saturated fat, cholesterol, sodium, and refined sugars and to provide adequate intake levels of minerals, vitamins, fiber, and complex carbohydrates. United Parcel Service (UPS) delivered the meals weekly in containers that kept the food frozen for 48 hours. The food company also provided education and counseling in the area of nutrition, exercise, and behavioral change (McCarron, 1997). After test marketing in 1998 in Ohio, the product's concept was withdrawn. Whether or not this concept will be revitalized in the same form or some other form in the future is in question. Other concepts in the functional food areas under discussion and investigation include the following:

- Modification of egg or dairy products to include high levels of vitamin E, carotenoids, special fatty acids, or proteins.
- Addition of plant sterols to margarine, mayonnaise, ice cream, etc. to inhibit the absorption of cholesterol.
- Specialty oils with eicosapentaenoic acid and docosahexaenoic acid.
- Calcium-fortified fruit juice with high absorbable calcium.
- Unique soluble fibers isolated and concentrated from plants to lower cholesterol.
- Breakfast cereal with special botanicals, vitamins, or minerals and antioxidants for certain disease conditions.

- Enhanced vegetables with high levels of anticarcinogen (sulphorane).
- Isolated components of soybeans, especially containing phytoestrogens and lignins.
- Pre- and probiotic cultures added to yogurt and other food systems.

SUMMARY

A broad range of products have been produced by various food technologies for use in the nutrition and health care area. With an understanding of the basic principles of formulation, food technology/processing, and clinical nutrition, these modalities can be utilized to prevent the wastage of body mass; to prevent, control, and/or alleviate acute, genetic, and chronic disease conditions; and to provide proper nutrition to most population groups. Scientists with this understanding help create better-quality, more stable products for the maintenance of health and management of specific disease conditions.

The major factors expected to affect the further development of medical foods are better clinical evidence relating specific dietary components to health and disease; the pervasive but necessary regulatory climate allowing proper and valid claims to be made about the healthfulness of specific foods; and the willingness of companies to invest in an area in which the population at risk is limited but the moral and ethical obligations of society are high. With respect to this population, there is a need to have the government come to closure quickly on defining the boundaries of medical foods regulation and instituting a simple and rapid procedure for clearance of the use of new ingredients and techniques in their manufacture. Once such a new procedure is in place, the food industry must then apply its technology, either alone or through some consortium, to benefit those with specific medical disorders.

Finally, state governments and the insurance industry must recognize that these new special medical foods are critical in sustaining life and maintaining the health and well-being of those with specific medical problems. Because of the low numbers of people with many of these diseases and the resultant difficulty in product distribution, there has been little incentive for the food industry to manufacture products on such a small scale with a small return on the investment. If the cost of these foods of "sufficient medical merit," used only under medical supervision, were covered under medical insurance, this would stimulate development and manufacture by the food and pharmaceutical industries.

Although a few basic principles of supplying nutrients to the hospitalized patient or compromised person have been identified and applied in the production of medical foods, this field of medical nutrition is still evolving. A number of problem areas await solution through future research. Factors expected to influence future developments include demographics of disease, advances in food processing technology, government regulations and their impact on private industry, and the potential for third-party payments for these

foods through medical insurance. Science and technology have worked hand in hand with marketing and promotional efforts to develop this area. Many products do save lives, with adverse events being extremely low or just too difficult to measure. Opportunities are still available for development of unique ingredients and novel processes that will improve both sensory quality and functionality of the products and will show beneficial clinical outcomes for the patients. Medical foods initially were only found in hospitals, but today the consumer is able to purchase them in grocery stores. Future growth opportunities are with the aging population and prevention or treatment of chronic disease states.

Additional pertinent reviews include the Federation of American Societies for Experimental Biology's report on medical food products (FASEB, 1991) and FASEB's report on scientific guidelines for review of enteral food products for medical purposes (Talbott, 1990).

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CHAPTER 30

FOOD FORTIFICATION

R. ELAINE TURNER

INTRODUCTION AND DEFINITION OF ISSUES

Fortified foods are such a familiar sight on grocery store shelves that most consumers take them for granted and pay only scant attention to key words such as "enriched," "added," "iodized," or "fortified." Fortification has its roots in public health policy to reduce the prevalence of nutrient deficiency diseases. Those policies have practically eradicated deficiency diseases such as goiter and rickets that were common at the beginning of the twentieth century (Crane et al., 1995). Improved nutritional quality is one of the five main reasons for using food additives according to the Food and Drug Administration (FDA, 1992):

> *"... to maintain or improve nutritional value. Vitamins and minerals are added to many common foods such as milk, flour, cereal, margarine to make up for those likely to be lacking in a person's diet or lost in processing."*

However, in our current era of nutritional excess, the focus of fortification has shifted from the provision of nutrient adequacy to the pursuit of optimal health and dietary intake. Today's consumers are more interested in foods that have added beneficial compounds such as antioxidant vitamins than in foods with less healthful substances like sugar and fat removed (Hollingsworth, 1997). Many may wonder whether fortification is truly serving public health needs or is simply another marketing tool, with the appropriate verbiage vying for label space and consumer attention. Health-conscious consumers not only look for foods with added health benefits but are also more likely to take vitamin/mineral supplements.

Fortification is one of many appropriate strategies for people to meet their nutritional needs. A recent position statement from the American Dietetic Association supports the use of fortified foods for this purpose (ADA, 2001):

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"It is the position of the American Dietetic Association (ADA) that the best nutritional strategy for promoting optimal health and reducing the risk of chronic disease is to wisely choose a wide variety of foods. Additional vitamins and minerals from fortified foods and/or supplements can help some people meet their nutritional needs as specified by science-based nutrition standards such as the Dietary Reference Intakes (DRI)."

In developing the Dietary Reference Intakes (DRI), the Food and Nutrition Board acknowledges the need for fortified foods or supplements in two specific instances: folic acid for women of childbearing age and vitamin B_{12} for individuals over the age of 50 (IOM, 1998). Fortification of common foods can more reliably reach target populations than recommendations for individual supplementation (ADA, 2001).

Careful thought must accompany the decision to fortify foods. As Borenstein (1971) points out, even though fortification may improve the nutritional value of a single food, it may have little effect on total diet quality when that food is consumed as part of a mixed diet. Fortification policies must focus on the following:

- Nutrients that are needed by the public at large;
- Nutrients that may have health benefits in quantities greater than recommended intake levels;
- Foods that are appropriate vehicles; and
- Fortification levels that minimize the potential for adverse effects or toxicity symptoms.

This chapter first briefly reviews the history of food fortification in the United States, followed by a critical review of current fortification policy and an outline of current health and safety issues related to food fortification. Among the issues explored are the following:

- What is the FDA's current fortification policy?
- What nutrients are appropriately added to food and in what amounts?
- What foods are appropriate vehicles for fortification?
- Is fortification safe?
- How does the recent interest in adding herbal and botanical compounds to foods fit into the FDA's fortification policy and what are the concerns related to this practice?

BACKGROUND AND HISTORICAL SIGNIFICANCE

For food science and nutrition professionals, the term "fortification" probably brings to mind three public health efforts: addition of iodine to salt, addition of

vitamin D to milk, and enrichment of cereal grain products with B vitamins and iron. Of course, there are many other examples of fortified foods, but these three examples provide the historical underpinnings for current fortification practices. In each case, the objective of fortification was to reduce the public's risk for nutrient deficiency and its associated consequences.

At the start of the twentieth century, nutrient deficiency diseases were widespread, even in the United States. Nutrition science had not yet identified the essentiality of specific vitamins and minerals, and medical science still focused on infectious etiology hypotheses for many of the diseases we now know as nutrient deficiencies. Areas of the Midwest, where soil iodine levels were low, had a high incidence of goiter (enlargement of the thyroid gland resulting from iodine deficiency). The presence of goiter was a major reason for rejection of men for service in World War I (Carpenter, 1995). In the South, pellagra (disease resulting from niacin deficiency) was the eighth or ninth leading cause of death by the late 1920s (Park et al., 2000). Beriberi (thiamin deficiency) and ariboflavinosis were also apparent, although not as common. Rickets (vitamin D deficiency) was primarily a problem in the industrialized cities of the Northeast. As nutrition science began to identify the connections between vitamins and minerals and deficiency diseases, public health efforts intensified to reduce nutrient deficiencies.

SCIENTIFIC BASIS AND IMPLICATIONS

Public Health Fortification Programs

Iodine and salt Although, by 1820, iodine was recommended to treat goiter, it was roughly 100 years later when studies documented the effectiveness of sodium iodide as a treatment for goiter (Mertz, 1997, Carpenter, 1995). In 1922, under the leadership of pediatrician David Cowie, the state of Michigan embarked on a major effort to market iodized salt. The effects were impressive; including a decline in goiter among children from 9.7% to 1.4% in 8 years (Carpenter, 1995). The Committee on Foods of the American Medical Association (AMA) went on to recommend voluntary iodization of table salt on a nationwide basis.

Today, iodized salt remains a major source of iodide in the U.S. diet. For salt to be labeled "iodized salt," iodide in the form of cuprous iodide or potassium iodide must be added in an amount not to exceed 0.01% (21CFR100.155). To clarify the purpose of the added iodide, the statement "*this salt supplies iodide, a necessary nutrient*" must appear on the label immediately following the name "iodized salt." Table salt that is not iodized must bear the label statement "*this salt does not supply iodide, a necessary nutrient.*" Typically, a teaspoon of iodized salt (~6 g) provides approximately 360–450 micrograms (μg) of iodide. The current RDA for iodide for adults is 150 μg/day (IOM, 2001).

Cuprous iodide and potassium iodide are regulated as direct food substances affirmed as generally recognized as safe (GRAS). Potassium iodide may be used as a nutrient supplement or in table salt (21CFR184.1634), whereas the use of cuprous iodide is limited to table salt (21CFR184.1265).

Vitamin D and milk Vitamin D is unique among the essential nutrients in that adequate quantities can be synthesized in the body if given enough exposure to ultraviolet (UV) light. However, for individuals who are not regularly exposed to sunlight and/or geographic regions where adequate sunlight for vitamin D synthesis is not available year-round, vitamin D is a dietary essential. Rickets, vitamin D deficiency in children, was prevalent in the northern U.S. in the early 1900s. By the early 1920s, it was known that rickets could be prevented by exposing young children to UV light or by giving them fish liver oil, a significant source of vitamin D (Carpenter, 1995).

Milk was identified as an appropriate vehicle for vitamin D fortification targeting children, and, once the structure of vitamin D was identified in 1932, milk fortification began almost immediately (Mertz, 1997). This effort was strongly supported by the Council on Foods and Nutrition (formerly the Committee on Foods) of the American Medical Association (AMA), (Shank and Wilkening, 1986). According to the standard of identity for milk (21CFR131.110), addition of vitamin D is optional, but if added, the amount of vitamin D is to be 400 international units (IU) per quart. This equates to 10 μg per quart or 2.5 μg per 1-cup (8 fl oz) serving. The current AI for vitamin D for children and young adults 5 μg/day. For older adults, the AI rises to 10 μg/day for those aged 51–70 and to 15 μg/day for those over age 70 (IOM, 1997).

Addition of vitamin D is also optional for other standardized dairy products such as acidified milk, cultured milk, concentrated milk, dry whole milk, yogurt, low-fat yogurt, and nonfat yogurt (21CFR131). However, vitamin D fortification is required for nonfat dry milk fortified with vitamins A and D to the same level as for milk and for evaporated milk so that each fluid ounce contains 25 IU (0.625 μg) (21CFR131). Vitamin D is also an optional additive for margarine (21CFR166.110). Under its status as a direct food substance affirmed as GRAS, vitamin D may be used in breakfast cereals and grain products subject to specific limitations (21CFR184.1950).

Although thought to be a disease of the past, rickets has been identified in several recent case reports (Biser-Rohrbaugh and Hadley-Miller, 2001, Tomashek et al., 2001, Carvalho et al., 2001). Although the risk for rickets is known to be higher among breastfed children who do not receive vitamin D supplementation (Tomashek et al., 2001), one of the recent reports linked rickets to inappropriate weaning of babies onto milk alternatives not fortified with vitamin D. According to the American Academy of Pediatrics, infants weaned from breast milk before 12 months of age should receive iron-fortified infant formula (which has a standardized level of vitamin D) and after 12 months should receive whole milk or a *nutritionally equivalent milk substitute* (AAP, 1997, 1999). Many parents are not aware of the nutritional differences between fortified cow's milk and milk alternatives.

Thiamin, riboflavin, niacin, and iron and cereal grain products The history of enrichment of cereal grain products in the U.S. has been well documented (Park et al., 2001). Nutritional deficiencies involving the B-vitamins thiamin, riboflavin, and niacin were apparent across the U.S., with the incidence of pellagra (niacin deficiency) in southern states the most prominent (Park, 2000). Among other factors, the growing popularity of refined grain products limited the amount of available thiamin, riboflavin, and niacin because these vitamins are more concentrated in the bran and germ layers of grains than in the endosperm. Recognizing the need for enhancements of the general food supply when nutrient needs were greater than the amounts in the usual diet, the Council on Foods and Nutrition of the AMA adopted a resolution in 1939 that encouraged restorative addition of nutrients to foods in the interest of public health (Park, 2001).

At about the same time as the AMA Council on Foods and Nutrition resolution, many bakers had began voluntarily using a high-quality yeast to enhance the amounts of B-vitamins in bread, and some began adding synthetic vitamins, although the cost for these was high. In the 1940s, many states enacted mandatory enrichment laws, requiring that bread, flour, and other cereal products sold in their states be enriched. By 1941, 30% of white flour and bread produced in the U.S. was voluntarily enriched, and by the end of 1942, 75–80% of family flour and bakery white bread was enriched with thiamin, dry milk, niacin, and iron (Park, 2001). Concurrently, the incidence of and mortality from pellagra steadily declined.

The FDA adopted the term "enriched" as specifically descriptive of nutrients added to flour in 1940, and the next year it released final rules for definitions and standards of identity for enriched and unenriched flour and farina. A War Food Order from the War Foods Administration required mandatory enrichment nationwide from January, 1943 through October, 1946. Since that time, the FDA has adopted final rules for enrichment of other cereal grain products. Enrichment of cereal grain products eradicated pellagra by the late 1950s (Park, 2000); dietary deficiency of niacin or riboflavin is extremely rare in the U.S. at present.

Contrary to popular belief, enrichment of grain products is not a federal mandate. States are free to enact their own laws or policies regarding the availability of enriched products. Federal authority lies only in the establishment of standards of identity for enriched products. At the present time, standards of identity exist for numerous cereal grain products. A complete list with appropriate CFR citations is given below.

Enriched bread, rolls, buns	21CFR136.115
Enriched flour	21CFR137.165
Enriched bromated flour	21CFR137.160
Enriched self-rising flour	21CFR137.185
Enriched corn meals	21CFR137.260
Enriched farina	21CFR137.305
Enriched rice	21CFR137.380

Enriched macaroni products	21CFR139.115
Enriched macaroni products with fortified protein	21CFR139.117
Enriched nonfat milk macaroni products	21CFR139.122
Enriched vegetable macaroni products	21CFR139.135
Enriched noodle products	21CFR139.155
Enriched vegetable noodle products	21CFR139.165

The standard of identity for enriched corn grits was revoked on June 3, 1996 (Park, 2001).

The current (1998) federal enrichment standards regarding the amounts of nutrients to be added to cereal grain products are given in Table 30.1. Addition of calcium and vitamin D are optional in cereal grain products, except for enriched self-rising flour, for which calcium is a mandatory nutrient.

TABLE 30.1. Enrichment Standards for Cereal-Grain Products.

Grain product	Thiamin (mg/lb)	Riboflavin (mg/lb)	Niacin (mg/lb)	Iron (mg/lb)	Calcium (mg/lb)	Vitamin D (IU/lb)
Bread, rolls, buns	1.8	1.1	15	12.5	600	—
Cornmeal	2.0–3.0	1.2–1.8	16–24	13–26	500–750	250–1000
Farina	2.0–2.5	1.2–1.5	16.0–20.0	≥13.0	≥500	≥250
Flour	2.9	1.8	24	20	960	—
Macaroni, noodles	4.0–5.0	1.7–2.2	27–34	13–16.5	500–625	250–1000
Rice	2.0–4.0	1.2–2.4*	16–32	13–26	500–1000	250–1000

Source: Park YK, McDowell MA, Hanson EA, Yetley EA. *Nutrition Today*. 2001; 36:124–137.

*The requirement for riboflavin in enriched rice is currently stayed pending final action on objections.

Typical serving sizes and nutrient amounts for the required enrichment nutrients are shown in Table 30.2 along with the current RDA values for adult men and women (ages 19 and above).

As of 1988, 14 states and the District of Columbia had no enrichment law or policy for any grain products. Only 4 states (Arizona, California, Florida, New York) have mandatory laws for enrichment of all grain products, 24 states mandate enrichment of some grain products, and the remaining 8 states have optional laws or policies (Park, 2001).

Thiamin (as thiamin mononitrate or thiamin hydrochloride), riboflavin (as riboflavin or riboflavin-5′-phosphate), and niacin (as niacin or niacinamide) all are direct food substances affirmed as GRAS (21CFR184). In all cases, they may be used in food with no limitation other than current good manufacturing practice. Iron in many forms (including elemental iron and ferrous sulfate) is also a direct food substance affirmed as GRAS. It may also be used in food with no limitation other than good manufacturing practice. It should be noted,

TABLE 30.2. Nutrient Amounts in Enriched Products and RDA Values for Adults.

Nutrient	Enriched bread (1 oz)	Enriched rice (1/2 cup)	Enriched egg noodles (1/2 cup)	RDA for males	RDA for females*
Thiamin	0.13 mg	0.13 mg	0.15 mg	1.2 mg/day	1.1 mg/day
Riboflavin	0.04 mg	0.01 mg	0.07 mg	1.3 mg/day	1.1 mg/day
Niacin	1.1 mg	1.2 mg	1.2 mg	16 mg/day	14 mg/day
Iron	1.3 mg	0.9 mg	1.2 mg	8 mg/day	18 mg/day

Sources: U.S. Department of Agriculture, Agricultural Research Service. 2001. USDA Nutrient Database for Standard Reference, Release 14. Nutrient Data Laboratory Home Page, *http://www.nal.usda.gov/fnic/foodcomp*; Pennington JAT. Bowes & Church's Food Values of Portions Commonly Used, 17th ed. Philadelphia: Lippincott-Raven Publishers, 1998.

*The RDA for iron declines to 8 mg/day for females over the age of 50.

however, that GRAS substances that are added to infant formula are subject to separate regulations under the Federal Food, Drug and Cosmetic Act (FDCA).

Folic acid and cereal grain products In the latter part of the twentieth century the link between periconceptional folate status and the incidence of neural tube defects became apparent. In 1992, the U.S. Public Health Service (PHS) recommended that all women who were capable of becoming pregnant consume 400 μg/day of folic acid (the synthetic form of the B-vitamin folate) to reduce their risk of having a neural tube defect-affected pregnancy (Crane et al., 1995). The scientific evidence supporting this recommendation led FDA to consider the possibility of food fortification with folic acid.

In 1996, FDA issued a final regulation to amend the standards of identity for enriched cereal-grain products to include folic acid. The appropriate folic acid enrichment levels are listed below:

Breads, rolls, buns	0.43 mg/lb
Cornmeal	0.7–1.0 mg/lb
Farina	0.7–0.87 mg/lb
Flour	0.7 mg/lb
Macaroni, noodles	0.9–1.2 mg/lb
Rice	0.7–1.4 mg/lb

At this level of fortification, a 1-oz (28 g) slice of enriched bread would provide 15 μg of folic acid (total folate = 25–40 μg DFE), and a 1/2-cup serving of enriched noodles or pasta would provide 90–95 μg of folic acid (total folate = 160–170 μg DFE) (Suitor and Bailey, 2000). This level of fortification is beyond the "restorative" levels for the other enrichment nutrients and parallels the addition of iodine or vitamin D to specific foods for the prevention of disease.

In 1998, the Food and Nutrition Board released DRI values for folate. For adults, the RDA is 400 μg/day. Furthermore, the report states, "... in view of evidence linking folate intake with neural tube defects in the fetus, it is recommended that all women capable of becoming pregnant consume 400 μg from supplements or fortified foods in addition to intake of food folate from a varied diet." (IOM, 1998). Analysis of expected intake of folate from all sources indicates that most of the population will meet or exceed the Estimated Average Requirement for folate; however, the majority of females of childbearing age still have intakes of synthetic folic acid below the recommended 400 μg/day (Lewis et al., 1999). A recent study suggests that the prevalence of neural tube defect-affected births has declined since the institution of folic acid fortification, but further study is needed to separate the impact of folic acid fortification from other possible factors (Honein et al., 2001).

Folic acid is approved as a food additive with specific conditions (21CFR172.345). As described above, folic acid is added in accordance with standards of identity for enriched cereal grains. Folic acid may be added to breakfast cereals at levels not to exceed 400 μg per serving and to corn grits so that grits contain no more than 1.0 mg of folic acid per pound. Folic acid is also approved for addition to infant formula, medical foods, foods for special dietary use, and meal replacement products.

Other Examples of Food Fortification

Vitamin A, milk, and margarine Vitamin A deficiency is relatively rare in the U.S., but it remains a major public health problem in many developing countries and is a leading cause of blindness worldwide. Vitamin A (retinol) is found naturally in whole milk, eggs, liver, and fish liver oils. The major precursor to vitamin A, beta-carotene, is found in deep green and yellow-orange vegetables and many orange-colored fruits such as mango, papaya, and cantaloupe. Although whole milk naturally contains approximately 75 μg of retinol per 1-cup (8 fl oz) serving, skim milk has only 2.5 μg per cup. Therefore, most nonfat and reduced-fat milks in the U.S. are fortified with vitamin A.

Vitamin A (retinol) is an optional additive for milk. If added, vitamin A must be present at a level of not less than 2000 IU (~600 μg) per quart (21CFR131.110). One cup (8 fl oz) of vitamin A-fortified milk would therefore provide approximately 150 μg of vitamin A. The current RDA for vitamin A for adults is 700 μg/day for females and 900 μg/day for males. Vitamin A must be added to nonfat dry milk fortified with vitamins A and D.

Vitamin A also must be added to margarine (21CFR166.110). Here, the required amount of vitamin A is 15,000 IU (~4500 μg) per pound. Therefore, 1 tablespoon of margarine would provide approximately 140 μg of vitamin A. In addition to added vitamin A, margarine may contain beta-carotene (a precursor to vitamin A in the body) as a color additive. As a GRAS substance, no limitations have been placed on the use of vitamin A other than good

manufacturing practices (21CFR184.1930). The same is true for beta-carotene (21CFR184.1245).

Calcium Calcium is a key nutrient for bone health. Calcium also is important for a wide variety of other functions including muscle contraction, blood clotting, and nerve impulse transmission. Calcium is found naturally in milk and other dairy products, which account for 73% of the calcium in the U.S. food supply (IOM, 1997). Other calcium-rich foods are Chinese cabbage, kale, broccoli, and tofu processed with calcium. Calcium intake and utilization are affected by a wide variety of factors including lactose intolerance, presence of oxalate and phytate (found mainly in whole grains and vegetables), and interactions with high protein and sodium intakes (IOM, 1997). Current median calcium intakes tend to be below the Adequate Intake (AI) level of 1000 mg/day for adults aged 19–50 years. For older adults, the AI rises to 1200 mg/day, and for teens the AI is 1300 mg/day. Without significant amounts of dairy products in the diet (a 1-cup serving of milk provides ~300 mg), these levels of intake are difficult to achieve.

Lack of calcium intake is a significant factor in the risk for osteoporosis in later life. Osteoporosis is a major cause of debilitation and loss of mobility in elders and accounts for approximately 1.5 million fractures each year (IOM, 1997). Improved calcium intake, especially during the childhood and teenage years, is recognized as a major part of preventive efforts. In recent years, calcium has been added to a growing number of foods including juices, juice/fruit beverages, cereal grain products, breakfast cereals, and others. Even dairy products are appearing on market shelves with "extra" calcium.

Calcium in 15 different forms (including calcium carbonate, calcium citrate, and calcium gluconate) is a direct food substance affirmed by GRAS (21CFR184). Current regulations allow addition of calcium in many of these forms to foods with no limitation except for good manufacturing practices. Calcium is an optional ingredient in enriched cereal grain products as described above.

Antioxidant nutrients As nutrition science has continued to study the role of various antioxidant compounds in the reduction of risk for chronic disease, interest in antioxidant fortification has grown. The antioxidant nutrients vitamin C, vitamin E, and selenium and the vitamin A precursor beta-carotene have become popular food additives as more evidence supports the importance of foods rich in antioxidant nutrients. Currently, no consistent evidence supports the routine use of antioxidant supplements as an effective tool in lowering heart disease or cancer risk.

Vitamin C (ascorbic acid) has GRAS status as both a nutrient and a chemical preservative (21CFR182.3013, 21CFR182.8013). Vitamin C is routinely added to juice and to juice/fruit drinks and other foods marketed to children such as fruit snacks and gummi bears. There is no limitation on the amount of vitamin C that can be added to foods. In fact, several beverage products have

vitamin C contents as high as 240–500% of the Daily Value (144–300 mg) per serving.

Vitamin E (α-tocopherol) is also a GRAS substance that can be added for its nutritional or preservative value (21CFR182.3013, 21CFR182.8890, 21CFR182.8892). Vitamin E has received much media attention for its hypothesized role as a substance that can reduce the risk of heart disease. To date, studies have not found that supplemental vitamin E will reduce heart disease risk. Vitamin E has been added to a variety of foods for its nutritive value, often accompanied by a structure/function claim related to the immune system, or the body's "natural defenses."

Other vitamins and minerals A variety of other vitamins and minerals can be added to foods. Some foods, like fortified breakfast cereals, provide the same variety and amount of those nutrients found in a vitamin/mineral supplement. Meal replacement bars and beverages are often heavily fortified with vitamins and minerals. Energy bars and beverages focus on added B-vitamins, which are important in the metabolism of food to yield energy. Sports drinks typically have added sodium and potassium for replacement of electrolytes lost during sweating. Zinc is currently a popular nutrient additive because of its reputation as an immune system enhancer. Cereals, energy bars, and beverages are also being developed and marketed specifically to women. These products focus on important nutrients for women such as calcium and folic acid but also on vitamin B_6 and vitamin B_{12}. Along with folic acid, these two B-vitamins may have a protective role in heart disease. In general, vitamins and minerals other than those described above are affirmed as GRAS and are able to be added to foods without restriction.

REGULATORY, INDUSTRIAL, AND INTERNATIONAL IMPLICATIONS

U.S. Food Fortification Policies

General FDA requirements Statements regarding food fortification by other government and health agencies predated the FDA's fortification policy. Both the AMA Council on Foods and Nutrition and the Food and Nutrition Board (FNB) of the National Academy of Sciences had previously released statements on food fortification; a joint statement released in 1968 endorsed fortification in the following circumstances (AMA, 1968):

1. The intake of the nutrient(s) is below the desirable level in the diets of a significant number of people.
2. The food(s) used to supply the nutrient(s) is likely to be consumed in quantities that will make a significant contribution to the diet of the population in need.

3. The addition of the nutrient(s) is not likely to create an imbalance of essential nutrients.
4. The nutrient(s) added is stable under proper conditions of storage and use.
5. The nutrient(s) is physiologically available from the food.
6. There is reasonable assurance against excessive intake to a level of toxicity.

These endorsements are consistent with fortification of salt with iodine, milk with vitamin D, and enriched grains with folic acid. However, this statement does not consider the restorative function of fortification (Borenstein, 1971). These same six principles were part of the Food and Nutrition Board's 1974 paper "Proposed Fortification Policy for Cereal Grain Products" (Mertz, 1997).

The FDA codified its fortification policy in 1980, and this policy was last revised in 1993 (21CFR104.20). In this policy, FDA lists 21 nutrients (protein, 12 vitamins, 8 minerals) that may be added to food for several listed reasons.

1. To correct a dietary insufficiency recognized by the scientific community and known to result in nutritional deficiency disease
2. To restore such nutrient(s) to a level(s) representative of the food before storage, handling, and processing
3. To balance the vitamin, mineral, and protein content
4. To avoid nutritional inferiority in a food that replaces a traditional food in the diet
5. To follow requirements of other regulations.

In regard to "nutrients added to correct a dietary insufficiency," there must be sufficient information available to identify the problem and the affected population groups, and the food selected for fortification must be a suitable delivery vehicle and not part of another federal regulation that requires, permits, or prohibits nutrient additions.

When nutrients are added for restorative purposes, the FDA requires that the losses of a specific nutrient be of a measurable quantity [2% of the Daily Reference Value (DRV) or Recommended Daily Intake (RDI)]; good manufacturing practices do not prevent the loss; all nutrients that are lost in measurable amounts are restored; and the food is not the subject of any other federal regulation related to the addition of nutrients. The FDA's own standards of identity for enriched grains conflict with this element of its fortification policy. Other vitamins and minerals, such as vitamin B_6 and zinc, are lost in measurable quantities (Weaver, 2001) but are not required to be replaced under current standards of identity.

Nutrients may be added to balance the protein, vitamin, and mineral content provided that the food contains at least 40 kcal per serving and contains all 21 nutrients listed in the policy.

Nutrient additions are appropriate when the nutrient is 1) stable under customary conditions of storage, distribution, and use; 2) physiologically available from the food; 3) present at a level at which there is reasonable assurance that consumption of the food containing the added nutrient will not result in an excessive intake; and 4) suitable for its intended purpose and in compliance with regulations governing the safety of substances in food.

The FDA fortification policy goes on to identify appropriate claims and label statements that may be made in accordance with each of the fortification scenarios. The terms "enriched," "fortified," and "added" may be used interchangeably except in the case of enriched grain products, where the word "enriched" is defined by other regulations.

In the opening statements of the fortification policy are several key phrases that describe the FDA's view of appropriate fortification practices. The agency acknowledges that fortification "can be an effective way of maintaining and improving the overall nutritional quality of the food supply" but also points out that random fortification could result in over- or under-fortification in consumers' diets and nutrient imbalances. Random fortification "could also result in deceptive or misleading claims." Finally, the agency states that it does not consider appropriate the fortification of fresh produce; meat, poultry, or fish products; sugars; or snack foods such as candies and carbonated beverages.

Other FDA policies Another FDA policy is relevant to the discussion of food fortification but is rarely cited. This policy is found in 21CFR Part 104: Nutritional Quality Guidelines for Foods, the same section as the fortification policy. The general principle of this policy is that a *nutritional quality guideline* would prescribe the minimum level or range of nutrient composition appropriate for a given class of food. Following a defined nutritional quality guideline would permit the label statement "*This product provides nutrients in amounts appropriate for this class of foods as determined by the U.S. Government*".

To date, the only specific nutritional quality guideline established is for frozen "heat and serve" dinners. The nutritional quality guideline identifies minimum levels of protein, vitamin A, thiamin, riboflavin, niacin, pantothenic acid, vitamin B_6, vitamin B_{12}, and iron that must be provided in such a dinner. The dinner must be composed of at least one or more sources of protein (meat, poultry, fish, cheese, or eggs), one or more vegetables or vegetable mixtures, and potatoes, rice, or a cereal-based product (other than bread or rolls). Nutrients may be added to achieve any of the required minimum levels but must be biologically available in the final product. Furthermore, when technologically practicable, iodized salt should be used and components should be selected to obtain a calcium-phosphorus ratio of 1:1.

Critique of Current Fortification Policy

Mertz (1997) reviews the FNB conditions for fortification in comparison to current FDA policy and fortification activities. One criticism is that "desirable levels of nutrients" have been redefined in recent years, and FDA policies, and in particular, RDI values for vitamins and minerals have not been updated to reflect recent changes, some of which are significant. Table 30.3 presents current RDA or AI values for vitamins and minerals for adults along with the RDI established in the regulations to implement the Nutrition Labeling and Education Act. Consumption surveys have identified that certain nutrients that are less frequently used in fortification are often consumed in marginal

TABLE 30.3. RDA/AI, RDI, and UL Levels for Vitamins and Minerals.

Nutrient	RDA or AI* Males	RDA or AI* Females	RDI†	UL‡
Vitamin A	900 μg	700 μg	1500 μg	3000 μg
Vitamin C	90 mg	75 mg	60 mg	2000 mg
Vitamin D	5 μg	5 μg	10 μg	50 μg
Vitamin E	15 mg	15 mg	9 mg	1000 mg**
Vitamin K	120 μg	90 μg	80 μg	
Thiamin	1.2 mg	1.1 mg	1.5 mg	
Riboflavin	1.3 mg	1.1 mg	1.7 mg	
Niacin	16 mg	14 mg	20 mg	35 mg**
Vitamin B6	1.3 mg	1.3 mg	2 mg	100 mg
Folate	400 μg	400 μg	400 μg	1000 μg**
Vitamin B12	2.4 μg	2.4 μg	6 μg	
Biotin	30 μg	30 μg	300 μg	
Pantothenic acid	5 mg	5 mg	10 mg	
Calcium	1000 mg	1000 mg	1000 mg	2500 mg
Phosphorus	700 mg	700 mg	1000 mg	4000 mg
Magnesium	400 mg	310 mg	400 mg	350 mg**
Iron	8 mg	18 mg	18 mg	45 mg
Zinc	11 mg	8 mg	15 mg	40 mg
Iodine	150 μg	150 μg	150 μg	1100 μg
Copper	900 μg	900 μg	2 mg	10000 μg
Selenium	55 μg	55 μg	70 μg	400 μg
Manganese	2.3 mg	1.8 mg	2 mg	11 mg
Chromium	35 μg	25 μg	120 μg	
Molybdenum	45 μg	45 μg	75 μg	2000 μg

* Values represent adults age 19–30 years. RDA/AI values for older adults may be higher or lower for some nutrients. Source: IOM, 1997, 1998, 2000, 2001.

† *Source:* 21CFR.

‡ *Source:* IOM: 1997, 1998, 2000, 2001.

** The UL for vitamin E, niacin, and folate apply to synthetic forms from supplements and fortified foods only; the UL for magnesium applies to pharmacological agents only.

amounts, especially vitamin B_6, zinc, magnesium, copper, and possibly chromium (Mertz, 1997).

Other aspects of FNB and FDA policy that need re-examining in current fortification practices are the "avoidance of imbalance" and "insurance against excessive intake" requirements. The addition of folic acid to enriched cereal grains and breakfast cereals has created concern about levels of intake that may mask the presence of vitamin B_{12} deficiency, particularly in elders. Fortification of many products with iron, and especially the lack of non-iron-fortified options, may put individuals at risk for excessive iron absorption and storage. Hemochromatosis, an iron storage disorder, affects a significant fraction of the U.S. population. Current fortification practices allow for unlimited levels for most vitamins and minerals. Until the FNB began setting Tolerable Upper Intake Levels (UL) for vitamins and minerals in 1997, there were few articulated standards for amounts of nutrients that were considered excessive. The UL is the "highest level of daily intake that is likely to pose no risks of adverse health effects to almost all individuals in the general population" (IOM, 1997). Intakes above the UL increase risk for adverse effects. Table 30.3 also includes established UL values to date. GRAS standards need to be re-evaluated in light of these values.

Mertz (1997) concludes that today's food fortification does not meet three of the FNB criteria: 1) not all nutrients whose intake is less than desirable are included, 2) imbalances have been created, and 3) excessive intake is possible. Other criticisms of current policy include the lack of nonfortified analogs for some foods with standards of identity (e.g., evaporated milk, margarine), the difficulties of finding nonenriched cereal-grain products, and the prohibition of fortification of certain foods, specifically meat and poultry products (McNamara, 1995, Theuer, 2000).

CURRENT AND FUTURE IMPLICATIONS

From a food safety perspective, there are a number of key issues to be examined related to current fortification policy and practices. The appropriateness of nutrients, the amounts being added, and the types of foods being fortified all have food safety implications. Another key issue is the appropriateness of food formulations that include added botanicals alone or in addition to nutrient fortification. This issue presents unique regulatory challenges that FDA is only beginning to address.

Quantities of Added Nutrients

Nutrient quantities are limited in only a few specific cases. Research in nutrition science is advancing daily, and as further nutrient relationships to optimal health are identified, it can be expected that food manufacturers will look to take advantage of media reports to help sell newly formulated fortified prod-

ucts. Taking a cue from the dietary supplement industry, food manufacturers are using simple but powerful key words to promote fortified products: "Immune," "Energy," "Stamina," "Think," "Memory," to name a few. Often, large quantities of nutrients are being added, many times the existing RDI for the particular vitamin or mineral.

As Table 30.3 illustrates, there is often a small gap between the current RDI and the newly established UL. For example, the UL for vitamin A is only twice the RDI; for calcium, iron, and zinc, the UL is only about two and one-half times the RDI. If individuals are eating several calcium- or iron-fortified foods, taking a dietary supplement, and consuming foods rich in calcium or iron, it can be quite easy to exceed the UL. Nearly half of the U.S. adult population uses vitamin or mineral supplements at least occasionally (ADA, 2001). FDA estimates that 20–30% of children age 1–8 years may exceed the UL for folic acid now that it is found in most breakfast cereals and all enriched cereal grain products (ADA, 2001). As already stated, the lack of limits on iron fortification is particularly concerning, considering that 12–14% of the population who are of northern European descent carry the gene for hemochromatosis, an iron storage disorder. It is quite difficult to find unenriched cereal grains or breakfast cereals with no added iron.

Table 30.3 also illustrates that there is a substantial gap between many RDI values and newly revised RDA or AI values. For example, the current adult RDA for vitamin B_{12} is 2.4 μg whereas the RDI is 6 μg. For biotin the gap is tenfold: the AI is 30 μg whereas the RDI is 300 μg. Revision of the RDI values to more nearly match current nutrient standards should be a priority. As these RDI values are revised, it would be appropriate to set limits on the amounts of nutrients that can be added to foods.

As the GRAS regulations currently state,

> "Any ingredient affirmed as GRAS in this part shall be used in accordance with current good manufacturing practice. For the purpose of this part, current good manufacturing practice includes the requirements that a direct human food ingredient be of appropriate food grade; that it be prepared and handled as a food ingredient; and that the quantity of the ingredient added to food does not exceed the amount reasonably required to accomplish the intended physical, nutritional, or other technical effect in food" (21CFR184.1).

With the bountiful, nutritious food supply available in the U.S., there is no need to fortify a single food at levels of 100% or more of the DV per serving without strong scientific evidence that intake levels exceeding these nutrient standards are in fact beneficial. A thorough examination of current dietary intakes from fortified foods and comparisons to UL levels would also be useful in setting reasonable target levels for fortification. In its position paper on food fortification, the American Dietetic Association encourages new guidelines to help prevent excessive nutrient intakes from fortified foods, meal replacements, and dietary supplements (ADA, 2000).

Assurance that stated levels of fortification are actually present in the food is another potential issue. An outbreak of vitamin D intoxication led to review of fortification quantities of vitamin D in milk and the documentation in 1992 of a range of vitamin D levels in milk samples (Holick et al., 1992). Only 29% of milk samples contained the required 80–120% of the amount of vitamin D stated on the label. Most milk samples were low in vitamin D, whereas 70% of samples of infant formula contained more than 200% of the stated amount. This led to a review of fortification procedures in many states (Hicks et al., 1996). The problem remains to be solved; a recent survey in Canada found a wide range of vitamin D levels in milk (Faulkner et al., 2000).

Appropriateness of Added Nutrients and Foods Being Fortified

The specific nutrients to be added and the specific foods to be fortified are additional considerations. In his review of current fortification policy, Mertz makes several reasonable suggestions to more effectively target fortification practices and at the same time avoid issues related to over-fortification (Mertz, 1997). One suggestion is to keep current policies but complement the existing standards of identify for cereal grain products by adding other nutrients of concern, such as vitamin B_6. Vitamin B_6 intake is marginal for many people. This vitamin is lost in substantial quantities when grains are processed but is not restored in current enrichment standards. Other nutrients to consider are vitamin E, magnesium, copper, and zinc.

A second option would be to designate breakfast cereals and grits instead of flour and baking products as fortification carriers. Standards of identity could be revised such that one serving would provide one-half of the RDA for all vitamins and minerals, except iodide, and standards of identity could be developed for products with and without iron (Mertz, 1997). In this scenario, commonly consumed foods would be used to deliver a wide range of nutrients. It may be more prudent to consider a value of one-fourth the RDA per serving, considering that individuals still would consume a wide variety of other nutrient sources and in light of the common use of nutrient supplements.

The third option proposed by Mertz (1997) was to develop standards of identity for a nutritional supplement containing one-half the RDA, again in versions with and without iron. This could be sold at a minimum cost, possibly with federal subsidy for individuals in the Special Supplemental Nutrition Program for Women, Infants and Children (WIC) and allowable for purchase with food stamps. This option might reduce or eliminate the need for cereal fortification and could reasonably lower the prices of breakfast cereals and other highly fortified foods. It is possible that FDA could develop a nutritional supplement under the existing "nutritional quality guidelines for foods" (21CFR104.5) and use the allowable government endorsement on the label.

Some nutritionists may argue that there could be better fortification choices than salt and whole milk. Salt (sodium chloride) in excess may aggravate blood pressure. For 30–50% of people with hypertension, reducing salt intake can

lower blood pressure. However, the prevalence of added salt in processed foods likely provides enough iodide exclusive of any salt added by the individual during cooking or at the table. Whole milk is an excellent source of nutrients but is also high in saturated fat and cholesterol—important targets for the reduction of blood cholesterol levels and heart disease risk. Consumers need to be educated that reduced-fat milks provide nutrition, including vitamin D, equal to that in whole milk.

Revisiting Fortification Policy

As previously stated, many principles in the FDA's current fortification policy and current fortification practices by the food industry are at odds with other viewpoints about the purpose of fortification, namely the principles endorsed by the Food and Nutrition Board in 1974. In his letter of August 3, 2000 to FDA, Richard Theuer proposes the adoption of the Codex General Principles for the Addition of Essential Nutrients to Foods. These general principles endorse addition of essential nutrients to achieve 1) restoration of nutrients lost during processing, 2) nutritional equivalence of substitute foods, 3) fortification, and 4) ensuring the appropriate nutrient composition for a special purpose food (FAO). The Codex principles define fortification as "... the addition of one or more essential nutrients to a food whether or not it is normally contained in the food for the purpose of preventing or correcting a demonstrated deficiency of one or more nutrients in the population or specific population groups...." Current regulated fortification practices such as iodizing salt, adding vitamin D to milk, and enriching cereal grains fit this definition, whereas adding five times the RDI of vitamin C to a juice beverage does not.

It may be difficult to rein in fortification activities by the industry, which are fueled by the public's current appetite for foods with health-*promoting* qualities. Consumer demand will continue to drive the market for fortified foods and push the limits of current regulations. According to Sloan, regulatory agencies have not updated policies or interpreted existing policies to stay ahead of the more innovative companies (Sloan, 1995; Sloan and Stiedemann 1996). Fortification efforts have been moving away from adding nutrients to products that are not nutrient dense and toward fortifying already nutritious foods, such as orange juice (Hollingsworth, 1997).

The Problem of Botanicals

The most pressing fortification issue is not one of nutrient amounts or appropriateness of foods, but one of fortifying products with nonnutrients, specifically botanical compounds. The market for herbally enhanced food products has exploded, from less than $20 million in sales in 1997 to $700 million in 2000. Juices and cereals have been common fortification targets, but herbs are appearing everywhere from snack foods to soups. As is the case with herbal supplements, many compounds have scant proof of efficacy and safety, and for

many the risk of adverse reactions and drug interactions is very real (Percival and Turner, 2001). Few botanical compounds have either GRAS or direct food additive approval, and thus may render many of these foods adulterated.

In January 2001, the FDA sent a general letter to the food industry addressing botanicals and other novel ingredients in conventional foods (FDA, 2001). This letter reminded the industry of the requirements for food additives to be approved or affirmed as GRAS. The FDA also reviewed the types of allowable claims on food labels, including the provision that structure/function claims on foods must be for effects that are achieved through the "nutritive value" of the food, and warning that structure/function claims that are not attributable to nutritive value render the food product a drug.

In June 2001, the FDA sent warning letters to several specific food companies who market beverages and breakfast cereals containing herbal additives. These letters indicate the FDA's position that current products are misbranded and adulterated and asked for the companies to not only provide written documentation of steps taken to correct violations but also provide the basis for concluding that the herbal additions are the subject of a prior sanction or GRAS. Furthermore, the FDA reminds the companies that the term "added" is a synonym for fortified and is only authorized to be used in conjunction with the addition of protein, vitamins, minerals, dietary fiber, or potassium.

These actions clearly state the FDA's position that, under current regulations, many botanical compounds are not appropriate to be added to food. Again, the public appetite for these botanicals in supplement form and the vast amount of media attention given to them is driving the market. The data related to the efficacy of a botanical compound after food processing are virtually nonexistent, so it is reasonable to conclude that much of the current fortification of foods with botanical compounds is done for marketing reasons rather than health reasons. The FDA's fortification policy states that nutrient additions are only appropriate when the nutrient is stable in the food and is physiologically available. Again, there is little evidence related to either the stability or bioavailability of botanicals when added to foods. For these reasons, it is critical that the FDA continue to take action to stop the proliferation of botanically enhanced foods until the science has time to catch up.

SUMMARY

Food fortification has been an effective public health measure over the last 80 years. Nutrient deficiency diseases that were once common have been all but eradicated, and inroads are being made for reducing neural tube defects associated with folate status. With the threat of nutrient deficiency behind us, it is time to re-examine food fortification policy in light of new dietary standards, medical efforts that are preventative rather than treatment oriented, and consumers with an insatiable appetite for the latest miracle nutrient, herbal, drink, or supplement.

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CHAPTER 31

SPORTS NUTRITION

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INTRODUCTION AND DEFINITION OF ISSUES

Ergogenic aid use is rooted in antiquity and is based on superstition and ritualistic behavior of athletes who believed that past performance was related to dietary intake or manipulation (Applegate and Grivetti, 1997). Soldiers preparing for battle were told to consume specific animal parts to confer agility, speed, or strength. In the twentieth century, scientific research supported the need for energy to fuel athletic performance and the importance of protein in muscle-building activities. Although the scientific value of dietary manipulation for athletic performance has been studied extensively, the popularity and use of ergogenic aids have preceded scientific substantiation of claims. Funding dietary research that may prevent cancer is considered more important than research that may support the use of ginseng to improve running performance.

Even the diets of elite athletes have received little attention (Grandjean, 1997). Most studies suggest that the range of nutrient intakes in elite athletes is great, as is intake of protein, fat, and carbohydrate. Protein intakes of elite athletes range from 1.0 to 4.3 g/kg body weight (Grandjean, 1997). Many unanswered questions about sports nutrition remain, but athletes are continually incorporating new dietary strategies and supplements into their daily intake.

BACKGROUND AND HISTORICAL SIGNIFICANCE

A discussion of the nutritional needs of athletes is hampered by the wide range of types of athletes. Athletic pursuits include activities that involve a range of activity from short bursts of speed to ultraendurance events that include days of uninterrupted exercise. Adding to the complexity are differences in nutrient

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needs associated with gender, age, environmental conditions, and training. To evaluate the nutritional impact of any diet or supplement requires a placebo-controlled trial. Most of the existing trials have been conducted with the most available subjects, generally fit male athletes that are easily recruited at an academic sports medicine department. Thus questions about children, women, obese subjects, etc. and their nutritional needs must be inferred from the existing data from fit male subjects.

This review will divide material into the following sections: macronutrients, micronutrients, fluids, and ergogenic aids. Because the topic covered by each of these sections includes a large amount of material, nutrients of current interest will be highlighted.

SCIENTIFIC BASIS AND IMPLICATIONS

Macronutrients

The calorie needs of athletes vary greatly depending on the sport. Whereas sports such as gymnastics require calorie restriction, ultraendurance sports may require upwards of 10,000 kcal daily. Elite female figure skaters were found to consume only 1,500 kcal per day, significantly less recommended (Ziegler et al., 2001). Thus, recommendations for macronutrient composition of calorie intake are difficult to support when total calorie intake varies so greatly. As a general recommendation, the nutritional recommendation for all Americans, with 30% of calories as fat, 55% as carbohydrate, and 15% as protein, could also be used with athletes.

Additionally confusing in this area is the fact that energy can be obtained from foods or from body stores. Thus, body stores of macronutrients will affect performance. Compared with the body's limited carbohydrate stores, triglyceride reserves are plentiful. In a healthy, untrained individual, between 70,000 and 100,000 kcal of energy is stored as fat (Hawley, 1998). Even highly trained athletes with little fat tissue have fat stores that far exceed their athletic requirements. As a stored source of energy, fat has an advantage over carbohydrate: The energy density is higher, whereas the relative weight is lower. Fatty acids are concentrated energy sources but require more oxygen than does the oxidation of carbohydrates.

Intensity of exercise also affects fuel use. Low-intensity exercise, such as walking, stimulates lipolysis, whereas high-intensity exercise maximizes carbohydrate breakdown. At all intensities a combination of protein, fat, and carbohydrate is used to fuel exercise. As exercise continues, body stores of carbohydrates are depleted and it is important that the athlete consume energy sources to fuel exercise if the exercise is prolonged.

Endogenous carbohydrate reserves are limited, and fatigue sets in when glycogen is depleted. Thus methods to enhance carbohydrate storage, preserve carbohydrate stores, and promote fatty acid oxidation will improve exercise

capacity. There is also a training effect in this equation. Well-trained athletes routinely store more glycogen, use their glycogen stores more slowly, and convert to fatty acid oxidation sooner than untrained athletes. Additionally, nutrition strategies have been developed to promote fat utilization and spare glycogen. This is particularly important because athletes have a difficult time following dietary recommendations for carbohydrate intake (Burkeet al., 2001).

Caffeine is the best-known ergogenic aid that alters macronutrient metabolism. The Medical Commission of the International Olympic Committee (IOC) first banned caffeine in 1962. Currently it is considered a restricted drug (an illegal dose is greater than 12 mg/dl in urine). Normal intake of caffeine from foodstuffs would not cause these illegal levels of caffeine. Evidence of a glycogen-sparing effect of caffeine is supported in most studies (Hawley, 1998). When compared with placebo, caffeine (150–250 mg) improves running and cycling performance in moderately or well-trained athletes who perform at or near their Vo_{2max}. Caffeine has no ergogenic effect on sprints or short events.

Carnitine has also been promoted as an ergogenic aid that can spare glycogen use and increase fatty acid oxidation. Carnitine does play an important role in the metabolism of fatty acids by transporting them into the mitochondria for beta-oxidation. Although carnitine is promoted to athletes for its ability to burn fatty acids, especially to athletes in sports such as wrestling where weight loss is desirable, few studies provide evidence that it has any effect (Hawley, 1998).

Another nutritional supplement that affects macronutrients is β-hydroxy-β-methylbutyrate (HMB). It is a metabolite of the essential branched-chain amino acid leucine and is produced in small amounts endogenously. HMB is hypothesized to be the bioactive component in leucine metabolism that regulates protein metabolism. Promoters suggest that high HMB levels decrease protein catabolism, thereby creating a net anabolic effect (Armsey and Green, 1997). Again, few studies have been conducted and no data are available on the safety aspects of HMB.

Medium-chain triglycerides, triglycerides with a chain length of between 6 and 10 carbons, have been promoted to athletes as ergogenic aids because they are emptied rapidly from the stomach and are absorbed nearly as quickly as glucose. Although these products appear to be useful to athletes, few studies find any benefits of MCTs. Additionally, some research has found that the large amounts of MCTs that may aid performance are not tolerated well and produce gastrointestinal symptoms.

Altering the macronutrient composition of the diet to enhance glycogen stores is generally accepted in sports nutrition. Methods to accomplish this objective vary. Historically, subjects were encouraged to go through a carbohydrate restriction a few days before a carbohydrate feeding to enhance glycogen stores. More recent studies provide evidence that by habitually consuming a high-carbohydrate diet (70% of calories as carbohydrate) and training, glycogen stores can be kept elevated. Some studies have found that endurance

athletes can adapt to high-fat diets and perform well on these diets, especially if the athletes are engaged in long-distance, endurance events.

Another popular concept in sports nutrition is the idea of getting into "the zone." "The zone" is defined as an euphoric state where body and mind work at peak efficiency. This state can be reached by altering the production of eicosanoids (Coleman, 1996). To control eicosanoids and enter the zone, athletes are advised to follow a dietary regimen of 30% protein, 40% carbohydrate, and 30% fat at each meal and snack. The protein content of the Zone diet is supposed to increase glucagon levels and maintain the proper balance between insulin and glucagon. Concerns with the Zone diet include the low carbohydrate intake that may impair athletic performance.

High-protein diets are not new to sports nutrition. In the nineteenth century it was believed that protein was the major exercise fuel, whereas in the twentieth century nutritionists emphasized that exercise has little effect on protein needs (Lemon, 1998). Recent research does provide evidence that active people have increased protein needs, although the usual high intakes of protein in the United States generally covers the needs of most athletes. Although the RDA for protein is 0.8 g/kg body weight regardless of physical activity, other recommendations for protein intake for athletes have been suggested. Lemon (1998) suggests that endurance athletes consume 1.2–1.4 g/kg body weight whereas strength athletes should consume 1.6–1.7 g/kg body weight. There are no indications of adverse health effects associated with high protein intake as long as kidney function is adequate. Additionally, studies that show increased losses of calcium in urine are associated with purified protein sources and not food protein sources that are naturally high in phosphate. Concerns with amino acid toxicities are not relevant when athletes consume intact proteins. Also, athletes on high-protein diets need to be encouraged to increase fluid intake to avoid dehydration.

Usual recommendations for carbohydrate intake in sports nutrition studies support high carbohydrate intakes with little discussion of carbohydrate composition. Burke et al. (1998) have suggested that different types of carbohydrate foods be consumed at different points in the carbohydrate loading process. Before exercise, a low-glycemic index meal should be eaten to promote sustained carbohydrate availability. During exercise, high-glycemic index foods are recommended (Table 31.1). These authors suggest that in the postexercise period high-glycemic index foods should be consumed to enhance glycogen storage by promoting greater glucose and insulin responses. Sport drinks on the market contain a variety of carbohydrate sources including glucose, sucrose, and glucose polymers.

Hawley and Burke (1997) have also suggested that meal frequency and timing are important variables in sports nutrition. They suggest that, often, smaller meals make sense because athletes may have gastric discomfort with infrequent large meals. Athletes need to work out schedules of eating that allow them to consume enough calories to meet needs and resynthesize glycogen.

TABLE 31.1. Examples of the Glycemic Index (GI) of CHO-Rich Foods

	Food	GI (glucose = 100)	GI (bread = 100)
High GI	Glucose	97	138
	Cornflakes	84	119
	Coco Pops	77	110
	Instant mashed potato	83	118
	Baked potato	85	121
	Sports drink	95	136
	Jelly beans	80	114
	White bread	70	101
	Wholemeal bread	69	99
	Weetabix	70	100
	Watermelon	72	103
	Honey	73	104
	Rice (low amylose)	88	126
Moderate GI	One-minute oats	66	94
	Muesli flake cereal	68	97
	Muffins (cake style)	62	88
	Soft drink	68	97
	Rice (high amylose)	59	83
	Arrowroot biscuit	66	95
	Ice cream	61	87
	Ripe banana	52	74
	Mangoes	55	80
	Orange juice	57	74
	Sucrose	65	92
	Porridge	61	87
Low GI	Mixed-grain bread	45	64
	All-bran cereal	42	60
	Milk	27	39
	Flavored yogurt	33	47
	Chocolate	49	70
	Unripe banana	30	43
	Apple	36	52
	Orange	43	62
	Pasta	41	59
	Baked beans	48	69
	Kidney beans	27	42
	Red lentils	26	36
	Fructose	23	32

Note. Values derived from studies where glucose is the reference food can be converted to the white bread standard by multiplying by 1.42.

Source: Burke et al., 1998.

Micronutrients

Although it is generally assumed that vitamin needs increase with exercise, little research data supports this position. The increased food intake associated with endurance exercise will usually supply more than adequate vitamins to fuel additional metabolism. The micronutrients that may be in short supply in athletes' diets are the minerals. This is particularly true for women. Endurance athletes are at risk of becoming iron deficient because of an imbalance between absorption of dietary iron and exercise-induced iron loss. Supplementation with iron to treat iron deficiency in athletes should be handled on an individual basis because iron supplementation studies find conflicting results (Nielsen and Nachtigall, 1998).

Athletes commonly eliminate red meat from their diets (Loosli and Ruud, 1998). Besides the decreased protein intake, red meat is an important source of trace minerals such as iron and zinc. Iron in red meat is particularly bioavailable. By eliminating red meat, women athletes, in particular, significantly decrease iron intake and also lower the availability of ingested iron. Zinc is also concentrated in red meat and is in low supply in women athletes' diets.

In 1992, the American College of Sports Medicine coined the term "the female athlete triad." This is a serious syndrome comprising three interrelated components: disordered eating, amenorrhea, and osteoporosis. This syndrome is related to the need to maintain a low body weight to excel in a sport. Sports most likely to be related to this triad include gymnastics, diving, and figure skating. Although prevention is the preferred method, once the triad occurs it must be treated. Often, amenorrhea must be treated with hormone replacement and does not respond to nutritional treatment. Nutritional treatment includes improved diet and maintenance of adequate body weight. Calcium intake is important but will not stop bone loss that is associated with amenorrhea. Oligoamenorrhea in long-distance runners, even with adequate dietary intakes, decreased bone mineral density significantly in the lumbar spine in a recent trial (Gremion et al., 2001).

Chromium is another micronutrient that is of concern to athletes. The primary function of chromium is to potentiate the effects of insulin and thereby alter glucose, amino acid, and fat metabolism. Chromium supplements have been related to increased muscle mass and decreased body fat. However, most experimental evidence does not support these claims (Clarkson, 1997). The prudent course of action for athletes is to consume foods rich in chromium and, if desired, take a supplement that contains the recommended amounts of chromium.

Fluids

Athletes are always at risk for dehydration. Dehydration causes reduced training capacity, reduced sports performance, and compromised thermoregulation and cardiovascular functions (Horswill, 1998). Continued physical exertion

TABLE 31.2. Fluid Intake Guidelines

Timing	Amount	Adaptation
Before exercise (2 h before)	Drink 500 ml (17 oz)[a]	None
During	Drink 600–1200 ml (20–40 oz) per h[a]	Drink 150–300 ml (5–10 oz) every 15–20 min
After exercise	Based on pre- and post-exercise body weight, drink enough fluid to restore body weight.	Drink 50% over and above the volume ingested to restore pre-exercise body weight. This compensates for urine losses, which may induce hypohydration when only 100% of fluid is consumed

[a] From American College of Sports Medicine position stand.

with these functions running at suboptimal levels will cause exhaustion or heat injury and hamper performance. Studies find that athletes may lose up to 3 liters per hour with exercise-induced sweating. Fluid intake guidelines, which have been developed by the American College of Sports Medicine, are given in Table 31.2.

It is always stressed that the most important fluid to replace is water, yet many sport nutrition drinks are on the market. Research supports that the characteristics of a fluid will impact the volume consumed (Horswill, 1998). Additionally, a range of factors influence the intestinal absorption of fluids (Table 31.3). These factors are useful in the formulation of sports drinks.

Ergogenic Aids

The difference between the agony of defeat and the ecstasy of winning is tenths of a second or less. The athletic product industry has responded to this reality with a thousand items that give athletes the extra burst of power to put them over the finish line first (Butterfield, 1996). Nutritional ergogenic aids can be divided into four categories. The categories include (a) products representing metabolic fuels, such as carbohydrate, lactate, and more recently, fat; (b) those representing cellular components that might be limited, such as creatine, creatine phosphate, carnitine, and various vitamins; (c) anabolic substances that may enhance performance by changing body composition, such as protein, energy, chromium, and vanadium; and (d) substances that may enhance recovery, such as fluid, electrolytes, and herbal products.

The number of products in each category is ever-expanding. Thus it is difficult to keep abreast of the latest products. Additionally, many body building products now use "stacking" of various ergogenic aids. These products include a variety of ergogenic aids and have not been tested together. Often athletes themselves, particularly athletes who are successful in a sport, promote these

TABLE 31.3. Factors Influencing Intestinal Absorption of Fluids

Factor	Description	Action
Concentration of carbohydrate	Range of 2.5–12% found in commercially available beverages.	Carbohydrates are transported actively across intestinal wall. When carbohydrate levels are too high (8%), free carbohydrate in gut lumen can counteract fluid absorption
Type of carbohydrate	Glucose polymers—(maltodextrins), sucrose, glucose, and fructose are typical choices—fructose should not exceed a 1:1 molar ratio with glucose.	Glucose and fructose (individually or as sucrose) facilitate transport. Solute transport across intestinal membrane creates osmotic pressure that draws water for absorption.
Presence of sodium	Macromineral, which is found in extracellular fluid.	Transported in intestinal membrane via glucose-sodium system. Resultant osmotic pressure draws water for absorption.
Osmolality	Particle content of the solution, primarily determined by carbohydrates, and electrolytes.	Osmolality has less of an impact when multiple transportable substrates are present in the fluid compared with when only one substrate is present

products. For this review, one substance from each category will be highlighted.

Metabolic fuels: Carbohydrates Ingesting a fluid containing carbohydrate during sustained exercise can increase endurance time (Horswill, 1998). The ingested glucose becomes a substrate for the muscle as muscle glycogen levels run low. The ergogenic effect of carbohydrate during prolonged exercise may be affected by the type of carbohydrate ingested. Glucose is oxidized at a higher rate than fructose when either is consumed alone. When a mixture of glucose and fructose is ingested, the rate of carbohydrate oxidation is significantly higher than the rate for glucose or fructose alone. Thus a mixture of carbohydrates may maximize the athlete's ability to use exogenous carbohydrates supplied during exercise.

Concentration of carbohydrate is an important variable to consider. Ranges of 2.5–12% are generally found in commercially available sport drinks. Saturation of transporters is found when carbohydrate levels are too high, usually greater than 8% (Horswill, 1998). The type of carbohydrate also affects intesti-

nal absorption of fluids. Glucose polymers—(maltodextrins), sucrose, glucose, and fructose are typical choices)—are optimal, with lesser amounts of fructose (not to exceed 1:1 molar ratio with glucose).

Cellular components: Creatine Creatine is an amino acid that in its phosphorylated form transfers phosphate to adenosine diphosphate (ADP) to maintain high levels of adenosine triphosphate (ATP) in muscle and thus provides energy for muscle activity (Feldman, 1999). The use of creatine supplements was suspected in the 1992 Olympic Games in Barcelona, Spain. Chevreul first identified creatine in meat extracts in 1835. Phosphocreatine, or creatine phosphate (CP), was identified in the late 1920s. Creatine is synthesized from arginine. Most of the total body creatine-CP pool is in muscle. Creatine biosynthesis rates are highest under anabolic conditions in young vertebrates with a good food supply and optimal levels of blood insulin, somatotropin, thyroxin, and testosterone.

Scientific evaluation of the effectiveness of creatine as an ergogenic aid is extensive. Studies are short-term and generally conducted with elite athletes. Body mass index tends to increase with creatine supplementation, especially in male subjects, with increases of 0.7–2 kg after 1–2 weeks of 20–25 g creatine/day. An association with decreased urinary volume suggests that water retention is occurring in muscle.

Creatine has been recommended as an ergogenic aid for athletes who engage in repeated bouts of brief, strenuous, high-intensity, maximal exercise. The weight gain and increase in muscle volume are considered desirable, although specific benefits of muscle bulk have not been reported. The recommended initial dose for athletes ranges from 15 to 30 g/day taken orally. After this period of "loading," 2–5 g/day is considered the maintenance dose. Muscle uptake of creatine is maximal during the initial few days of high-dose supplementation. Combining creatine with a simple sugar such as glucose may increase transport into the muscle. The initial large dose of creatine increases the creatine content of muscle by 20–50%.

Little is known about the safety of creatine. A recent letter to *The Lancet* described the occurrence of glomerulosclerosis in a patient with nephrotic syndrome, which reversed when the supplement was discontinued (see Feldman, 1999). The authors recommended measuring albumin excretion in subjects taking creatine. The increased nitrogen load to the kidneys may increase the chance for azotemia in people with impaired renal function. Users of creatine have reported muscle cramping, tears and pulls, dehydration, gastrointestinal distress, nausea, and seizures, but these side effects have not been detailed in scientific studies. The FDA has advised consumers to consult a physician before using creatine.

Creatine, unlike some other ergogenic aids that fall into the class of controlled substances, is a dietary supplement containing an amino acid that is provided in a meat-containing diet and can be synthesized by the body. Use of creatine is widespread in professional and amateur sports. Additional research

is needed on the long-term effects of this supplement, especially in growing children where it is used widely in athletics.

Anabolic substances: Nonprescription steroids Mark McGwire's use of androstenedione increased public awareness, but the substance has been popular with bodybuilders for many years. Bodybuilders call these substances, which are classified as dietary supplements, "prohormones." The president of a supplement company predicted in *Sports Illustrated* that McGwire's androstenedione use would boost annual sales from $5 million to $100 million.

Once ingested, androstenedione converts to testosterone, as do the dietary supplements dehydroepiandrosterone (DHEA) and androstenediol. The FDA banned DHEA in 1996, but manufacturers began selling it as a nutritional aid rather than a therapeutic drug. DHEA was identified in 1934 as an androgen produced in the adrenal glands. It is a precursor to the endogenous production of both androgens and estrogens. It is available in wild yams, which are sold in many health food stores as a source of DHEA. As a precursor to androgenic steroids, DHEA may increase the production of testosterone and provide an anabolic steroid effect (Armsey and Green, 1997). Promoters claim that this compound slows the aging process and is a "fountain of youth."

Only a few randomized, double-blind, placebo-controlled studies on the effects of DHEA supplementation have been published. Two studies demonstrated significant increases in androgenic steroid plasma levels, along with subjective improvements in physical and psychological well-being, while supplementing with 50 gm/day for 6 months or 10 mg/day for up to 12 months. Its effect on healthy individuals younger than 40 years old is virtually unstudied.

Few adverse effects from the supplement have been reported. Irreversible virilization in women, including hair loss, hirsutism, and voice deepening have been reported, as has irreversible gynecomastia in men, which may result from an elevation in estrogen levels. Concern has also been raised that DHEA may increase risk of uterine and prostate cancer because it elevates levels of estrogen and testosterone. There are no human studies that support the long-term safety of these substances or their ergogenic effects. There is particular concern with young people because steroid use can cause premature closure of the growth plate.

Enhanced recovery Recovery from exercise depends on replenishing muscle glycogen levels. Some research suggests that adding protein to hydration beverages helps to stimulate recovery of muscle after exercise. Because dietary protein stimulates the secretion of insulin and other hormones such as gastric inhibitory polypeptide (GIP) that augment insulin action, the rate of glycogen synthesis could be amplified with protein intake.

Other nutrients important to recovery include fluids, carbohydrates, and perhaps herbal products. Some herbal products contains caffeine, which is known to help spare glycogen stores. Ginseng has been promoted as an aid for recovery, yet only testimonial data support its use (Bahrke and Morgan, 1994).

Adequate intake of carbohydrates is crucial to recovery of glycogen levels. Additionally, some data support the importance of the timing of this carbohydrate intake. There is a brief window of opportunity after glycogen-depleting exercise when glucose uptake (and glycogen resynthesis) is substantially enhanced (Lemon, 1998). Athletes are encouraged to consume carbohydrate (about 2 g/kg body weight) shortly after exercise.

REGULATORY, INDUSTRIAL, AND INTERNATIONAL IMPLICATIONS

Aggressive marketing has led athletes to use nutrition supplements in hopes of improving performance (Armsey and Green, 1997). These aids are costly and potentially harmful, and the ergogenic claims are based on little or no scientific evidence. Nutritional supplements are a lucrative business in the United States, with consumers willing to pay billions of dollars for alleged benefits. Supplements receive little regulation by the FDA. The lack of regulation leads to outrageous advertising, impurities in manufacturing, and potentially dangerous reactions among supplement users.

In September 1998, the American College of Sports Medicine issued a statement urging the FDA to scrutinize supplements such as androstenedione. The Dietary Supplements Health and Education Act (DSHEA) of 1994 limits FDA regulation of dietary supplements. In an editorial in *The New England Journal of Medicine*, editors Marcia Angel and Jerome Kassirer criticized Congress for weakening the FDA's jurisdiction over dietary supplements. They cited specific examples of problems related to dietary supplement use. One involved a bodybuilder who had a central nervous system reaction to a supplement containing butyrolactone that he took to stimulate growth-hormone production. Many scientists feel that the legal loophole that allows the sale of substances that are only one enzymatic step away from the real thing needs to closed.

Costs of nutritional supplements are also an issue for athletes. Armsey and Green (1997) calculated the costs of a loading dose of creatine at $7.20 per day for a week. The maintenance dose then costs $3.60 per day. Brand-name protein powder is $9.80 per day, whereas generic protein powder costs $2.80 per day. In contrast, tuna, a very high-quality protein costs $2.80 per day for the same amount of protein. Nutritionists will note that tuna contains other nutrients besides protein and also is a food, which adds to mealtime enjoyment.

CURRENT AND FUTURE IMPLICATIONS

The sports nutrition market is extremely lucrative and should continue to grow. Particularly attractive supplements include those that build muscle and decrease fat. These products find use both in sports nutrition and in the weight control market. A popular juice drink at a local sports club includes the fol-

lowing ingredients: calcium, ginseng, *Gingko biloba*, chromium picolinate, whey protein, creatine, echinacea, and designer protein. This concept of stacking is becoming more popular with athletes. Thus not only do we not know what any individual ingredient does for the athlete, we are now challenged with a mixture of untested nutritional treatments.

Kelly (1997b) reviewed supplements of current interest to endurance athletes. These include *Panax ginseng*, *Eleutherococcus senticosus*, carnitine, choline, coenzyme Q_{10}, pyridoxal-α-ketoglutarate, pyruvate, and performance drinks. In an earlier review (Kelly, 1997a) he reviewed the nutritional supplements of current interest to strength athletes. These include creatine monohydrate, HMB, whey protein, phosphatidylserine, and selected amino acids and minerals. These popular supplements are always evolving, so it is difficult for the health professional to keep ahead of the field.

The group that needs them most does not consume most sports nutrition supplements and products. Endurance athletes completing a 24-hour run obviously need sports bars, drinks, and meal replacements. Middle-aged, overweight golfers probably have little need for these products. Gymnasts consuming few calories need to take supplemental nutrients to provide deficiencies. A recent position statement states that nutritional ergogenic aids should be used with caution and only after careful evaluation of the product for safety, efficacy, potency and whether it is a banned or illegal substance. (American College of Sport Medicine, American Dietetic Association, Dietitians of Canada, 2000). Thus use of these products must be evaluated on an individual basis after the athlete's usual dietary intake is evaluated by a nutritionist.

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INTERNET RESOURCES

Gatorade Sports Science Institute. *http://www.gssiweb.com/*
The Gatorade Sports Science Institute provides information targeted toward athletic trainers, physicians, coaches, and nutritionists. Visitors to the site can find out what's new in the field, review past issues of review papers, and post questions for response.

Penn State Sports Medicine Newsletter Homepage. *http://cac.psu.edu/~hgk2/index.html*
Articles from the Penn State Sports Medicine Newsletter are featured at this all-text

site. The newsletter, a monthly publication of the Center for Sports Medicine at Pennsylvania State University, is written for a general audience and includes information on sports nutrition and exercise for general health.

The Physician and Sports Medicine Online. *http://www.physsportsmed.com/index.html*
Read about nutrition, exercise, injury prevention and fitness at this site from the Physician and Sports Medicine Online, a division of The McGraw-Hill Companies. Provides abstracts from the current issue and articles from previous issues.

CHAPTER 32

DIETARY SUPPLEMENTS

CATHY L. BARTELS and SARAH J. MILLER

INTRODUCTION AND DEFINITION OF ISSUES

Herbal and nonherbal medicines are popular worldwide, with the branded nonprescription herbal medicine market estimated to be worth almost $1.2 billion in 1994 (DeSmet and Brouwers, 1997). Their consumption continues to rise yearly, with annual sales of approximately $4 billion and sales increasing by 20% per year since the early 1990s (Anonymous, 1998a; Canedy, 1998; Eisenberg et al., 1998; Greenwald, 1998). American consumers are increasingly turning to herbal and related remedies for promotion of wellness and cure or palliation of illnesses. The widely quoted 1990 survey by Eisenberg et al. found that herbal medicine had been used in the past year by 3% of adult respondents (Eisenberg et al., 1993). A follow-up survey by the same group in 1997 found that over 12% of adult respondents reported using herbal medicine in the past year (Eisenberg et al., 1998). A recent review quotes a range of 3–93% of the U.S. population as herb users, with variability because of differing definitions of herbs as well as length of use (Winslow and Kroll, 1998). With the increasing use of herbal medicines, it is important for health care practitioners, who often receive little or no formal training regarding these products, to become familiar with them and be aware of the regulation of this market.

There are currently over 500 different herbal products marketed in the U.S. (Tyler, 1995). According to the Complete German Commission E Monographs, the 14 herbs listed as top sellers in the U.S., in decreasing order, are ginkgo, ginseng, garlic, echinacea and goldenseal (tied), St. John's wort, saw palmetto, grapeseed extract, evening primrose oil, cranberry, valerian, bilberry, milk thistle, and kava kava. With the exception of goldenseal, all of these products are undergoing some form of pharmacological or clinical research, particularly in western Europe (Blumenthal et al., 1998). Mass marketing data from 1997–98 indicate a slight shift in the U.S. top sellers, listing ginkgo, St.

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John's wort, ginseng, garlic, echinacea, saw palmetto, kava kava, and valerian as the top sellers in decreasing order (Brevoort, 1998).

BACKGROUND AND HISTORICAL SIGNIFICANCE

Abood reviewed the history of dietary supplement regulation in 1999 (Abood, 1999). Much of the controversy in this area has centered on the U.S. Food and Drug Administration's (FDA) desire to regulate dietary supplements as drugs, whereas the industry has pushed to have them regulated as foods. This is understandable, because foods are scrutinized to a much lesser extent than drugs in terms of premarket approval and labeling and marketing standards. Regulations were enacted in 1973 that restricted the over-the-counter dosage content of certain vitamin and mineral products. These regulations were rescinded after their challenge by the dietary supplement industry in court. In 1976, Congress passed an amendment to the Federal Food Drug and Cosmetic Act, known as the Proxmire amendment, which restricted the FDA's authority to regulate these products.

In the early 1990s, the FDA investigated tightening of the regulation of dietary supplements. The Nutritional Labeling and Education Act (NLEA) of 1990 gave the FDA authority to regulate health-related claims of foods and food supplements (Abood, 1999). A huge public outcry to Congress followed, allegedly promoted by the health food industry. The public was led to believe, for example, that vitamins might become prescription-only items under tighter FDA controls. Apparently Congress received more mail on this issue than any other since the Vietnam War! This led to the Dietary Supplement Act of 1992, which prevented the FDA from passing regulations for a year. Eventually, Congress passed legislation that became known as the Dietary Supplement Health and Education Act (DSHEA) of 1994, which classified dietary supplements as foods. Some key elements of the Act are outlined below. The reader is referred to other sources for a more complete discussion of DSHEA (Anonymous, 1995a; Blumenthal, 1994; Glade, 1997; Abood, 1999).

DSHEA defines dietary supplements to include products containing vitamins, minerals, herbs, amino acids, and other dietary substances for use to supplement the diet by increasing total dietary intake. Dietary supplements are excluded from regulation as either food additives or drugs. An interesting corollary of the definition is that these substances can be marketed as dietary supplements even if they have previously been designated by the FDA as drugs, antibiotics, or biologics, as long as they previously were marketed as dietary supplements before being classified as drugs, antibiotics, or biologics and before October 15, 1994. On the other hand, if a product was not marketed as a dietary supplement before being recognized by the FDA as a drug, antibiotic, or biologic, it cannot be marketed as a dietary supplement.

Whereas the burden of proof of safety for food additives and drugs lies with the manufacturer, under DSHEA the burden of proof of safety for dietary

supplements lies with the FDA. DSHEA allows information from books, articles, or scientific abstracts to be used in conjunction with the sale of a dietary supplement. The information must not be false or misleading, must not promote a particular manufacturer or brand, must present a balanced view of the scientific information, must be physically separate from the products, and must not have any information appended to it. The FDA again bears the burden of proof that the literature is false or misleading. One author has made the point that although the material is required to be balanced, there is no provision for enforcement (Anonymous, 1995a).

One of the most interesting and controversial aspects of DSHEA relates to statements of nutritional support. Manufacturers may make claims in the labeling of dietary supplements regarding a product's effect on structure or function of the human body or general well-being, although they must state in the labeling that such statement "has not been evaluated by the Food and Drug Administration" and that the product "is not intended to diagnose, treat, cure, or prevent any disease." Manufacturers are prohibited from making claims that a product is useful in diagnosis, treatment, or cure of any specific disease or class of disease. This distinction is obviously somewhat nebulous.

One of the most encouraging aspects of the DSHEA legislation was its establishment of the Office of Dietary Supplements within the National Institutes of Health. The purposes of this office are to collect and compile data from studies of dietary supplements and to conduct and coordinate scientific study on supplements.

DSHEA established a Commission on Dietary Supplement Labels to study label claims and statements. The results of the studies of this commission were issued as rules by the FDA in late 1997 and took effect in 1999. Under these rules, dietary supplements are required to be labeled with a "Supplement Facts" panel that looks very much like the "Nutrition Facts" label on foods (U.S. FDA, 2001a). In addition, the FDA issued statements to help manufacturers determine whether a claim reflects effects on body structure or function or whether a claim crosses over into the diagnosis, treatment, cure, or prevention category (U.S. FDA, 2001b). In 1998, the FDA proposed rules on structure/function claims, which again set off a firestorm of controversy, with the industry accusing the agency of trying to change the definition of disease and thus limiting information that could be placed on the label of some dietary supplements and expanding the agency's oversight over botanicals (Federal Register, 2001). In the final rules on this topic issued by the FDA in January 2000, the definition of disease reverted back to preexisting narrow definitions, much to the delight of the dietary supplement industry (U.S. FDA, 2001c)

The Federal Trade Commission (FTC), which shares jurisdiction with the FDA over dietary supplements, has issued guidance for advertisers to help clarify their policies to help ensure more truthful advertisements (U.S. FTC, 2001a). This guide provides examples to illustrate how the policies apply in the actual practice of advertising.

Some new products coming onto the market over the past several years have

further muddied the waters in regard to what is a drug versus what is a food versus what is a dietary supplement. Generally, drugs can claim to treat or cure disease if the FDA approves these claims. The FDA also allows a few foods and dietary supplements to carry health-related claims. For example, some foods and dietary supplements containing calcium can carry the claim that they reduce the risk of osteoporosis. As another example, some foods that contain oats can claim to lower the risk of heart disease. In recent years, margarines containing plant stanols and sterols that inhibit cholesterol absorption have been marketed. In the premarketing process, there was considerable debate as to whether these products would be marketed as dietary supplements or as foods (Anonymous, 1998b). Since their marketing, the FDA has allowed these products to make claims regarding their use and reduction of coronary heart disease (U.S. FDA, 2001d). Therefore, it is important for patients not only to tell their physician or other health care practitioner about their dietary supplement use (which they frequently don't disclose) but also to give a history of use of other health products such as these foods. The term "nutraceutical" is increasingly being used for foods, dietary supplements, or medical foods that may be useful in the prevention or treatment of disease. The reader is referred to an article by the American Botanical Council that discusses the complexity of trying to regulate the addition of herbs to foods, exemplified by the recent trend to add ginseng and guarana (a commercial caffeine source) to various beverages (Blumenthal, 2000).

Under DSHEA, the U.S. has become one of the developed countries of the world with the least restrictive access to herbal and related remedies. For a manufacturer to bring a dietary supplement to market as a drug in the U.S., the product must be shown to the FDA to be safe and efficacious under prescribed conditions of use for a targeted patient population. This is a very expensive process (in the range of hundreds of millions of dollars), which will not be explored for products that are often not patentable, especially if these products can be brought onto the market as dietary supplements requiring little or no safety or efficacy data. Some herbal experts have advocated for a system similar to that in Germany, where proof of absolute safety and reasonable proof of efficacy are required to bring herbal and related products onto the market as drugs. This process is much less expensive and more realistic from the manufacturers' point of view (Tyler and Foster, 1996). Such a process could be limited to products promoted for minor illnesses and not include products promoted for serious disorders (DeSmet, 1997).

One problem with the lack of regulation of dietary supplements in the U.S. is that it has led to a lack of standardization of commercial products. Even if clinical studies have been conducted in a foreign country on a particular herb, there is usually no guarantee that a product sold in this country under the same herbal name will contain the same ingredients in the same quantities studied elsewhere. A widely publicized example of this possibility concerns commercially available ginseng. A widely quoted but obscure 1979 study of commercially available ginseng showed that many of the products contained no ginse-

nosides, the ingredient considered to be biologically active. A study published in the lay literature in 1995 showed that the amount of active ingredient varied severalfold among brands labeled as containing the same amount (Anonymous, 1995b). This was recently corroborated in the scientific literature (Harkey et al., 2001).

Part of the difference between brands and between lots could be due to the natural chemical variability of plants. The geographic location of plant growth, growth conditions, date of harvest, and conditions of harvesting, drying, and storage may influence the chemical makeup considerably (Bauer and Tittel, 1996). Differences in extraction techniques and the existence of chemically different varieties of many plants may also explain variations (Bauer and Tittel, 1996). Ideally, some sort of standardization of active ingredients should increase consumer confidence, although even this effort may be plagued by the shortcoming of not knowing which ingredient or ingredients of a plant contribute to pharmacologic activity.

SCIENTIFIC BASIS AND IMPLICATIONS

Echinacea

Echinacea (*Echinacea angustifolia, E. purpurea, E. pallida*) includes plants commonly known as purple or American coneflower, black sampson, black-eyed Susan, and snakeroot (Blumenthal et al., 1998; Hobbs, 1994; Olin, 1997). These plants have daisylike rose to purple or white flowers crowned with a prominent cone, and they are found throughout North American prairies, plains, and open woodlands (Blumenthal et al., 1998; Hobbs, 1994; Olin, 1997; Tyler, 1993). Native Americans used echinacea as a remedy for colds, flu, and infections (Hobbs, 1994; Olin, 1997). The first commercial preparation was made in the early 1900s, when extracts were often used as anti-infectives (Hobbs, 1994; Olin, 1997; Tyler, 1993). Since then, this preparation has undergone several clinical trials, and the plant continues to be used topically for wound healing and internally as an immunostimulant.

Clinical studies Extracts of echinacea contain several different pharmacologically active constituents including alkylamides, alkaloids, caffeic acid derivatives, chicoric acid, essential oils, flavonoids, polyacetylenes, and polysaccharides (Chavez and Chavez, 1998a; Melchart et al., 1994; Olin, 1997; Tyler, 1994). The alkylamides, the chicoric acids and related glycosides, and the high-molecular-weight polysaccharides are believed to possess nonspecific immunostimulatory activity (Chavez and Chavez, 1998a; Tyler, 1996).

Echinacea is most commonly used as an immunostimulant to provide supportive therapy for colds, flu, and chronic infections of the respiratory tract and lower urinary tract as well as topically for slow-healing wounds and chronic ulcerations. Most clinical studies were conducted in Germany, using the

aboveground plant parts or the fresh root of *E. purpurea* administered as injections or applied locally (Blumenthal et al., 1998; Chavez and Chavez, 1998a; Tyler, 1993).

Early in vitro and animal studies demonstrated the immunostimulant effects of extracts of echinacea. Studies have suggested that these effects are due to stimulation of phagocytosis caused by promotion of the release of tumor necrosis factor by lymphocytes, increasing cellular respiratory activity and leukocyte mobility (Olin, 1997; Tyler, 1993). In addition, antihyaluronidase activity has been demonstrated by several echinacea isolates, which may limit the progression of certain degenerative inflammatory diseases such as rheumatoid arthritis or osteoarthritis (Olin, 1997). Inhibition of leukemia cells both in vitro and in vivo has also been demonstrated with echinacea extracts (Olin, 1997).

More than 300 articles have been published on echinacea since 1930 (Chavez and Chavez, 1998a). Several small trials in humans have shown that echinacea extracts administered either subcutaneously or orally significantly stimulated cell-mediated immunity compared with placebo (Chavez and Chavez, 1998a; Olin, 1997).

A meta-analysis published in 1994 reviewed 26 controlled clinical studies, 25 of which were published between 1961 and 1993 in German journals. Eighteen of the twenty-six trials were randomized, and eleven were double-blinded. Single-plant extracts were used in 6 of the trials, and the remaining 20 trials used combination products containing echinacea together with other ingredients. Nineteen trials evaluated efficacy for prophylaxis or curative treatment, four trials evaluated reduction of side effects of antineoplastic drugs, and three trials studied immunomodulation. The authors reported that 30 of the 34 study groups demonstrated efficacy with echinacea compared with control groups, but most of the studies lacked strong methodological quality, making the results difficult to interpret (Melchart et al., 1994).

In a small German study conducted in 15 patients with advanced metastatic colorectal cancer, Echinacin® (60 mg/m^2) was given intramuscularly once daily and then twice weekly, as part of an immunostimulant regimen consisting of cyclophosphamide and thymostimulin. The mean survival time was 4 months, and two patients survived for longer than 8 months, suggesting that this form of adjuvant therapy may increase survival time in patients with colorectal cancer (Lersch et al., 1992).

A second review was published in 1998 examining 13 randomized, double-blind, placebo-controlled trials of echinacea specifically for prevention or treatment of upper respiratory tract infections (URTIs). Eight of the nine trials for the treatment of URTIs reported a benefit against the URTI symptoms. The four trials for prevention of URTIs failed to show statistically significant evidence for prophylactic efficacy (Barrett et al., 1999).

A third review was published in 2000 examining five clinical trials of echinacea for the treatment or prevention of URTIs. Three of these studies concluded that echinacea was efficacious for the treatment of the common cold, but methodological flaws make the results unclear. Two studies showed that

echinacea was ineffective for treating or preventing URTI symptoms (Giles et al., 2000).

Although evidence for echinacea's efficacy is inconclusive, it does appear to be a safe and effective treatment for URTIs to decrease the time to resolution of signs and symptoms of the common cold.

Availability and dosage Echinacea is available in several different dosage forms in the U.S., including a hydroalcoholic tincture extract, capsules, and a tea (Tyler, 1993). Some of the fresh juice preparations of *E. purpurea* are standardized to contain a minimum of 2.4% β-1,2-fructo-furanosides (Chavez and Chavez, 1998a). The dose of echinacea depends on the potency and preparation of the product. One dose is equivalent to 6–9 ml of expressed juice, two tablets or capsules (usually around 500–1000 mg of the ground herb), 30–40 drops of the extract, 0.7–1.5 ml of tincture, or 4–8 ounces of a strong tea made from the ground root (Blumenthal et al., 1998; Chavez and Chavez, 1998a; Tyler, 1996). For the *treatment* of active cold or flu, echinacea should be taken as often as every 2 hours until symptoms begin to resolve. The dose should then be reduced to anywhere from twice daily to five times daily for up to 1 week. For *prevention* of recurrent infections, echinacea may be taken two to three times daily for 1–2 weeks per month. Continued use of any echinacea product should not exceed 8 weeks, to avoid overstimulation of the immune system (Blumenthal et al., 1998; Tyler, 1993). After a "herb holiday," the echinacea may be restarted for another 8 weeks. The extract may also be used externally in the treatment of superficial wounds, and the liquid formulations may also be used as a mouthwash in the treatment of pyorrhea and gingivitis (Tyler, 1993).

Concerns with use Adverse effects to echinacea are rare, although allergies can occur, especially in those allergic to members of the Asteraceae family, including sunflowers and ragweed (Chavez and Chavez, 1998a; Tyler, 1994). Parenteral administration has rarely resulted in localized symptoms of fever and allergic reactions (Chavez and Chavez, 1998a; Melchart et al., 1994). Many echinacea tinctures contain concentrations of alcohol ranging from 15% to 90% and may not be suitable for certain populations (Chavez and Chavez, 1998a). There currently is no information available regarding potential drug interactions, nor are there any known contraindications. Echinacea should not be used in patients with progressive systemic diseases such as tuberculosis, multiple sclerosis, human immunodeficiency virus (HIV) infection, leukosis, collagenosis, and other autoimmune diseases (Blumenthal et al., 1998). It should probably be avoided during pregnancy because of the lack of information in this population.

Garlic

Garlic (*Allium sativum*) is a perennial bulb belonging to the lily family (Liliaceae), and it is a relative of the leek, onion, and other related species. The

bulbs of these plants contain the aromatic sulfur-based compounds that contribute to the characteristic odor and taste (Olin et al., 1997; also see Chapter 33). Garlic has been used traditionally as a diuretic, disinfectant, expectorant, and diaphoretic, and it was used during the Middle Ages to cure deafness. The Native Americans used it as a remedy for earaches, scurvy, and flatulence (Olin et al., 1997; Tyler, 1993). Garlic has undergone several clinical trials particularly looking at its potential role in the prevention and treatment of atherosclerosis and hypertension.

Clinical studies Controversy exists in the clinical literature regarding the role of regular consumption of garlic in several disease states, particularly its effects on serum lipoproteins and cholesterol. Allicin is believed to be responsible for some of the pharmacologic activity of garlic (Olin et al., 1997; Tyler, 1993). Animal and human studies have shown that garlic can reduce blood sugar levels, has antibacterial activity approximating 1% of the activity of penicillin, has antioxidant activity, increases the tone of intestinal smooth muscle and increases peristalsis, increases fibrinolytic activity, and inhibits platelet function by interfering with thromboxane synthesis. In addition, there is some evidence in humans that garlic may have anticarcinogenic effects by acting as an immunostimulant and by inhibiting the growth of cancerous cells (Olin et al., 1997; Tyler, 1993).

A recently published double-blind, randomized, placebo-controlled crossover trial examined the effects of a steam-distilled garlic oil preparation on serum lipoproteins and cholesterol in 25 hypercholesterolemic patients. The patients received either 5 mg of the garlic preparation or placebo twice daily for 12 weeks, followed by a 4-week washout period, after which they were crossed over to the other treatment arm for an additional 12 weeks. The steam-distilled garlic oil preparation was found to have no significant effect on serum lipoproteins, cholesterol absorption, or cholesterol synthesis compared with placebo (Berthold et al., 1998). However, a major flaw with this study lies in the garlic preparation that was used. Garlic oil is a commercial product formed when the water-soluble thiosulfinates from crushed garlic are transformed by steam distillation to oil-soluble allyl sulfides. In vitro studies have shown that the allyl sulfides may not be as active as the thiosulfinates. Products based on the steam-distilled oil of garlic have been shown to not contain alliin, which is essential in forming allicin (Lawson, 1998). A better representation of whole garlic is allicin-standardized garlic powder tablets, and this type of garlic preparation has been shown to have significant cholesterol-lowering effects (Warshafsky et al., 1993).

Two recent meta-analyses have demonstrated that treatment with allicin-standardized garlic powder tablets resulted in sustained reductions of 9–12% in total cholesterol (Warshafsky et al., 1993; Silagy and Neil, 1994). Doses ranged from 600 to 900 mg daily of dried powder preparations, 10 to 20 g of fresh, high-allicin garlic; or 1 g of aqueous extract. Patients demonstrated significant lowering in cholesterol levels (by approximately 10%) after 1–3 months of

therapy with the various garlic dosages. A third meta-analysis of 13 randomized, double-blind, placebo-controlled trials concluded that garlic was superior to placebo in reducing total cholesterol levels. Ten of these trials used the 300 mg of standardized garlic powder (Kwai®), one used a spray-dried powder, one used an essential oil, and one used steam-distilled oil. Dosages ranged from 10 mg to 900 mg daily, and durations ranged from 8 to 20 weeks. The pooled results showed that garlic reduced total cholesterol level from baseline (by approximately 5.8%), significantly more than placebo ($P < 0.01$) (Stevinson et al., 2000).

A randomized, double-blind, placebo-controlled study determined the lipid-lowering effects of garlic powder tablets in patients with hypercholesterolemia. Patients either received 300 mg of garlic powder (Kwai®; $n = 28$) or placebo ($n = 22$) three times daily for 12 weeks. There were no significant changes in serum lipids or lipoproteins in either arm of the study (Isaacsohn et al., 1998). Another randomized, double-blind, placebo-controlled trial determined the effect of garlic on LDL and HDL subclass patterns and distribution. Patients either received 300 mg of garlic powder (Kwai®; $n = 25$) or placebo ($n = 25$) three times daily for 12 weeks. There were no significant changes in total cholesterol, LDL or HDL cholesterol, or LDL or HDL subclass distribution. The only significant finding ($P = 0.01$) was a greater reduction in LDL mean peak particle diameter in the pattern A garlic and placebo groups compared with the pattern B group. The implications of this latter finding are unclear (Superko and Krauss, 2000).

The conflicting data found in the literature pertaining to the potential lipid-lowering effects of garlic remain confusing and unresolved at this point in time. Further studies are needed before any conclusions can be drawn in this area.

Availability and dosage Garlic is available in the U.S. as the fresh bulb or cloves, distilled garlic oil capsules, oil-based garlic preparations, garlic aged in aqueous alcohol, certain "deodorized" garlic capsules (often containing parsley), encapsulated, dried, powdered garlic that is not enteric coated for acid resistance, and enteric coated tablets or capsules (Olin, 1997; Tyler, 1993; Tyler, 1996). Many of the commercial forms of garlic are labeled as "allicin rich" (Olin, 1997; Tyler, 1993).

For the prevention of atherosclerotic disease, garlic should be dosed in the range of 2–5 g of fresh garlic, 8 mg of essential oil of garlic, 0.4–1.2 g of dried powder, or 10–15 g of cooked garlic per day (Blumenthal et al., 1998; Olin, 1997; Tyler, 1993).

Concerns with use Adverse effects reported with garlic consumption are mild and typically include heartburn, flatulence, gastrointestinal distress, allergic reactions, asthmatic reactions after repeated exposure to garlic dust, and changes in the odor of the skin and breath (Blumenthal et al., 1998; Olin, 1997; Tyler, 1993). Contact dermatitis may occur after exposure to garlic bulbs or juice, and there is a report of a single 25-ml dose of fresh garlic extract causing

burning of the mouth, esophagus, and stomach together with lightheadedness, nausea, and sweating. Persons taking aspirin or other anticoagulants should avoid eating large amounts of garlic as this may reduce the blood clotting time (Blumenthal et al., 1998; Olin, 1997; Tyler, 1993).

Ginkgo

The ginkgo, maidenhair tree, or kew tree (*Ginkgo biloba* L.) is one of the oldest living trees on this planet, dating back over 200 million years. The tree lives to be over 1000 years old, grows to about 125 feet, and has fan-shaped leaves (Olin, 1997; Salvador, 1995; Tyler, 1993). Ginkgo has been used as a health remedy since 2800 BC. The leaves and seeds were used in traditional Chinese medicine to treat asthma and chilblains, as a digestive aid, and to prevent drunkenness (Olin, 1997; Tyler, 1993). In modern China, the leaves and fruit are still used for treating lung and heart problems, and the nut (pak ko) is used to treat respiratory problems such as wheezing and coughing, urinary incontinence, and spermatorrhea (Salvador, 1995).

Ginkgo leaf extract was first studied in Germany in the 1950s for the treatment of a variety of disorders including memory impairment, hearing loss, vertigo, and tinnitus. Since 1965, a concentrated standardized leaf extract (GBE or EGb 761) has been used in Europe for the treatment of cerebral insufficiency and peripheral vascular disease (Chavez and Chavez, 1998b; Salvador, 1995).

Clinical studies Ginkgo leaf extract contains various flavonol and flavone glycosides, ginkolides, bilobalide, and various other compounds. Commercial manufacturers standardize and concentrate the extract of the dried leaves of *G. biloba* (GBE) to contain 24% flavonol heterosides, 6% terpene lactones (ginkgolides and bilobalide), and 7% proanthocyanins (Chavez and Chavez, 1998b). In addition, the German Commission E Monograph requires a maximum acceptable level of 5 parts per million (ppm) of ginkgolic acid, a strongly allergenic component of the fruit pulp and seed cover that may also be found in the leaves (Blumenthal, 1997). The U.S. currently has no set standards for ginkgolic acid. Most clinical studies with ginkgo used the extract designated EGb 761, which contains the 24% ginkgo-flavone glycosides and 6% terpenoids. A similar product, designated LI 1370, contains 25% ginkgo-flavone glycosides and 6% terpenoids (Massey, 1999; Curtis-Prior et al., 1999).

GBE has several proposed physiological effects including maintenance of venous and arterial vascular tone, decreased blood viscosity, serving as a free radical scavenger to prevent membrane damage, increasing tolerance to ischemic conditions, inhibiting platelet-activating factor, having a beneficial effect on neurotransmitter disturbance and cerebral receptor numbers, and possessing anti-infective properties (Chavez and Chavez, 1998b).

More than 70 clinical trials have been conducted with GBE, many evaluating its efficacy for dementia and peripheral vascular diseases (Chavez and

Chavez, 1998c). Various trials have also looked at the effects of GBE for a variety of other indications including memory impairment, concentration difficulties, colitis, vertigo, coronary bypass surgery, depression, tinnitus, cochlear deafness, headache, asthma, chronic active hepatitis B, hyperlipidemia, impotence, premenstural syndrome and idiopathic cyclic edema, senile macular degeneration, stroke, and hypovolemic shock (Chavez and Chavez, 1998c). However, with the possible exceptions of vertigo and certain forms of deafness, the efficacy of ginkgo in any of these conditions has yet to be determined.

GBE has demonstrated moderate efficacy in the treatment of vertigo, with 47% of patients reporting relief of symptoms versus 18% in the placebo group (Chavez and Chavez, 1998c; Olin, 1997; Salvador, 1995). In patients with hearing disorders secondary to vascular insufficiency of the ear, treatment with GBE resulted in improvement in auditory measurements in 40% of patients (Chavez and Chavez, 1998c).

More than 20 clinical studies have been published examining the effects of GBE on cerebral insufficiency, memory impairment, Alzheimer disease and vascular dementia, cerebro-organic syndrome, multi-infarct dementia, and idiopathic cognitive impairment. Various studies have shown that GBE stimulates cerebral blood flow by promoting vasodilation and improving blood flow both in the arteries and capillaries (Tyler, 1993).

A review of 40 published clinical trials evaluating the use of GBE for treating cerebral insufficiency in humans reported that 39 of the 40 trials reported positive results with GBE. However, 32 of the 40 studies had major methodological flaws, and the results of the remaining 8 studies were difficult to interpret. Although a few of the studies demonstrated an improvement in patients' symptoms, the authors suggested that treatment with GBE for longer than 6 weeks is required for any improvement to be noted. The authors also compared the methodologies of these studies to methodologies used in clinical studies evaluating the use of ergoloid mesylates (co-dergocrine) for cerebral insufficiency. On the basis of this comparison, the authors concluded that the clinical evidence for GBE is similar to that for ergoloid mesylates for cerebral insufficiency (Kleijnen and Knipschild, 1992a; Kleijnen and Knipschild, 1992b).

A more recent U.S. clinical trial examined the effects of GBE (EGb 761) in early-stage dementia (LeBars et al., 1997). In this 52-week randomized, double-blind, placebo-controlled study, patients received either GBE 120 mg daily ($n = 166$) or placebo ($n = 161$). Outcome measurements included the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), the Geriatric Evaluation by Relatives Rating Instrument (GERRI), and the Clinical Global Impression to Change (CGIC). The GBE-treated group demonstrated significant improvements in the three primary outcome measurements, cognitive impairment, and daily living/social behavior, compared with the placebo group. No significant differences were seen in the CGIC.

Another recent randomized, double-blind, placebo-controlled trial examined the efficacy of ginkgo extract EGb 761 in older people with dementia or age-associated memory impairment. Patients were randomized to receive ginkgo

160 mg/day ($n = 84$), ginkgo 240 mg/day ($n = 82$), or placebo ($n = 48$) for a 12-week period. Subjects exposed to ginkgo were then randomized to either continue to receive ginkgo or to receive placebo for an additional 12-week period. The results showed no effect on the outcome measures for the ginkgo-treated patients compared with placebo, and no beneficial effects were noted with the higher dose or the prolonged duration of treatment with ginkgo (van Dongen et al., 2000).

Studies have demonstrated positive changes in short-term memory in healthy adults and in elderly patients with mild to moderate memory impairment. The speed of information processing assessed by the Dual Coding Test was shown to improve significantly in 18 elderly patients with memory impairment 1 hour after receiving a single 320-mg or 600-mg dose of EGb 761 (Allain et al., 1993). A double-blind, placebo-controlled trial involving 27 elderly patients with mild to moderate memory impairment showed an improvement in the Digit Copying Test of the Kendrick battery after administration of GBE 40 mg three times daily for 24 weeks compared with placebo (Rai et al., 1991).

A review of six trials evaluating the effectiveness of GBE for the treatment of intermittent claudication in elderly patients found that treatment was successful in 75% of patients after 3–6 months with doses of 120 mg/day (Kleijnen and Knipschild, 1992a). Several other clinical trials have demonstrated that GBE is useful in the management of peripheral vascular disorders such as Raynaud disease, acrocyanosis, intermittent claudication, and postphlebitis syndrome (Chavez and Chavez, 1998c; Olin, 1997; Salvador, 1995).

A recent meta-analysis evaluated the efficacy of GBE for the treatment of intermittent claudication. A total of eight randomized, placebo-controlled, double-blind trials were included in the analysis. A significant difference was found in the increase in pain-free walking distance with ginkgo compared with placebo (Pittler and Ernst, 2000).

Two clinical studies have evaluated the efficacy of GBE for the treatment of impotence (Sikora et al., 1989; Ernst, 1996). An open trial using GBE for sexual dysfunction secondary to use of selective serotonin reuptake inhibitors (SSRIs) has enrolled over 100 patients thus far. Patients received an average GBE dose of 120 mg daily titrated up to 480 mg daily, with an 84% positive response rate (McCann, 1997).

Ginkgo does appear to be safe and effective for the treatment of dementia, intermittent claudication, and vertigo, although evidence is currently conflicting and inconclusive.

Availability and dosage GBE is available in the U.S. in capsules, tablets, concentrated liquids, sublingual sprays, and bars and as a cola drink. The most common dosage forms are tablets and capsules containing 40, 60, or 120 mg of the extract. The extracts should be standardized to contain 24% flavone glycosides and 6% terpenes (Chavez and Chavez, 1998c; Tyler, 1993; Tyler, 1996).

The typical recommended dose of GBE is 40–60 mg twice to three times daily, but higher daily dosages may be required for certain conditions (Blumenthal et al., 1998; Chavez and Chavez, 1998c; Salvador, 1995; Tyler, 1993;

Tyler, 1996). Duration of therapy is not clearly defined, but in most trials 4–8 weeks of therapy was required before positive effects were observed (Blumenthal et al., 1998; Chavez and Chavez, 1998c).

Concerns with use Few adverse effects have been reported with the use of GBE. Occasionally, headache, gastrointestinal upset, and dizziness have been reported (Blumenthal et al., 1998; Chavez and Chavez, 1998c; Olin, 1997; Salvador, 1995; Tyler, 1993; Tyler, 1996). Large doses of GBE may cause nausea, vomiting, diarrhea, and restlessness (Tyler, 1993). GBE should not be used during pregnancy because of its effect on the arachidonic acid pathway (Chavez and Chavez, 1998c). Although the ginkgo seed is edible, large amounts (=50 seeds) may be toxic, resulting in tonic/clonic seizures, loss of consciousness, convulsions, fever, emesis, and dyspnea (Olin, 1997; Salvador, 1995). Contact with ginkgo fruit pulp has been associated with severe allergic reactions including erythema and edema with the rapid formation of vesicles accompanied by severe itching. The symptoms typically last 7–10 days. The pulp should not be ingested as ingestion has been reported to cause pruritus, stomatitis, perioral erythema, rectal burning, and painful spasms of the anal sphincter (Olin, 1997; Salvador, 1995). A cross-allergenicity exists between ginkgo fruit pulp and poison ivy, and individuals with a history of allergic reaction to poison ivy should be extremely careful when handling any portion of the ginkgo plant (Salvador, 1995). GBE should not be taken concomitantly with anticoagulant or antiplatelet drugs because of its inhibitory effect on platelet-activating factor; the combination may prolong bleeding time (Chavez and Chavez, 1998c; Tyler, 1993).

Ginseng

Ginseng consists of the dried rhizomes and roots of several *Panax* species, namely *P. ginseng* C.A. Meyer (Asian or Korean ginseng), *P. quinquefolium* L. (American ginseng), and *P. pseudoginseng* Wallich (san qui, tienchi, or sanchi ginseng) (Olin, 1997; Tyler, 1993; Tyler, 1996). Siberian ginseng, or eleuthero, is often sold under the general name of "ginseng" even though the plant belongs to an entirely different genus (*Eleutherococcus senticosus* Maxim., also referred to as *Acanthopanax senticosus* Harms) (Tyler, 1993).

Ginseng has traditionally been used as a general tonic, an appetite stimulant, and an aphrodisiac, to quiet the spirit and to give wisdom, to treat blood and bleeding disorders, and to relive the symptoms of aging, cancer, and senility (Olin, 1997; Tyler, 1993). It is currently advertised as an "adaptogen," or performance and endurance enhancer, and it is believed to increase resistance to stress and to strengthen general vitality and overall body functions (Tyler, 1993; Tyler, 1996).

Clinical studies Ginsenosides are believed to be responsible for many of the beneficial effects of ginseng (Keung, 1994; Tyler, 1996). Many claims are associated with the use of ginseng, and it has been used in the treatment of anemia,

diabetes, insomnia, weakness, fatigue, gastritis, sexual impotence, menorrhagia, vomiting, atherosclerosis, depression, edema, hypertension, and ulcers (Tyler, 1993). There is some evidence to suggest that ginseng may reduce the stressful effects of temperature changes, diet, restraint, and exercise, raise mental and physical capacity, and protect against neurosis, radiation sickness, and some cancers (Blumenthal et al., 1998; Olin, 1997; Tyler, 1993). However, efficacy has not adequately been demonstrated in human clinical trials.

A recent review of 16 double-blind, randomized, placebo-controlled trials reported the effects of ginseng root extract on physical performance, psychomotor performance and cognitive function, immunomodulation, diabetes mellitus, and herpes simplex type II infections. Seven of the sixteen trials investigated the effects of ginseng root extract on physical performance in young, active participants during submaximal and maximal exercises on cycle ergometers. Four of these studies reported no improvement on physical performance, whereas three reported a significant decrease in heart rate and an increase in maximal oxygen uptake compared with placebo. Five of the sixteen trials investigated the effects of ginseng on psychological functions. Three of these studies reported significant improvements in mental arithmetic, abstraction tests, and selective memory tests with ginseng, whereas two reported no improvement. One of the sixteen trials reported the effects of ginseng on newly diagnosed type II diabetes mellitus patients. A reduction of the fasting blood glucose level was reported with ginseng compared with baseline, and the HbA_{1C} was significantly reduced in patients who received 200 mg of ginseng. One of the sixteen trials reported a significant beneficial effect of ginseng on the frequency, severity, and duration of herpes simplex type II infections compared with placebo (Vogler et al., 1999).

Two additional studies have been published examining the effects of ginseng root in type II diabetes mellitus. These studies reported significant reductions in postprandial glycemia in subjects with type II diabetes when 3 g of ginseng was administered either 40 minutes before or together with the glucose challenge. In nondiabetic subjects, significant reductions were observed only when ginseng was taken before the glucose challenge. Ginseng dosages greater than 3 g had no further effect on postprandial glycemia (Vuksan et al., 2000a; Vuksan et al., 2000b).

The available evidence for the beneficial effects of ginseng on physical performance and psychological function is contradictory and conflicting. Further studies are needed before any conclusions can be drawn in this area.

Availability and dosage Ginseng is available in the U.S. as fresh and dried roots, extracts, solutions, capsules, tablets, cosmetics, sodas, teas, and chewing gum (Olin, 1997; Tyler, 1993). Many of these products are standardized based on their ginsenoside content. However, some preparations contain little to no ginseng or have been adulterated with other compounds such as phenylbutazone, aminopyrine, or mandrake root (Olin, 1997; Tyler, 1995).

The recommended oral dose of ginseng extract standardized to contain 7%

ginsenosides is 100–300 mg three times daily, which is approximately equivalent to 3 g of the crude root daily. Although the optimal duration of therapy is not specified, one reference recommends therapy for up to 3 months, with repeat courses as needed (Blumenthal et al., 1998; Tyler, 1996).

Concerns with use Side effects with ginseng are usually mild and typically diminish after the first few days of use or with a dosage reduction. The most commonly reported adverse effects include nervousness and excitation (Olin, 1997; Tyler, 1993). Ginseng contains gingkoic acids, potent contact allergens, and an allergic risk is possible (Blumenthal et al., 1998). Ginseng has also rarely been reported to cause estrogenic effects in women, inability to concentrate, and a possible Stevens–Johnson syndrome (Olin, 1997; Palmer, et al., 1978; Punnonen and Lukola, 1980; Greenspan, 1983; Chosidow et al., 1996; Tyler, 1993). The only known contraindication to ginseng use is for individuals with elevated blood pressure (Blumenthal et al., 1998).

Ginseng has the potential to interact with several different medications. Ginseng has been reported to possess hypoglycemic effects, and caution should be used in patients with labile blood glucose levels (Olin, 1997). Ginseng induces both cytochrome P450 and NADPH-cytochrome *c* reductase and has the potential of interacting with other medications metabolized by these enzymes (Keung, 1994). Interactions between ginseng and warfarin (reduced International Normalized Ratio or INR), phenelzine (a monoamine oxidase inhibitor or MAOI), digoxin, and alcohol have been reported in the literature (Janetzky and Morreale, 1997; Jones and Runikis, 1978; Keung, 1994; McRae, 1996).

St. John's Wort

St. John's wort (*Hypericum perforatum* L.) is also commonly called klamath weed, John's wort, amber touch-and-heal, goatweed, and rosin rose (Olin, 1997; Tyler, 1993; Upton, 1997). This aromatic perennial herb is found throughout Europe, Asia, and North America. It has been used traditionally for the treatment of depression and anxiety, as an anthelmintic, to treat minor hemorrhages, as a diuretic, and as a tea for bedwetting children. An olive oil extract of the fresh flowers (red oil) has been taken internally for the treatment of anxiety and applied externally for the treatment of hemorrhoids. St. John's wort is now commonly used for the treatment of depression and anxiety (Chavez and Chavez, 1997; Olin, 1997; Tyler, 1993; Upton, 1997).

Clinical studies Hypericum contains several pharmacologically active compounds including hypericin and pseudohypericin, flavonoids, naphthodianthrones, tannins, and proanthocyanins. St. John's wort has been extensively studied in the treatment of depression. In addition, several clinical trials have investigated its antiviral activity, wound healing properties, and antineoplastic activity (Chavez and Chavez, 1997; Upton, 1997).

Hypericin and pseudohypericin have demonstrated in vitro and in vivo inhibitory activity against a variety of encapsulated viruses, including HIV and herpes simplex virus types 1 and 2 (Chavez and Chavez, 1997; Upton, 1997). VIMRxyn® is a synthetic hypericin currently undergoing antiviral trials. However, a recent phase I study reported that hypericin given orally in doses of 0.05 and 0.10 mg/kg/day had no detectable anti-hepatitis C virus (HCV) activity after an 8-week treatment period in patients with chronic HCV infection (Jacobson et al., 2001). Hypericum extracts have also demonstrated in vitro activity against several gram-negative and gram-positive bacteria (Olin, 1997). Patients treated with a burn ointment prepared from hypericum flowers demonstrated more rapid healing of their second and third degree burns than those treated with conventional methods (Upton, 1997).

Numerous studies have demonstrated the efficacy of hypericum in the treatment of depression. The proposed mechanisms of action are unclear but may include inhibition of monoamine oxidase, serotonin reuptake inhibition, and alteration of biogenic amine synthesis (Chavez and Chavez, 1997; Upton, 1997). A meta-analysis of 23 randomized trials with a total of 1757 outpatients with mild to moderate depression was recently published (Linde et al., 1996). Twenty of the twenty-three trials were double blind, one was single blind, and two were open label. All preparations used contained standardized hypericin ranging from 0.4 to 2.7 mg, and most of the trials had durations of 4–8 weeks. In this analysis, hypericum extract preparations were found to be superior to placebo and comparable to maprotiline, imipramine, and amitriptyline, with fewer side effects.

Two recently published randomized, double-blind multicenter studies comparing hypericum extract with imipramine also reported that St. John's wort was at least as effective as imipramine and more effective than placebo for the treatment of mild to moderate depression (Woelk, 2000; Philipp et al., 1999). Another study reported that hypericum extract was at least as effective as sertraline in the treatment of mild to moderate depression (Brenner et al., 2000). In contrast, one study compared the efficacy of St. John's wort extract with placebo in patients with major depression and found that St. John's wort was not effective (Shelton et al., 2001).

Although some of the clinical evidence for St. John's wort's efficacy in depression is contradictory, it does appear to be a safe and effective treatment for mild to moderate depression.

Availability and dosage St. John's wort is available in various commercial dosage forms ranging from tablets and capsules to teas, tinctures, and oil macerates. Several standardized extracts, yielding from 0.3% to 2.7% hypericin per daily dose, are also available (Upton, 1997).

The recommended average daily dose for the treatment of mild to moderate depression is 300 mg of standardized extract (standardized to 0.3% hypericin) three times daily for 4–6 weeks, or 2–4 g of hypericum daily (Blumenthal et al., 1998; Upton, 1997).

Concerns with use Adverse effects to hypericum are rare and most commonly include fatigue, allergic reactions, and gastrointestinal effects (Chavez and Chavez, 1997; Olin, 1997; Upton, 1997). Hypericin ingestion can cause a photosensitivity reaction, particularly in fair-skinned individuals. Contact photosensitivity may occur after handling any of the fresh plant parts (Olin, 1997; Upton, 1997). Animal studies have shown that St. John's wort has uterotonic and possible abortifacient properties and should therefore be avoided in pregnancy (Shipochliev, 1981).

Several references indicate monoamine oxidase (MAO) inhibition with hypericum. However, considering the lack of reports of MAO inhibition types of drug interactions after widespread use of hypericum throughout Europe, it is unlikely this type of herbal-drug interaction would occur. Patients should be warned of the potential risk with serotonin reuptake inhibitors and tyramine-containing foods until more conclusive evidence becomes available (Upton, 1997). There have recently been reports of St. John's wort interacting with several drugs, including cyclosporine, digoxin, indinavir, oral contraceptives, serotonin-reuptake inhibitors, theophylline, and warfarin, possibly as a result of CYP3A4 induction or an interaction with the P-glycoprotein drug efflux pump (Broughton and Denham, 2000).

Glucosamine and Chondroitin Sulfate

Glucosamine is an intermediate in glycosaminoglycan (GAG) synthesis and is found in chitin, mucoproteins, and mucopolysaccharides (Chavez, 1997). Chondroitins are GAGs that contain mucopolysaccharides and are found in mammalian cartilaginous tissues (Chavez, 1997). Chondroitins increase the resistance and elasticity of cartilage and inhibit the action of certain enzymes, such as human leukocyte esterase, which degrade old cartilage (Morreale et al., 1996). Chondroitin and glucosamine are both required for the synthesis of proteoglycans, essential components of articular cartilage. Exogenous administration of glucosamine and chondroitin may inhibit cartilage deterioration (Heil, 1997).

Clinical studies A randomized, double-blind, parallel study compared oral glucosamine sulfate 500 mg three times daily with ibuprofen 400 mg three times daily for a 4-week period. One-hundred ninety-nine patients with osteoarthritis of the knee were enrolled in the trial. Response rates were comparable between the two treatment groups at the end of the 4-week period (48% for glucosamine, 52% for ibuprofen; $P = 0.67$), although the ibuprofen group showed a trend toward more rapid response (Muller-Fabender et al., 1994).

A randomized, double-blind, placebo-controlled trial compared oral glucosamine hydrochloride 500 mg three times daily to placebo for an 8-week period. Ninety-eight patients with osteoarthritis of the knee were enrolled in the trial. The authors reported that there was no significant difference in pain reduction between the glucosamine hydrochloride and placebo groups. However, sec-

ondary measurements of pain indicated that glucosamine hydrochloride demonstrated favorable effects in some patients (Houpt et al., 1999).

Another recent randomized, placebo-controlled, double-blind trial compared oral glucosamine 500 mg three times daily with placebo for an 8-week period in 98 patients with osteoarthritis of the knee. The authors reported that glucosamine was no better than placebo in reducing pain from osteoarthritis of the knee (Rindone et al., 2000).

A recent meta-analysis reviewed seven trials of 372 patients taking chondroitin sulfate for the treatment of osteoarthritis. Chondroitin sulfate was found to be significantly superior to placebo after 120 or more days of treatment; however, it was often given concomitantly with analgesics or nonsteroidal anti-inflammatory drugs, making interpretation of the results difficult (Leeb et al., 2000).

Chondroitin sulfate 400 mg orally three times daily was compared to diclofenac sodium 50 mg three times daily in a randomized, multicenter, double-blind, placebo-controlled study enrolling 146 patients with osteoarthritis of the knee (Morreale et al., 1996). Patients were randomized to receive either chondroitin sulfate for 3 months followed by placebo for 3 months or diclofenac sodium for 1 month followed by placebo for 5 months. The diclofenac group showed a faster response rate and decreased pain after 1 month compared with the chondroitin group ($P < 0.01$). The authors claimed that response at 4, 5, and 6 months was significantly greater with chondroitin compared with diclofenac. However, because of the different durations of therapy for the two treatment arms, these results are difficult to interpret.

A recent meta-analysis evaluated the combination of glucosamine and chondroitin for the treatment of osteoarthritis of the knee or hip. Fifteen double-blind, randomized, placebo-controlled trials of 4 or more weeks' duration were included in the analysis. The authors reported moderate to large beneficial effects with either preparation but the beneficial effects were reduced when only high-quality or large trials were considered (McAlindon et al., 2000).

One trial examined the effects of the combination of glucosamine, chondroitin, and manganese ascorbate for degenerative joint disease (DJD) of the knee or lower back. Thirty-four men with DJD of the knee or lower back were enrolled in this 16-week randomized, double-blind, placebo-controlled crossover trial of a combination of 1500 mg/day glucosamine hydrochloride, 1200 mg/day chondroitin sulfate, and 228 mg/day manganese ascorbate. The authors reported that the combination therapy significantly relieved the symptoms of knee osteoarthritis but was inconclusive for effects on spinal DJD (Leffler et al., 1999).

As yet there have been no clinical trials comparing glucosamine sulfate with chondroitin sulfate. The current evidence appears to be fairly consistent in support of glucosamine for the treatment of osteoarthritis of the knee, whereas more data are needed regarding chondroitin sulfate or the combination of glucosamine and chondroitin in this setting.

Availability and dosage Glucosamine sulfate is available as 500-, 750-, and 1000-mg tablets and capsules. Chondroitin sulfate is available as 400-mg tablets and capsules. Many combination products are available, typically at dosages of 500 mg of glucosamine sulfate and 400 mg of chondroitin sulfate.

Glucosamine sulfate is typically dosed at 500 mg orally three times daily for the treatment of osteoarthritis (Heil, 1997). Chondroitin sulfate has been given at 200–400 mg orally three times daily for the treatment of osteoarthritis (Morreale et al., 1996). Optimal duration of therapy for either agent has not been established.

Concerns with use Adverse effects with either glucosamine sulfate or chondroitin sulfate appear to be minimal and most typically include gastrointestinal symptoms, headache, drowsiness, insomnia, and skin rash. Either product is contraindicated in patients with a previous hypersensitivity to them (Heil, 1997). Chondroitin sulfate administered up to 10 mg orally daily for periods of up to 6 years has not been associated with adverse effects or laboratory abnormalities (Morreale et al., 1996).

Melatonin

Melatonin is a neurohormone produced by the pineal gland near the center of the brain from the precursor tryptophan (Brzezinski, 1997; Olin, 1997; Sack, 1998). Endogenous melatonin production is much higher in children than adults, peaking in early childhood and declining steadily with age (Brzezinski, 1997; Sack, 1998). Endogenous melatonin is thought to play a role in setting the sleep-wake cycle to a 24-hour length, the onset of puberty, and reproduction (Brzezinski, 1997; Sack, 1998). In the early 1990s, melatonin began to be marketed in the U.S. as a dietary supplement. Several claims are associated with the use of melatonin, including benefits for sleep, aging, cancer treatment, and sexuality (Brzezinski, 1997; Sack, 1998).

Clinical studies Although there are many case reports and small trials suggesting that low-dose melatonin can promote sleep and prevent or alleviate jet lag, large controlled trials have not been performed. In one study of 37 travelers melatonin 8 mg was shown to be superior to placebo in alleviating morning fatigue and evening drowsiness ($P < 0.01$), but it had no effect on mood or sleep quality (Claustrat et al., 1992). A double-blind, placebo-controlled trial examined the effect of melatonin on jet lag in 52 cabin crew members on international flights. One group received 5 mg melatonin daily for 3 days before the trip and continued this dose for 5 days after arrival (early melatonin group). The second group received 5 mg melatonin daily only for the 5 days after arrival (late melatonin group). Subjects in the late group reported less overall jet lag and sleep disturbances and more rapid recovery of both energy and alertness than the early group (Petrie et al., 1989). In another randomized, double-blind, placebo-controlled study in 257 travelers, no significant difference

was reported between the placebo group and those receiving one of three melatonin regimens (Spitzer et al., 1999).

A randomized, placebo-controlled, double-blind, crossover trial compared melatonin supplementation to placebo. Fifteen emergency physicians were given melatonin 5 mg orally or placebo for 3 consecutive nights after night-shift duty, followed by crossover to the opposite agent after another 3 nights. There was no difference between the two groups in recovery, sleep quality, tiredness, or cognitive function (Wright et al., 1998).

In another randomized, double-blind, placebo-controlled study the effects of melatonin on sleep disturbances during the first 4 weeks of treatment with fluoxetine in patients with major depressive disorder were studied. Ten patients were treated with fluoxetine plus 5–10 mg slow-release oral melatonin, and nine were given fluoxetine plus placebo. The patients treated with melatonin reported significant improvement in sleep variables compared with the placebo group (Dohberg et al., 1998).

In another randomized, double-blind, placebo-controlled crossover trial the effects of melatonin on delayed sleep phase syndrome were studied. Twenty subjects were randomized to receive either placebo or 5 mg of melatonin daily for 4 weeks, followed by a 1-week washout period, and then given the other treatment for an additional 4 weeks. The patients treated with melatonin reported significant improvement in sleep onset latency compared with placebo but no effect on total sleep time, sleepiness, fatigue, and alertness (Kayumov et al., 2001).

The conflicting data found in the literature pertaining to the potential benefit of melatonin in sleep disorders and in alleviating jet lag remain confusing and unresolved at this point in time. Further studies are needed before any conclusions can be drawn in this area.

Availability and dosage Various dosage forms of melatonin are available in the U.S., including sublingual tablets, lozenges, capsules, and tablets. Combination products containing valerian and/or vitamin B_6 are also available. Melatonin is available commercially either in a synthetic form or a "natural" form derived from extracts of animal pineal glands. Some authors recommend avoidance of the "natural" forms because of the possibility of viral transmission (Olin, 1997). Most commercial brands of melatonin are available as 0.3-, 1-, 1.5-, 2-, or 3-mg tablets (Olin, 1997).

Dosages used in clinical trials for the treatment of insomnia ranged from 1 to 5 mg taken anywhere from 30 minutes to 2 hours before bedtime (Brzezinski, 1997; Olin, 1997). For prevention of jet lag, melatonin 5 mg daily for several days before departure and several days after arrival has been suggested in the literature (Brzezinski, 1997; Petrie et al., 1989).

Concerns with use Adverse effects with melatonin are usually minor and typically include headache, transient depression, nightmares, nausea, insomnia, low sex drive, and morning grogginess. In psychiatric patients, melatonin has

aggravated depressive symptoms (Brzezinski, 1997; Olin, 1997). There are several concerns with the use of melatonin. One concern is that high doses could have unknown long-term effects. A second concern is the lack of quality control of commercially available products. In one comparison of melatonin products, some products showed evidence of poor formulation and/or poor quality (Hahm et al., 1999).

REGULATORY, INDUSTRIAL, AND INTERNATIONAL IMPLICATIONS

The activities of the United States Pharmacopoeia (USP), which sets standards for prescription and nonprescription drugs in the U.S, can help the consumer in choosing quality dietary supplement products. Products can carry the USP or National Formulary (NF) designation only if they meet criteria for quality, strength, purity, and packaging. For an herbal to be included in the USP, several major studies must support its efficacy and no major studies can show lack of efficacy (Murray, 1998). Standards for botanical products with FDA-approved or USP-accepted uses are published in the USP. Standards for botanicals without FDA- or USP-accepted uses but with evidence for use and no evidence of significant safety risk are published in the National Formulary (NF). Standards for botanicals without FDA- or USP-accepted uses and with safety risks will not be published. At the present time, only a limited number of botanical monographs are included in the USP or NF, but standards development for additional entities continues (U.S. Pharmacopoeia, 2001a)

In early 2001, the USP initiated a voluntary pilot certification program for dietary supplements (U.S. Pharmacopoeia, 2001b). Under this program, dietary supplement manufacturers will work with the USP. The manufacturer will test ingredient samples, and these test results will be reviewed by the USP. The USP will also practice some oversight to see that participating product manufacturers are in compliance with good manufacturing practices (GMPs) and will do postmarketing product surveillance. The pilot program should last less than a year and is to be followed by the full-fledged program. Under this program, manufacturers who adhere to the criteria, standards, and procedures set forth by the USP will be granted the use of a proprietary USP certification mark; this mark will be distinct from the USP or NF designation referred to above.

ConsumerLab.com is a group that tests commercial dietary supplements for content and purity (ConsumerLab, 2001). Complete information regarding the commercial products tested and those that passed and failed content and purity criteria requires a subscription fee.

In 2000, the FDA issued draft guidelines for the botanical industry that were aimed to clarify certain regulatory requirements for botanicals marketed as drug products (U.S. FDA, 2001e). These guidelines explain to the industry when a botanical drug may be marketed under an over-the-counter drug monograph and when FDA approval of a new drug application is required.

In 1992, Congress established the Office of Alternative Medicine (OAM) within the National Institutes of Health (NIH) to evaluate alternative remedies, which include herbal products. The budget for this office initially comprised $2 million of the NIH's $10 billion budget, an amount termed "homeopathic" by the Office's first director (Berkenwald, 1998). This Office was upgraded in 1999 to the National Center for Complementary and Alternative Medicine (NCCAM), with an increased budget. The Center is now able to fund its own research grants and other projects directly rather than requiring collaboration with other institutes or outside agencies. Trials currently under way that are being funded by NCCAM can be viewed on the NCCAM website (National Center for Complementary and Alternative Medicine, 2001).

Another endeavor funded by the OAM (and now the NCCAM) is the complementary medicine (CM) area of the Cochrane Collaboration. The Cochrane Collaboration exists to produce, maintain, and disseminate systematic reviews on all topics in health care and also maintains a registry of controlled trials, known as the Cochrane Controlled Trials Registry. Ezzo et al., outlined the importance of this CM field (Ezzo et al., 1998). MEDLINE searches of CM topics usually yield only a portion of all known trials; Ezzo et al. outline several reasons for this. First, many of the CM trials appear in journals not indexed by MEDLINE. Second, CM articles appear in journals not indexed by any electronic database. Third, there are CM studies that have never been fully published in any journal. When addressing publication bias, Ezzo et al. question whether CM journals tend to publish results favoring CM treatments, whereas conventional medical journals tend to publish results not favoring CM treatments. The fact that results of many studies of certain CM topics, including some related to herbal remedies, are almost exclusively published initially in languages other than English contributes to the lack of knowledge of and bias against many of these therapies found in the United States. Hopefully, the CM area of the Cochrane Collaboration will be able to cut through some of these problems and provide useful information to health care practitioners and the lay public in this country.

In the widely quoted surveys of unconventional medicine use in the U.S. by Eisenberg et al., the majority of patients who used unconventional therapy did not inform their medical doctor of this use (Eisenberg et al., 1993; Eisenberg et al., 1998). Because herbal remedies contain pharmacologically active constituents with potential for adverse effects and interactions with other drugs, this nondisclosure can obviously complicate conventional medical therapy. Eisenberg has published an approach for promotion of discussion of alternative medical therapy by patients emphasizing patient safety, documentation in the medical record, and the importance of shared decision-making (Eisenberg, 1997).

In recent years, reports of misadventures with herbal remedies have been reaching the conventional medical literature at increasing rates. For example, several cases of herbal misadventures were published in a single issue of the *New England Journal of Medicine* in late 1998. Classification schemes for

organizing herbal misadventures have been published and are useful for discussion of this topic (Drew and Myers, 1997; Ernst, 1998).

The classification scheme of Drew and Myers (1997) divides adverse effects of herbals into two major categories, intrinsic and extrinsic. Intrinsic type A reactions include predictable toxicities based on the pharmacologic properties of a preparation. For example, ephedra found in Ma huang has sympathomimetic properties and has been associated with cases of significant hypertension, heart attack, and stroke (Nightingale, 1996). Interaction with pharmaceuticals is another example of an intrinsic type A reaction that again may be predictable based on the pharmacokinetics and pharmacodynamics of the pharmacologically active ingredients in herbal products. The reader is referred to reviews of drug-herb interactions (Miller, 1998; Heck et al., 2000). Some of the more significant drug-herb interactions recognized to date involve the anticoagulant warfarin. Effects of feverfew, garlic, ginger, ginkgo, and ginseng on platelet activity require special caution in the use of these herbs in conjunction with warfarin (Miller, 1998). Allergic reactions to medicinal plants, TYPE B intrinsic reactions, are real possibilities; Ernst lists many such possibilities (Ernst, 1998).

Under Drew and Myers' classification, extrinsic adverse effects are those associated with failure of good manufacturing practices. Examples of these types of adverse events were presented in the *New England Journal of Medicine* articles referred to above. Slifman reported digitalis toxicity due to ingestion of a contaminated plaintain product, whereas Beigel reported lead poisoning in a patient taking an Indian herbal remedy for diabetes (Slifman et al., 1998; Beigel et al., 1998). Ko highlighted inconsistencies and adulteration of Asian patent medicines (Ko, 1998). Ernst supplies a table of contaminants repeatedly found in herbal remedies (Ernst, 1998). The problem of incorrect preparation of an herbal remedy by end users was illustrated in a recent report of two cases of lead poisoning in a married couple who prepared Kombucha tea in a ceramic pot, resulting in leaching of lead from the ceramic glaze (Phan et al., 1998). Inappropriate labeling and/or advertising of dietary supplements is illustrated by a product purchased by Texas Department of Health investigators that was labeled as causing "no side effects" and that listed wild Chinese ginseng as the only ingredient (Centers for Disease Control, 1996). Laboratory analysis revealed a content of 45 mg of ephedrine and 20 mg of caffeine in a single tablet. The label on the product instructed users to take five tablets, which would result in an ephedrine dosage approximately 11 times the usual recommended over-the-counter dosage of ephedrine-containing products. An interesting case of mandrake toxicity illustrates the possibility of misidentification leading to adverse events (Frasca et al., 1997). Two different plants are commonly called mandrake. The patient bought and ingested material from *Podophyllum peltatum* containing the substance podophyllotoxin, which is used topically to treat venereal warts. He thought he was taking the "other" mandrake, the hallucinatory plant *Mandragora officinarum*.

The true incidence of adverse reactions to dietary supplements is unknown. The Adverse Drug Reactions Advisory Committee (ADRAC) of the Com-

monwealth Department of Health and Family Services of Australia received only 154 reports relating to alternative medicine in the 25-year period between 1972 and 1997 (Drew and Myers, 1997). Drew and Myers commented on this statistic, stating that given the widespread use of these therapies, they must either carry a low risk of adverse effects or such effects must be significantly underreported (Drew and Myers, 1997). They concluded that underreporting is likely, at least in Australia, based on the following observations: 1) ADRAC has not actively encouraged the reporting of adverse effects of alternative medicine; 2) alternative medicine use is not routinely included in drug histories or in reports of adverse effects; and 3) the public perception that "natural" products are safe biases against associations being made between alternative medicine products and adverse effects. Of course, underreporting of adverse events is a problem with allopathic medicine as well.

Davidoff (1998) pointed out that many alternative medicine systems are characterized by the conviction that the cause and also the remedy for most illness lie within the mind and spirit of the patient. He suggested that because therapeutic success and failure in alternative systems often thus "belong" primarily to the patient, this may help explain the lack of reports of toxicities; he calls this phenomenon the "responsibility paradox."

Evidence from parts of the world where herbal remedies have been more heavily used in a traditional sense gives support to the concept that the incidence of adverse effects is actually more like what would be expected from agents with potentially active pharmacologic moieties. In a Taiwanese study, herbal remedies ranked third among the categories of medicines causing adverse effects in patients admitted to a department of medicine (Ernst, 1998). Ernst also quotes a study from the Philippines that identified herbal medicine use as one of the main risk factors for nasopharyngeal carcinoma. He quotes another study from Hong Kong that indicated that 0.2% of all admissions to two general wards of a Hong Kong hospital were due to adverse reactions to Chinese herbal drugs.

The Institute for Safe Medication Practices (ISMP) points out that DSHEA does not require postmarketing surveillance and reporting of adverse events by supplement manufacturers (Anonymous, 1998b). ISMP has compiled a list of several organizations in the United States and elsewhere that accept voluntary reports of adverse events involving herbal products, although this list is fluid (Anonymous, 1998b). Reports to the FDA MEDWATCH program involving dietary supplements can be made by phone (1-800-FDA-1088) or FAX (1-800-FDA-0178) or through the FDA website (U.S. FDA, 2001f). Concerns or complaints regarding dietary supplement advertising practices may be made to the FTC via phone (1-877-FTC-HELP) or online (U.S. FTC, 2001b).

The Medical Herbalism website accepts reports of herbal adverse events and passes them on to the FDA, to the PhytoNet European group described below, or to medical herbalists who request such information; the route of the report is dependent on the choice of the reporter (Medical Herbalism, 2001). PhytoNet is a resource based in England and serving the European community that accepts adverse event reports regarding herbal products (PhytoNet, 2001).

CURRENT AND FUTURE IMPLICATIONS

Herbal and nonherbal dietary supplements have seen an explosive growth in pharmacies and other mass-market retail outlets throughout the U.S. A survey published by Prevention Magazine/NBC News in 1997 estimated that 60 million adult Americans, or 30% of all adults, had used herbal medicines in 1996, spending an average of $54 per person annually, for an estimated total of $3.24 billion (Johnston, 1997; see Tyler, 1996).

Because so many consumers use dietary supplements, every health care professional needs to be able to provide accurate, reliable, and unbiased information about these products. Clinicians in the U.S. often are hesitant to recommend these products because of the misconception that they have not been studied sufficiently. However, clinical studies have been published for several of these products. It is the responsibility of all health care providers to weed through the available information on dietary supplements to determine which products are safe and effective and which products should be avoided.

General recommendations for counseling patients regarding use of herbal and related remedies have been published (Cirigliano and Sun, 1998; Huxtable, 1992; Vance, 1997) and include the following:

1. Patients should be specifically asked about use of these products, and use should be documented in the medical record.
2. "Natural" does not necessarily mean safe.
3. Interactions between these products and conventional medications do occur; the patient's health care practitioners, including the pharmacist, should be apprised of use of these products.
4. Quality and standardization of these products is often lacking. Look for sealed containers offering protection from light and complete labeling showing ingredients, botanical names for plants, amounts of ingredients, manufacturer name and address with telephone numbers, expiration dates, and lot numbers. Some manufacturers sell only to licensed health care practitioners; this may be a sign of higher-quality products.
5. These products should be avoided by women contemplating pregnancy or currently pregnant or lactating.
6. These products should not be taken in larger than recommended dosages. Large quantities of any one herbal preparation should be avoided. Herbs should probably not be taken on a daily basis for long periods of time (more than several weeks at a time).
7. Some of these products are known to be toxic and should be avoided. The pharmacist is often the health care professional with the best access to information on these toxicities.
8. Infants, children, the elderly, and those with serious medical conditions should not use these products without professional advice.
9. An accurate diagnosis and discussion of treatment options with a health

professional should occur before the patient uses these products for any potentially serious health condition.

10. These products should be discontinued if signs of adverse events such as allergy, skin rashes, headaches, or gastrointestinal upset occur. Adverse events should be documented in the patient's medical record.
11. Herbal medicine should not be confused with homeopathy. Homeopathy uses plant drugs in miniscule amounts, whereas herbal medicine uses potentially therapeutic dosages.
12. Misinformation abounds, especially on the Internet and in health food stores. Advertising is often misleading.

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CHAPTER 33

FUNCTIONAL FOODS AND NUTRACEUTICALS

RONALD H. SCHMIDT and R. ELAINE TURNER

INTRODUCTION AND DEFINITIONS OF ISSUES

In many parts of the world, there has been a recent explosion of consumer interest in the "health enhancing" value of foods, food ingredients, or food derivatives. Food products are currently being marketed, or are being developed, that either naturally contain or are formulated to contain certain biologically active components or ingredients. A detailed description of the burgeoning number of these functional foods and ingredients is beyond the scope of this chapter, and the topic has been thoroughly covered in other publications (Hasler, 1998; Wildman, 2001a; Oomah and Mazza, 2000).

There remains some debate over the terminology to describe and classify this food category. Such foods and food ingredients have been described by a variety of terms including: functional foods, nutraceuticals, vitafoods, foodaceuticals, phytochemical foods, pharmafoods, and designer foods (Oomah and Mazza, 2000). The term "functional foods," which was introduced in Japan in the mid-1980s, is currently the most widely adopted term (Arai, 1996). The terms "functional foods" and "nutraceuticals," are most commonly used in the U.S. and are sometimes used interchangeably. However, it is currently generally accepted that *nutraceuticals* refers to "chemicals" found as naturally occurring components of foods that provide health benefits, whereas *functional foods* are "foods" or "food ingredients" that "provide a health benefit beyond the traditional nutrients they contain" (Wildman, 2001b). In Canada, the term "functional foods" is used to describe those foods with "demonstrated physiological benefits and/or reduced risk of chronic disease, but which are similar in appearance to conventional foods and are consumed as part of the diet." The Canadian definition for nutraceuticals is reserved for those therapeutic products that are produced from food but sold in pill, powder, or other medicinal

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form (Scott, 1996). In Europe, a functional food refers to "any food which has been adequately demonstrated to beneficially affect one or more target functions in the body, beyond normal nutritional effects, in a way which is relevant to either the state of well being and health and/or the reduction of the risk of a disease" (Haumann, 1999).

With an estimated market value of approximately $28.9 billion, the functional food category has been identified as the leading trend in the U.S. food industry (Meyer, 1998, Sloan, 2000). As the "baby boomers" (currently comprising approximately 45% of the U.S. population) grow older, it is expected that this trend will continue. After years of being told what to cut out of their diets, health-conscious baby boomers are much more receptive to *adding* functional foods to reduce risk of chronic disease. In addition, functional foods may eliminate or at least delay the need for pharmaceutical drugs (and their associated side effects) for controlling blood pressure or blood cholesterol.

Epidemiological studies and well-designed clinical trials have provided evidence for the efficacy of many of the biologically active ingredients or components being promoted in certain functional foods. However, for other agents, there has been little to no investigation of efficacy, and/or the results have been inconsistent. In addition, the widespread use of some of these ingredients, in a variety of food environments as well in combination with other biologically active agents, raises some concerns and long-term safety issues that require further investigation.

BACKGROUND AND HISTORICAL SIGNIFICANCE

The belief in the health benefits of foods dates back to approximately 2500 years ago when Hippocrates proclaimed, "Let food be thy medicine and medicine be thy food" (Hasler, 1998; Wildman, 2001a; Oomah and Mazza, 2000). The use of certain "magic potions" for the treatment of disease has been recorded for many past civilizations.

Historical accounts of the U.S. and other countries in the late nineteenth and early twentieth centuries indicate widespread consumer interest in therapeutic food products (Deutsch, 1977). Many illegal formulations (the so-called "snake oils") accompanied by outrageous claims were being brought to the marketplace. In fact, such products, and the legal entanglements involved in their regulation, played a major role in the initiation, development, and evolution of the U.S. food regulatory system. The functional foods movement, however, really started in the late 1970s (Oomah and Mazza, 2000), with consumer interest accelerating in the late 1980s. Research interest was punctuated by the announcement of a $20 million research project by the National Cancer Institute in 1989 to investigate the anticarcinogenic properties of citrus, flax, aged garlic extract, licorice extract, soybean meal, and umbelliferous vegetable juice beverages. The development of improved research capabilities with regard to isolation of specific food components and efficacy evaluation has led to bet-

ter understanding of the role of some of these components and will prove or disprove many claims made by our ancestors.

SCIENTIFIC BASIS AND IMPLICATIONS

Classification of Functional Ingredients

There are a number of ways that biologically active food ingredients can be grouped: by food source, by chemical nature, by mechanism of action, or even by purported effect in the body. Wildman (2001b) proposed that such substances be grouped by food source, which recognizes the primary dietary source of the nutraceutical component. This classification scheme, with examples of substances that are either accepted or purported nutraceutical substances, is presented in Table 33.1.

Functional Components from Plant Sources

Phytochemicals There is considerable evidence that many components of a plant-based diet can reduce the risk of chronic diseases, especially cancer (Oomah and Mazza, 2000; Hasler, 1998). There are 14 classes of these compounds, termed phytochemicals, which are known or believed to have cancer-preventive properties (Caragay, 1992) including sulfides, phytates, flavonoids, glucarates, carotenoids, coumarins, monoterpenes, thiocyanates, phythalides, and polyacetylenes. Phytochemicals are present to varied degrees in garlic, green tea, soybeans, cereal grains, licorice roots, flaxseed, and plants from the cruciferous, umbelliferous, citrus, solanaceous, and cucurbitaceous family (Oomah and Mazza, 2000).

TABLE 33.1. Examples of Nutraceutical Substances Grouped by Food Source

Plants		Animals	Microbial
β-Glucan	Allicin	Conjugated linoleic acid (CLA)	*Saccharomyces boulardii*
Ascorbic acid	δ-Limonene	Eicosapentaenoic acid (EPA)	*Bifidobacterium bifidum*
γ-Tocotrienol	Genestein	Sphingolipids	*B. longum*
Quercetin	Lycopene	Choline	*B. infantis*
Luteolin	Hemicellulose	Lecithin	*Lactobacillus acidophilus* (LC1)
Cellulose	Lignin	Calcium	*L. acidophilus* (NCFB 174B)
Lutein	Capsaicin	Ubiquinone (Coenzyme Q_{10})	*Streptococcus salvarius* subspp. *thermophilus*
Gallic acid	β-Ionone	Selenium	
Perillyl alcohol	α-Tocopherol	Zinc	
Indole-3-carbonol	β-carotene		
Pectin	Nordihydrocapsaicin		
Diadzein	Selenium		
Potassium	Zeaxanthin		

Source: Wildman, 2001b.

Soluble fiber components It is scientifically proven that consumption of foods rich in soluble fiber (e.g., β-glucan) can reduce total and low-density lipoprotein (LDL) cholesterol and, thus, reduce the risk of coronary heart disease. It has been shown that 3 g of β-glucan would be required to achieve a 5% reduction in serum cholesterol (Hasler, 1998). After the approval of the first food specific health claim for foods containing oat bran by the U.S. Food and Drug Administration (FDA) in 1997, there has been considerable interest in amending a variety of food products with this ingredient. The soluble fiber health claim was extended to include soluble fiber from psyllium seed husk in 1998 (Hasler, 1998).

Soybean components Members of the Leguminosae plant family, especially soybean, are considered to be primary sources of phytoestrogens (e.g., isoflavones) and other physiologically active components (Oomah and Mazza, 2000). It has been purported that soy protein and related components can play a preventive and therapeutic role in cardiovascular disease, cancer, osteoporosis, and alleviation of menopausal symptoms. As a result, there has been a tremendous interest in the promotion of soy and soy-based products for these therapeutic properties by the food and pharmaceutical industries.

The most well-documented physiological property of soy is the cholesterol-lowering effect of the isoflavones. However, the exact mechanism for the hypocholesteremic effect has not been elucidated and the research data regarding this effect are inconsistent. In fact, dietary isoflavones were not effective at lowering cholesterol in some recently published studies (Hodgson et al., 1998). However, in 1999, the FDA approved a health claim for soy protein and reduced risk of coronary heart disease based on evidence supporting the role of soy protein in lowering blood cholesterol. The claim notes that 25 g per day of soy protein are needed, along with a diet low in saturated fat and cholesterol.

Potential anticarcinogens found in soybeans include protease inhibitors, phytosterols, saponins, phenolic acids, phytic acids, and isoflavones. Again, the isoflavones have been the most investigated. The suggested relationship between a diet high in soy isoflavones and reduced estrogen-dependent cancer is based on the low mortality from breast, colon, and prostate cancer in Southeast Asia. However, the epidemiological relationship between soy intake and cancer risk has not been shown consistently (Messina et al., 1997), and clinical intervention trials have not been done (Hasler, 1998).

Because Asian women, in general, report much a lower incidence of hot flashes and night sweats during menopause compared with Western women, it is suggested that there is a relationship between soy intake and alleviation of menopausal symptoms (Hasler, 1998). Although there has been some indication of these effects in clinical investigations, further research is needed to prove or *disprove* this theory. The isoflavone β-estradiol, an isoflavone extracted from soybeans, is currently being marketed as a prescriptive oral estrogen for managing menopause.

Flaxseed components Among the oilseeds, flaxseed is the most prominent source of the essential omega-3 fatty acid α-linolenic acid. Omega-3 fatty acids have been shown to be important in visual and brain development. Because of the high level of α-linolenic acid in flaxseed, there has been considerable research investigation of the use of this oilseed as a feed additive in poultry, cattle, and pigs to increase the level of this fatty acid in eggs, milk, and meat.

More recently investigated biologically active components of flaxseed are the fiber-associated phenolic compounds (lignans). The lignans of flaxseed are precursors for the mammalian lignan enterdiol and its oxidation product enterolactone, which are structurally similar to estrogens and may play a role in prevention of estrogen-related cancers. Although further research and epidemiological investigation is needed, flaxseed has been shown to decrease tumors of the colon and mammary gland in rodents (Thompson, 1995).

Flaxseed has also been shown to prevent the decline in renal function in patients with lupus nephritis and other forms of renal disease and may have hypocholesterolemic properties through reduction in total and LDL cholesterol (Oomah and Mazza, 2000, Hasler, 1998).

Vegetable components

Tomatoes Lycopene (a carotenoid) from tomatoes may reduce the risk of cancer and the risk of mycocardial infarction because of modulation of cholesterol metabolism. Of the suggested benefits of lycopene, the relationship between tomato consumption and reduced risk of prostate cancer has received the most attention based on a prospective cohort study involving 47,000 men (Giovannucci et al., 1995). In this study, the men who consumed tomato products 10 or more times per week had less than one-half the risk of prostate cancer. The probable mechanism for cancer reduction by lycopene is related to its antioxidant properties.

Cruciferous vegetables On the basis of epidemiological evidence, consumption of cruciferous vegetables (e.g., broccoli, cabbage, brussels sprouts, cauliflower) may be associated with reduced risk of breast, colon, gastric, and prostate cancer (Oomah and Mazza, 2000, Hasler, 1998). This has been primarily attributed to the relatively high level of glucosinolates (e.g., indole-3-carbinol) and other compounds (e.g., dithiolthiones, sulfonates). Indole-3-carbinol is under investigation as a cancer chemopreventive for the mammary gland.

Allium vegetables Allium vegetables include garlic, leek, and onion. Of these, the suggested health benefits of garlic have been highly publicized for many years. Garlic has historically been used as a spice as well as a remedy for common ailments, with reputed medicinal properties including antibiotic activity (antibacterial and antifungal), antihypertensive properties, inhibition of platelet aggregation, reduction of cholesterol, and cancer chemopreventive properties.

The most notable biological active garlic compound is allicin, an amino acid produced enzymatically when garlic cloves are crushed. Allicin further breaks down to a variety of sulfurous compounds (Block et al., 1992). Allium vegetables also contain bioactive sapogenins. Although there is epidemiological evidence that garlic may be effective in reducing cancer risk and may have a preventative role in cardiovascular disease, not all of the studies have been conclusive and clearly defined mechanisms have not been established (Hasler, 1998).

Fruit components The primary biologically active components of fruits, in general, are the flavonoids and other antioxidants. These compounds have been associated with reducing the risk for a variety of degenerative diseases. Dietary antioxidants, in general, increase the plasma antioxidant capacity and thus inhibit atherosclerosis and cardiovascular disease (Meltzer and Malterud, 1997). Antioxidants also have a potential role in cancer prevention.

Citrus Citrus fruits are good sources of the limonoin phytochemicals (e.g., limonene). Evidence has been accumulating to support the cancer-preventive properties of limonene (Hasler, 1998). Perrillyl alcohol, a limonene metabolite, is being evaluated for clinical chemoprevention (Ripple et al., 1998).

Cranberry The most noted therapeutic property of this fruit is the prevention and treatment of urinary tract infection. This effect is related to the inhibition of the adherence of *Escherichia coli* to uroepithelial cells, possibly caused by fructose and a nondialyzable polymer (Schmidt and Sobota, 1988).

Grapes On the basis of epidemiological studies, a possible relationship may exist between red wine consumption and reduced risk of cardiovascular disease. Much of the attempt to explain this relationship has focused on the flavonoid compounds associated with the grape skins, which may prevent the oxidation of LDL cholesterol. However, the relationship has been questioned in a recent California study (Klatsky et al., 1997). Furthermore, alcohol consumption, in general, has adverse effects on the risk of several degenerative diseases, including many cancers.

Functional Foods from Animal Sources

Omega-3 fatty acids Fish oil is a good source of polyunsaturated fatty acids (PUFA), especially omega-3 fatty acids, which are essential for normal growth and development. It has been suggested that omega-3 fatty acids may prevent hypertension, arthritis, other inflammatory and autoimmune disorders, and cancer (Oomah and Mazza, 2000). A relationship between diets high in omega-3 fatty acids and reduced risk for Cardiovascular disease (CVD) by lowering serum cholesterol and triglycerides has been suggested since the observation that Eskimos have low incidence of CVD despite a high-fat diet (Bang and

Dyerberg, 1972). However, there are some inconsistencies and a lack of agreement in the scientific community regarding the role of omega-3 fatty acids and CVD (Hasler, 1998). Other purported benefits of omega-3 fatty acids included reduced insulin resistance and reduced inflammation in rheumatoid arthritis. Both of these areas require further investigation.

Conjugated linoleic acid Foods from ruminant animal sources (e.g., beef, lamb, dairy) are a good source of conjugated linoleic acid (CLA), a fatty acid that has potential antioxidant and anticarcinogenic properties. This beneficial fatty acid is formed by the natural process of biohydrogenation of dietary linoleic acid by ruminant bacteria in these animals (Watkins and Yong, 2001). CLA is found to a lesser extent in a variety of other foods such as seafood, turkey, and vegetable oils. CLA has been shown to be effective in suppressing stomach and mammary tumors in laboratory animals (Ip and Scimeca, 1997). In addition, dietary CLA has been associated with reduced risk of congestive heart disease (Lee et al., 1994). A study performed in mice suggests that dietary CLA may also play a role in weight reduction by reducing fat deposition and increasing lean body mass (Park et al., 1999).

The biohydrogenation process is affected by type of feed, season, genetic variation, and management practices (Watkins and Yong, 2001). There has been considerable interest in creating "designed" dairy and beef products with increased or enhanced CLA levels through alteration of agricultural practices.

Functional Foods Involving Microorganisms

Probiotics Since Metchnikoff's first observation that the unique longevity of the Bulgarians might be associated with yogurt in their diet, there has been considerable interest in the health benefits of foods containing "therapeutic microoganisms" (Deutsch, 1977). The current terminology, *probiotics*, is used to describe foods that are either produced by or contain live microorganisms that possess therapeutic or health benefits (Farnsworth, 2001). The microorganisms primarily associated with a probiotic effect are the lactic acid bacteria and, to a lesser extent, some yeasts. The largest category of foods containing lactic acid bacteria is fermented or cultured dairy products and/or nonfermented products that are amended with these beneficial bacteria. Other lactic acid-containing fermented foods that may contain these microorganisms include fermented vegetable products (e.g., sauerkraut, fermented pickles), sourdough bread, and fermented sausages. A general listing of probiotic lactic acid bacteria found in dairy products is presented in Table 33.2.

Lactic acid bacteria, in general, constitute an integral part of a healthy gastrointestinal microecology. These bacteria, by their presence or by antimicrobial substances (e.g., bacteriocins; lactoperoxidase system) that some bacteria produce, control the proliferation of undesirable bacteria in the gut. Certain types of lactic acid bacteria colonize or implant in the intestinal tract (e.g., *L. acidophilus* in the small intestine, *Bifidobacteria* in the large intestine).

TABLE 33.2. A General Listing of Potentially Probiotic Lactic Acid Bacteria and Dairy Product Source

Bacteria	Dairy product source
Bifidobacterium	
B. bifidum	Amended products (e.g., A/B/C milk)
B. longum	Amended products
B. infantis	Amended products
B. breve	Amended products
B. adolescentis	Amended products
Lactobacillus	
Lb. acidophilus	Yogurt and related products; amended products (e.g., A/B/C milk)
Lb. delbreuckii subsp. *bulgaricus*	Yogurt (predominant starter culture used)
Lb. casei	Amended products (e.g., A/B/C milk)
Lb. rhamnousus (strain GG)	Amended products
Lb. fermentum	Kefir
Lb. plantarum	Kefir
Lb. brevis	Amended products; some cheeses
Lb. helveticus	Amended yogurt products; some cheeses
Lactococcus	
L. lactis subsp. *lactis*	Cheese, buttermilk, sour cream
L. lactis subsp. *cremoris*	Cheese, buttermilk, sour cream
Leuconostoc	
Ln. lactis	Buttermilk, kefir, sour cream
Ln. mesenteroides subsp. *cremoris*	Buttermilk, kefir, sour cream
Ln. mesenteroides subsp. *dextranicum*	Buttermilk, kefir, sour cream
Streptococcus	
S. salivarius subsp. *thermophilus*	Yogurt (predominant starter culture used)

The impact of the therapeutic properties of lactic acid bacteria is affected by many factors including microbiological factors (e.g., species and strain variation), host factors (e.g., host reactivity, health condition), and dietary factors (e.g., other types of food consumed). Other therapeutic benefits that have been associated with specific strains of these microorganisms (Farnsworth, 2001; Fernandes et al., 1987) are listed below:

- Reducing the symptoms associated with lactase (β-galactosidase) deficiency;
- Enhancing immune function;
- Prevention of infantile diarrhea;
- Anticholesterolemic properties;
- Prevention of urinary tract infections; and
- Reduced risk of cancer (especially colon cancer)

Yogurt has been the most investigated cultured dairy product with regard to health benefits. The most generally accepted therapeutic effect of yogurt bacteria is its role in reducing the symptoms of lactase deficiency. In addition to the traditional dairy products, unique cultured dairy products are being developed (e.g., acidophilus yogurt, yogurt drinks, kefir, and a variety of other fermented products using various strains of lactic acid bacteria). Kefir is a fermented, mildly carbonated yogurtlike drink that contains a wide variety of lactic acid bacteria as well as some potentially beneficial yeast. Kefir is highly varied throughout the world with regard to ingredients and composition (both microbiological and ingredients), and manufacturing methods.

There is considerable interest in amending dairy products with specific strains of lactic acid bacteria. Many of these products are not fermented, and they appeal to that segment of the population that does not like the more acidic fermented products. For example, a product termed sweet acidophilus milk was released in the 1970s. This nonfermented product, amended with *Lb. acidophilus*, had the taste and consistency of traditional milk. Today, milk products amended with *Lb. acidophilus*, *Bifidobacteria*, and *Lb. casei* are on the market in the U.S. (generally termed A/B/C milk) and other parts of the world. The current trend is to use human isolates, which are considered to be more biologically active (e.g., *Bifidobacterium* strains, *Lb. Casei* GG, *Lb. acidophilus* LC1, *Lb. acidophilus* NCB 1748).

Prebiotics The term *prebiotics* is defined as nondigestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of a limited number of bacteria in the colon (Gibson and Roberfroid, 1995). The goal of prebiotic use is to increase the number of beneficial bacteria such *Lactobacillus* and *Bifidobacteria* in the colon. The response to prebiotics is variable and is affected by many host-related factors (e.g., initial level of target bacteria, susceptibility, health condition, medications). Thus prebiotic ingredients (e.g., indigestible carbohydrates such as inulin or oligofructose) are often used in combination with probiotic microorganisms (termed *symbiotic foods*) (Roberfroid, 1998).

Herbals and Their Application to Functional Foods

Certain plant components (e.g., herbs, botanicals) have perceived and demonstrated health benefits (Percival and Turner, 2001). Although a wide variety of these products are currently being sold as dietary supplements, there is considerable current interest by the food industry to amend food products with these potentially biologically active components. A general listing of the most common herbs and their alleged function is presented in Table 33.3.

Some of the herbals listed in Table 33.3 are available in Europe as prescription drugs. For example, *Gingko biloba* is prescribed in Germany for the treatment of cerebral disturbances and circulatory disorders, and St. John's wort is widely prescribed in Europe as an antidepressant (Percival and Turner, 2001).

TABLE 33.3. Classification of Common Herbs and Alleged Action or Function

Herb	Active ingredient	Alleged function
Impact on nervous system		
Ginkgo biloba	Flavonoid glycoside; diterpene lactones	Enhanced memory, cognition
Kava kava	Lactones	Anti-anxiety, relaxation
St. John's wort	Hypericin, flavonoids, naphthodianthroms	Antidepressant
Valerian root	Valepotriates, valerenic acid, sesquiterpenes	Sleep inducement
Impact on heart/circulation		
Hawthorn	Flavonoids	Cardiac insufficiency
Impact on immune system		
Echinacea	Echinosides, caffeic and ferulic acids, glycoproteins and polysaccharides	Boosts immune system
Others (astragalus, cat's claw, goldenseal, pau d'arco)		
Ginseng	Saponins (ginsenosides), Eleutherosides	Anti-stress, immunostimulant
Impact on digestive system		
Peppermint oil	Menthol	Irritable bowel disease
Ginger	Ginerols and gingerdiols, volatile oils	Antiemetic, nausea
Impact on respiratory system		
Licorice root	Glycyrrhetic acid, triterpene, saponins, flavonoids, isoflavonoids	Expectorant
Impact on urinary system		
Cranberry	Not defined (possibly benzoic acid, fructose, nondialyzable polymers)	Bacteriostatic action in urinary tract
Others (blueberry, bilberry, bearberry)		
Saw palmetto	Not defined	Benign prostatic hyperplasia
Impact on liver		
Milk thistle	Silymarin—a complex of many flavonolignans	Supports healthy liver function
Impact on musculoskeletal system		
Feverfew	Sesquiterpene lactones	Migraine prophylactic

Source: adapted from Percival and Turner, 2001.

TABLE 33.4. Food Products Containing Herb Ingredients

Herb ingredient	Food product
Ginkgo biloba	Snack bars (*Brain Broo*™, *Think*™, *Brain Wash*™, *Wise Guy*™)
St. John's wort	Beverages (teas, juice blends); soups; snack foods
Kava kava	Beverages (kava juice, kava beverages); snacks/candy (kava chips, kava chocolate)
Valerian root	Beverages ("relaxing" teas and related products)
Hawthorn	Beverages [*Intelligence*™ (ginkgo and hawthorn); *Relaxation Cocktail*™ (hawthorn, kava, and chamomile]; snack bars (*HeartBar*™)
Echinacea	Beverages (teas, juice blends); soups; snack foods

Ginkgo is also being investigated in the treatment of Alzheimer disease and other forms of dementia. Valerian is approved in Germany as a mild sedative. The top three best-selling herbal dietary supplements in the U.S. include (in rank order) *Ginkgo biloba*, garlic, and Echinacea.

Examples of food products that have been amended with herb ingredients are presented in Table 33.4.

Safety Issues and Concerns

A general rule of thumb regarding functional foods containing physiologically active components might be *a little may be good, but more may not be better.* Safety is a critical concern regarding the use of these compounds. For example, some phytochemicals that demonstrate anticarcinogenic properties may, in fact, be carcinogenic at high concentrations, as has been shown for allyl isothiocyanate (Hasler, 1998). Of special concern are those compounds that are involved in estrogen metabolism (e.g., soy phytoestrogens or isoflavones). For example, genistein has been shown to promote tumor development in animals (Rao et al., 1997).

With regard to herbals and botanicals, concerns have been raised regarding the lack of standardization or the confusion with regard to the correct identity of the substance. The potency of these components is affected by geographic as well as environmental factors. In addition, because the active ingredient(s), in many cases, is not known, there is little standardization among preparations (Percival and Turner, 2001). Not all extracts from the same genus are physiologically active, and some may cause adverse reactions if consumed. Improper identification has been blamed for "poisoning" of individuals taking an herbal supplement purported to be plantain that in fact contained an extract from a similar but toxic plant, *Digitalis lanata* (Slifman et al., 1999).

Additional safety concerns regarding herbals and botanicals include the lack of sufficient safety data for many of the active ingredients, the possibility of poisonous contaminants, the potential for allergic reaction, the risks of con-

sumption by children, and potential interactions with other medicines. Several herbs have been shown to have adverse effects (Percival and Turner, 2001). Although many of these adverse effects are not serious (e.g., headaches, gastrointestinal disturbance, dizziness, etc.), some can be very serious, especially in highly affected individuals. The dangers of some herbs (e.g., chaparral, ephedra, blue cohosh, yohimbe) have been well documented.

Relatively little is known about the cumulative risks of these physiologically active ingredients, the risk of using these agents in combination with other nutraceuticals or food ingredients, or the impact of certain types of food processing on these ingredients. In addition, further investigation is needed to evaluate potential drug interactions and contraindications for certain segments of the population.

REGULATORY, INDUSTRIAL, AND INTERNATIONAL IMPLICATIONS

Regulatory Definition

The only country with a specific regulatory definition as well as an approval process for functional foods is Japan (Arai, 1996), where they are licensed and regulated as *foods for specified health use (FOSHU)* and are eligible to bear a seal of approval. In the U.S. there is currently no definition for functional foods in FDA regulations. Thus functional foods fall obliquely between dietary supplements, defined under the Dietary Supplement Health and Education Act (DSHEA) discussed in Unit 7.7 and foods, defined under the Federal Food, Drug and Cosmetic Act (FDCA).

Regulation of Functional Foods

Definition and classification Under FDCA, the distinction between *foods* and *drugs* is very clearly defined. Furthermore, *special dietary foods* (e.g., medical foods) and *dietary supplements* are also clearly defined (see Chapters 29 and 32). Thus, until a more specific regulatory category is defined, functional foods, which are marketed and sold as foods, are regulated as foods. If a claim is made or if the product purports to diagnose, cure, mitigate, treat, or prevent disease, it is considered a drug and subject to all appropriate regulations regarding preapproval for efficacy, safety, and labeling. The medical foods category (see Chapter 29) is only allowed for products that meet specific dietary needs of a specific population (e.g., hypoallergenic foods, foods for individuals with diabetes or phenylketonuria). Thus any mention of disease will cause the product to be classified as an unapproved drug. The definition is less clear with regard to functional foods and dietary supplements. If a product is labeled and marketed as a dietary supplement, it should be so presented in form and presentation for sale (e.g., not sold as a food or alongside similar traditional foods in the marketplace). The general philosophy of FDA might be characterized as: *if it looks like a food, acts like a food, and is marketed like a food, it is a food.*

Labeling issues According to FDA regulations under FDCA, any label information on food products must not be false or misleading in any part. This includes: the statement of identity (or name), the ingredient list, the identity of the manufacturer, packer, or distributor, nutrition information, and any other claim or statement made regarding the product.

Health or therapeutic claims Issues regarding misleading health claims made for certain ingredients had a major impact in the passage of the Nutrition Labeling and Education Act (NLEA) in 1990. Since NLEA, any claim considered a health claim must be specifically approved by the FDA (FDA, 2001). Of the list of approved health claims, those that directly or indirectly relate to functional foods are those that suggest a relationship between:

- Soluble fiber from certain foods and risk of CHD;
- Fiber-containing grain products, fruits, and vegetables and cancer;
- Fruits, vegetables, and grain products that contain fiber, particularly soluble fiber, and risk of CHD;
- Soy protein and risk of CHD; and
- Plant sterol/stanol esters and risk of CHD.

Health claims may be proposed at any time but must be supported by either significant scientific agreement or an authoritative statement from a recognized government entity to be considered for approval. To date, no health claims have been approved regarding herbal or botanical ingredients. Health claims for the benefits of probiotic bacteria have been under consideration but, to date, have not been approved by the FDA.

Since passage of DSHEA, other types of claims, called *structure/function* claims, have become prevalent on dietary supplement labels. These types of claims are not held to the same stringent regulations regarding health claims as are foods. In particular, there is no standard such as significant scientific agreement for structure/function claims, and these claims do not have to be submitted to the FDA for approval. A structure/function claim is a label statement regarding the effect of a component on a body function or structure (e.g., "promotes urinary tract health") or on general well-being (e.g., "gives energy"). The use of structure/function claims on dietary supplements must be accompanied by the following disclaimer: "This statement has not been evaluated by the FDA. This product is not intended to diagnose, cure, mitigate, treat or prevent disease". The "rules" for use of structure/function claims on foods are less well defined; however, current regulations require that such claims for food derive from the "nutritive value" of the food. This implies that a claim such as "calcium builds strong bones" on a calcium-fortified food product would be acceptable whereas a claim for the immune-enhancing properties of Echinacea on a soup label would not.

Ingredient/food additive labeling Any food additive used in a food product must be either under a specific food additive regulation or generally recognized as safe (GRAS) under FDCA. For approval, additives must be shown to be safe as well as beneficial. A controversial issue with DSHEA is that additives used in dietary supplements are not held to the same stringent approval process. The FDA has recently begun to take action against manufacturers using herbal additives that do not have GRAS or approved food additive status in foods.

In general, additives and ingredients must be listed in the ingredient statement of a food product by their common or usual name (Schmidt, 2000). Some ingredients may require additional clarifying phrases which are specifically addressed (FDA, 2001). The ingredient listing should not be false or misleading in any way.

CURRENT AND FUTURE IMPLICATIONS

There are some scientific inconsistencies regarding functional foods. Although there is considerable and even overwhelming evidence that some of the physiologically active components from plant, animal, and microbial sources may provide health benefits, the evidence for others is not that clear. In addition, a great deal is still unknown regarding the identification and impact of the physiologically active ingredients, how they interact with other ingredients and with each other, and the effects of processing on their structure and function. Approval of functional ingredients should be based on sound scientific principles, and a regulatory definition is needed for the functional foods category.

The high level of interest in functional foods is expected to continue. New technological advances will increase the knowledge base regarding the efficacy and properties of functional ingredients in food systems. Use of scientific techniques such as genetic modification will provide increased levels of these ingredients in plants and microorganisms as well as the potential for new physiologically active components. Although functional foods definitely have a place in our diet, these foods should not be used to mitigate a nutritionally inadequate diet or an unhealthy lifestyle.

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PART VIII

WORLD-WIDE FOOD SAFETY ISSUES

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CHAPTER 34

INTERNATIONAL ORGANIZATION FOR STANDARDIZATION ISO 9000 AND RELATED STANDARDS

JOHN G. SURAK

INTRODUCTION

The global marketplace creates opportunities and concerns for customers. This marketplace allows customers a greater selection of economically priced goods and services. However, these customers have a greater concern, that of whether products will meet stated quality requirements. International standards provide tools to reduce customer concerns and allow communication across cultural and language barriers. This chapter focuses on using ISO 9001 and ISO 9004 to help food processors develop an efficient and effective quality management system.

BACKGROUND AND HISTORICAL SIGNIFICANCE

The International Organization for Standardization (ISO) is a nongovernmental organization located in Geneva, Switzerland. It was formed in 1947 with the mission of developing a common set of manufacturing, trade, and communications standards to facilitate international trade. ISO is made up of 138 nations (ISO, 2001). Countries are represented at ISO by the national standards organizations (Table 34.1; ISO, 2001).

The short name for the International Organization for Standardization, "ISO," was taken from the Greek word *isos*, meaning equal. This name was selected by the organization because its mission is to create equal or uniform standards. ISO did not intend to develop this acronym based on one of the organization's official names. ISO has three official names, one each in English,

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TABLE 34.1. Examples of Standards Organizations That Belong to ISO

Canada	Standards Council of Canada
France	Association française de normalisation
Germany	Deutsches Institut für Normung
Mexico	Dirección General de Normas
United Kingdom	British Standards Institute
United States	American National Standards Institute

Source: ISO, 2001

French, and Russian. For example, ISO's French name is *Organisation Internationale de Normalisation.*

ISO standards are voluntary standards and are developed in response to market-driven forces. This process leads to harmonization in the global marketplace and thus the reduction of "technical barriers" to trade. In 1951, ISO published its first standard, which was titled. "Standard reference temperature for industrial length measurement." As of December 31, 2000, ISO had published 13,025 standards and technical reports that cover a wide variety of subjects (ISO, 2001). These standards provide a common set of rules, guidelines, and definitions of characteristics of products to ensure that products, processes, and services are fit for use.

A consensus process is used to develop the standards. Consensus is achieved through the voluntary involvement of all interested parties in the industrial sector in which the standard is being developed. Typically, manufacturers, suppliers, users, consumer groups, governmental agencies, and professional and research organizations are represented during the standards development process. The standards are developed using the following consensus process:

- Formally recognize that an international standard is needed.
- Develop the technical scope of the standard.
  This is done by a technical committee (TC) that consists of experts from countries interested in the subject matter.
- Build a consensus.
  This process begins when countries negotiate the detailed specifications of the standard.
- Approve the standard in two parts.
  The draft international standard (DIS) is generated and published when two-thirds of the ISO members who have actively participated in the standard development process approve the DIS.
  The International Standard is generated and published when 75% of member nations of ISO cast a positive vote for the DIS.

Voting on the standards is done by the standards organizations that are members of ISO. [The United States is represented by the American National Standards Institute (ANSI)]. Because only one standards organization is allowed to represent a each nation, each nation is allowed only one vote during the approval phase of a standard.

In 1979, ISO perceived a need to harmonize the large number of international, national, regional, and industrial standards related to quality management systems. In response to this issue, ISO formed the "Ad Hoc Task Force for the International Organization for Standardization Technical Committee 176," or TC 176. TC 176 was charged with developing a single quality management set of standards. The committee used existing quality management standards such as ANSI/ASQC Z1.8, ANSI/ASQC Z1.15, British Standard (BS) 5750, and Military Standard (MIL STD) 9858A as source material. The first version of the ISO 9000 standards was published in 1987.

ISO requires that all of its standards be reviewed every 5 years. This review is conducted to ensure that the standards remain current with technology and that industrial practices do not become nontariff barriers to trade. Just after publication of the 1987 version of the ISO 9000 series of standards, TC 176 started to work to revise the standards. The Technical Committee stated that the second version would contain only minor revisions and that the third version would contain major revisions. The second version was published in 1994. The general structure of the 1987 and the 1994 standards were identical. The third revision was published on December 15, 2000. Significant changes were made to this version, including the following:

- Using a process management structure. Tables 34.2 and 34.3 compare the structure and content of the 1994 edition and the 2000 edition of ISO 9001.
- Using quality management system wording rather than using contractual wording.
- Incorporating more concepts of Total Quality Management (TQM).
- Reducing the number of standards in the ISO 9000 series. ISO 9002 and ISO 9003 have been withdrawn as international standards. Table 34.4 lists the current standards in the ISO 9000 series.

The United States adopted ISO 9000, 9001, and 9004 as official U.S. standards that describe a quality management system. These standards are published as the ANSI/ISO/ASQ Q9000, Q9001, and Q9004 standards respectively (ASQ, 2000a; ASQ, 2000b; ASQ, 2000c).

SCIENTIFIC BASIS AND IMPLICATIONS

Management Systems and Quality Management Systems

A management system can be defined as what an organization does to manage processes or activities. Typically, as a company grows larger in size, it becomes

TABLE 34.2. Comparison of ISO 9001:1994 Requirements to ISO 9001:2000 Requirements

ISO 9001-1994		ISO 9001-2000	
1	Scope	1	Scope
2	Normative reference	2	Normative reference
3	Definitions	3	Terms and definitions
4	Quality system requirements		
4.1	Management responsibility		
4.1.1	Quality policy	5.1	Management commitment
		5.3	Quality policy
		5.4.1	Quality objectives
4.1.2	Organization		
4.1.2.1	Responsibility and authority	5.5.1	Responsibility and authority
4.1.2.2	Resources	6.1	Provision of resources
		6.2.1	Competence, awareness and training
4.1.2.3	Management representative	5.5.2	Management representative
4.1.3	Management review	5.6.1	General
		8.5.1	Continual improvement
4.2	Quality System		
4.2.1	General	4.1	Quality management system
		4.2.2	Quality manual
4.2.2	Quality system procedures	4.2.1	General
4.2.3	Quality planning	5.4.2	Quality management system planning
		7.1	Planning of product realization
4.3	Contract review		
4.3.1	General		
4.3.2	Review	5.2	Customer focus
		7.2.1	Determination of requirements related to the product
		7.2.2	Review of requirements related to the product
		7.2.3	Customer communication
4.3.3	Amendment to a contract	7.2.2	Review of requirements related to the product
4.3.4	Records	7.2.2	Review of requirements related to the product
4.4	Design control		
4.4.1	General		
4.4.2	Design and development planning	7.3.1	Design and development planning
4.4.3	Organizational and technical interfaces	7.3.1	Design and development planning
4.4.4	Design input	7.2.1	Determination of requirements related to the product
		7.3.2	Design and development inputs
4.4.5	Design output	7.3.3	Design and development outputs
4.4.6	Design review	7.3.4	Design and development review

TABLE 34.2. *(Continued)*

ISO 9001-1994		ISO 9001-2000	
4.4.7	Design verification	7.3.5	Design and development verification
4.4.8	Design validation	7.3.6	Design and development validation
4.4.9	Design changes	7.3.7	Design and development changes
4.5	Document and data control		
4.5.1	General	4.2.3	Control of documents
4.5.2	Document and data approval and issue	4.2.3	Control of documents
4.5.3	Document and data changes	4.2.3	Control of documents
4.6	Purchasing		
4.6.1	General		
4.6.2	Evaluation of subcontractors	7.4.1	Purchasing process
4.6.3	Purchasing data	7.4.2	Purchasing information
4.6.4	Verification of purchased product	7.4.3	Verification of purchased product
4.7	Control of customer-supplied product	7.5.4	Customer property
4.8	Product identification and traceability	7.5.3	Identification and traceability
4.9	Process control	6.3	Infrastructure
		6.4	Work environment
		7.5.1	Control of production and service provision
		7.5.2	Validation of processes for production and service provision
4.10	Inspection and testing		
4.10.1	General	7.1	Planning of product realization
		8.1	General
4.10.2	Receiving inspection and testing	7.4.3	Verification of purchased product
		8.2.4	Monitoring and measurement of product
4.10.3	In-process inspection and testing	8.2.4	Monitoring and measurement of product
4.10.4	Final inspection and testing	8.2.4	Monitoring and measurement of product
4.10.5	Inspection and test records	7.5.3	Identification and traceability
		8.2.4	Monitoring and measurement of product
4.11	Control of inspection measuring and test equipment		
4.11.1	General	7.6	Control of monitoring and measuring devices
4.11.2	Control procedures	7.6	Control of monitoring and measuring devices

TABLE 34.2. *(Continued)*

ISO 9001-1994		ISO 9001-2000	
4.12	Inspection and test status	7.5.3	Identification and traceability
4.13	Control of nonconforming product		
4.13.1	General	8.3	Control of nonconforming product
4.13.2	Review and disposition of nonconforming product	8.3	Control of nonconforming product
4.14	Corrective and preventive action		
4.14.1	General	8.5.2	Corrective action
		8.5.3	Preventive action
4.14.2	Corrective action	8.5.2	Corrective action
4.14.3	Preventive action	8.5.3	Preventive action
4.15	Handling, storage, packaging, preservation and delivery		
4.15.1	General		
4.15.2	Handling	7.5.5	Preservation of product
4.15.3	Storage	7.5.5	Preservation of product
4.15.4	Packaging	7.5.5	Preservation of product
4.15.5	Preservation	7.5.5	Preservation of product
4.15.6	Delivery	7.5.1	Control of production and service provision
4.16	Control of quality records	4.2.4	Control of quality records
4.17	Internal quality audits	8.2.2	Monitoring and measurement process
		8.2.3	Monitoring and measurement of product
4.18	Training	6.2.2	Competence, awareness, and training
4.19	Servicing	7.5.1	Control of production and service provision
4.20	Statistical techniques		
4.20.1	Identification of need	8.1	General
		8.2.3	Monitoring and measurement of process
		8.2.4	Monitoring and measurement of product
		8.4	Analysis of data
4.20.2	Procedures	8.1	General
		8.2.3	Monitoring and measurement of process
		8.2.4	Monitoring and measurement of product
		8.4	Analysis of data

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TABLE 34.3. Comparison of ISO 9001:2000 to ISO 9001:1994

ISO 9001:2000		ISO 9001:1994 Corresponding Element	Changes in the revision	
Number	Title		Type	Description
1	SCOPE	1		
1.1	General		Enhanced	Achieve customer satisfaction
1.2	Applications		NEW	General description of the application of the standard Permissible exclusions limited to clause 7 Cannot limit the organization's ability to fulfill customer or regulatory requirements
2	NORMATIVE REFERENCES	2		
3	TERMS AND DEFINITIONS	3		Terms and definitions are given in ISO 9000:2000 Definitions of ISO 8402 apply "Supplier" is used instead of "subcontractor" Term "Product" applies to both products and services
4	QUALITY MANAGEMENT SYSTEM			
4.1	General requirements	4.2.1	Increased emphasis	Continual improvement
			Clarifies	Steps necessary to implement a quality management system REQUIRED DOCUMENTS
4.2	Documentation requirements			Gives an indication of the documentation that will be required
4.2.1	General	4.2.1 4.5.1		Indication of required documentation REQUIRED DOCUMENTS
4.2.2	Quality manual	4.2.1	Enhanced	Specify and justify any exclusions in quality manual The quality manual shall have a description of the sequence and interaction of the processes of the quality management system REQUIRED DOCUMENTS

TABLE 34.3. *(Continued)*

ISO 9001:2000		ISO 9001:1994 Corresponding Element	Changes in the revision	
Number	Title		Type	Description
4.2.3	Control of documents	4.5.1 4.5.2 4.5.3		REQUIRED DOCUMENTS AND PROCEDURE
4.2.4	Control of quality records	4.16		REQUIRED DOCUMENTS AND PROCEDURE
5	MANAGEMENT RESPONSIBILITY			
5.1	Management commitment	4.1	Increased emphasis	Top management commitment Ensure that subclauses a, b, c, and e, are linked to Clause 6
5.2	Customer focus	4.3.2	NEW	Top management ensures that customer needs and expectations are determined and converted into requirements with aim to achieve customer satisfaction
5.3	Quality policy	4.1.1	Enhanced	Top management establishes the quality policy Commitment to increase effectiveness of quality management system Frame work for establishing and reviewing quality objectives
5.4	Planning			
5.4.1	Quality Objectives	4.1.1	Enhanced	Quality objectives at relevant functions and levels in organization Quality objectives are measurable and consistent with quality policy REQUIRED DOCUMENTS

5.4.2	Quality Management System Planning	4.2.3	Revised	Ensures managing of change included in planning Maintains the integrity of the quality system when changes are planned and implemented
5.5	Responsibility, Authority, and Communication			
5.5.1	Responsibility and authority	4.1.2.1		
5.5.2	Management representative	4.1.2.3	Clarified	Top management shall appoint management representative
			Increased authority	Promote awareness of customer requirements
5.5.3	Internal communications		NEW	Ensure communications between various levels and functions of the quality management system and communications on the effectiveness of the quality management system
5.6	Management review	4.1.3	Enhanced	Address key input and output requirements of management review
5.6.1	General	4.1.3		REQUIRED RECORDS
5.6.2	Review input			Give attention to customer feedback, process performance and product conformance, status of preventive and corrective, changes that can effect quality management system
5.6.3	Review output			Give attention to improvement of quality management system, it processes and improvement of product related to customer requirements
6	RESOURCE MANAGEMENT			
6.1	Provision of resources	4.1.2.2	Clarified	Provide resources in a timely manner and improve processes of the quality management system and address customer satisfaction
6.2	Human resources			
6.2.1	General	4.1.2.2		

TABLE 34.3. *(Continued)*

ISO 9001:2000		ISO 9001:1994 Corresponding Element	Changes in the revision	
Number	Title		Type	Description
6.2.2	Competence, awareness, and training	4.18	Enhanced	Need to include competence and awareness, in addition, to training REQUIRED RECORDS
6.3	Infrastructure	4.9		Need to maintain the infrastructure needed to achieve conformity to product requirements
6.4	Work environment	4.9		Determine and manage the work environment needed to achieve product requirements
7	PRODUCT REALIZATION			ISO 9001:1994 uses the term "Process Control"
7.1	Planning of product realization	4.2.3 4.10.1	Clarified	Pay special attention to subclauses a and d REQUIRED RECORDS
7.2	Customer-related processes			
7.2.1	Determination of requirements related to the product	4.3.2 4.4.4	NEW	Added requirements include product requirement not specified by customer by necessary for intended or specified use and obligations related to product, including regulatory and legal requirements and any requirements determined by the organization
7.2.2	Review of requirements related to the product	4.3.2 4.3.3 4.3.4		REQUIRED RECORDS
7.2.3	Customer communication	4.3.2	NEW	Effective liaison with customer to meet customer requirements
7.3	Design and development			
7.3.1	Design and development planning	4.4.2 4.4.3		REQUIRED DOCUMENTS

7.3.2	Design and development inputs	4.4.4	Enhanced	Includes performance requirements from customer or market REQUIRED RECORDS
7.3.3	Design and development outputs	4.4.5		REQUIRED DOCUMENTS
7.3.4	Design and development review	4.4.6	Enhanced	Design and development reviews must be systematic If a problem is identified during review, follow-up actions shall be proposed and subsequent follow-up actions shall be recorded REQUIRED RECORDS
7.3.5	Design and development verification	4.4.7		REQUIRED RECORDS
7.3.6	Design and development validation	4.4.8		REQUIRED RECORDS
7.3.7	Control of design and development changes	4.4.9	Enhanced	Determine the effect of the change on constituent parts or delivered product Changes must verified and validated before implementation REQUIRED RECORDS
7.4	Purchasing			
7.4.1	Purchasing process	4.6.2		REQUIRED RECORDS
7.4.2	Purchasing information	4.3.3		
7.4.3	Verification of purchased products	4.6.4 4.10.2		
7.5	Product and service operations			
7.5.1	Control of production and service provision	4.9 4.15.6 4.19		REQUIRED DOCUMENTS
7.5.2	Validation of process for production and service provision	4.9	Enhanced	Carry out process validation REQUIRED RECORDS

TABLE 34.3. *(Continued)*

ISO 9001:2000		ISO 9001:1994 Corresponding Element	Changes in the revision	
Number	Title		Type	Description
7.5.3	Identification and traceability	4.8 4.10.5 4.12		REQUIRED RECORDS
7.5.4	Customer property	4.7		REQUIRED RECORDS
7.5.5	Preservation of product	4.15.2 4.15.3 4.15.4 4.15.5		
7.6	Control of measuring and monitoring devices	4.11.1 4.11.2		REQUIRED RECORDS
8	MEASUREMENT, ANALYSIS AND IMPROVEMENT			
8.1	General	4.10 4.20.1 4.20.2		Monitoring, measurement, analysis and improvement processes needed to demonstrate conformity of product, ensure conformity of quality management system and improve effectiveness of quality management system Determine the need for and use of applicable methodologies including statistical techniques
8.2	Measurement and monitoring			
8.2.1	Customer satisfaction		NEW	Monitor information on customer satisfaction and/or dissatisfaction as one of the measurements
8.2.2	Internal audit	4.17	Enhanced	Auditors selected to ensure objectivity and impartiality of audits REQUIRED RECORDS AND PROCEDURE

8.2.3	Monitoring and measurement processes	4.9 4.20.1 4.20.2	Enhanced	Method to demonstrate ability of processes to achieve planned results REQUIRED RECORDS AND PROCEDURE
8.2.4	Monitoring and measurement of product	4.10.2 4.10.3 4.10.4 4.10.5 4.20.1 4.20.2		REQUIRED RECORDS
8.3	Control of nonconforming product	4.13.1 4.13.2		REQUIRED RECORDS AND PROCEDURE
8.4	Analysis of data	4.20.1 4.20.2	Enhanced	In addition to using the traditional statistical techniques, analysis of data is a means for determining where the quality management system can be improved. Defines which data must be analyzed Customer satisfaction, conformance to product requirements, characteristics and trends for opportunities for preventive action, and suppliers
8.5	Improvement			
8.5.1	Continual improvement	4.1.3	Clarified	Need to plan and manage the process for continual improvement of the quality management system. Need to use quality policy, objectives, internal audit results, analysis of data, corrective and preventive actions, and management review
8.5.2	Corrective action	4.14.1 4.14.2		REQUIRED RECORDS AND PROCEDURE
8.5.3	Preventive action	4.14.1 4.14.3		REQUIRED RECORDS AND PROCEDURE

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TABLE 34.4. Standards That are Part of the ISO 9000 Series

ISO 9000:2000	Quality management systems—Fundamentals and vocabulary
ISO 9001:2000	Quality management systems—Requirements
ISO 9004:2000	Quality management systems—Guidelines for performance improvements
ISO 10005:1995	Quality management—Guidelines for quality plans
ISO 10006:1997	Quality management—Guidelines for quality in project management
ISO 10007:1995	Quality management—Guidelines for configuration management
ISO/DIS 10012	Quality assurance requirements for measuring equipment—Part 1: Metrological confirmation system for measuring equipment
ISO 10012-2:1997	Quality assurance for measuring equipment—Part 2: Guidelines for control of measurement processes
ISO 10013:1995	Guidelines for developing quality manuals
ISO 10014:1998	Guidelines for managing the economics of quality
ISO 10015:1999	Quality Management—Guidelines for training
ISO 16949:1999	Quality systems—Automotive suppliers—Particular requirements for the application of ISO 9001:1994
ISO 19011	Guidelines on quality and/or environmental management system auditing

Adapted from ISO, 2001

important that processes become standardized to ensure consistency in producing products and delivering services. This is done to reduce variation that can occur as the product is manufactured or the service is delivered. Some of the sources of variation include day-to-day variation, person-to-person variation, or location-to-location variation in performing the same activity or process.

ISO 9001 is an auditable standard that describes the basic quality management system requirements an organization must address to demonstrate its ability to provide products and services that meet customer and regulatory requirements. ISO 9004 is a guidance standard that describes the quality principles that must be addressed to increase the organization's effectiveness in meeting business goals. These standards are based on the following principles (ISO, 2001):

- Customer focus
- Leadership
- Involvement of people
- Process approach
- Systems approach to management
- Continual improvement

- Factual approach to decision making
- Mutually beneficial supplier relations.

Customer Focus

A company's survival depends on its customers. Therefore, it is imperative that the company understands the customer's current and future needs. This critical information must be used to develop products and services that will not only meet the customers' needs but strive to exceed the customers' expectations. The standard requires that companies measure customer satisfaction and dissatisfaction.

Leadership

The ISO 9001 recognizes that executive management is responsible for establishing and maintaining the overall quality management system for a company. This responsibility includes developing and implementing the quality policy and quality objectives, providing resources to maintain the quality system, and ensuring that an environment exists so that employees can meet the company's objectives. In addition, executive management is responsible for increasing the effectiveness of the quality management system.

The standards also are practical in nature. They allow the appointment of a management representative. This person is typically assigned the responsibility of dealing with the day-to-day activities of the quality management system. This person must report to the senior management on quality matters regardless of the other responsibilities the person holds.

The standard also requires management review. Reviews are conducted periodically to ensure the continued effectiveness of the quality management system. The management reviews should not be confused with quality audits, but these high-level reviews are performed to ensure the overall suitability and effectiveness of the quality management system. Input for these reviews should come from a number of sources including quality audits, customer feedback, marketplace evaluations, operational performance data, status of corrective and preventive actions, self-assessment, reviews of continuous improvement processes, and changes that can occur to the quality management system.

Involvement of People

The company must motivate and enable all of its employees so they can reach their full potential, thus enabling the company to achieve its goals.

Process Approach

A process is defined as a "set of interrelated activities that transform inputs into outputs." ISO makes extensive use of this definition. First, a process model is

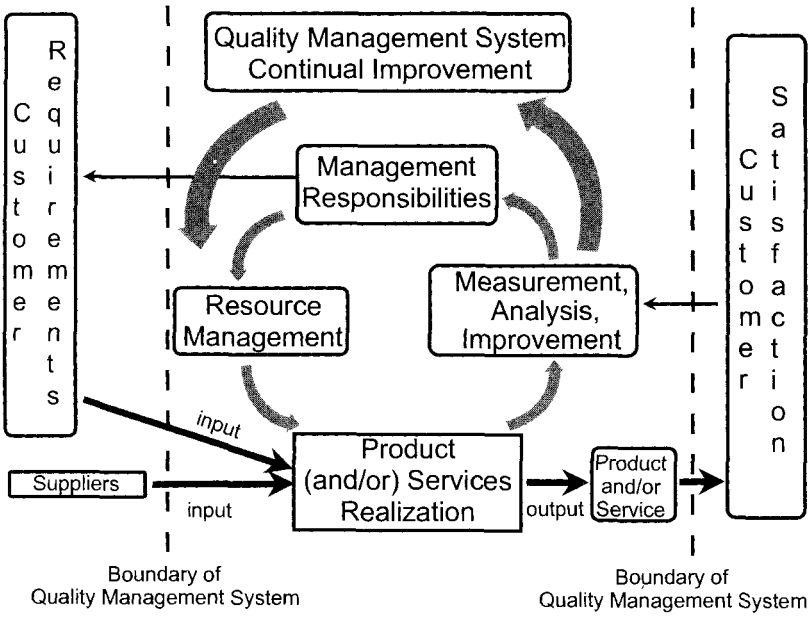

Figure 34.1. Copyright 2001, J.G. Surak. Used with permission of author. Source: ASQ, 2001b.

used to define the relation of the various elements of a quality management system (Fig. 34.1). The process model is also used to further define the relationship between inputs, value-added activities, procedures, measurements, and outputs (Fig. 34.2). The inputs include materials (ingredients or components), machines, time, and finances. Procedures may or may not be documented. (See the section on documentation). Monitoring and measurement opportunities are used to provide feedback and feed-forward information on the process and product quality.

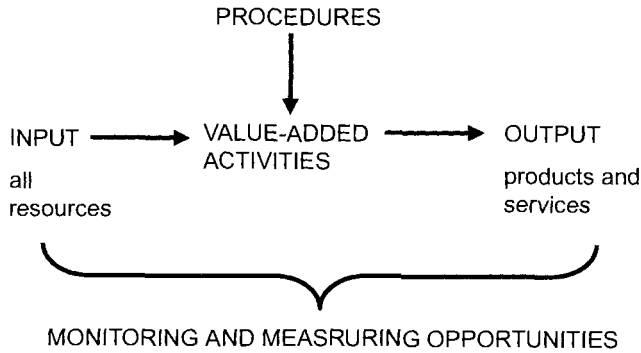

Figure 34.2. Copyright 2001, J.G. Surak. Used with permission of author. Source: ISO, 2001.

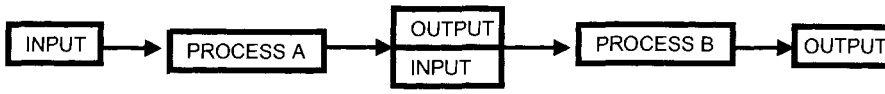

Figure 34.3. Copyright 2000, J.G. Surak. Used with permission of author.

Systems Approach for Management

The standard recognizes that processes do not operate in isolation. The output of one process usually becomes an input into another process (Fig. 34.3). These processes link together to form a system. Therefore, if a company is to be effective and efficient in meeting its goals, the company must manage the all of the processes as a system rather than trying to manage each process individually.

Continual Improvement

To compete in the global marketplace companies must improve the overall efficiency and effectiveness of operations. Continual improvement is the tool that allows this to take place. It has the following forms:

Technological breakthroughs
Incremental improvements.

Incremental improvements, also known as continuous improvement, include corrective and preventive actions. Companies should incorporate a plan-do-check-act cycle (PDCA cycle) into management of the continual improvement process.

Corrective actions provide a tool to assist a company in correcting known or identified problems. An effective corrective action program is designed not only to contain the existing problem but also to determine the root cause of the problem so that appropriate action can be taken to prevent reoccurrence.

Preventive actions are to be taken when the company identifies potential problems. This requires the continual analysis of various forms of quality data and implementation of strategies to prevent the occurrence of problems. Sources of information that can help the preventive action process include customer response information including complaints, market analysis, analysis of process and operational data, and audit results. Statistical techniques can help the company evaluate these data.

Factual Approach to Decision Making

Facts rather than assumptions are used as the basis for making decisions. This requires the monitoring and measurement process. The objective is to use data to generate information and knowledge to make appropriate decisions. Pro-

cesses may be controlled by using either a feedback or feed-forward system. To properly control processes, companies must identify the following: key product or process characteristics, sampling plans (which include targets, specifications, frequency of sampling), measurement methods, analysis plan, and action plan. The measurement process is not just limited to manufacturing. The company must measure other parameters such as customer satisfaction and effectiveness and efficiency of critical processes.

Mutually Beneficial Supplier Relations

ISO 9001 recognizes that the manufacturing process goes beyond the company. Therefore, companies within the supply chain are interdependent and should actively work together to meet customer needs and ultimately exceed customer expectations.

Documentation

The 2000 version of ISO 9001 has a decreased emphasis on documentation as a means to achieve the quality requirements. The standard only requires the following six documented procedures:

- Control of documents
- Control of records
- Internal audit
- Control of nonconforming product
- Corrective action
- Preventive action.

The standard requires the following documentation:

- Quality policy
- Quality objectives
- Quality manual
- Documents required to ensure the effective planning, operation, and control of the company's processes
- Records required by the standard.

Whether or not a company may actually reduce the amount of documentation will depend on the following:

- Size of the company
- Types of activities
- Complexity of processes
- Competence of personnel.

The following are questions that a company can ask when developing the documentation system:

- What is the effect of a no documented procedure or work instruction on the quality of products or services?
- What is the risk of customer dissatisfaction?
- What are the statutory or regulatory requirements?
- What is the effect of a nondocumented procedure or work instruction on process efficiency or effectiveness?

Table 34.3 summarizes places where documents must be maintained.

Documentation allows for the common understanding of how processes are to be done. Thus documents are effective tools to ensure that processes are performed in a consistent manner. They are developed to help employees do their jobs. Documents should be written at a level that enables an experienced, trained, and knowledgeable employee do his or her assigned tasks. The quality records provide proof to various stakeholders that the proper activities have taken place. In addition, the standardization of processes and the measuring of process performance is the first step in continuous improvement.

The standards require that all documented procedures must be controlled to ensure that employees have the correct and the most up-to-date procedures. In addition, there are requirements that ensure that all records be controlled and retained for a specified amount of time. To achieve the requirements of the standard, most companies use a three-tier system to document the processes. This system is supported by a fourth layer that consists of various quality records (Fig. 34.4).

The first tier is the quality manual. The quality manual serves as a master document and defines the company's philosophy to achieve stated customer requirements. It also defines how the company will achieve the elements of ISO 9001. An international standard (ISO 10013-1995) provides guidelines for developing quality manuals (Table 34.5).

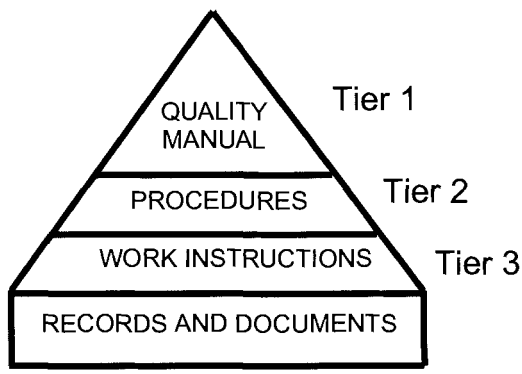

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TABLE 34.5. Suggested Organization of a Quality Manual as Defined by ISO 10013-1995

Title, scope, field or application
Table of contents
Introduction about manual and organization
Quality policy and objectives of the organization
Description of the elements of the quality system—References to documented procedures
Optional Sections
Definitions
Guide to quality manual—Tells what is where in the manual
Appendix of supportive material

Source: ASQ, 1995

The next level of documentation is the procedures. Procedures provide a means to control critical activities for an individual department or for interdepartmental activities.

The third tier of the documentation system is the work instructions. Work instructions provide the step-by-step activities that must be carried out so an individual can perform a specific job.

The entire documentation system is supported by quality records and other documents. The quality records provide proof to various stakeholders that an activity has been carried out properly. Examples of these documents that must be controlled include production records, specifications, drawings, recipes, formulas, regulations, and standards. These documents are subject to periodic revision, and employees must be able to reference the latest edition.

Implementing the Quality Management System

ISO 9001 does not provide specific instructions on how to build the quality system. Companies must understand and interpret the standard as it develops and customize the quality management system to meet its needs. Issues that must be addressed during the implementation of the ISO 9001-based quality management system include the industry sector, business environment, size of the company, customer needs and requirements, current status of the quality system, and corporate culture. These issues are best addressed by the company if it desires to have an effective and efficient quality management system.

The standard allows for some customization of the quality management system. If a company cannot apply a certain requirement of ISO 9001, it may be possible to exclude the requirement from the quality management system. Clause 1.2 (Application) defines the permissible exclusions. The standard permits only exclusion of requirements in Clause 7 (Product Realization). If this is done, the excluded requirement must be defined and justified in the quality manual. However, it should be noted that a company cannot claim compli-

ance to ISO 9001, "if the excluded requirement affects the company's ability or responsibility to provide a product (or service) that meets customer or applicable regulatory requirements" (ASQ, 2000b).

Table 34.6 describes a generic implementation process. The first step is management commitment to develop an ISO 9001-compliant quality management system. The development of a quality management system is a time-consuming task. It requires the commitment of the company at all levels in the organization. Upper management must see this process as a priority item for the company. In addition, upper management will need to take an active role in the development of the system. If a company has an existing senior management quality council, this council can assume the management responsibility for the implementation of the quality management system.

TABLE 34.6. Generic Process for Implementing a Quality Management System

Management commitment
Develop an implementation plan and time table
Develop an understanding of ISO 9000
Appoint an ISO 9000 implementation team
Start management review
Develop an understanding of the company's current quality system
Document and implement operational and quality documents that have not been documented
Start documenting the system wide procedures
Start internal quality audits
Determine gaps between the current quality system and the ISO 9000 standard
Document appropriate procedures to fill the gap
Continue to improve the quality management system

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Senior management should also set a realistic time line for implementation. This time line should be flexible to meet unforeseen problems. One company allocated 4 hours per week per professional for about 6 months to ensure complete documentation of the quality management system. It took the company about 12 months to complete the registration process.

Typically, senior management will appoint an implementation team to manage the project on a day-to-day basis. This team must develop an understanding of the standard and the basic principles of quality management. Once the training is completed, the team should develop a systematic understanding of the company's existing manufacturing practices and control procedures. This can be done by flow diagramming the processes from purchasing through sales and servicing and then documenting those processes. As part of this process the company must assess the following:

- How is the company meeting customer needs and requirements, especially with regard to product quality, delivery, and services?

- What sort of standard operating procedures (SOPs), including manufacturing and quality control quality assurance procedures, have been developed and implemented?
- Where are the bottlenecks that keep the company from effectively meeting customer needs?

The implementation team must determine the extent of documentation, because the 2000 version of the ISO 9001 has a reduced amount of required documentation. It is suggested that documentation belongs to the employees of the system. Therefore, it is important to involve all employees in the documentation of the company's processes. In addition, the documentation teams should document the processes as they actually exist, not the ideal process. It can be expected that the documentation team will identify a number of shortcomings in the manufacturing. These shortcomings must be categorized as critical and minor issues. Critical issues may require immediate attention.

During its ISO 9001 implementation process, one company discovered that a large number of the quality problems were attributed to the lack of equipment maintenance. This company did not want to permanently expand the size of the engineering department. Therefore, an outside company was subcontracted to repair the equipment. At the same time, an effective preventive maintenance program was implemented.

Companies should consider delaying the implementation of solutions to the minor problems until the initial documentation process is completed. Every time a problem is addressed, there will be a delay in the completion of the documentation process. Therefore, companies that try to fix all of the problems immediately may find themselves in a continuous loop trying to fix problems rather complete the ISO 9001 implementation process. Management must make critical decisions as to which problems to solve immediately and which problems to delay solving until latter.

After the documenting of the existing quality system, gap analysis is conducted to determine where the existing quality system meets or does not meet the standard. This step is the customizing part of the process, and it ensures that all critical issues that can affect product quality have been addressed.

Once the quality management system has been completely documented and implemented, the company can then allocate resources to fine-tune the system and to eliminate the root causes of the minor problems.

Internal Quality Audits

ISO 9001 requires that food processing companies carry out internal quality audits of the entire quality management system much like a financial audit. Quality audits help the food processor in the following ways:

- Assist in determining the effectiveness of the quality management system.
- Provide part of the input for management review.

- Verify that the quality activities comply with the planned activities.
- Determine whether the requirements of the quality management system are being met.

Internal quality audits should be started as soon as the documented procedures are implemented. This provides a number of additional benefits to the company:

- Allows the internal auditors to gain experience in the audit process.
- Allows the employees to gain experience in being audited (this reduces the audit fear factor).
- Provides feedback to senior management during the implementation process.

Auditors should use formal quality audit procedures. The following provides an outline of this procedure:

Planning for the audit
  Prepare the audit schedule
  Notify the auditee
  Select the team
  Develop audit records and checklists
Performing the audit
  Hold opening meeting
  Conduct audit
  Hold caucus meeting of the audit team
  Hold exit meeting
Reporting audit results and follow-up
  Prepare and deliver the audit report
  Follow up on corrective action requests
  Close the audit.

All phases of the quality management system should be audited at least once a year; however, the audit process can be done in segments. The entire system does not have to be audited at a single time.

Certification, Registration, and Accreditation

There is some confusion over these three terms as they are used as part of the ISO 9001 registration process. Part of the confusion stems from how various countries interpret the terms certification and registration.

Certification is a process of awarding a document that states that an organization has met certain requirements. For example, if a registrar determines

that a company's quality management system meets or exceeds the requirements of ISO 9001, this registrar will issue a certificate that testifies to this fact.

Registration is the process of listing the certified company in a public registry. For example, after a company has been certified to either ISO 9001, the registrar will then list the company in a public registry with the scope of the certification, address, and contact person.

Accreditation is a process by which an authoritative body gives formal recognition that an organization can perform certain tasks. For example, the Registration Accreditation Board (RAB), in the U.S. gives formal recognition that a registrar has met certain minimal requirements. This allows the registrar to do the following: 1) conduct third-party audits of other companies' quality management systems, 2) certify that these quality management systems meet the requirements of ISO, 3) publish the list of certified companies in a public registry. There are numerous authoritative bodies around the world with respect to ISO 9001 certification. These include Dutch Council for Accreditation or (*Raad voor Accreditiatie*, RvA) in The Netherlands and the United Kingdom Accreditation Systems (UKAS) in Great Britain. The accreditation agencies are national in origin and can accredit companies to carry out the ISO 9001 registration process. These accreditation agencies audit the registrars according to ISO Guide 62:1998. This ISO standard provides a set of international requirements for the operation of a registrar. Currently, memorandum of understanding exist between the major accreditation agencies around the world, so that the registration that is issued by an accredited registrar is recognized by the other countries.

In the United States, the terms "registration" and "certification" are used interchangeably. This has been done because all companies that have a site certified to an ISO 9001 quality management standard will also be registered. Most British quality literature will distinguish between certification and registration.

Registering the Quality Management System

As of July, 2001, 69,116 sites were certified to an ISO 9000 standard worldwide (World Preferred, 2001). These numbers include the certification and registration of 34,634 sites in the United States, 11,375 sites in Canada, and 1,556 sites in Mexico. In addition, as of July, 2001, 288 food processing sites were registered in North America (Quality Digest, 2001. This included 148 certificates in the United States, 120 certificates in Canada, and 20 certificates in Mexico (Quality Digest, 2001).

These companies typically use the following process to seek registration (Surak, 1993):

- Implement ISO 9001
- Select an ISO 9001 registrar
- Obtain preassessment audit (optional)

- Make improvements
- Conduct document review
- Obtain formal assessment of the management system
- Fix any minor discrepancies
- Obtain certification and registration by a registrar
- Maintain the registration.

The formal registration process is costly and time-consuming. In addition, the transfer of certificates from one registrar to another may not be a simple process. (Even though there is reciprocity between the accreditation agencies, this reciprocity does not extend to the registrars). The transfer of the registration process may cost the company both time and money. The Independent Association of Accredited Registrars (IAAR) suggests that both the old and new registrars work with the company to ensure that the transfer of registration will occur without undue hardship, bureaucracy, or cost to the company (IAAR, 1999).

Selection of a registrar is a critical step. During the selection process the company should interview several registrars and determine the compatibility of the company and the potential registrar. The company seeking the registration process should approach this decision using the same procedures as in a new business partnership. Table 34.7 provides a series of questions that can be used to interview perspective registrars.

After the registrar is selected, the registrar will conduct a document review that typically consists of determining whether the quality manual complies to the appropriate ISO 9001 standard. This review can be off-site rather than at the company. Registrars may carry out this review at the registrars' headquarters. Registrars use this practice to ensure a consistent review of quality manuals from company to company.

Once the registrar approves the quality manual it becomes a fixed document. The quality manual is the document that sets out the quality philosophy for the company. Revisions to the manual cannot be made without notifying and obtaining approval from the registrar. It should be noted that this approval process only applies to the quality manual. The company can revise procedures, work instructions, and other documents and records without approval by the registrar, However, revisions of these documents and records must be carried out with proper internal procedures.

Some companies elect to incorporate a preassessment audit as part of the registration process. This mini-audit is designed to determine the readiness of the company for the assessment audit. During the preassessment audit, the auditor will look at only a part of the quality management system. Certain areas are selected by the auditor because past experiences have demonstrated that these areas tend to be the weak links in the proper development of the quality management system.

The assessment audit will typically be conducted by an audit team and will take several days to complete. The size of the team and length of the audit are

TABLE 34.7. Questions That Can Be Used to Interview A Potential Registrar

Audit process
- How many audit days will it take to audit the site?
- How are the number of audit days determined?
- What are the rights to object to the audit team, especially with a perceived conflict of interest?
- How are corrective actions requests handled?
- What is the time frame of handling corrective action requests?
- What is the appeal process for corrective action requests of audits?
- What is the timing of the audits and surveillance audits?
- If auditors are contracted by the registrar and also work as consultants, how does the registrar deal with conflicts of interest?
- Do the auditors perform any other services for the registrar other than conducting audits?

Certification and registration
- What is the scope of registration for the registrar?
- How long are the certificates effective?
- How many ISO 9000 certificates have been issued, How many are still active?
- What are the requirements governing the use of the registrar's ISO 9000 symbol?
- Is the registration process easy to understand?
- What is the process used to maintain registrations?
- What is the appeals process for registration and corrective action?

General aspects of the registrar
- Does the registrar have an interest in working with the company—Is there a customer focus?
- How does the registrar notify clients of rule changes?
- How did the registrar work with the clients with the 1994 revisions? What do they plan to do to assist in implementing the 2000 revision?
- Does the registrar provide training or consulting or a company associated?
- How are the registration activities separate from the consulting and training activities?
- Are any of registrar's employees including governing board members, owners, auditors involved in consulting and training activities? If so, what is the nature of these activities and how does the registrar deal with conflicts of interest?
- How is confidentiality maintained with all personnel associated with the registrar?
- How long has the registrar been in business?
- What are contingency plans in the event of a business failure?
- In what state is the registrar incorporated?

Relation of the registrar with the food processing industry or any other industrial sector
- What are the specific qualifications and experiences of the owners, governing board, and auditors, in working in the food processing industry?
- How many clients does the registrar have with the food processing industry?

References
- Obtain a list of references both from the auditor and from a public register
- What were the experiences with the auditor, both positive and negative?
- There should be unequivocal support of the registrar

TABLE 34.7. *(Continued)*

Costs
What are the first-year costs?
What are the subsequent year costs?
Are there discounts for registration of multiple sites?
Will there be any additional costs when the system is first assessed to the 2000 revision of the standards?

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a function of the size and complexity of the site that is being audited. The International Accreditation Forum published guidelines on the number of audit days required to complete both certification and surveillance audits (IAF, 1996).

The audit is conducted according to standard quality management audit practices. During the audit the team determines whether the procedures and work instructions conform to the quality manual and whether the employees are following the procedures and work instructions.

On completion of the audit, the audit team recommends to the registrar whether the company should be certified to the appropriate ISO 9001 standard. The registrar will determine whether to issue the certificate or to deny certification because of findings that were identified during the audit. If certification is denied, the registrar will determine what type of follow-up is required to close out the findings and complete the audit process (The actions may include a complete second audit of the site before issuing the certificate).

Once the certificate is issued, the company must take appropriate actions to maintain and improve the quality management system. This is done through several processes including management reviews, internal quality audits, and registrar's surveillance audits. Many registrars will issue the certificate for a period of 3 years. During the first 2 years, surveillance audits will be conducted twice a year. Each audit will cover approximately one-half of the quality management system. During the third year, the registrar will conduct a single audit of the complete quality management system. On completion of the third-year audit, the registrar will issue a new 3-year certificate.

If a company fails to maintain it, the quality management system slowly deteriorates and loses its effectiveness. If the deterioration of the quality management system is too severe, the registrar may elect to withdraw the certificate and remove the company's name from the public registry. This action has been taken 334 times in the United States (ISO, 2001).

REGULATORY, INDUSTRIAL, AND INTERNATIONAL SIGNIFICANCE

Benefits of Implementing ISO 9001

Obtaining ISO 9001 certification is a voluntary process. Therefore, companies that seek registration must understand the reasons for undertaking the process

and the benefits they receive. Many companies have listed a number of benefits from ISO 9001 registration, which include:

- Staying in business—a major customer requires registration
- Expanding into new markets such as international markets
- Anticipating customer requirements
- Decreasing the number of customer audits
- Increasing customer satisfaction
- Using a recognized quality logo as a marketing tool
- Increasing the efficiency of operations
- Better control of operations
- Decreasing production costs
- Increasing the ability to identify inconsistencies in production
- Increasing quality to customers
- Improving production and efficiency.

In addition, several surveys have indicated that most companies save money by implementing a quality management system (Table 34.8). Surak and Wells further analyzed this data and reported that the break-even period for small companies was 2.78 years, whereas the break-even point for medium and large companies was slightly less than 1 year. This study looked at all costs, including internal costs for implementation, consulting costs, and registration costs.

Liability Issues

Recently, some legal scholars have investigated the liability issues regarding ISO 9001 registration. In a recent book, Dr. James Kolka (1998) points out some interesting legal observations, which include the following:

- A well-constructed and effective quality management system should stand the scrutiny of a legal challenge.

TABLE 34.8. Financial Costs and Benefits of Implementing ISO 9001

Size of company	Costs			Benefits		Break-even period, years
	Internal	External	Registrar	One-time Savings	Annual or on-going savings	
<$11 million	$51,000	$20,000	$11,500	$14,000	$23,000	2.78
$100–200 million	$166,000	$50,000	$23,700	$102,000	$160,000	0.86
>$1 billion	$321,000	$88,000	$27,400	$164,000	$295,000	0.98

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- A nonregistered company that does not have an internal quality assurance system that meets or exceeds the requirements of ISO 9001 is vulnerable to an legal challenge on each element of ISO 9001.

Documentation is a two-edged sword. It can benefit a company that has a well-designed, properly functioning quality management system. However, documentation can also weaken the legal position of a company that has a poorly designed or poorly functioning quality management system. One way to avoid problems is to develop the quality management system beyond the minimum requirements that are described in either ISO 9001. In a legal case, an attorney could use ISO 9004 to interpret ISO 9001 (Kolka, 1998).

ISO 14000

In recent years, there has been an heightened awareness of environmental issues around the world. As a direct result of this awareness, ISO created a series of environmental standards known as the ISO 14000 family of standards.

The ISO 14000 family of standards will eventually consist of over 20 standards and technical reports (Table 34.9). These standards address a wide variety of environmental issues including environmental management systems, environmental performance, labeling, auditing, and life cycle assessment.

Two of these standards have attracted interest from organizations that wish to implement an environmental management system. ISO 14004 is a guidance standard that advises organizations on developing an environmental management system. ISO 14001 is a standard that describes the elements of an environmental management system (Table 34.10). The environmental management system should be designed to allow the organization to achieve and control its stated environmental performance goals.

ISO 14001 is not designed to be a substitute for environmental laws and regulations. Therefore, the standard does not establish environmental performance levels or rate of environmental performance improvement. Each individual company must define the levels of environmental performance by taking into account environmental laws and regulations and other environmental requirements to which the company subscribes.

ISO 9001 and HACCP

It is recommended that food processors do *not* combine their ISO 9001 quality management system with their HACCP system. These two systems have two different objectives. HACCP is a food safety management system that is designed to ensure the safe production of food. The ISO 9001 quality system is designed to meet customer requirements. In addition, HACCP has moved from being a technical issue to being both a regulatory and a technical issue. Therefore, the primary customers of the two systems differ (the regulatory agency

TABLE 34.9. The Issued and Proposed ISO 14000 Family of Standards

Environmental management system	
ISO 14001	Environmental management systems—Specifications with guidance for use.
ISO 14004	Environmental management systems—General guidelines on principles, systems and supporting techniques.
Environmental management system auditing	
ISO 14010	Guidelines for environmental auditing—General principles.
ISO 14011	Guidelines for environmental auditing—Audit Procedures—Auditing environmental management systems
ISO 14012	Guidelines for environmental auditing—Qualification criteria for environmental auditors
ISO/WD 14015	Environmental assessment of sties and entities
Environmental labeling	
ISO 14020	Environmental labels and declarations—General principles
ISO 14021	Environmental labels and declarations—Self-declared environmental claims
ISO 14024	Environmental labels and declarations—Environmental labeling Type I—Guiding principles and procedures
ISO/WD/14025	Environmental labels and declarations—Environmental labeling, Type III—Guiding principles and procedures
Environmental performance evaluation	
ISO 14031	Environmental management—Evaluation of environmental performance evaluation—Guidelines
ISO 14032/TR	Environmental management—Environmental performance evaluation—Case studies illustrating the use of ISO 14031
Environmental assessment	
ISO 14040	Environmental management—Life cycle assessment—Principles and framework
ISO 14041	Environmental management—Life cycle assessment—Goal and scope definition and inventory analysis
ISO 14042	Environmental management—Life cycle assessment—Life cycle impact assessment
ISO 14043	Environmental management—Life cycle assessment—Life cycle interpretation
ISO/TR 14048	Environmental Management—Life cycle assessment—Life cycle assessment data documentation format
ISO/TR 14049	Environmental Management—Life cycle assessment—Examples for the application of ISO 14041
Vocabulary	
ISO 14050	Environmental management—Vocabulary
Environmental aspects in products standards	
ISO 14061	Information to assist forestry organizations in the use of the environmental management systems standards ISO 14001 and ISO 14004
ISO Guide 64	Guide for the inclusion of environmental aspects in product standards

Source: ISO, 2001

TABLE 34.10. Environmental Management System Structure

EMS paragraph number	Element	Description
4.1	GENERAL	The organization shall develop an EMS
4.2	ENVIRONMENTAL POLICY	The long-term commitment to the environment
4.3	PLANNING	Translation of environmental commitment into actions
4.3.1	Environmental aspects	Identify environmental impact of the organization
4.3.2	Legal and other aspects	Access to laws, regulations, and other requirements
4.3.3	Objectives and targets	Environmental goals and performance requirements
4.3.4	Environmental management programs	Plans of action to achieve objectives and targets
4.4	IMPLEMENTATION & OPERATIONS	Programs to achieve objectives and targets
4.4.1	Structure and responsibility	Roles and responsibilities to facilitate environmental management
4.4.2	Training, awareness, and competency	Training needs for employees who can significantly impact the environment
4.4.3	Communication	External and internal communications of environmental issues
4.4.4	EMS documentation	Maintaining appropriate information regarding EMS
4.4.5	Document control	Process to ensure everyone has correct documents
4.4.6	Operational control	Control of operations that have a significant environmental impact
4.4.7	Emergency preparedness and responsiveness	Identify potential emergencies and develop procedures to respond to the emergencies
4.5	CHECKING AND CORRECTIVE ACTIONS	Review of environmental activities that will lead to improved environmental performance
4.5.1	Monitoring and measurement	Monitor key activities and track environmental performance
4.5.2	Nonconformities and corrective and preventive actions	Identify and correct problems and prevent reoccurrence
4.5.3	Records	Maintain records of environmental performance
4.5.4	EMS audits	Verification that EMS is operating as intended
4.6	MANAGEMENT REVIEW	Senior management review to ensure suitability, adequacy, and effectiveness of the EMS

Source: ASQ, 1996

and the customer). Both systems may have some shared components; however, the systems need to be developed, managed, and audited separately. HACCP and the quality management system must each be recognized as a critical and important component in the company's survival.

FUTURE IMPLICATIONS

Future of ISO 9001

TC 176 plans to continue to receive feedback on the ISO 9000 family of standards from experts and from organizations that use the standards. This feedback will become the basis for future revisions. The Technical Committee plans to integrate quality assurance and quality management concepts from sector-specific initiatives and from various international quality awards.

CONCLUSION

Food processing companies should have a properly functioning quality management system that ensures that the company will provide products and services that meet customer requirements. ISO 9001 provides the definition for this minimal quality management system. However, companies must determine whether or not to seek external certification and registration of the quality management system. This is a business decision. Food processors must determine whether there will be an adequate return on the investment for this effort. Currently, there are no directives from the European Union mandating that food processing companies must have their quality management systems certified to an appropriate ISO 9001 standard. Any requirements for mandating ISO certification for food processing companies is market driven by customers.

In addition, a quality management system that only meets the requirements of either ISO 9001 is not guaranteed to address a number of critical marketplace issues including:

Achieving a competitive marketplace advantage
Ensuring efficiency and superiority of operational performance
Delighting the customer.

To achieve these objectives, the company must incorporate the concepts addressed in ISO 9004.

In addition, food processors cannot afford to let a quality management system stagnate. This system must continually evolve and improve, if the company is to meet the needs of the customer in the global marketplace.

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Ketula, J., and Roberts, K. 2001. ISO 9000:2000 In a Nut Shell, 2nd Edition. Paton Press, Chico, CA.

Peach, R.W., Peach, B., and Ritter, D.S. 2000. The Memory Jogger 9000/2000. GOAL/QPC, Salem, NH.

INTERNET RESOURCES

The following websites provide information on ISO 9000 and related standards:
American National Standards Institute, *http://www.ansi.org/*
American Society for Quality, *http://www.asq.org/*
Standards Council of Canada, *http://scc.ca*
International Association of Accredited Registrars, *http://iaar.org/*
International Organization for Standardization, *http://iso.ch*
Registrar Accreditation Board, *http://www.rabnet.com/index.shtml*
World Preferred, *http://worldpreferred.com*

CHAPTER 35

IMPACT OF FOOD SAFETY ON WORLD TRADE ISSUES

ERIK LICHTENBERG

INTRODUCTION AND DEFINITION OF ISSUES

International and regional treaties implemented in the mid-1990s have achieved significant progress in removing tariff barriers to agricultural trade. For example, under the Uruguay Round of the General Agreement on Tariffs and Trade (GATT), completed in April 1994, developed country signatories committed to cutting internal support for agriculture by 20% and export subsidies by 36% by the year 2000. Existing nontariff barriers were converted into tariffs; for example, import quotas were converted into tariff rate quotas in which high tariffs are levied on imports above certain levels. Tariffs on individual agricultural commodities must be cut by at least 15% by the year 2000, and agricultural tariffs overall must be cut by an average of 36%. Signatories also agreed to establish minimum access import quotas in the form of low tariff quantities in markets where import barriers had been prohibitive. Low tariffs had to be set for at least 3% of the market, rising to 5% by the year 2000. Similarly, under the North American Free Trade Agreement (NAFTA), ratified in 1993, the United States, Canada, and Mexico agreed to phased elimination of tariffs on virtually all agricultural commodities by the year 2008 and a ban on the introduction of new tariffs or quotas. Under the Treaty of Asuncion, implemented in 1995, Argentina, Brazil, Paraguay, and Uruguay created a "common market of the southern cone" (Mercosur), a partial customs union featuring phased reductions in tariffs combined with a common external tariff. Chile subsequently joined the customs union but declined to implement the common external tariff. The Single European Union Act, which took effect in 1987, and the Treat of Maastricht of 1993 both furthered economic integration within the European Union (EU) with the ultimate goal of creating a single European market.

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In this context, sanitary and phytosanitary concerns, and food safety issues specifically, are likely to assume greater prominence in world trade. Increased liberalization should lead to increased trade in terms of both volume and variety of products. Disputes over sanitary and phytosanitary issues are likely to become more common as a result. In addition, sanitary and phytosanitary standards remain one of the few remaining options for imposing import barriers that might be sanctioned under international trade law. Thus, one might expect disputes to arise from attempts to use food safety and other sanitary and phytosanitary standards to pursue longstanding protectionist goals.

This chapter reviews the role of food safety in international trade policy. The first section discusses the economic rationale for food safety regulation. The subsequent section discusses the economics of alternative forms of food safety regulation and differences in regulation at the national, regional, and international levels. It also touches briefly on the history of food safety concerns in international trade. Finally, it reviews provisions of major trade agreements relating to sanitary and phytosanitary standards in general and food safety in particular. The ensuing section examines the impact of these provisions to date. It also discusses the pros and cons of harmonization and other measures for ensuring food safety in world trade. The final section discusses issues that may become important in the future.

BACKGROUND INFORMATION AND HISTORICAL SIGNIFICANCE

Food safety regulation plays an essential role in modern food economies. As countries develop economically, a growing share of the population leaves agriculture and acquires food from others via market transactions. Lacking firsthand knowledge of how the foods offered in the market are grown and processed, consumers have no means of verifying food safety before they purchase. Moreover, if and when they do fall ill, they may find it difficult to pinpoint the role of individual foods in creating that illness to prove liability and thus obtain compensation for damage. As a result, the food industry may have little or no incentive to ensure safety, particularly if it is cheaper to produce food by using unsafe additives or maintaining unsanitary conditions during transport, storage, or processing (Antle, 1995; Roberts et al., 2002).

These conditions may hinder market development. Lacking means of verifying safety, consumers may become convinced of a general lack of safety and will limit purchases as a consequence. If safety is unobservable *ex ante* or *ex post*, individual firms interested in increasing market share by producing safer products may not be able to distinguish themselves from those making false claims of safety. The ultimate logical conclusion of such a process is a complete breakdown of the market altogether.

Government food safety regulation becomes essential in this context (Sykes, 1995; Antle, 1995). Food safety is largely unobservable, making it difficult to distinguish safe food from unsafe food. Much food is sold in bulk or in

processed forms in which individual components cannot be distinguished. Private measures such as testing and labeling by independent, nongovernmental agencies cannot ensure against fraud and are thus inadequate for ensuring that food is safe. (Compare, for example, the role of Consumers Union ratings of branded appliances or Underwriters Laboratories certification of electrical equipment in promoting product quality.) Government agencies, in contrast, have the power and capacity to monitor food processing to ensure that proper sanitary policies are followed and that foods are free of dangerous contaminants. They can acquire legal authority to prevent unsafe foods from entering channels of commerce. They can levy fines or impose other penalties on firms refusing to follow proper safety procedures.

Historically, food safety regulation in Europe and the U.S. came into being in the late nineteenth and early twentieth centuries, precisely at the time their populations were changing from predominantly rural to predominantly urban (see, for example, Burnett and Oddy, 1994). Scandals involving unsafe additives, false and misleading advertising, and unsanitary processing methods gave impetus to food safety legislation and the creation of food safety agencies. Scientific and technical progress in chemistry and microbiology gave these agencies the wherewithal to define and enforce standards objectively.

SCIENTIFIC BASIS AND IMPLICATIONS

Economics of Food Safety Regulation

Government agencies have regulated food safety in two major ways: (1) by establishing product standards that specify acceptable food characteristics, including additives and contaminant levels, and (2) by requiring that food be produced according to specified processing and production methods (PPMs). The former is essentially a performance standard: The government regulates the finished product to ensure that it contains only safe ingredients. Foods that do not conform to product standards cannot be sold legally. They are subject to seizure, and those attempting to sell them may be liable for civil or, in some cases, criminal penalties. The latter forms of government regulation enhance food safety indirectly by requiring the use of production methods that inhibit contamination (Sykes, 1995; Antle, 1995). The safety of the resulting product is imputed from the production methods used rather than observed directly.

Tolerances for pesticide residues or chemical additives in foods are examples of product standards. Hazard Analysis Critical Control Point (HACCP) and state and local health department regulations governing sanitary food preparation are examples of PPMs.

The choice between these two approaches depends on their relative cost and on feasibility considerations. In general, a regulatory agency should seek to attain its desired level of safety at a minimum total cost to society, including costs imposed on regulated firms and on consumers as well as the government's

costs of promulgating and enforcing regulations. The sheer size of the food industry makes continuous government monitoring excessively expensive. Instead, regulations must be formulated and enforced in ways that give the industry incentives to comply in providing the desired level of safety. Thus, to enforce product standards effectively, a regulatory agency must combine inspection of a sufficiently large share of total sales volume with penalties for violations large enough to serve as an effective deterrent. If penalties cannot be set large enough—either because they are limited by legislation or because bankruptcy limits them de facto—inspection may be quite expensive. In such situations, PPMs may be more cost effective. In other situations, limitations in analytical chemistry methods may make inspection infeasible or feasible only in ways that lead to excessive disruption of trade. In these situations, too, it may be more cost effective to require PPMs that can be enforced by a system of periodic inspections and fines. The imposition of HACCP requirements on the U.S. seafood industry, for example, was motivated largely by the high cost of achieving effective regulatory monitoring in an industry characterized by widely dispersed processing facilities (Unnevehr and Jensen, 1996). The identification of key safety-enhancing measures to be undertaken at critical control points allows firms to achieve compliance with safety requirements with minimal formal testing. The record keeping requirements of the program allow the FDA to use periodic inspections to monitor compliance.

Domestic Versus International Food Safety Regulation

Methods that are suitable domestically, however, may not be suitable internationally. From an importing country's perspective, exporters' standards—be they product standards or PPMs—may be viewed as unreliable. Importing countries lack the ability to enforce their own standards outside their borders. They may not consider adequate either other countries' nominal standards or those countries' technical capacity and political will to enforce adequate standards. Importing countries may suspect, for instance, that foreign laboratories will provide fraudulent certification of food safety, with active or passive connivance from underfunded government regulatory agencies or from government ministries anxious to maintain hard currency export earnings. Exporting countries, in contrast, may view importing countries' standards as arbitrary or unnecessary to ensure adequate safety. Inspection to ensure compliance with importing countries' product standards may impose high costs on importers in the form of increased spoilage, reduced shelf life, lower quality, or delays in marketing (e.g., missing peak seasonal demand periods). Politically, exporters may be unwilling to grant the cession of sovereignty implicit in accepting other countries' certification or policing of their food safety systems.

Differences in history, culture, and income lie at the root of such difficulties. Notions of what constitutes a food product and how those products are made are integral parts of culture. People from different cultures differ in their understanding of what bread is and how it should be made, for example. Such

cultural differences may result in different perceptions of risk and safety as well. Consider, for example, differences in the regulation of food additives. In the U.S., flavoring agents, colorants, hormones, antibiotic residues, pesticide residues, materials leached from packaging, detergents, and decontaminants are all considered additives. In Japan, only flavoring agents and colorants are considered additives. The U.S. and the EU regulate natural and synthetic food additives according to the same criteria. Japan does not regulate natural additives at all, whereas its regulations governing synthetic additives are far more stringent than those in the U.S. and the EU. The Japanese approach has been justified on historical and cultural grounds, namely, that natural additives have traditionally been derived from other foods and have thus been shown to be safe in practice (Vogel, 1995).

Income is also an important determinant of food safety regulation. People with higher incomes—and, by extension, the populations of higher-income countries—demand greater levels of safety. In other words, higher-income populations are willing to pay more for a given reduction in foodborne risk than poorer populations. Higher-income populations also tend to demand greater reliability in regulation, specifically, lower probabilities that regulatory measures will result in levels of risk exceeding those considered acceptable (Lichtenberg and Zilberman, 1988). Finally, higher-income countries have the wealth and technical expertise to provide levels of safety and reliability that poorer countries are often unable to afford. As a result, wealthier countries typically have more stringent forms of food safety regulation.

Although there are legitimate reasons for accepting differences in risk perception and demand for safety as a basis for differences in regulation, there are also numerous instances in which they have been used mainly as a cover for imposing import restrictions. For example, Japan's strict regulation of chemical additives has made it difficult for the U.S. and the EU to export processed foods to Japan. Similarly, until 1986, Japan classified imported mineral water as a soft drink and, on that basis, required that it be sterilized and packaged in glass containers, measures that increased the cost substantially.

Food Safety Regulation Under Regional and International Trade Agreements

Food safety regulation in the European Union Despite the elimination of tariffs within the EU, sanitary restrictions severely inhibited intra-European trade in foods until quite recently (Vogel, 1995). Each country had its own standards for foodstuffs such as bread, jam, beer, vinegar, pasta, sausage, and most other staples as well as food and feed additives. Other countries' products typically did not comply with these standards, albeit mainly for historical and cultural reasons rather than reasons of safety. A famous example is Germany's beer purity law, which persisted largely unchanged from 1516 until recently. In contrast to other European countries, Germany did not allow any product made from ingredients other than malted barley, hops, yeast, and water to be

sold as beer. As recently as 1988, a European Commission report identified 218 nontariff barriers preventing the creation of a single European food market (Vogel, 1995). These barriers included specific import restrictions, packaging and labeling requirements, restrictions on specific ingredients, and content regulations. Restrictions on vegetable fat content in chocolate and ice cream were the most prominent of these, accounting for 40% of the total.

The 1979 *Cassis de Dijon* decision by the European Court of Justice created an important opening to broader trade in foods within the EU by instituting the principle of equivalence, requiring each country to accept the standards of others unless it could demonstrate that its own restrictions were necessary to protect public health. It also established the effect of regulation (as opposed to nominal intent) as the criterion for assessing import restrictions. Measures that effectively restricted imports were ruled illegitimate even if they did not nominally discriminate against imports specifically. The Single European Act of 1987 further broadened the application of these principles within the EU. It eliminated the ability of one nation to veto Union-wide food safety standards by requiring a supermajority for ratification rather than unanimous consent. It augmented pressure for agreement on harmonization by granting the Council of the EU the option of declaring as equivalent all national laws, regulations, and administrative practices that had not been harmonized by the end of 1992. Since 1987, European Commission actions and European Court decisions have removed many of the barriers to trade imposed by differing national food safety and purity standards.

Food safety regulation under GATT The Uruguay Round included a new agreement devoted specifically to the application of sanitary and phytosanitary measures (GATT, 1994). This agreement attempts to limit the illegitimate use of such measures as technical barriers to trade. It introduced several important new elements into international trade law. In particular, it sets new standards for accountability in setting food safety standards that should inhibit the use of food safety standards as means of restricting imports.

Nondiscriminatory impact The agreement accepts the position taken by the European Court in the *Cassis de Dijon* decision establishing discriminatory effect rather than discriminatory intent as the criterion for determining whether sanitary and phytosanitary measures are technical barriers to trade. In particular, the degree of protection of human life and safety must be consistent across regulations and must not result in discrimination against imports relative to domestic products. Members should attempt to minimize trade effects of their sanitary and phytosanitary regulations, avoiding in particular distinctions that result in discrimination or disguised restrictions on trade.

Scientific basis of regulation Article 5 of the agreement requires GATT members to ensure that food safety measures are based on risk assessments using internationally accepted techniques and taking into account all relevant

scientific and technical evidence. Article 3 permits members to impose stricter standards than those adopted internationally, but only if they can show that those standards result in higher levels of safety. Members must thus be able to document the scientific basis of their food safety regulations.

Equivalence According to Article 4 of the agreement, an exporting country's sanitary and phytosanitary measures must be accepted as equivalent to an importing country's if the exporting country can objectively demonstrate this to be so on the basis of internationally accepted techniques and information.

Transparency Article 7 and Annex B of the agreement require members to publish sanitary and phytosanitary regulations and provide them to trading partners. Members are required to establish a contact point to provide answers to inquiries about their regulations, risk assessment methods, control and inspection procedures, and any other regulatory measures used to establish regulations. They will also furnish documentation of these regulatory procedures if requested.

Harmonization Article 3 of the agreement encourages (but does not require) the establishment, recognition, and user of common sanitary and phytosanitary measures. It identifies the Codex Alimentarius Commission (CAC) as the source for food safety standards relating to food additives, veterinary drug and pesticide residues, contaminants, sampling and analysis methods, and codes and guidelines of hygienic practice.

Enforcement of these provisions is much stronger under the new GATT agreement than under its predecessors (Steger and Hainsworth, 1998). The agreement established a new body, the World Trade Organization (WTO), to oversee its implementation and handle disputes. The WTO comprises permanent entities that handle dispute resolution. The new agreement contains specific timelines and procedures for establishing review panels, rendering decisions, and considering appeals. It also prohibits unilateral actions by member states, including determinations that violations have occurred, retaliatory actions, or refusal to accept WTO decisions. As a result of these institutional and procedural changes, the number of dispute settlement cases brought under GATT has increased markedly in the few years since ratification. Particularly noteworthy is the fact that cases brought by developing countries have made up a larger share of the total volume of cases than under previous GATT regimes. It appears that developed countries' ability to impose procedural delays and to refuse unilaterally to recognize GATT decisions had largely deterred developing countries from using GATT to bring complaints.

It should be noted that, even with these strengthened enforcement provisions, the WTO has no power to alter any nation's own laws or regulations even though it may declare them contrary to international trade law. The only recourse the WTO can offer parties found to have been injured is the right to impose countervailing measures against offending parties. This right may not

give the offending parties sufficient incentive to comply with WTO rulings, as we discuss below in the context of the U.S.–EU dispute over hormone-treated beef.

Food safety regulation under NAFTA The sanitary and phytosanitary provisions contained in Chapters 7 and 9 of NAFTA are similar to those of GATT, but they grant more discretion to individual countries (Johnson and Beaulieu, 1996). Like GATT, they disallow the use of sanitary and phytosanitary standards as nontariff barriers to trade and insist that such standards have a sound scientific basis. In contrast to GATT, they give each signatory greater discretion over the level of protection it feels obligated to provide its citizens and the types of scientific evidence it must provide to defend its standards.

Nondiscriminatory impact Article 712 of NAFTA specifies that sanitary and phytosanitary standards may not arbitrarily discriminate against imports, that they be adopted and applied only to the extent necessary to achieve an appropriate level of protection, and that they not be used with either a view to or an effect of creating a disguised restriction on trade. These provisions are weaker than the corresponding provisions of GATT because they allow levels of protection to differ across products.

Scientific basis of regulation Article 712 of NAFTA requires signatories to ensure that any sanitary or phytosanitary standards adopted are based on scientific principles and risk assessment and that they not be retained when a scientific basis no longer exists. Article 715 specifies that these risk assessments take into account relevant methods, techniques, scientific evidence, production methods, inspection, sampling and testing methods, and environmental conditions. These provisions, too, are weaker than those of GATT. NAFTA does not specify that scientific data and information offered in support of standards must provide sufficient evidence to justify them. It does not require the data provided and risk assessment methods used to conform to international norms. Nor does it specify that all relevant scientific and technical evidence be taken into account. Moreover, NAFTA allows each signatory to determine the level of protection it deems appropriate, giving each signatory substantial leeway in interpreting the available scientific evidence.

Equivalence Article 714 of NAFTA requires each importing country to treat an exporting country's sanitary and phytosanitary standards as equivalent to its own if the exporting country provides adequate scientific evidence that its standards achieve the level of protection required by the importing country. An importing country can refuse to treat an exporting country's sanitary and phytosanitary standards as equivalent if it offers a scientific basis for determining that the exporting country's standards do not achieve the appropriate level of protection. These provisions, too, are weaker than those of GATT because they do not specify the degree of scientific proof required.

Transparency Article 718 of NAFTA requires signatories to publish new standards and to notify other signatories in writing. Article 719 requires signatories to establish a single entity to handle all inquiries. Articles 714 and 715 require signatories to provide the scientific basis of their risk assessments and of any determination that an exporting country's standards do not achieve their desired level of protection.

Harmonization Article 713 of NAFTA requires signatories to use international standards, guidelines, and recommendations as the basis of their own sanitary and phytosanitary standards. Standards that conform to international standards are presumed to be scientifically justified. However, any signatory is free to adopt standards that are more stringent than the corresponding international standards.

Looking toward the future, NAFTA authorizes various forms of technical assistance for improving any signatory's sanitary and phytosanitary standards (Article 720). NAFTA envisions a variety of types of technical assistance, including research, processing technologies, infrastructure development, and the establishment of national regulatory agencies. Credits, donations, and grants to acquire technical expertise, training, and equipment are permitted.

NAFTA requires signatories to resolve disputes over sanitary and phytosanitary standards under NAFTA procedures. (In all other disputes, signatories may choose to handle disputes under GATT instead of NAFTA.) Chapter 20 of NAFTA establishes specific timetables and procedures for filing complaints, conducting consultations to reach voluntary agreements, establishing dispute resolution panels in cases where agreement cannot be reached, providing evidence, making determinations, filing appeals, and complying with decisions.

Food safety regulation in Mercosur Participants in Mercosur have focused mainly on tariff reductions. Although working groups on technical standards and on agriculture do exist, they have accomplished little to date. Over the past year or so, the stability of Mercosur has been drawn into question as marked differences in trade and macroeconomic policies have created dramatic new trade imbalances between Brazil and Argentina.

REGULATORY, INDUSTRY, AND INTERNATIONAL IMPLICATIONS

Enforcement of Food Safety Provisions

Experience to date suggests that recently adopted restrictions on sanitary and phytosanitary standards will limit, but not eliminate, the use of food safety standards as a means of creating artificial import barriers. Two cases involving beef provide cases in point: the U.S.–EU dispute over hormones and the Britain–France dispute over British beef.

The U.S.–EU dispute over hormones in beef dates back to 1985, when

the European Council of Ministers voted to ban both the use of all growth-promoting hormones in beef production and the sale of beef produced using hormones (see Vogel, 1995 for an extensive discussion of this dispute). At the time, such hormones were legal and in use in about half the member states of the EU. The ban was motivated by a series of scandals involving two hormones that had previously been banned by the U.S. and other countries for use in dairy production and had not been used in beef. European Commission technical committees concluded that most hormones would be safe under appropriate conditions, including maximum residue limits. Nevertheless, the Commission instituted bans on meat produced using hormones, effective in 1987.

Its decision had two apparent motivations. One was popular pressure from consumer groups whose concern over potential health effects had been heightened by the prior use of the hormone DES, a possible carcinogen whose use had long been banned in the U.S. and other countries. Another was a desire to maintain the financial viability of the EU's Common Agricultural Policy as it related to meat. The Common Agricultural Policy provided support for European meat producers by stockpiling meat to keep prices high. High European meat prices led to increased imports, forcing the EU to stockpile ever larger quantities of meat to maintain prices. The hormone ban simultaneously limited imports and reduced supplies of meat from EU producers (because of lower meat productivity in the EU).

Most countries exporting beef to the EU were not affected by the ban. The U.S. was affected. Three of the five hormones used in the U.S. are natural in origin and are not regulated in the U.S. on the grounds that the levels in beef were not discernibly different from those found naturally. The U.S. sets tolerances for residues for the two other hormones, which are synthetic. The U.S. appealed to the CAC, whose Technical Committee on Residues of Veterinary Drugs agreed that the hormones posed no risk and thus that the ban was a classic barrier to trade. The CAC itself, however, refused the U.S. request to declare the hormones safe. Neither bilateral negotiations nor adjudication under GATT led to a resolution of the dispute. Attempts to settle the dispute through GATT were blocked by the EU's insistence on the right to establish its own scientific standards for determining safety. In 1996 the U.S. took its case to the WTO set up to enforce the Uruguay Round Agreements. The EU was unable to show that this restriction was health related. In 1998, the WTO ruled against the EU, giving it until May 1999 to drop its ban. In July 1999, the WTO allowed the U.S. to impose punitive duties on $116.80 million worth of EU products as compensation for the ban.

This case shows both the strengths and limitations of the Uruguay Round sanitary and phytosanitary agreements. The EU was made accountable for providing sound scientific basis for its ban. It lost its case because it was unable to do so. Thus the Uruguay Round agreements made the EU more accountable for its actions. The WTO was able to render a decision, which had not been possible previously under GATT. Nevertheless, the WTO's ability to enforce

compliance is no greater than GATT's had been before 1994, that is, highly limited. The U.S. can impose punitive duties that are sanctioned under international law, but those duties are unlikely to benefit beef producers harmed by the EU ban. Moreover, those duties may be insufficient to force the EU to remove the ban.

A similar lesson can be drawn from the current impasse between Britain and France over imports of British beef. In the 1980s, a new disease appeared in British cattle herds, bovine spongiform encephalopathy (BSE) or "mad cow disease." BSE is similar to scrapie, a disease of sheep. It is believed to have been transmitted to beef herds via the use of sheep brains in cattle feed. In 1995, consumption of beef with BSE was linked to occurrences of Creutzfeldt-Jakob disease, a rare but fatal human brain disease. The EU subsequently banned exports of British beef within the EU until British herds could be certified as free of BSE. France and Germany refused to accept the recent determination of an expert panel that BSE had largely been eradicated from British beef herds, so that British beef could be considered safe. Furthermore, France has promised to continue to ban imports of British beef regardless of whether it wins its appeal to the European Commission. Thus, even though the European Commission has considerably greater power than the WTO, it may still lack sufficient authority to force member states to abide by its decisions.

Impacts of Trade on Food Safety

It has been argued that expanded trade in general—and provisions like those of GATT and NAFTA in particular—tend to undermine food safety by forcing countries like the U.S. to accept imports produced under less stringent protective regulations. From this perspective, efforts to expand trade are likely to set off a "race to the bottom" in which producers relocate their operations to exploit opportunities for reducing production costs afforded by more lax regulation. For example, production of fruits and vegetables might gravitate to less developed countries with less stringent regulation of pesticides and sanitation procedures.

In most cases, however, the opposite has occurred. Producers in countries with less stringent regulation frequently comply voluntarily with food safety procedures of those with more stringent regulation (for export crops at least) to ensure access to lucrative export markets. For example, Central American exporters of fruits and vegetables for the U.S. market have trained growers to comply with U.S. pesticide regulations. Mexican growers exporting to the U.S. have developed laboratory certification programs for pesticide residues to enhance compliance with U.S. pesticide residue tolerances (GAO, 1992).

Failure to comply with U.S. residue regulations imposes two kinds of penalties on exporters. In the short run, noncompliant shipments can be refused entry. Shipments of firms or countries discovered to be out of compliance are subject to more frequent inspections in the future, imposing a cost on exporters in terms of delays in marketing and, possibly, a greater frequency of rejected

shipments. These penalties appear to be sufficient to ensure that exporters largely comply with U.S. pesticide residue regulations. FDA surveillance data consistently indicate that the rate of residue violations is no greater for imports than for domestic U.S. products. Moreover, the majority of violations are due to pesticides not registered for use in the U.S. because of the lack of a market rather than safety concerns (Food and Drug Administration Pesticide Program, 1987–1998).

Occurrences of illness due to contamination of imports may also have detrimental effects on demand for imports, giving exporters an incentive to maintain safety as a means of maintaining a market for their products. In 1997, over 1000 citizens of the U.S. were made ill by *Cyclospora* on raspberries imported from Guatemala. In response, the FDA first suspended and subsequently banned further imports of Guatemalan raspberries into the U.S. until Guatemalan growers could install improved sanitation procedures. Because the U.S. accounted for 80% of the market for Guatemalan raspberries, the ban had a catastrophic effect on the industry, driving a number of growers out of business. Guatemalan growers have since promised to install water filters and improve sanitation in handling.

In these cases, the effect of trade has been to upgrade food safety in exporting countries rather than downgrade it in importing countries. As noted above, richer countries typically have stricter regulatory systems. They also have a greater demand for imports. The positive correlation between regulatory stringency and level of demand creates incentives for a "race to the top," that is, for exporters to adopt stricter food safety standards and enhance their technical capabilities in food handling (at least for exports) to ensure access to more lucrative markets.

Advantages and Limitations of Harmonization

Arguments over the desirability of harmonization of food safety standards have followed similar lines. Opponents of harmonization worry that efforts to harmonize standards could force countries to accept less stringent protection in the food system. Proponents argue that harmonization of food safety standards would facilitate world food trade by allowing the food industry to exploit economies of scale in producing uniform products and by eliminating food safety as a pretext for imposing arbitrary import restrictions.

The European experience does not bear out the fears of opponents of harmonization. Harmonization efforts in the EU have resulted primarily in more restrictive, rather than more lax, food safety standards (Vogel, 1995). Despite substantial differences among EU countries in terms of income, technological capacity, national food traditions, and regulatory capabilities, in most cases harmonization has led to the imposition of standards that are stricter than those of the average EU member. In a number of cases (e.g., hormones in beef and dairy cattle), the EU has imposed food safety standards stricter than considered warranted by its own scientific advisory bodies.

U.S. opponents of harmonization have focused on the standard setting procedures used by the CAC, the entity identified by GATT as the appropriate vehicle for standardizing food safety regulations. For example, the CAC does not use the same procedures for setting pesticide residue tolerances as the U.S. Environmental Protection Agency (EPA). The U.S. General Accounting Office (GAO) conducted a comparison of U.S. and Codex pesticide residue tolerances in 1991. It found that the two were comparable only in 38% of the cases it could identify. Lack of comparability was due equally to lack of a U.S. tolerance (for pesticides not used in the U.S.) and to incompatible definitions of residues (indicator compounds only versus a pesticide and all its metabolites). U.S. and Codex residue tolerances were equal in almost half the cases where they were comparable. Codex tolerances were more stringent in about a third of the cases, and U.S. tolerances were more stringent in the remaining sixth (GAO, 1991). U.S. tolerances appeared to be more stringent in cases of pesticides identified as probable carcinogens. For the 15 chemicals identified as probable carcinogens, the U.S. standard was stricter than Codex in 55% of cases and equal in an additional 18%. However, these cases accounted for a tiny minority of the total number of cases, 15 out of 1,257, too small a number to provide a basis for firm conclusions.

In sum, there is little evidence to support the assertion that harmonization efforts under recent trade agreements will undermine food safety regulation. Codex standards are frequently stricter than U.S. standards. CAC decisions are influenced strongly by the U.S. and the EU, whose populations have a high demand for food safety and which have stringent regulatory systems for food safety. Moreover, Codex, GATT, and NAFTA do not prevent any nation from adopting stricter food safety standards as long as it can provide a sound scientific basis for its decision.

At the same time, harmonization is unlikely to be a panacea for eliminating unwarranted differences in food safety standards. Longstanding differences in culture and perceptions of risk make it difficult to reconcile national differences in overall approaches to regulation and in the significance attributed to different types of risk. The U.S., for example, has traditionally placed much greater emphasis on cancer than other adverse health effects. The EU exhibits much greater concern about genetically modified foods that have gained wide acceptance in the U.S. For example, the EU prohibits the use of recombinant bovine growth hormone in dairy production, whereas the U.S. has refused to permit labeling of milk produced with bovine growth hormone on the grounds that testing indicates no statistically discernible differences in product characteristics. Despite considerable debate at the time of its introduction, U.S. consumers have evinced little concern about bovine growth hormone in milk in subsequent years (Aldrich and Blisard, 1998). Similarly, the EU forbids the importation of crops genetically engineered for herbicide tolerance and insect resistance despite regulatory approval, widespread use, and broad consumer acceptance in the U.S. and Canada.

Reconciling such differences is essential for harmonization. But reconciling

such differences may take far too much time for harmonization to be useful. Moreover, efforts at harmonization can be stalled or blocked by individual countries with a strong interest in preventing agreement. The case of European integration is instructive in this regard (Vogel, 1995). Until 1980, efforts to create a single European food market focused on harmonization of product standards. Because unanimous consent was required for the adoption of any standard, the European Commission was able to reach agreement on directives for only nine products between 1952 and 1979. Agreement on standards for mineral water took 11 years. Agreement on standards for jellies, jams, marmalades, and chestnut puree took 14 years. The CAC has found it no less difficult to reach agreement on controversial topics. As noted above, for example, political differences between the U.S. and the EU led the CAC to refuse to make a determination on the safety of hormones in beef production.

National differences in cultural and historical conceptions of food, perceptions of risk, entrenched regulatory customs, demand for reductions in risk, and uncertainty about risk make harmonization difficult. These difficulties are compounded by the desire of some nations to use sanitary and phytosanitary standards to maintain import restrictions to protect domestic industry. As in the European case, mutual recognition of standards, accountability for the scientific basis of standards, and transparency will likely result in more rapid expansion of trade than formal harmonization.

FUTURE IMPLICATIONS

Trade in raw and processed foods continues to expand. The U.S., for example, exported $31.3 billion worth of processed foods in 1997, accounting for over half of U.S. agricultural exports and about 5% of total U.S. exports (Handy and Neff, 1998; U.S. Department of Agriculture, 1999). U.S. exports of processed foods grew at an average of 4.2% in real terms between 1990 and 1997. U.S. imports of processed foods amounted to $30.1 billion in 1997 and grew in real terms at an average annual rate of 2.9% between 1990 and 1997.

Trade liberalization measures for agricultural products achieved in recent years include the Uruguay Round of GATT, the North American Free Trade Agreement, Mercosur, and continuing European integration. These liberalization measures will likely expand world trade in food and feeds. By removing artificial barriers to trade, they allow countries to exploit natural comparative advantages in agriculture, leading to cheaper food and feed worldwide.

Expanded trade will likely make disputes over food safety standards more common. National differences in foods, regulatory systems, perceptions of risk, demand for safety, and demand for regulatory reliability will persist. Justifiable differences in regulation will thus persist as well. Accountability for providing a rationale for food safety standards based on recognized international scientific methods appears to be the most promising mechanism for weeding out food

safety standards instituted for the purpose of protecting domestic industry rather than protecting public health.

To date, expanded trade has served to bolster food safety measures in less developed countries rather than undermine them in developed countries. Less developed countries have had to upgrade their technical and regulatory capabilities to ensure that exports meet developed country standards. Strict food safety standards based on internationally accepted scientific principles, meanwhile, remain defensible under international trade agreements.

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INTERNET RESOURCES

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Economic Research Service, U.S. Department of Agriculture, *http://www.econ.ag.gov*

Food and Agricultural Organization, *http://www.fao.org*

Foreign Agricultural Service, U.S. Department of Agriculture, *http://www.fas.usda.gov*

U.S. Food and Drug Administration, *http://vm.cfsan.fda.gov*

U.S. Mission to the European Union, *http://www.useu.be*

U.S. Trade Representative, *http://ustr.gov*

World Trade Organization, *http://www.wto.org*

CHAPTER 36

UNITED STATES IMPORT/EXPORT REGULATIONS AND CERTIFICATION

REBECA LÓPEZ-GARCÍA

INTRODUCTION AND DEFINITION OF ISSUES

Food safety has assumed primary importance in today's food import and export market. Recent crises have prompted the development of diverse programs that are based on control of the supply chain as a whole. Thus concepts such as Food Safety "From Farm to Fork" have gained not only popularity but also support from both local governments and international agencies. The U.S. government is no exception. The United States Food and Drug Administration (FDA) is charged with, among other things, safeguarding the food supply by prohibiting adulterated or misbranded foods. This includes domestic and imported foods and food products. Therefore, all imported products are required to meet the same standards as domestic goods. Imported foods must be pure, wholesome, safe to eat, and produced under sanitary conditions. Considering the amount of food being marketed and consumed, the FDA may be faced with an significant challenge.

Ensuring food safety is the work of all parties involved (see Table 36.1) because no federal, state, or local system can reasonably guarantee safety without the cooperation of food handlers and food processors at all levels. This may be complicated when imported foods are considered because the FDA lacks the authority to inspect food processing operations in foreign countries. Additionally, imported food may enter the U.S. through diverse ports of entry, seaports, airports, overnight carrier hubs, and border crossings, and the volume of products is continuing to grow. With the increased number of products coming in through different ports of entry, it is impossible to sample and analyze all shipments that come to every port of entry. Thus the U.S. government has established several systems to monitor food entry into the country.

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TABLE 36.1. The U.S. Food Safety Team

U.S. Department of Agriculture (USDA)

Enforces standards for wholesomeness and quality of meat, poultry, and eggs produced in the United States. USDA food safety activities include inspecting poultry, eggs, and domestic and imported meat; inspecting livestock and production plants; and making quality (grading) inspections for grain, fruits, vegetables, meat, poultry, and dairy products.

Bureau of Alcohol, Tobacco and Firearms (ATF)

Is responsible for enforcing the laws that cover the production, distribution, and labeling of alcoholic beverages, except wine beverages that contain less than 7% alcohol, which are the responsibility of FDA. ATF and FDA sometimes share responsibility in cases of adulteration or when an alcoholic beverage contains food or color additives, pesticides, or contaminants.

Centers for Disease Control and Prevention (CDC)

A branch of the Department of Health and Human Services, CDC becomes involved as a protector of food safety, including responding to emergencies, when foodborne diseases are a factor. CDC surveys and studies environmental health problems. It directs and enforces quarantines, and it administers national programs for prevention and control of vector-borne diseases (diseases transmitted by a host organism) and other preventable conditions.

Department of Justice

When the problem with a food is a violation of federal law, marshals from the Department of Justice are the agents who seize products. The Justice Department's attorneys take suspected violators of food safety laws to court.

Environmental Protection Agency (EPA)

Among its many duties, EPA regulates pesticides. It determines the safety of new pesticide products, sets tolerance levels for pesticide residues in foods (which FDA enforces), and publishes directions for the safe use of pesticides.

Federal Trade Commission (FTC)

FTC's Bureau of Consumer Protection has, among its duties, the regulation of advertising of foods.

Food and Drug Administration (FDA)

FDA, a part of the Department of Health and Human Services' Public Health Service, is responsible for ensuring the safety and wholesomeness of all foods sold in interstate commerce except for meat, poultry, and eggs, all of which are under USDA jurisdiction. FDA develops standards for the composition, quality, nutrition, and safety of foods, including food and color additives. FDA also sets standards for certain foods and enforces federal regulations on labeling, food and color additives, food sanitation, and safety of foods. FDA inspects food plants, imported food products, and feed mills that make feeds containing medications or nutritional supplements for animals destined as food for humans. FDA monitors recalls of unsafe or contaminated foods and can have illegally marketed foods seized.

TABLE 36.1. *(Continued)*

National Marine Fisheries Service (NMFS)
A part of the Department of Commerce, NMFS is responsible for seafood quality and identification, fisheries management and development, habitat conservation, and aquaculture production. NMFS has a voluntary inspection program for fish products. Its guidelines closely match regulations for which FDA has enforcement authority.

State and Local Governments
State and local government agencies cooperate with the federal government to ensure the quality and safety of food produced within their jurisdictions. FDA and other federal agencies help states and local governments develop uniform food safety standards and regulations and assist them with research and information.

Foreign Governments
Governments of at least 40 nations are now partners with the United States in ensuring food safety through memoranda of understanding that cover some two dozen food products, including shellfish. International cooperation is expanding in areas of food product inspection, certification, quality assurance, education and training, product studies, and regulatory standards.

BACKGROUND AND HISTORICAL SIGNIFICANCE

Regulatory Requirements for Importing Food into the United States

The legal authority for the control of imported foods is found in Section 801 of the Food, Drug and Cosmetic Act (FDCA), where it is basically stated that all imported food must comply with United States laws and regulations and that the U.S. Customs (Department of Treasury) and FDA (Department of Health and Human Services) will cooperate in this by ensuring that imported food is in compliance. These agencies exercise judgment through sampling, relabeling, or reconditioning to bring food into compliance or through detention and destruction of noncomplying products when appropriate (Vetter, 1996). In 1999, U.S. President Clinton directed the Secretary of Health and Human Services and the Secretary of the Treasury to take action to further protect U.S. consumers from unsafe imported foods. This was done because, although most importers comply with U.S. food safety requirements, a few importers may sidestep U.S. laws and bring unsafe or contaminated food into the country (Department of Treasury and Department of Health and Human Services, 1999).

Adulteration and Misbranding

As mentioned above, imported foods must meet the requirements of applicable laws and regulations governing foods that are produced and marketed in the United States. These are broad statements, but in essence this means that a

food must not be adulterated or misbranded if it is going to enter the American marketplace.

Adulteration is a condition that may cause a food to be hazardous to the health of a consumer or render it aesthetically unpleasant. The food does not have to actually be hazardous or unpleasant; it is enough that the food may have been under conditions in which contamination may have occurred for it to be considered adulterated. The FDCA lists five ways in which a food may be considered adulterated:

- It contains a poisonous or deleterious substance
- It is prepared, packed or held under insanitary conditions
- Its economic value has been reduced without proper labeling
- It contains an unsafe color additive
- It is a confectionery product and contains substances specifically prohibited
- It is margarine or butter and is unfit for food

To avoid charges of adulteration, the food should be processed under good manufacturing practices, include only approved additives or substances that are generally recognized as safe (GRAS), and be in compliance with Defect Action Levels for unavoidable contaminants.

The term "misbranding" deals with statements or claims that are, or are not, made for a food on its label or in its labeling. The misbranding provisions of the FDCA are intended to protect consumers from being confused or deceived by false or misleading statements. It is important to distinguish between the terms "label" and "labeling." "Label" is on the package; "labeling" accompanies the package and includes the label. A properly "labeled" food may be considered misbranded if its "labeling" is false or misleading. Usually, misbranding is quite clear and unequivocal: a required declaration is either not present on the required location or not present at all. In other cases, substantial judgment is involved in determining misbranding. Section 403 of the FDCA lists the following 16 conditions under which a food might be considered misbranded:

- Its labeling is false or misleading
- It is offered for sale under the name of another food
- It is an imitation of another food and not properly labeled
- Its fill of container is false or misleading
- Its package does not contain:
  Name and address of manufacturer, packer, or distributor
  Statement of net quantity of contents
- Required statements are not prominent and conspicuous
- It is a standardized food and does not comply with the standard

- It is subject to a Standard of Quality or Standard of Fill and does not comply with the Standard
- Ingredients are not declared as required
- It is a food for special dietary use and does not comply with regulatory requirements
- Artificial colors, flavors, or chemical preservatives are not declared as required
- It does not meet requirements for declaration of pesticides on raw agricultural products
- It contains a color additive, and the declarations on the package are not in compliance with regulatory requirements
- Its packaging or labeling is in violation of the Poison Prevention Packaging Act of 1970
- It contains saccharine, and the packaging does not bear the required warning statement
- It contains saccharine and is offered for sale at an establishment that does not post the required warning statement

To avoid a charge of misbranding, the food must comply with all labeling requirements. Although this may not be directly related to food safety, it is perhaps, one of the most difficult prerequisites for an exporter to meet because of the wide variation in labeling legislation from country to country.

IMPORT PROCEDURES (FDA, 1996)

Before starting the exportation/importation process, several steps can be taken to speed food entry. Before the shipment is made, it is important to determine that the product to be imported is legal and to have a private laboratory examine samples and certify the product(s). Although certification by a private laboratory is not conclusive, it may help to determine the processor's ability to produce safe, acceptable products. Certification of the shipment by a private laboratory will not guarantee approval of the shipment if a problem is detected by the FDA. It is important to become acquainted with legal requirements including those of the FDA and any other government agency involved before contracting a shipment. It is important to know the food importing procedures described below (Fig. 36.1).

Notification of U.S. Customs by the Importer

The first step for any food importation is to notify U.S. Customs (USC). The importer or agent must file entry documents at a location specified by USC within 5 working days of the date of arrival of a shipment at a port of entry.

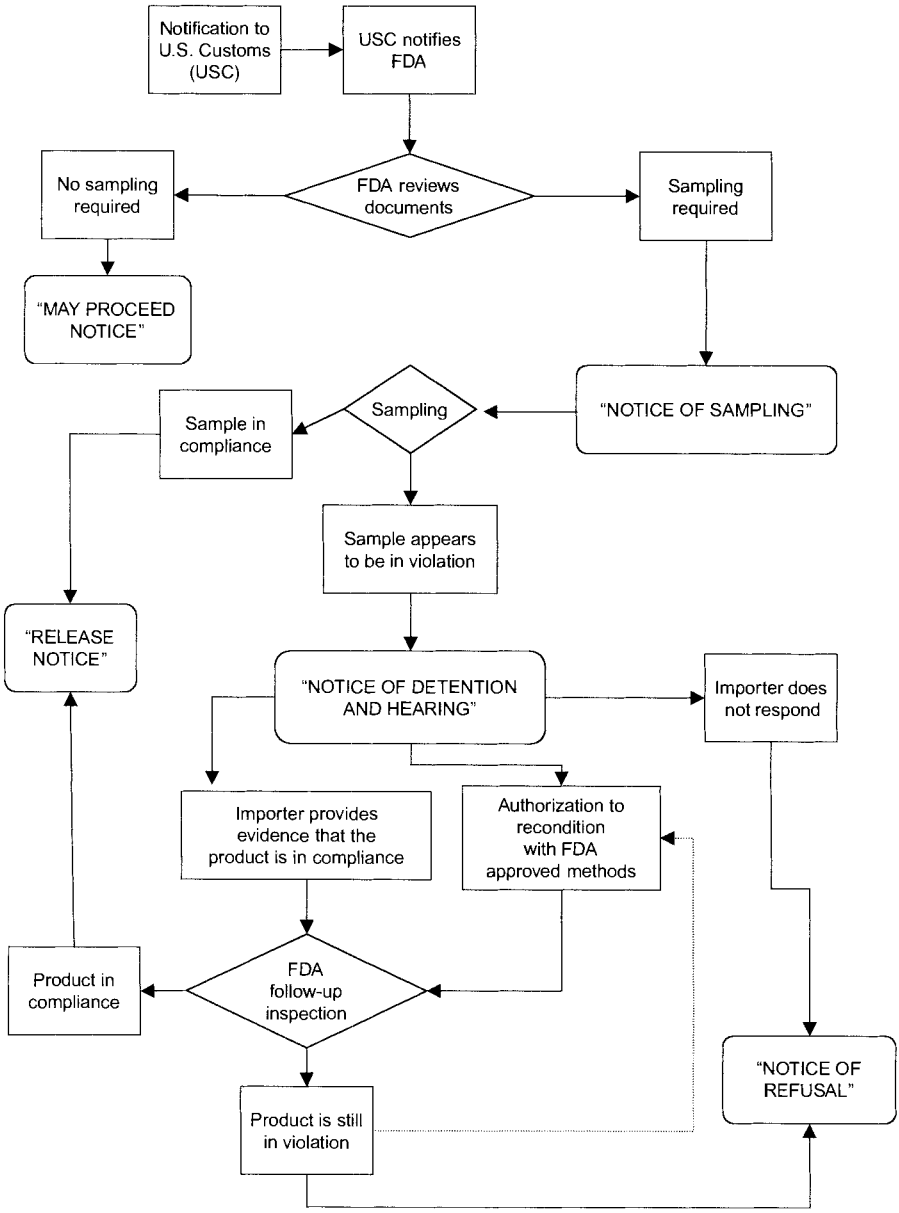

Figure 36.1. Food importing procedures

FDA Notification and Sampling Decision

The FDA is notified of an entry of a regulated food through:

- Duplicate copies of customs entry forms [CF3461, CF3461 ALT, CF7501, electronic filing through Automatic Manifest System (AMS) or alternative]
- Copy of a commercial invoice, and
- Surety to cover potential duties, taxes, and penalties

The FDA reviews the importer's documents and determines whether sampling of the shipment is necessary. Sampling may include a physical examination, wharf examination, or sample examination.

If the decision is to sample, the importer is notified. If sampling is not required, the FDA sends a "May Proceed Notice" to USC and the importer. At this point, the shipment is released as far as the FDA is concerned.

Sampling

On the basis of the nature of the product, FDA priorities, and the past history of the commodity, the FDA may decide to sample; it then sends a "Notice of Sampling" to USC and to the importer. A sample is collected, and the shipment must be held intact pending further notice. The sample is sent to an FDA District Laboratory for analysis.

Results of Sampling

If the FDA analysis finds the sample to be in compliance with requirements, a "Release notice" is sent to USC and to the importer.

If FDA determines that the sample "appears to be in violation of the Food Drug and Cosmetic Act and other related Acts," a "Notice of Detention and Hearing" is sent to USC and the importer. This notice specifies the nature of the violation and gives the importer 10 working days to present evidence of the eligibility of the shipment for entry. At this point, it is possible for the importer or a designated representative to introduce either oral or written testimony as to the admissibility of the shipment.

The FDA conducts a hearing concerning the admissibility of the product. This is an opportunity to present relevant matters and submit pertinent evidence. Several situations may occur:

The importer presents evidence indicating that the product is in compliance such as certified analytical results of samples, examined by a reliable laboratory, which are within the published guidelines for levels of contaminants and defects in food for human use. The FDA will collect samples

again to determine compliance with guidelines. If the new sample is in compliance, A "Release Notice" with the statement "Originally detained and now released" is sent to USC and the importer. If the sample is not in compliance, the importer may submit an Application for Authorization to Recondition (described below).

The importer submits an "Application for Authorization to Recondition or to Perform Other Action" (FDA Form FD 766). Through this form, the importer requests permission to try to bring the product into compliance by relabeling or other action or by converting it to nonfood use. A detailed method for bringing the food to compliance must be provided. The FDA evaluates the reconditioning procedure, and a bond is required for payment of liquidated damages. If the FDA approves the importer's reconditioning procedures, the approved application contains the statement "Merchandise Should Be Held Intact Pending the Receipt of FDA's Release Notice". Should the FDA disapprove the applicant's reconditioning procedure based on experience that shows that the proposed method will not succeed, a second and final request will not be considered unless it contains meaningful changes in the reconditioning operation to ensure a reasonable chance of success.

When the importer completes the reconditioning procedures, the FDA is informed that the product is ready for new inspection, and the FDA conducts a follow-up inspection based on the authorized reconditioning procedures.

If the reconditioned product is in compliance, a "Release Notice" is sent to all parties involved. If the product is still not in compliance, the product is rejected.

If the importer or designated representative neither responds to the "Notice of Detention and Hearing" nor requests an extension of the hearing period, the FDA issues a "Notice of Refusal of Admission" to the importer. All recipients of the documentation generated previously starting with the "Notice of Sampling" are sent a copy of the "Notice of Refusal".

After a "Notice of Refusal" is issued, FDA must receive a notification from USC verifying that the shipment was destroyed or exported under the direction of USC.

Costs of Sampling

The FDA will cover the costs of sampling if the product is found to be in compliance. However, the importer is charged for the costs of shipments that are in violation as well as for the costs of supervising reconditioning and/or relabeling, even if the violation is minor and the product is "Released with Comment."

Detention Without Physical Examination (DWPE)

Sometimes, the FDA will detain a product as soon as entrance into the United States is registered. The administrative procedure of detaining a product without physical examination is based on past history and/or information indicating that the product may be violative. The product will remain detained until the shipper or exporter provides evidence that it complies with FDA guidelines and standards. On rare occasions, the FDA will identify products of an entire country or geographic region for detention if a particular violative condition is widespread. This situation is not very common, and it only occurs when other avenues to resolving the problem have been exhausted.

Additional Forms

Low-acid canned foods In addition to required entry documents certain products require specific information to be presented to the FDA either at the time of importation or before importation. Under the Low Acid Canned Food Program, foreign firms must register and file processing information before shipping any low-acid canned food or acidified low-acid canned food to the United States. The information must be specific for each product to ensure compliance with registration and process filing requirements. The forms required for these products include Establishment Registration (FDA2541) and Process Filing Forms FDA2541a—Food Process Filing for All Methods Except Low-Acid Aseptic and FDA2541c—Food Process Filing for Low Acid Aseptic Systems. Registration is mandatory for any products in these categories. The filing forms can be obtained directly from the Regulatory Food Processing and Technology Branch, Division of HACCP Programs, Center for Food Safety and Applied Nutrition or on-line. It is important to maintain communication with this office to ensure proper handling of importation of these products. Low-acid canned foods that come to any port of entry are verified through their filed Food Canning Establishment Number.

Milk and cream Importation of milk and cream (including sweetened condensed milk) is subject to the requirements of the Federal Milk Import Milk Act, which states that a permit is required to import milk into the United States. To apply for a permit to ship or transport milk or cream into the United States, the actual shipper must complete the permit forms and address them to the Commissioner of Food and Drugs, Food and Drug Administration, Department of Health and Human Services (21CFR1210.20).

Plant and animal products The United States Department of Agriculture (USDA) is responsible for the inspection of meat and meat products, poultry and poultry products, and plant and plant products. Under the USDA, the Animal and Plant Health Inspection Service (APHIS) is responsible for

enforcing regulations for the import and export of plants and animals and certain agricultural products. APHIS import requirements depend on both the product and the country of origin. Plants and plant materials must be accompanied by a phytosanitary certificate issued by an official of the exporting country. Livestock and poultry must be accompanied by a health certificate, also issued by an official of the exporting country.

All commercial shipments of meat and meat products are subject to USDA regulations and must be inspected by APHIS and by the Food Safety and Inspection Service (FSIS) before release by USC. Meat and poultry (including game and fowl) can only be imported from approved countries and plants. All imported meat and poultry products must comply with the same requirements as domestic meats. Sampling and testing at the point of slaughter can be done under an arrangement that ensures that procedures and methods used are in accordance with USDA requirements. At the port of entry, all meat products are checked for transportation damage, species, labeling, general condition, proper certification, and residue levels. Residue levels must have certification.

To determine whether a country is eligible to export meat to the U.S., the USDA evaluates the country's whole inspection system. The country's laws, regulations, directives, and other written materials that govern inspection are reviewed as well as the administrative and on-site procedures. After a country is granted eligibility to export to the U.S., the FSIS relies on the country's inspection authorities to certify plants and carry out inspections. The country's adherence to the requirements determines the number of reinspections to which it is subjected; FSIS may conduct up to four reinspections a year (FAS, 1999).

Import Alerts

Import alerts have been developed as guidance documents that identify and disseminate import information of interest to FDA field offices. This information includes problems or violative trends and identifies problem commodities and/or shippers that require detention without physical examination.

Computerization

With the increased number of shipments coming into the United States, the FDA designed a system that aids the agency in making its admissibility determinations to ensure safety and quality of the foreign-origin products under the FDA's responsibility. The Operational and Administrative System for Import Support (OASIS) enables the FDA to handle the increasing number of shipments more efficiently. OASIS has also significantly speeded up the time within which FDA makes its determinations for imported products. This system routes electronic admissibility decisions to 2200 importers agents' computers within minutes after shipment data are transmitted electronically to the FDA. With this system, up to 85% of the shipments are now cleared without the submission of paper documentation. This computerized system also helps in

targeting probable problem areas through an automated screening function. OASIS is combined with USC's Automated Commercial System (ACS). With the combination of these two automated systems, the FDA is provided with immediate data on imported products, provides information on potential problems, and maintains national historical data files to develop profiles on specific products, shippers, and manufacturers as well as import alerts.

Guidelines for Automated Entry Screening on OASIS (FDA, 2000)

To import through OASIS, the importer must identify the actual FDA manufacturer (site-specific location where the product is manufactured, produced, or grown) and FDA shipper (actual shipper of the product identified on freight bills or bills of lading; often the same as the USC invoicing party).

FDA-regulated foods such as low-acid canned foods *always* require evidence that they were produced in a facility that is registered and licensed and has listed its products with the FDA. For these products, the site-specific location is the FDA manufacturer and must be submitted as such. This is specific for each manufacturing location because specific processing conditions have been filed and approved. The name and address of corporate headquarters or another plant location, intermediate supplier, or warehousing facilities are not acceptable. For products that do not have mandatory registration or licensing requirements the manufacturer is identified on the entry documents, and that information must be transmitted to OASIS.

Consolidators such as agricultural co-ops are often transmitted as the FDA manufacturer and FDA shipper. This is acceptable; however, if the product is detained after sampling, the entire shipment will be detained, regardless of the actual FDA manufacturer. Thus, consolidators should make an effort to determine the actual FDA manufacturer.

Memoranda of Understanding

FDA does not have the authority to inspect foreign food manufacturing plants. Therefore, it relies primarily on sampling and examination at port of entry and on memoranda of understanding (MOUs) with governments or agencies from other countries. Examples of MOUs for the movement of foodstuffs between the U.S. and other countries include (Vetter, 1996):

Compliance Policy Guide (CPG 7156.01) between the FDA and the Department of Agriculture and Food of Ireland. In this agreement, the government of Ireland agrees that it will sample, analyze, and certify shipments of casein and caseinates that are produced in Ireland and exported to the U.S.

Compliance Policy Guide 7156.03 between the U.S. and the Republic of Philippines, which covers raw and cooked frozen shrimp and frozen fruits and fruit purees.

Compliance Policy Guide 7156b.03 between the U.S. and Mexico, which refers to raw agricultural products and includes provisions for the countries to inform each other when changes are anticipated in legislation or regulations governing the movement of agricultural products between the two countries.

EXPORT REQUIREMENTS

Exportation generally involves more paperwork than domestic commercialization because compliance with the laws of two countries is needed. The first step is to comply with the requirements imposed by the U.S. on exports, the next step is to identify the import requirements imposed by the target country, and the final step is to obtain the appropriate certificates.

Generally, agricultural exporters do not have to obtain an export license, which is usually reserved for products with military or commercial uses. However, it is important to identify the U.S. export licensing requirements to verify that U.S. trade restrictions due to embargoes, domestic shortages, or other reasons are not being violated.

Certification for Export

FDA Certificates for export of foods and cosmetics A certificate of export can be obtained from the FDA for FDA-regulated foods. This document will generally indicate that the product is regulated by the FDA and that the company is not the subject of any enforcement action by the agency. Such certificates are not guarantees and do not imply certification of the product's safety and quality. The FDA issues them on request from a U.S. processor. The certificates are issued assuming the product meets the requirements of 801(e) of the FDCA. The product is in accordance with the specifications of the foreign purchaser and is not in conflict with the laws of the country to which it is intended to be exported; and the particular shipment is not sold or offered for sale in domestic commerce. To obtain a certificate for export, the company must present an original label or a detailed draft version of the current label; sufficient information for each product for which a certificate is requested so the reviewer can properly identify the product; adequate identification of the actual manufacturer of each product; and the following statement:

> "The requester hereby presents and acknowledges that the company is aware that in making this request the company is subject to the terms and provisions of Title 12, Section 1001, United States Code which makes it a criminal offense to falsify, conceal, or cover up a material fact; make any materially false, fictitious, or fraudulent statement or representation; or make or use any false writing or document knowing the same to contain any materially false, fictitious, or fraudulent statement or entry."

Certificates of export can be requested from the FDA's Center for Food Safety and Applied Nutrition.

USDA Agricultural Marketing Service (AMS) grading and certification The USDA Agricultural Marketing Service (AMS) has recognized that to stay competitive in today's market, U.S. agriculture has to produce locally but think globally. The AMS's mission is to become a strong partner in expanding markets for U.S. agricultural products. To accomplish this, the AMS's role centers on quality grading and certification programs that are user funded. Basically, grading involves determining whether a product meets a set of quality standards whereas certification ensures that certain specifications that have been contracted have been met. AMS commodity graders frequently work together with other USDA agencies such as the Farm Service Agency (FSA) and the Foreign Agricultural Service (FAS) that are also involved in export assistance. AMS certification services are usually requested by U.S. companies involved in exportation of agricultural commodities to a country with specific import requirements. Although certification is not a guarantee, it usually helps avoid rejection of shipment or delay in delivery once the product reaches its foreign destination. When exporting, it is important to avoid a delay in delivery because this may lead to product deterioration and may affect the image of U.S. quality, hampering future export business.

The AMS also provides a Quality Systems Verification Program for the meat industry. Under this program, the AMS provides independent third-party verification of a supplier's documented quality management system. This program supports the U.S. meat and livestock export industry by promoting world-class quality and international competitiveness.

Dairy products exported to the European Union, where there are special requirements, are also certified by AMS. AMS also provides laboratory testing for exporters of domestic food commodities on a fee basis. These analyses are in keeping with the sanitary and phytosanitary requirements of importing countries.

USDA Animal and Plant Health Inspection Service (APHIS) export permit services This agency offers assistance to farmers and exporters by providing phytosanitary inspection and certification for agricultural commodities exported to foreign countries. Phytosanitary certificates verify that the products have been inspected and are free of regulated pests and diseases. Every year, this agency certifies over 300,000 shipments for different countries that have vastly different requirements for agricultural products. To facilitate management of all this information, a database was developed. This database, called EXCERPT, allows officers as well as industry members to access export information. If a U.S. exporter wanted to export a particular commodity to a particular country, EXCERPT would provide him with the information that must be included in the phytosanitary certificate. Other useful information that can be obtained through EXCERPT includes a complete list of endangered plant

species and their current status; a list of commodities that are not eligible to be exported to specific countries; changes in countries' entry requirements; and ports that are authorized to certify for export endangered and threatened plants protected by the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES). With the use of the extensive information available on this database, U.S. exporters usually do not run into complications with phytosanitary issues. However, in cases where American goods arrive at a foreign port of entry and are denied admission, the agency will try to negotiate with foreign plant health authorities on behalf of the U.S. exporter.

NMFS Export certification for seafood and aquaculture Through the 1946 Agricultural Marketing Act, the National Oceanic and Atmospheric Administration (NOAA)/National Marine and Fisheries Service (NMFS) provides a voluntary inspection service. The NMFS Seafood Inspection Program includes a variety of professional inspection services to ensure compliance with all applicable food regulations. Additionally, it provides product quality evaluation, grading, and certification on a product lot basis. Under this program, the exporter may display official marks such as the U.S. Grade A, Processed Under Federal Inspection (PUFI), and lot inspection marks. Services provided by NOAA include establishment sanitation inspection; process and product inspection and product grading; product lot inspection; training programs; and consultation nationwide in U.S. territories and in foreign countries. Products eligible for inspection include whole fish, formulated products, and fish meal products used for animal food.

Other Resources for American Exporters

Import requirements are diverse and may vary from country to country and are also specific for raw and processed commodities and may change depending on a multitude of factors. Several resources are available for consultation by potential exporters. Most of these databases are available online and their web page addresses are provided in the Internet Resources section.

Food and Agricultural Import Regulations and Standards (FAIRS) reports These reports contain descriptions of import procedures and lists of useful contacts by country. The reports provide generic technical requirements and standards for consumer-ready food products pertaining to food additives, labels, pesticide residues, and food sanitation.

Library of export requirements The Food Safety and Inspection Service (FSIS), through the library of export requirements, presents information on foreign country export requirements for meat and poultry products. Two types of documents are available in the Export Library, the Export Notices and the Country Requirements. The Export Notices are intended to be a rapid method of dissemination of new and urgent export information. Such information is

eventually included in the Country Requirements. These files contain information obtained by FSIS through direct government-to-government communication with country officials. Country Requirements contain information in the areas of product eligibility, labeling, processing requirements, documentation, other requirements and plant eligibility. If a country is not found in the database, then it can be assumed that nothing is known about its export requirements.

CONCLUSIONS: THE UNITED STATES IN THE INTERNATIONAL TRADE FRAMEWORK

International trade of food has grown exponentially in the past decades and with this, there is an increased awareness of the safety, quality and labeling of food products moving in the international marketplace. In the U.S., the FDA's traditional monitoring and border inspection approaches for imported products may no longer be as effective as the sole means of ensuring the safety of food imported into the U.S. and food exported to other markets. Consequently, the U.S. government, through the Center for Food Safety and Applied Nutrition (CFSAN), has developed and implemented new strategies to deal with imported foods. These new approaches are based on cooperative efforts with governments and industries in producing countries to achieve a higher level of protection for U.S. consumers and to prevent safety problems at their source.

By the same token, the rules of international trade have also changed significantly. International trade agreements have introduced new requirements that affect how food products are regulated and inspected. International food safety, quality and labeling standards have been developed through international consensus with the Codex Alimentarius Commission. Although some of these standards are still under development, they have become more numerous and their use is now a benchmark for foods moving in international trade. The United States is an active participant in the Codex Alimentarius Commission and has played and will continue to play a major role in ensuring that these standards are based on sound scientific principles and are protective of the health of consumers.

United States regulatory agencies in charge of ensuring food safety at all levels of the supply chain will continue to evolve. Regulation of food and food safety is a dynamic process, and therefore, all agencies involved will have to continuously adapt their requirements to ensure the safety of American consumers and to promote American products in the global marketplace.

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Foreign Agricultural Service (FAS). 1999. Food and Agricultural Import Regulations and Standards Report.

U.S. Food and Drug Administration. Code of Federal Regulations 21CFR1210.20. Regulations under the Federal Import Milk Act.

U.S. Food and Drug Administration. 2000. FDA Manufacturer and FDA Shipper Data Transmission Requirements. Division of Import Operations and Policy.

U.S. Food and Drug Administration. 1996. Industry Activities Staff Flyer. Center for Food Safety and Applied Nutrition.

U.S. Food and Drug Administration. 2000. Industry Activities Staff Flyer. Center for Food Safety and Applied Nutrition.

Vetter, J.L. 1996. Food Laws and Regulations. American Institute of Baking, Manhattan, KS.

INTERNET RESOURCES

http://www.fas.usda.gov/scriptsw/attacherep/
Food and Agricultural Import Regulations and Standards (FAIRS)

http://www.fsis.usda.gov/OFO/export/explib.htm
Food Safety and Inspection Service Library of Export Requirements

http://www.aphis.usda.gov/import.html
USDA Animal and Plant Health Inspection Service (APHIS)

http://www.ams.usda.gov/
USDA Agricultural Marketing Service

http://seafood.nmfs.noaa.gov/
Seafood Inspection Program

http://www.fas.usda.gov/
United States Foreign Agricultural Service: The Foreign Agricultural Service (FAS) of the U.S. Department of Agriculture (USDA) works to improve foreign market access for U.S. products. FAS operates programs designed to build new markets and to improve the competitive position of U.S. agriculture in the global marketplace.

http://www.cfsan.fda.gov/
Center for Food Safety and Applied Nutrition, United States Food and Drug Administration. CFSAN's homepage provides links to many of the programs and resources described in this chapter.

OTHER RESOURCES

Agricultural Marketing Service (AMS)

AMS Processed Products Branch
Room 0709, South Building
Washington, DC 20250-6456
Phone: (202)720-4693
Fax: (202)690-4119

Cheese, Milk, and Dairy Products
AMS Dairy Division
Room 2750, South Builiding
Washington, DC 20250-6456
Phone: (202)720-3171
Fax: (202)720-2643

Customer Service Standards for Quality Grading and Certification, Fresh Fruits, Vegetables, and Specialty Crops
Room 2056, South Building
Washington, DC 20250-6456
Phone: (202)720-5870
Fax: (202)720-0393

Laboratory Testing Division, Standardization Branch
AgBox 0222
Phone: (202)720-2158
Fax: (202)720-6496

Meat and Meat Products
Meat Grading & Certification
Livestock and Seed Division
Room 2628, South Building
Washington, DC 20250-6456
Phone: (202)720-1246
Fax: (202)690.4119

Poultry and Eggs
AMS Poultry Division
Room 3938, South Building
Washington, DC 20250-6456
Phone: (202)720-3271
Fax: (202)690-3165

Animal and Plant Health Inspection Service (APHIS)-Plant Protection Quarantine
APHIS-PPQ, Permit Unit
4700 River Road, Unit 136
Riverdale, MD 20737-1236
Phone: (301)734-8645 Fax: (301)734-5786
Information retrieval system: (301)734-8645

Animal and Plant Health Inspection Service (APHIS)-Veterinary Services
APHIS-VS
National Center for Import/Export
4700 River Road, Unit 40
Riverdale, MD 20737-1231
Center for Food Safety and Applied Nutrition

U.S. Food and Drug Administration
200 C Street, S.W.
Washington, D.C. 20204

Commissioner of Food and Drugs
Food and Drug Administration
Department of Health and Human Services
5600 Fishers Lane, Rockville, MD 20857

Export Services, Phytosanitary Issues Management
USDA-APHIS-PPQ
4700 River Road, Unit 140
Riverdale, MD 20737
Telephone: (301)734-8537
Fax: (301)734-3249

Food Safety Inspection Service
International Programs
Room 341-E Whitten Building
Washington, DC 20250
Telephone: (202)720-3473
Fax: (202)690-3856

National Technical Information Service (NTIS)
Information on HACCP
U.S. Department of Commerce
5285 Port Royal Road
Springfield, VA 22161

Regulatory Food Processing and Technology Branch
Division of HACCP Programs
Center for Food Safety and Applied Nutrition
200 C Street S.W., Washington, DC 20204

Seafood Inspection Program
1315 East-West Highway
Silver Spring, MD 20910
Telephone: (301)713-2355
Fax: (301)713-1081
Toll Free: 800-422-2750
Contributed by Rebeca López-García
Logre International Food Science Consulting

CHAPTER 37

EUROPEAN UNION REGULATIONS WITH AN EMPHASIS ON GENETICALLY MODIFIED FOODS

J. RALPH BLANCHFIELD

INTRODUCTION AND DEFINITION OF ISSUES

To understand the laws and regulations relating to genetically modified (GM) foods in the European Union (EU), one needs to have some knowledge of the EU legislative structure and how it works and some background about GM, how it is carried out, what its potential benefits are, the concerns (whether real or speculative) to which it gives rise, and the issues that the EU GM-related legislation is intended to address.

BACKGROUND AND HISTORICAL SIGNIFICANCE

EU Legislative Structure

Information on most matters relating to the EU may be found by using links on the EU Web site *http://europa.eu.int/index-en.htm*.

The EU structure is complex, as might be expected in a union of 15 sovereign nations (Member States). The main EU institutions and their functions are listed at *http://europa.eu.int/inst-en.htm*.

For purposes of food legislation, however, the key institutions are:

- The *Council of Ministers*, consisting of one Minister from each Member State; the composition varies according to the subject; for food matters it is the Agriculture Ministers. Between meetings there are working committees of officials from each Member State.

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- The *EU Commission*, which is run collectively by Commissioners who are appointed by the Member States and approved by the European Parliament but who, once appointed, owe allegiance to the EU and not to the countries that appointed them. It is staffed by employed officials. The Commission is divided into 26 *Directorates General (DGs)*, each controlled by a Commissioner, dealing with different subjects. Food legislation is the responsibility of DG Consumer Policy and Consumer Health (sometimes referred to by the French abbreviation DG Sanco and formerly designated DG 24), which has a website at *http://europa.eu.int/comm/dgs/health_consumer/index_en.htm.*
- The relevant *Scientific Committees* responsible for providing expert advice; the Scientific Steering Committee (SSC) and, in the case of food, the Scientific Committee for Food (SCF) and the Scientific Committee on Veterinary Measures relating to Public Health (SCVMPH).
- The *Economic and Social Committee*, an advisory committee comprising representatives of manufacturers, trade unions, agriculturalists, professions, consumer bodies, and officials from Member States' governments. The Commission and Council may seek its opinion on any matter but are obliged to seek its opinion on any draft legislation. The Committee may itself proactively issue an opinion where it sees fit.
- The *European Parliament*, which has a consultative role and, in particular, can affect the passage of Commission recommendations to the Council of Ministers.
- The *Court of Justice*, which is independent of other EU bodies, is composed of Judges and Advocates General and reviews the legality of acts by the Parliament and Council and by the Council and Commission. It is also the final arbiter on matters of interpretation of EU legislation and the final court of appeal in matters of legal dispute and for imposing penalties where a Member State is not fulfilling its EU obligations.
- To add to the foregoing complex structure, in January 2002 the Council of Ministers adopted the Regulation establishing the European Food Safety Agency (EFSA). Its main task is to provide scientific advice and support for Community legislation and policies in all fields having a direct or indirect impact on food and feed safety. It will give independent information on these matters and communicate on risks in the food chain to the general public. The Regulation sets out the guiding principles of EU food legislation, involving a major overhaul of the EU food safety. A key element is the responsibility of food and feed businesses to ensure that only safe food/feed is placed on the market, and that unsafe foods/feedingstuffs are withdrawn from the market. It will also set up a Rapid Alert System for Feedingstuffs by integrating information on contaminated feed into the existing Rapid Alert System for Food. It will allow for rapid communication between the Member States on dangerous substances found in feed and its possible recall. It is intended also to make it mandatory for businesses to

have systems in place for tracing from whom they have purchased foods and to whom they have supplied them. On 28 June 2001 the EU Council of Ministers accepted the proposals and some of the amendments that were proposed by the Parliament.

In simplified summary, food legislation is formed by recommendations from the DG Consumer Policy and Consumer Health of the Commission to the Council of Ministers. Drafts from the Commission go first to a succession of meetings of the officials from Member States, where, ideally, differences in approach are resolved, but in practice these meetings often involve "horse trading" and compromises and are the main reason why the process is sometimes lengthy. During this period, drafts (and often a succession of drafts) are widely circulated by the national government departments for public consultation.

The main forms of legislation, including food legislation, are EU Directives and EU Regulations. When adopted, the full text of the Directive or Regulation is published in that day's "L" issue of the Official Bulletin of the European Communities [quoted in references as "OJ L" followed by volume number date and page(s)]. Food-related texts are accessible to authenticated subscribers on-line at *http://europa.eu.int/eur-lex/en/lif/reg/en_register_152030.html*. The measures in a Directive must, within a limited time from the date of its adoption, be given legal effect by national legislation in each Member State. By contrast, a Regulation takes immediate force in all Member States. Although national legislation is not necessary to bring a Regulation into force, it is customary for national legislations to mirror it, providing for enforcement machinery and penalties for noncompliance.

SCIENTIFIC BASIS AND IMPLICATIONS

Food biotechnology is the application of biological techniques to food crops, animals, and microorganisms to improve the quality, quantity, safety, ease of processing, and production economics of food. It thus includes the traditional food manufacturing processes used for bread, beer, cheese, and various fermented milk products.

The most recent application of biotechnology to food is genetic modification (GM), also known as genetic engineering, genetic manipulation, gene technology, and/or recombinant DNA technology. The collective term "Genetically Modified Organisms," or GMOs, is used frequently in regulatory documents and in the scientific literature to describe plants, animals, and microorganisms that have had DNA introduced into them by means other than by combination of an egg and a sperm or by natural bacterial conjugation.

Random genetic variation occurs naturally in all living things and is the basis of evolution of new species through natural selection. Even before its scientific basis was understood, mankind took advantage of this natural variation

by selectively breeding wild plants and animals and even microorganisms, such as yogurt cultures and yeasts, to produce domesticated variants better suited to the needs of humans.

Traditional selective breeding methods are based on the transfer of genetic material between individuals of the same species. Many changes to food materials brought about by gene technology are no different in essence from those which can take place in nature, except that the gene technologist speeds them up and channels them to drastically reduce their random nature. Thus within-species GM involves few fundamentally new issues. However, gene technology also makes it possible to move genes between different species. This property makes the technique revolutionary in terms of the potential benefits that it may bring but it has also caused concern regarding issues of safety, ethics, consumer choice, and environmental impact.

How is GM technology carried out? In simple terms, the gene technologist uses a "cutting-copying-pasting" approach to transfer genes from one organism to another. For this, bacterial enzymes are used that recognize, cut, and join Deoxyribo Nucleic Acid (DNA) at specific locations acting as molecular "scissors and tape." However, the selected gene is copied billions-fold, with the result that the amount of original genetic material in the modified organism is immeasurably small. Because DNA does not always readily move from one organism to another, "vehicles" such as plasmids (small rings of bacterial DNA) may be used; alternatively, some plant cells may be transformed by "shooting" small particles coated with the new DNA into the target cell using a special type of gun, the "Gene Gun." The modified cell can then be used to regenerate a new organism.

By currently available methods, however, only small numbers of cells subjected to genetic modification procedures are successfully modified. Furthermore, the regeneration of whole plants or animals from culture cells may take months or years. Consequently, it is necessary to identify the modified cells in a culture mix by using "marker genes" closely linked to the genetic material to be transferred. Antibiotic resistance has often been used to "tag" genes so that they can be detected easily and rapidly at the cellular level in the laboratory, providing a basis for selection. The use of antibiotic marker genes has, however, been a source of concern, and other methods are becoming available. In a development reported in *Science* in May 1999, researchers at the University of Hawaii have demonstrated the use of sperm to transport "foreign" DNA into an egg. It has a relatively high rate of success, is technically simple to carry out, has potential for transferring larger pieces of DNA, and is applicable to animals.

What Are the Potential Benefits of GM?

For the development of improved food materials, GM has the following advantages over traditional selective breeding:

- It allows a much wider selection of traits for improvement, for example, not only pest, disease, and herbicide resistance achieved to date in plants

but also potentially drought resistance, improved nutritional content, and improved sensory properties.
- It is faster and lower in cost.
- Desired change can be achieved in very few generations.
- It allows greater precision in selecting characteristics.
- It reduces the risk of random occurrence of undesirable traits.

These advantages could, in turn, lead to a number of potential benefits, especially in the longer term, for the consumer, industry, agriculture, and the environment:

- Improved agricultural performance (yields)
- Ability to grow crops in previously inhospitable environments (e.g., via increased ability of plants to grow in conditions of drought, salinity, extremes of temperature, consequences of global warming), leading to improved ability to feed an increasing world population at a reduced environmental cost
- Improved sensory attributes of food (e.g., flavor, texture)
- Improved nutritional attributes (e.g., the successful EU research project funded by the Rockefeller Foundation, resulting in increased vitamin A content in rice, helping to prevent blindness among children in Southeast Asia)
- Improved processing characteristics, leading to reduced waste and lower food costs to the consumer.

GM has huge potential for mankind in medicine, agriculture, and food. In food, the real benefits are not the early instances that have been appearing so far, but its longer-term benefit to the world—and especially the third world—of the potential for developing crops of improved nutritional quality and crops that will grow under previously inhospitable conditions (see above), thereby contributing to elimination of hunger and malnutrition while helping to prevent the otherwise inevitable pressure to encroach on natural resources. Even today, there are 800 million people in the third world who regularly do not receive enough food to alleviate hunger, much less to provide adequate nutrition; this will be greatly worsened as a result of the world's increasing population over the coming decades.

It is frequently argued by some that there is more than enough food to feed the world and all that is needed is "fairer distribution" (which so far mankind has signally failed to achieve)—or a variant of that argument, "the real problem is not shortage of food, it is poverty." Whatever may be done by way of improved yields through conventional methods, attempted population control, and fairer distribution would, however, be inadequate for the future. The important point is not only how to feed the world now but addressing and trying to solve the problem of "How shall mankind feed the world in a few decades when the world's population has doubled, with most of the increase in the

poorest parts of the world?" Food science cannot by itself solve a problem that has such huge political and economic dimensions. However, the problem will not be solved without food science and, in particular, the possibilities that may be opened up by GM. The Nuffield Council on Bioethics, in its May 1999 Report on "Genetically modified crops: the ethical and social issues," not only adopted this position, but referred to it as a compelling moral imperative. The Council also stressed that this is something that should not be left to commercially oriented R&D, but must be promoted by governments and international agencies.

Food scientists and technologists can support the responsible introduction of GM techniques *provided that* issues of product safety, environmental concerns, ethics, and information are satisfactorily addressed so that the benefits that this technology can confer become available both to improve the quality of the food supply and to help feed the world's increasing population in the coming decades.

What Are the Concerns About GM?

Many concerns about GM have been aired, some of them genuine, based on hazard analysis and risk assessment; some speculative and without scientific basis (often presented as though they were evidence based); and some that are urban myths.

Increasingly at the heart of the debate over GM is the fundamental matter of the roles of science and society in relation to "new" science-based developments such as GM.

Science depends on gaining knowledge, organizing it into a coherent structure, and applying it. It is society's tool and method for doing so. However, we can never know everything there is to know about a topic. So the one certain thing about life is that nothing in life is certain. Science cannot prove that anything is "safe" (i.e., absence of harm) because "absence of evidence" is not "evidence of absence." Thus any policy purportedly based on requiring science to prove safety is unrealistic.

In real life, decision and action by society to meet its needs must be based not on certainty but on using the best knowledge available at the time and on skillful selection of areas for urgently needed research. In the absence of certainty decision and action must involve the combination of risk analysis and the precautionary principle, which are two inseparable sides of the same coin. These lie at the very crux of any discussion on the application of GM.
Risk analysis (RA) consists of

1. Risk assessment, a task for scientists who are experts both in the topic and in the methodology of risk assessment. Risk assessment should take account of the likelihood of a risk occurring and its seriousness if it does occur and should be applied not only to a potential course of action but also to failure to take that action and to alternative courses of action;

2. Risk communication, a multidirectional interchange of information and interpretation among legislators, the scientific community, and the rest of society, which should be an ongoing process; and
3. Risk management, for legislators to carry out on behalf of society in the light of 1 and 2.

The precautionary principle (PP) is a concept familiar to, and used by, food scientists and technologists. It is at the heart of the Hazard Analysis Critical Control Point (HACCP) preventive food safety system.

However, various concepts and interpretations of PP abound, and a widely quoted concept regards PP as a preferred alternative to RA and its components. It is important to understand that in real life PP and RA are inextricably linked and must be pursued together.

A commonly expressed (but unrealistic) approach demands that PP must be invoked

- Where the scientific evidence for safety is insufficient, inconclusive, or uncertain, or
- Where preliminary scientific evaluation suggests that effects on the environment, health, or safety may be unacceptable and/or inconsistent with the chosen level of protection

and PP may be applied

- Without waiting for the reality and seriousness of those risks to become fully apparent.

This fails to recognize that science can never produce conclusive results and cannot deal in certainty. Moreover, experience teaches that the situation envisaged is most likely to arise in areas (such as biotechnology) where there are strong ideological agendas, in pursuit of which some individuals, including, unfortunately, some scientists, present unsubstantiated speculation, assumptions, and guesswork as though they were "preliminary objective scientific evaluation." This sometimes takes the form of published purported "research papers" that on scrutiny turn out to be merely the authors' speculations and opinions, complete with references to similar papers by like-minded individuals.

If that sort of presentation is considered enough to bring a development to a halt and, as we have seen, scientific evidence is always insufficient and science cannot prove anything to be safe, it can then be argued in perpetuity, both by its ideological opponents and by scientists who see further research as a funding opportunity, that the development should not be resumed "until we know more."

Purported "preliminary objective scientific evaluation" should, therefore, always be very carefully scrutinized to ensure that there is a broad scientific consensus that it is based on some hard scientific evidence.

On February 2, 2000, the EU Commission issued a "Communication on the Precautionary Principle." This is on-line at *http://europa.eu.int/comm/dgs/health_consumer/library/pub/pub07_en.pdf*.

It is an oft-repeated environmental truism that we hold the world in trust for future generations. It would be a betrayal of that trust and an abdication of responsibility by the present generation if science were to limit itself to collecting and providing information about current biotechnology applications or if society were to limit itself to arriving at verdicts about them. To make available to future generations the huge benefits in quantity and quality of food that biotechnology can bring, while minimizing pressure on land and water supplies and minimizing the use of agricultural chemicals, society needs to foresee, identify, address, and solve problems. The main tool that society has for addressing and solving safety and environmental problems is science.

Thus the real questions to be answered are not "Is it safe?" and "Is it environmentally friendly?" but "What do we have to do to make it safe?" and "What do we have to do to make it environmentally friendly?" Recognition of this is the touchstone of sincerity and objectivity for us all.

How do we go about it? The author's contribution on behalf of the Institute of Food Science & Technology (IFST) to the OECD on-line Forum for the Paris Biotechnology Consultation on November 22, 1999, explained how. This constructive approach is to prevent hazards giving rise to risks. The established methodology for this, used by those responsible for safety in food production and distribution, is a systematic methodology called HACCP.

Those working in food technology in industry will be very familiar with HACCP. For any who are not, in brief, the specific system concerned is studied and the hazards are identified. "Critical control points" are then established, where controls are operated (measures and limits to prevent hazards causing risks, and monitoring to ensure that the controls are working effectively). A food technologist or engineer designing a new system or redesigning an existing one first uses the HACCP approach to design it so as to avoid as far as possible "built-in" hazards and then applies HACCP to the resulting system.

So, instead of identifying possible hazards and crying, "Look at these scary dangers" (the passive "victim" approach), society should require the case-by-case application of the food safety HACCP approach to GM. The further development of GM technology holds out the potential for such indispensable benefits for humanity's future that any other approach would be indefensible. For those who wish to explore the HACCP methodology further, some useful on-line and print references are included in the Literature Cited and Internet Resources sections.

A most thorough and balanced study of the ethics, environmental impacts, and social aspects of GM was carried out in 1998 under the auspices of the Nuffield Foundation. The Nuffield Council on Bioethics carried out a widespread public consultation using a questionnaire posing questions on the ethical, environmental, and social issues and issued a comprehensive report on

its conclusions and recommendations, "Genetically modified crops: the ethical and social issues" *http://www.nuffieldbioethics.org/file/library/pdf/gmcrop.pdf.* This is a very lengthy report, but for those interested in gaining awareness of these issues, it will repay careful study.

More recently, a joint report on "Transgenic Plants and World Agriculture" was published jointly in July 2000 by the Brazilian Academy of Sciences, the Chinese Academy of Sciences, The Indian National Science Academy, the Mexican Academy of Sciences, the National Academy of Sciences of the U.S., The Royal Society (UK), and the Third World Academy of Sciences. It is available in printed form, published by The Royal Society, and it may be accessed on-line as a pdf file at *http://www.royalsoc.ac.uk/policy/rep_gr.htm.*

Safety

To produce food by any new technology, including gene technology, there must be appropriate safeguards to protect human and animal health. Most countries in the Western hemisphere started developing regulatory controls long before any GM foods became available to consumers. These controls were developed not because of identified safety problems but because of a lack of previous experience of GM foods. Although many of the early concerns regarding the safety of GM foods have not materialized, the precautionary approach remains to ensure that no new hazards are created.

When considering safety in relation to GM, generalizations cannot validly be made. Instances must be considered and studied in a case-by-case way, and each case should be assessed in relation to the food involved, as ready for consumption, whether by humans or by animals.

Regulations in most countries involve, but, importantly, are not limited to, the concept of substantial equivalence. This concept was developed in the late 1980s by several national regulators, refined and given international recognition by OECD in 1993, and further refined in the FAO/WHO Consultation of Experts in 1996 with particular reference to foods produced by modern biotechnology. It is based on the idea that existing organisms used as food or food sources can serve as a basis for comparison when assessing the safety for humans of modified foods or ingredients. If a new food or component is considered to be substantially equivalent to an existing food or component the concept holds that it can be treated in the same manner with respect to its safety and nutritional assessments.

Acceptability or nonacceptability is established by determining whether a novel food is substantially equivalent to an analogous conventional food in terms of composition, nutritional properties, toxin and allergen content, the amount consumed, the type of processing (industrial or domestic) that the food might undergo, and consumption by vulnerable groups of people (e.g., infants and the elderly). Foods are assigned to three categories

1. Products that are shown to be substantially equivalent to existing foods or food components
2. Products that are substantially equivalent to existing foods or food components except for defined differences
3. Products that are not substantially equivalent to existing foods or food components

Where differences are identified, extensive animal feeding and toxicological trials are required. The establishment of substantial equivalence is an analytical exercise that has to be approached carefully. The comparison may be a simple task, or very lengthy, depending on the nature of and experience with the foods or components being compared. It must also contain a dynamic element to take into account the fact that the continuing modification of a food will require that the most recent novel food is compared with an appropriate former novel food and not necessarily with the original and traditional counterpart.

At this point it should be mentioned that the EU Commission has introduced stricter interpretation rules that result in some differences between the EU and the U.S. Food and Drug Administration (FDA) in their respective applications of substantial equivalence (see below).

An understanding of substantial equivalence is key to understanding the basis of GM regulatory controls. This brief outline may be supplemented by studying the text of the Report of the Joint FAO/WHO Consultation on Biotechnology and Food Safety at *http://www.fao.org/es/esn/biotech/tabconts.htm*.

Reference has already been made to the reason for the use of antibiotic marker genes and the reason for moving to other methods. Although the transfer of antibiotic resistance from a marker gene contained in a GM plant to a microorganism normally present in the human gut has not been demonstrated experimentally, it has been suggested that the potential risk, however small, of spreading resistance to therapeutic antibiotics could have serious health consequences and therefore should be avoided. In the absence of reliable data, the U.K. Advisory Committee on Novel Foods and Processes (ACNFP) has erred on the side of caution and has recommended against the use of antibiotic resistance marker genes.

There are no inherent grounds for assuming that GM foods are more—or less—allergenic than traditional foods. However, when developing any novel foods, including GM foods, care must be taken that allergenicity is not inadvertently introduced into the diet. This requires assessment of the allergenicity of a new protein by predictive methods, experimental testing, and a postmarketing surveillance based on traceability.

The testing of GM products for suspected allergens can be done by an IgE test with serum from sensitive individuals (see, e.g., Herian et al., 1990). However, there is also a need to test products where genes have been inserted from sources not known to be allergenic. Astwood et al. (1996) have developed a

method. Stability of a protein or protein fragments to digestion in simulated gastric fluid (SGF) may be used to assess the potential allergenicity of a protein.

It is worth mentioning here three supposed safety concerns that have been given wide publicity but are in fact urban myths. These are the L-tryptophan story, the brazil nut allergen story, and the events surrounding Arpad Pusztai and his potato experiment.

The L-tryptophan story A frequently repeated account, quoted as established fact in a key debate about GM in the U.K. House of Commons in February 1999, alleges GM as the cause of the disease that caused 1500 illnesses and 37 deaths in the U.S. in 1989. The story refers to the so-called eosinophiliamyalgia syndrome (EMS) associated with some dietary supplements containing the amino acid L-tryptophan.

The illnesses and death did occur, but the rest of the story is untrue. In reality, extensive investigation traced the cause to an impurity in L-tryptophan made by just one of its several chemical manufacturers, all in Japan. The culprit was Showa Denko KK of Tokyo (the fourth-largest chemical manufacturer in Japan, which had some 80% of the market for L-tryptophan).

L-Tryptophan is manufactured by a fermentation that also results in the formation of a number of secondary substances. To produce L-tryptophan of a purity necessary for human ingestion, the fermentation product mixture has to go through purification processes to remove impurities, by-products, and cellular debris, including treatment with activated carbon and reverse osmosis.

Investigation of the records of Showa Denko KK showed that in the critical period (December 1988 to June 1989) they made a number of simultaneous changes to the manufacturing protocols . One of these was the use of the fermentation organism *Bacillus amyloliquefaciens* that had been genetically altered to increase the production of L-tryptophan. But this was accompanied by the partial bypassing of the reverse osmosis purification procedure and a halving of the amount of activated carbon used, thus failing to carry out the purification effectively. Subsequent research showed that in consequence the procedure left behind some 60 impurities and also found significant correlation between the development of EMS and the reduction of the activated charcoal.

Sporadic cases of EMS have occurred linked with L-tryptophan made with the conventional (non-GM) organism, demonstrating that GM was not involved but suggesting occasional inadequate purification.

There have been several attempts to explain the precise mechanism by which the syndrome occurred. One involves a residual impurity, 1,1′-ethylidenebis-[tryptophan] (EBT), which then broke down to give 1-methyl-l,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (MTCA), a substance that was thought to have been involved in the EMS syndrome. Another suggests that it was the result of a reaction between two (or more) impurities. Like so many food poisoning outbreaks investigated after the event, the exact mechanism is unlikely

now to be conclusively proved, but it was nothing to do with GM. Thus the "tryptophan" story was not a consequence of GM or of tryptophan itself, but an impurity or impurities left in as a result of short-cutting by a particular chemical manufacturer.

The brazil nut allergen story With the currently much greater recognition of food allergens as a food safety issue, the possible introduction of allergenicity by genetic modification is a concern; and the apocryphal story of "people made sick by a brazil nut gene transferred into soy" has become a widely believed urban myth.

In fact, such a product never came on the market, and nobody ever ate any such product. Soy protein is deficient in methionine, and a seed company, Pioneer Hi-Bred, wanted to investigate the possibility of producing a soybean with increased methionine content, by transferring a brazil nut gene to soy. With any research involving any gene transfer, it is routine standard procedure to investigate whether any allergenicity could be thereby transferred. In this instance, many people are allergic (some very seriously so) to soy itself, but it was important to investigate whether such a transfer would make the resulting soy allergenic also to people who were allergic to brazil nuts. The research was carried out at the University of Nebraska, a leading center for allergenicity research. Perhaps not surprisingly, the researchers found that brazil nut allergenicity was transferred to the experimental material. Pioneer Hi-Bred announced that the research project was discontinued, and the results were published in a peer-reviewed journal (Nordlee et al., 1995).

The Pusztai potato experiment This has received considerable publicity. It relates to the purported adverse effects on rats of GM potatoes in which lectins had been inserted and the associated TV program and media interviews given by Dr. Pusztai. Lectins, which are complex plant proteins, appear to act as pest deterrents in plants, and lectin insertion into a crop plant by GM has been investigated as a means of enhancing pest resistance.

The story has been greatly confused by contradictory reports as to exactly what happened and as to the supposed ill-treatment of the researcher concerned—mostly culled from the media and claims by Pusztai himself and activists keen to exploit the situation. Fortunately, a first-hand history is now available. In March/April 1999 the United Kingdom (U.K.) House of Commons Parliamentary Select Committee on Science and Technology investigated GM, and on Monday, March 8, 1999 they held a hearing at which Dr. Pusztai and his friend Dr. Stanley Ewen and Professor Philip James, Director, and Dr. Andrew Chesson, Head, of the Nutritional Chemistry Unit of the Rowett Research Institute (RRI), all appeared and were examined.

The written statement submitted by the RRI gives a first-hand historical account (and, incidentally, is sympathetic to Pusztai and disposes of the various myths that have been put around about him and his treatment). For a verbatim account of all the evidence submitted by RRI and by Pusztai himself, and for

the Select Committee's conclusions, see U.K. House of Commons, Select Committee on Science and Technology, *http://www.publications.parliament.uk/pa/cm199899/cmselect/cmsctech/286/9030801.htm* and *http://www.publications.parliament.uk/pa/cm199899/cmselect/cmsctech/286/28602.htm*.

The study that caused the controversy has since been reviewed twice by the Audit Committee, by the Royal Society, by the U.K. Advisory Committee on Novel Foods and Processes (ACNFP), by the U.K. Committee on Toxicity, and by the Nuffield Council on Bioethics. All found the experiment flawed, poorly designed, and incapable of leading to meaningful conclusions. There is, however, agreement that adequate *in vivo* tests need to be developed before a new GM crop with a lectin insert is released for either human or animal consumption.

As the RRI Audit Committee stated:

> "The research was preliminary and not part of the process of testing specifically genetically modified crops destined for commercial use.... However, the purpose of the research remains valid. It was part of a larger programme designed to identify possible candidate genes, and their implications, for possible future use in the genetic modification of crops to enhance the crops' resistance to pests."

Although investigations into this case have shown that the problems were not directly related to the genetic modification as originally claimed (and still perpetuated by some), they emphasize that a greater awareness of the possible areas of concern is needed when assessing the safety of GM foods.

Environmental

Early regulatory controls over the release of GM crops were, of necessity, developed on an ad hoc basis because of the virtual absence in the 1980s of quantitative data on the ability of GM organisms to survive in the environment. However, in recent years evidence has accumulated so that regulations and guidelines can now be developed on a more rational basis, but there is a continuing need for studies on the possible risks of GM crops to the agricultural environment. In the last few years, the U.K. government has responded to this need by funding over 20 projects in this area at a cost of over £4 million. Clearly, regulations will need continuous revision and updating as new data become available.

In the EU Member States, any release of GMOs into the environment has been governed by national regulations implementing EU Directive 90/220/EEC (implemented in the U.K. as part of the Environment Protection Act). In the U.K., at present no GM crops are being grown commercially. An experimental release, such as a field trial of a food crop, requires consent from the government. Applications for consent must include a considerable volume of data and a detailed assessment of the risk of harm to human health and the environment. If a risk is identified or there is some uncertainty about the level

of risk, the applicant may propose measures to manage or eliminate the risk. The applications are scrutinized by the Advisory Committee on Releases into the Environment (ACRE), a group of independent experts who advise the government on whether consent should be given and whether extra conditions should be imposed before consent is given. All releases are advertised locally, and details are made available via a Public Register. Release sites are subject to inspection by the Health and Safety Inspectorate, and those making the release are required to report any incidents that may occur during and after the completion of the trials. On the one hand, this openness and transparency is admirable, but on the other hand the public information has been seized on by organized gangs of terrorist activists who invade and destroy the trials.

After agreement between the Council of Ministers and the European Parliament, the European Commission at its meeting in July 2000 proposed a strategy for a revised Directive 90/220 (see below).

The objective is to protect health and the environment when

- Carrying out the deliberate release into the environment of GMOs for any purposes other than placing on the market within the European Community
- Placing on the market GMOs as, or in, products within the European Community

The data required (other than for higher plants) are information concerning the

1. GMO characteristics of donor and recipient (or, where appropriate, parental) organisms and vector characteristics of modified organism
2. Conditions of release and the receiving environment
3. Interactions between the GMO and the environment characteristics affecting survival, multiplication, and dispersal interactions with the environment
4. Monitoring, control, waste treatment and emergency response plans.

The data required for GM higher plants are information relating to the

1. Recipient and/or parental plant
2. Specific genetic modification
3. GM plant
4. Site of release
5. Manner of release
6. Control, monitoring, post-release, and waste treatment plans

Since 1987, more than 25,000 field trials of GM plants have been carried out in 45 countries without adverse environmental consequences. Furthermore, the rate of field-testing has increased rapidly, especially in the U.S., where the

number of trials has doubled each year since 1987. In terms of field releases, the EU lags well behind North America. More than 70% of field trials were conducted in the U.S. and Canada followed in descending order by Europe, Latin America, and Asia, with very few trials conducted in Africa. These trials represent considerable accumulated evidence in support of a favorable safety and environmental record for the new gene technology.

However, the relevance of environmental data obtained from small field trials to large-scale sowing on several million acres of land has been questioned. Toward the end of the 1990s, more than 80 GM variants of several food crops including maize, rapeseed, and soybean, had received regulatory approval in the U.S. and Canada for large-scale sowing and use in foods. It has been estimated that in 2001 52.6 million hectares (130 million acres) of land were planted worldwide with transgenic crops. By far the largest acreage of land planted with GM crops has been in the U.S. and Argentina, although plantings in China and Canada have also been significant.

Past experience with introductions of new species to environments where they are not naturally present has shown that potential problems may take several generations to manifest themselves. Possible cross-pollination from GM crops to non-GM crops is of concern to organic farmers, who fear that, if it occurs, their produce could no longer be said to be "organic" and to those who wish to have the right to choose non-GM foods. There is also concern that traits such as herbicide resistance may spread to weeds and that the problem of insect resistance may be aggravated. It has been suggested that the adoption of insect-resistant crops by farmers worldwide may lead to the extinction of certain insect species (e.g., Lepidoptera), thereby reducing the biodiversity of the planet. Environmental regulation is difficult to enforce when there are no clear standards against which the performance of a product can be measured (e.g., how many birds, butterflies, and wild flowers should there be on a farm and to what extent can their numbers be affected before the environment is harmed?).

Ethical

Mankind has been manipulating nature from the very start of agriculture. Moreover, nature itself carries out random GM through accidental mutation. All present-day food plants (and animals) are GM, most by traditional or accidental methods. For this reason we cannot really talk about non-GM foods—we should speak of "traditional GM" to distinguish it from "new GM." Whichever method is used, the same risk analysis and risk assessment should be (and are) carried out. As regards within-species GM there is no fundamental difference between traditional GM and modern GM except that the latter is more precise, more capable of providing desired characteristics unaccompanied by disadvantageous ones, and more rapid. "Trans-species GM," however, produces results that could not be achieved by traditional methods, and this can give rise to perceived religious dietary concerns or fears of cannibalism or aesthetic concerns or worries about "interfering with nature."

The officially appointed U.K. Committee on the Ethics of Genetic Modification and Food Use, chaired by the Rev. John Polkinghorne, carried out a wide public consultation and issued a report in September 1993 on all of the moral and ethical issues involved. This was accepted by the U.K. government and welcomed by the Institute of Food Science and Technology. The Committee found that the concerns were misconceptions rather than of real substance, arising from lack of knowledge, outside the scientific community, of just what was involved.

Because any gene extracted from one species for copying into another is not itself inserted but is copied in the laboratory and diluted millions of times before a single gene is transferred, the chance that the original gene would be found are much less than the chance of recovering a particular drop of water from all the oceans of the world. If this were widely understood, fears of cannibalism or of contravening religious food taboos would be seen to be unwarranted. Unfortunately, this fact does not make good media copy, whereas sensational "cannibalism" scare stories do.

The Polkinghorne Committee's conclusions were:

- Genetic modification of food and medicines is here to stay. It is not something to be stopped, and it would not be ethically right or necessary that it should be;
- There is no reason for any ban on the use of copy genes of human origin or from animals subject to dietary restrictions, but scientists working in this field should be discouraged from using such genes where alternatives would be equally effective;
- Products containing such copy genes should be labeled to enable consumers to make informed choices;
- Government and industry should look for ways of explaining genetic modification to the general public.

Because what is transferred to the "host" is not the DNA direct from the donor but a laboratory copy of it—in familiar terms, it is cut-copy (billions of times over)-and-paste rather than cut-and-paste—the perceived concerns are mistaken, but no less real for that.

As a matter of interest that not many people realize, we are in fact all cannibals—everyone is continuously shedding skin cells, which of course contain their DNA. We are all ingesting the DNA of people around us, or who, for example, have previously been in the same room or public transport.

Reference has already been made to the more recent Report of the Nuffield Council on Bioethics, which covers all the ethical considerations in great depth.

In the U.K., English Nature (the U.K. government's statutory adviser on wildlife and natural features) monitors developments that may affect wildlife and advises on how any damaging effects might be avoided. Its environmental concerns about GM of crops are summarized as a series of questions and answers in its press briefing of 21 June 1999, covering issues such as:

- Are GMOs harmful to the environment?
- What is English Nature's position on commercial growing of GM crops?
- Who is doing research and how long will it take?
- Won't GM crops reduce the amount of pesticides and therefore benefit wildlife?
- Will genes from GM crops spread to wild plants?
- These crops are widely grown in the U.S. What is the effect on wildlife there?
- Is the regulatory regime for GMOs adequate?
- Should there be statutory control of growing GM crops?

In seeking action, English Nature is:

- Pressing government and the biotechnology industry for a delay in commercial introduction of genetically modified herbicide-tolerant (GMHT) and insect-resistant (IR) crops until research is completed and results assimilated,
- Calling for more ecological research to be started now, and
- Working to change the regulatory system to include much greater consideration of the potential effects of GM crops on wildlife

and it believes that only statutory control of how GM crops are grown will ensure that wildlife is protected.

Socio-economic

Much of the vocal antagonism to GM expressed by its opponents appears to consist of antipathy to large companies engaged in GM and to the socio-economic system that allows large companies to exist and thrive. This is, however, not specific to GM, for similar antipathy is expressed about other products and activities and the existence of large companies.

One recent socio-economic concern has been about the potential for misuse of the so-called terminator genes that prevent seeds from germinating. Although patents exist for terminator technology, it is not yet available commercially. There are fears that large corporations might use such genes in all their GM crops to prevent farmers from storing seed and that plants that produce barren seed could make life more difficult for poor farmers in the developing world. However, farmers would only buy these seeds if they found an overall advantage in doing so; otherwise, they could continue to grow conventional cultivars and save the seed in the traditional way. Furthermore, if cross-pollination occurs, GM plants with terminator genes could transfer their sterility to other plants grown nearby. However, on the positive side, terminator technology could ensure that GM plants do not themselves become weeds.

Another concern involves the general question of patents in relation to GM and, more particularly, whether genes can or should be patentable. By analogy with computer language, the procedure of inserting a gene into an organism is not "cut-and-paste" but "cut-copy (billions of times over)-and-paste." The laboratory-generated copies from that procedure are in every way exact copies of the copied original but are not the original. Precise details of patent law vary from country to country, but in principle, patents are intended to protect inventions and to give the inventor monopoly for a limited time to benefit from the invention. Whether it is the original gene or DNA fragment, or a lab-generated exact copy, these are not "inventions" and ought not to be patentable. A gene is a pre-existing thing, and identification of a gene and its function is a "discovery" rather than an "invention." However, an invention is often a novel combination of pre-existing things, and it is not those things but the combination of them that may be accepted as an invention and therefore patentable. Generally, patent law requires novelty and also that the combination and its claimed benefits would not be obvious to those "skilled in the art." If these principles are valid, then someone inventing a novel combination involving a gene can patent the combination, but cannot use patent law to prevent someone else from using that gene for other purposes (or even patenting a different combination involving that gene).

Information

Information (and particularly label information) about the GM status of foods or ingredients is a topic with polarized views that do not lend themselves to an intermediate position. On the one hand, it is argued that if a food or ingredient has been approved as "safe," the method of production is irrelevant and need not be stated. On the other hand, it is argued that provision of that information is necessary for informed consumer choice, including the consumer who wishes to choose GM and the consumer who wishes to avoid GM for whatever reason—even an irrational reason or whim.

As seen below, the EU Commission adopts the latter position whereas the U.S. FDA adopts the former.

Potential Benefits Versus Concerns

There are two ways of dealing with developments with associated problems and uncertainties. One is to reject or ban the developments. The other is to address and solve the problems and to accept that there are no certainties in any aspect of life. Fortunately, in the long run mankind has generally adopted the second course; otherwise, we would still be living in the Stone Age. Looking at more recent times, there would be no electricity; the first passenger flight would not have taken place, so there would be no air travel; the first surgical operation would never have been carried out so there would be no surgery; the first anesthesia would never have been used, so there would be no anesthetics (it is

worth recalling that the medical profession of the day prevented Queen Victoria from having anesthesia with the birth of her first seven children ("not natural, not proved safe, not sufficient testing, what about the long term effects?")—the list could be endlessly extended. Exactly the same arguments were used in the early decades of the twentieth century to try to prevent the legalization of milk pasteurization. We can be thankful that it was eventually legalized, and over the last seven decades has saved untold numbers of lives that would otherwise have continued to be lost to milk-borne tuberculosis—second only to clean water as the most important public health measure ever adopted.

REGULATORY, INDUSTRIAL, AND INTERNATIONAL IMPLICATIONS

Factors Affecting EU Approach to Regulating GM

In the EU, the general legislative approach throughout its existence has been that if anything can conceivably be regulated, regulate it. So the EU built a comprehensive system and machinery for considering and approving (or otherwise) applications for approval of specific lines of GMOs and for controlling the release of GMOs into the environment. Likewise, it adopted from the outset the principle of informed consumer choice, which has led to increasingly comprehensive measures, initially voluntary and then by legislation, to provide distinctive labeling of GM foods. In this, as in other aspects, the nature and extent of the regulatory provisions has been influenced by the governments of the Member States, reflecting a public opinion influenced by the factors discussed below. Some observers, mainly in the U.S., conclude that the driving force is protectionism and a not very well hidden trade barrier. Of course, every government wants to protect its own industry and will ingeniously find ways of creating trade barriers if it can, and no doubt the EU Member States' governments are no different in that respect. However, in this instance the dominant driving force is something quite different—the fact that the Commission, the European Parliament, and European retailers and manufacturers are all highly sensitive to an extremely strong anti-GM attitude of European consumers, who don't care about protectionism any more than the anti-GM activist organizations that deliberately and skillfully engineered that consumer attitude.

Differences from the U.S. Regulatory Approach

In contrast, in the U.S. the FDA has, despite increasing pressure, refused to require distinctive labeling of GM materials, on the grounds that it has determined that they are substantially equivalent to the non-GM versions. That being so, their method of production is irrelevant. However, note that Dan Glickman, U.S. Agriculture Secretary in the previous Administration, said at the time that "if the consumers demand labeling—even if we think it doesn't

convey a lot of good stuff—we're probably going to end up with a labeling scheme." Subsequently, the FDA has held a number of public hearings on the subject.

The absence of distinctive labeling in the U.S. means that most U.S. consumers have not had their attention drawn to the presence of GM foods or ingredients (although in the past period this situation has been gradually changing). Most of those who have been aware of it have evidently been reassured by approval on the part of both the FDA and the EPA. This has, in turn, has been one of the factors making U.S. consumers much less susceptible (thus far) than European consumers to the kind of activist campaign that has dramatically affected public opinion in the EU and especially in the U.K.

Another major difference is that, in the definition of substantial equivalence still used in many countries including the U.S. and Canada, the presence of degraded novel DNA or protein does not preclude a GM food from being considered substantially equivalent to a conventional food. However, in Europe the concept of substantial equivalence was redefined in December 1997. Only highly processed foods derived from GM crops, such as highly refined oil, white sugar, and starch hydrolysates, are considered substantially equivalent to their conventional counterparts on the grounds that neither DNA nor protein would be expected to be present after the processing that these foods receive. All other ingredients derived from GM crops, such as flour and protein extracts, require a full safety evaluation, as they may contain novel DNA and/or protein in either intact or degraded form. Thus lecithin from GM soybean, used extensively as an emulsifier in many processed foods, would be considered substantially equivalent to conventional lecithin in North America but not in the U.K. and the rest of the EU.

CURRENT AND FUTURE IMPLICATIONS

Factors Affecting EU Public Opinion

Public opinion on GM in the EU, and particularly the U.K., changed dramatically between January and May 1999. This did not just happen. It was "engineered"—skillfully planned by a consortium of "fundamentalist" anti-GM organizations, and brilliantly organized and executed. The plan was first spotted on one of the complex network of listservs operated by those groups—and for those who monitor those listservs it is a real eye-opener how effectively they use the Internet not merely to exchange information but to plot and plan activities such as intimidating manufacturing companies and retailers, marches, demonstrations, rioting, uprooting of experimental plants, destruction of property. The plan to focus on Europe was hatched at a meeting hosted by the Green Parties, with the participation of "the usual suspects" in St, Louis, Missouri, in July 1998. It was planned to be launched in January 1999 to coincide with the World Summit on the Environment in Columbia.

Reasons that are often quoted for the turnaround of European and especially U.K. public opinion are in fact not the reasons for the turnaround but rather the underlying factors that made the public susceptible to being manipulated by a intensive propaganda campaign.

The main factor that made the public susceptible was neophobia—the fear of the new—in combination with the following factors:

1. In Europe there was voluntary labeling at first and then legislation provided for distinctive labeling of GM foods and ingredients, so that many consumers were aware of eating GM foods;
2. The public, as a result of BSE and various food scares, was and is distrustful of governments, wary if not distrustful of science and scientists, and susceptible to suggestions of new food scares;
3. The "first generation" of GM foods were those that were relatively easy to produce and that would commend themselves to the biotech companies' immediate "customers," farmers, thus enabling the companies that developed them to obtain a rapid commercial return on their research investment; however, the products did not offer consumers a readily perceivable benefit (reduced pesticide and herbicide use is in fact a benefit, but not readily perceivable to the consumer at the point of purchase).

None of the factors changed significantly between January and May 1999, yet public attitude was dramatically changed.

The plan, capitalizing on the above factors, effectively utilized the Internet and was amplified by the media, highlighting problems and uncertainties, some real, some pure speculation, some spin-doctored, and some just urban myths, combined with vandalizing of experimental crop trials and intimidation and threats to companies and major retailers (picketing, organized bombarding of companies and named individuals therein with letters and phone calls, activists in white "space suit" simulated protective clothing invading supermarket aisles). The purpose was to get GM legally banned; if that failed, the fall-back aim was to scare the public and intimidate industry so that the result would be the virtual equivalent of a ban.

In these circumstances is hardly surprising that by mid-1999 the U.K. public became turned against GM, and that, reacting to their customers' views and "pressure" from these organizations, major retailers and manufacturers decided to exclude GM foods and ingredients.

The first to succumb was Sainsbury. (Actually, Iceland announced prohibition of GM much earlier, but not as a result of this propaganda—the then-chairman of Iceland was personally anti-GM.) Other major supermarket groups quickly followed Sainsbury, and each tried to outdo the others in advertising that they were squeakier-clean than the others.

It is difficult to blame them. Even apart from the threats and intimidation, their boards had a responsibility to look at their respective bottom lines, pro-

vided that food safety was not thereby compromised. Nevertheless, when these major retailers, followed by major manufacturers like Unilever and Nestle, made their announcements, headlined by the media, that gave a further message to the public that GM foods and ingredients were "bad."

Where does distinctive labeling fit into this picture? The attitude of the EU and its Member States (and indeed of IFST) toward distinctive labeling has been that the principle of informed consumer choice (i.e., that a consumer is given on the label sufficient information on which to make a decision, for whatever reason, on whether or not to purchase that product) takes precedence over the valid arguments used by the FDA [and The Institute of Food Techologists (IFT)] to justify the lack of need for distinctive labeling.

However, note the paradox—distinctive labeling made the mass of consumers aware that they had been consuming GM foods, bringing neophobia into play and helping to make the public susceptible to the anti-GM propaganda campaign. So distinctive labeling, introduced in pursuance of informed consumer choice, has substantially contributed in Europe to destruction of such choice, as it is now virtually impossible to purchase a GM food.

Since mid-1999, that same coalition of groups has been carrying out targeting of consumers, intimidation of manufacturers, and vandalizing of experimental crop trials in the U.S. The process was greatly intensified in 2001, as a result of a meeting of the top planners of the opposition at Blue Mountain Lake, New Jersey, and has been widened by a large number of national and local groups, many masquerading under the cloak of "environmental protection."

An example of "environmental protection" by the self-styled "Earth Liberation Front" was setting fire to Catherine Ives's Agricultural Biotechnology Sustainability Project laboratory and office on the Michigan State University campus on New Year's Day 2000. In 2001, similar acts of mindless terrorist firebombing have been perpetrated at the University of Oregon and the Center for Urban Horticulture at Washington University, destroying the office and laboratory of Prof. Toby Bradshaw, presumably because of his basic research into the genetics of fast-growing hybrid poplars. However, the action also destroyed many irreplaceable books, historical documents, and photographs belonging to the faculty, staff, students, and volunteers who have worked there for the past 20 years. In addition, it severely damaged research efforts aimed at conserving endangered plant species, ecological restoration of wetlands, creating environmentally sound urban landscapes and gardens, and discovering the patterns of plant regeneration after the eruption of Mount St. Helens. Outreach programs such as vegetable gardening classes for low-income families were also affected.

It is interesting to note that the anti-GM campaign has, more recently, begun to be extended to similar intensive targeting of consumers, intimidation of manufacturers, and vandalizing of experimental crop trials in the U.S.

This will take much longer than the five months that sufficed in Europe. Why? Because, in the continuing absence of distinctive labeling, the majority of

U.S. consumers are not aware of eating GM foods, and most of those who are aware are also aware that the FDA, the USDA, and the EPA have approved them. This explains why the anti-GM coalition is focusing so heavily on demands for mandatory distinctive labeling in the U.S.

Detection and Analysis of GM Materials

Effective regulatory control over GMOs is crucially dependent on the existence of reliable analytical methods for detection and identification of specific genes and for quantification where, for example, a threshold limit is set. Until the mid-1990s, in the absence of reliable analytical methods, it was impossible to determine whether a food or food ingredient had been genetically modified. More recently, however, new methods have been developed based on the polymerase chain reaction (PCR)—a method for several-million-fold amplification *in vitro* of specific DNA sequences known as nucleotides or "primers." Compared with the millions of bases in the DNA in an organism, and the 100 bases in an average gene, it has been discovered that primers as short as 21–24 bases in length can act as a unique "fingerprint" for a gene.

PCR-based assays involve the following three basic steps:

1. DNA extraction and purification
2. PCR amplification of DNA
3. Gel electrophoretic analysis of PCR reaction products

The EU Institute for Health and Consumer Protection have started a series of Training Courses on "The Analysis of Food Samples for the Presence of Genetically Modified Organisms". The courses are intended to teach molecular detection techniques to laboratory personnel that have a good level of analytical knowledge, but that have no or little expertise in this specific domain.

Although none of these new techniques has been validated internationally as of July 2001, many laboratories are already using them routinely to meet the growing demand for detection and labeling of foods containing GM ingredients or components and for Identity Preserved (IP) certification. It is expected that validation and harmonization of methodologies will occur in the near future.

EU Directives and Regulations Concerning GM

Relevant regulatory information has been given under various headings in the foregoing text but, for convenience, is collected under this heading.

Regulations on novel foods and novel food ingredients The principal legislation is EU Regulation No. 258/97 of the European Parliament and of the Council of 27 January 1997 concerning novel foods and novel food ingredients. (OJ L43, 14.2.97, pp 1–7).

The Novel Foods Regulation applies to the placing on the market within the EU of foods and food ingredients that have not previously been used for

human consumption to a significant degree and that fall into the following categories:

- Foods and food ingredients containing or consisting of GMOs within the meaning of Directive 90/220/EEC (see below)
- Foods and food ingredients produced from, but not containing, GMOs foods and food ingredients with a new or intentionally modified primary molecular structure
- Foods and food ingredients consisting or isolated from microorganisms, fungi, or algae
- Foods and food ingredients consisting of or isolated from plants and food ingredients isolated from animals, except for foods and food ingredients obtained by traditional propagating or breeding practices and having a history of safe food use
- Foods and food ingredients to which has been applied a production process not currently used, where that process gives rise to significant changes in the composition or structure of the foods or food ingredients that affect their nutritional value, metabolism, or level of undesirable substances.

The novel foods and food ingredients must not present a danger for the consumer, mislead the consumer, or differ from the foods or food ingredients that they are intended to replace to such an extent that their normal consumption would be nutritionally disadvantageous for the consumer. Derogations are available for foods and food ingredients that according to expert scientific opinion are substantially equivalent to existing foods in respect of their composition, nutritional value, metabolism, intended use, and level of undesirable substances contained therein.

These particular regulations did not apply to GM-derived food additives, flavorings, and extraction solvents. On this basis soy lecithin derived from GM soy would not have required an indication that it is derived from GM sources (but see below).

However, proposed amendments to Directives 95/31/EC (sweeteners), 95/45/EC (colors), and 96/77/EC (miscellaneous additives) have been under discussion that would alter purity criteria so that:

> "Food additives that are prepared by production methods or starting materials significantly different from those included in the evaluation of the Scientific Committee on Food (SCF), shall be subject to a new safety evaluation by the SCF. If starting material is or is derived from a GMO, it shall always be considered to be a significantly different source."

The EU Novel Foods Regulation also specifies the assessment procedures that must be carried out before a novel food can be placed on the market and makes provision for objections to be raised by interested parties. A procedure for reassessment of novel foods is included if they subsequently appear to be

endangering human health and for a review of the regulations within 5 years from implementation in any case.

The Novel Foods Regulation has been in force for more than 4 years. There have been relatively few applications for full approval of GM food sources or ingredients, some of them by the "substantial equivalence" notification route.

Releases into the environment Council Directive 90/220/EEC of 23 April 1990 controlled the deliberate release into the environment of genetically modified organisms [OJ L117, 8 May 1990, p. 15; amended by Commission Directive 94/15/EC (OJ L103, 2214/94, p. 20) and Commission Directive 97/35/EC (OJ L169, 27/6/97, p. 72)].

Under this Directive, a manufacturer or importer must submit a notification to the national competent body of a Member State where the product is to be first placed on the market before undertaking a deliberate release into the environment of a GMO or placing it on the market.

The notification should contain a technical dossier of information including a full risk assessment. The Member State that receives the notification examines the dossier, and in the case of a negative evaluation the notification is rejected.

In the case of a favorable opinion, the dossier is forwarded to the European Commission and all the competent authorities of the other Member States, who have the right to raise objections. If there are no objections, the competent authority that carried out the original evaluation grants the consent for the placing on the market of the product, which may then be placed on the market throughout the European Union.

In case of objections, a decision must be taken at Community level. The Commission seeks the opinion of its Scientific Committees before drafting a Decision, which is put forward to the Regulatory Committee composed of representatives of Member States for favorable opinion. Otherwise, a proposal is put forward to the Council, which decides by qualified majority. If no Council decision is taken within 3 months the Commission takes the decision. In any case, in accordance with Directive 90/220/EEC, the Commission is ultimately obliged to adopt measures to authorize a GMO if the application fulfils current EU legislation and if it is not rejected by unanimity in the Council or if the Council fails to act within the fixed deadline.

GMOs must undergo a scientific assessment of risks to human health and the environment before receiving Community authorization. Risk assessments are performed on a case-by-case basis.

The safety assessment takes into account of the following:

- How the GM was developed—including the source of the genes to be introduced and detailed molecular analysis of the modified plant and organism. The process can be likened to that of "cutting" and "pasting" where pieces of DNA are cut out of the donor organism and pasted into a recipient organism. It is necessary to establish which genes are incorporated and where in the recipient genome they are incorporated.

- Risk associated with the gene products in the plant, mainly proteins. It is necessary to know that the gene does not encode for a protein that is toxic to humans or does not produce an allergic response. It must also be established that insertion of the gene(s) does not result in unexpected effects.
- Investigation of the possibility that the inserted gene may be transferred to bacteria. This has particular relevance to the possible transfer of antibiotic resistance genes.

Council Directive 90/220/EEC has now been superseded by Directive 2001/18/EC providing for deliberate release of GMOs into the environment Meanwhile, at a Commission meeting in July 2000, a strategy was proposed for relaunching the authorization procedure for GMOs on the basis of a reinforced framework for approval under a revised Directive 90/220/EEC after agreement between the Council and the European Parliament.

It includes the following:

- Anticipating the key provisions (labeling, traceability, monitoring etc) of the revised Directive 90/220/EEC before they are transposed in all Member States based on legally enforceable voluntary commitments. The new requirements will be incorporated into the individual authorizations of GMO products granted on the basis of the existing Directive 90/220/EEC.
- A comprehensive set of labeling provisions in the food sector that would cover GMOs and products derived from GMOs
- An initiative on a traceability system for GMOs and possibly products derived from GMOs
- Filling in the gaps in current legislation concerning GMOs

In November 2000, the Commission issued Working Document ENV/620/2000 setting out detailed proposals.

Containment EU Council Directive 90/219/EEC on the contained use of genetically modified microorganisms (OJ L117, 8 May 1990, pp. 1–14), as amended by Council Directive 98/811EC of 26/10/98 (OJ L330, 5 December 1998, p. 13), which provides the circumstances and conditions under which GMOs (including fermentation organisms) require consent for contained use, is administered in the U.K. by the Department of Food, Environment, and Rural Affairs (DEFRA) and implemented in the U.K. by:

- The Environmental Protection Act 1990, Part VI, Genetically Modified Organisms, Sections 106–127. Section 106 states that this Part (i.e., Part VI) has effect for preventing or minimizing any damage to the environment that may arise from the escape or release from human control of genetically modified organisms.

- The Genetically Modified Organisms (Risk Assessment) (Records and Exemptions) Regulations 1996 (SI 1996/1106) restricts the import and acquisition of GMOs under Section 108 (1)(a) of this Act.
- The Genetically Modified Organisms (Contained Use) Regulations 1992 (SI 1992/3217)
- [The Genetically Modified Organisms (Contained Use) Regulations 1993—now revoked]
- The Genetically Modified Organisms (Contained Use) (Amendment) Regulations 1996 (SI 1996/967)
- The Genetically Modified Organisms (Contained Use) (Amendment) Regulations 1996 (SI 1998/1548)

Labeling Before May 1997, labeling of GM foods in many countries, including the U.K., was not explicitly mandatory. Nevertheless, some European food manufacturers and retailers labeled GM foods on a voluntary basis (e.g., the Co-op's vegetarian cheese prepared with GM chymosin and Sainsbury's and Safeway's GM tomato paste) to allow consumers to exercise choice and to gain consumer confidence. Labeling guidelines developed by a number of bodies including the independent Food Advisory Committee in 1993 (revised in 1996) and the Institute of Grocery Distribution in 1997. These guidelines took into account the need for labeling of novel foods that contain material (e.g., allergens) that may have implications for the health of some sections of the population (e.g., infants or the elderly) as well as those that contain "ethically sensitive genes." The latter include foods that contain copy genes originally derived from humans or from animals that are the subject of religious dietary restrictions (e.g., pig genes for Muslims) or any animal genes for vegetarians. Much of the provision on ethically sensitive genes has been based on the findings of the U.K. Polkinghorne Committee, which reported on the ethics of genetic modification in 1993.

On May 15, 1997, the EU Novel Foods Regulation (258/97) was made, controlling the placing on the market and making the labeling of GM foods or foods obtained from GMOs mandatory in the European Union if, on the basis of a scientific assessment, they were judged not to be substantially equivalent to an existing food (for a definition of substantial equivalence, see pp. 765–6). Article 8 of the Novel Foods Regulation requires foods and food ingredients containing or consisting of GMOs and foods and food ingredients produced from (but not containing) GMOs to be labeled so as to inform consumers of any characteristic or property that makes the food or food ingredient different from an equivalent existing food or food ingredient. Not only must the modified characteristic or property be identified, the method by which it was obtained must be indicated. The regulation allowed voluntary labeling to indicate the absence of any genetic material.

However, specific lines of GM soy and GM maize approved under the Deliberate Release Directive 90/220 and consumed to a significant degree

before the Novel Foods Regulation came into effect on May 15, 1997, were therefore outside the scope of that Regulation.

To deal with that situation, on November 1, 1997 Commission Regulation 1813/97 was adopted, which made food ingredients from those crops subject to the same distinctive labeling provisions as those contained in the Novel Foods Regulation. This regulation also stated that detailed Community Rules on labeling would be adopted as soon as possible in accordance with the requirements of Article 8 of Regulation 258/97. In line with this provision, Council Regulation No 1139/98 (OJ L159, 3/6/98, p. 4) came into effect on October 1, 1998. As later amended by Regulation 49/2000, it requires that where a food consists of more than one ingredient, the words "produced from genetically modified soya" or "produced from genetically modified maize," as appropriate, shall appear in the list of ingredients. This wording can be shortened to "genetically modified" where an ingredient is already listed as being produced from soya or maize or where it is used as a footnote, linked by an asterisk to "soya*" or "maize*." This regulation applies to foods delivered as such to the final consumer.

EU Regulation 50/2000 applies similar requirements to the labeling of GM derived additives and flavorings but extends beyond GM soy or maize to any GM source.

In the U.K., this requirement was taken one step further in early 1999 by the announcement that labeling of GM soy and maize will be required not only for manufactured products but also in restaurants, cafes, delicatessens, and sandwich shops. Since it is not always practically possible for catering establishments to provide labeling at the point of sale, the Food Labelling (Amendment) Regulations 1999. S.I. 1999/747 (UK) allow such establishments to inform customers about GM foods via their staff. The availability of this information must also be indicated on the menu or on a prominent notice. In addition, information must also be made available to customers who place telephone orders for take-away food. The Regulations allowed for a 6-month lead-in time (i.e., to September 1999) to enable reprinting of menus and staff training. The selling of foods containing GM material where this has not been properly declared can now be prosecuted and fined up to £5,000.

Regulation 1139/98 also requires that validated testing methods be established so that the presence or absence of GM materials can be scientifically determined. To deal with adventitious contamination of foods or food ingredients with GM materials, a threshold for detection of genetically modified DNA would be set at or below which foods would not need to be labeled. A negative list of processed foods in which any genetically modified DNA or protein present would have been destroyed is also to be drawn up under the Regulation. Foods may only be exempted from distinctive labeling if they contain less than an agreed threshold level of GM material.

Regulation 49/2000 of January 11, 2000 set the threshold at 1% of a single ingredient food or, in a multi-ingredient food, 1% of each ingredient considered separately, but only if the manufacturer can demonstrate that the ingredient

has been obtained from a non-GM source (but note that this only permits exemption from distinctive labeling for food or ingredients below the threshold; it does not permit such foods to be designated as "GM-free"—however, the EU Commission's program of future work foreshadows the development of a Regulation for the labeling of GM foods). Of course, effective regulatory control in relation to a threshold limit is crucially dependent on the existence of a validated, reliable analytical method for detection, identification, and quantification of specific genes, and as yet (September 2002) no method has been validated by the EU.

The original expectation was that the food components compared should be key nutrients and toxicants rather than tiny fragments of degraded DNA and associated proteins. The Regulation recognized that in some cases it would not be possible to segregate foods that contain genetically modified and conventional produce (e.g., soybeans imported from the U.S.). In such circumstances, the Regulation recognized that providing other information for the consumer (e.g., point-of-sale leaflets) indicating that GMOs may be present fulfilled the labeling obligation.

Enforcement of these measures are carried out by Member States' authorities.

Since July 2000 discussions and work have been proceeding in the Commission, the Council of Ministers, and the European Parliament to provide a comprehensive and stringent regime, replacing the previous piecemeal measures covered in the various pieces of legislation and based on

- A mandatory traceability system for GMOs and possible products derived from GMOs or with the assistance of GMOs
- A comprehensive set of labeling provisions that would cover GMOs and products derived from GMOs or with the assistance of GMOs

After agreement had been reached by the Council of Ministers, on July 25, 2001, the Commission issued a statement:

> "The European Commission adopted today an important legislative package on genetically modified organisms (GMOs) which establishes a sound community system to trace and label GMOs and to regulate the placing on the market and labelling of food and feed products derived from GMOs. The new legislation is intended to provide a trustworthy and environmentally safe approach to GMOs, GM food and GM feed. The package consists of a proposal[1] for traceability and labelling of GMOs and products produced from GMOs and a proposal[2] on regulating GM food and feed. It will require the traceability of GMOs throughout the chain from farm to table and provide consumers with information by labelling all food and feed consisting of, containing or produced from a GMO. It will establish a 'one door—one key' procedure for the authorisation of GMOs for food and feed, including the deliberate release into the environment. This procedure will consist of a single scientific assessment, carried out by the scientific committees of the European Food Authority. The new system as proposed today

> ensures a tight and stringent regulatory framework on the use of GMOs in Europe and closes existing legal gaps whilst addressing legitimate concerns of the economic operators. It meets the requests by Member States governments, the European Parliament and consumer organisations and has been drafted in close dialogue with all stakeholders and Member States. Two further proposals relating to GM seed will be brought forward in autumn. Today's proposals are subject to co-decision with the European Parliament and the Council and should enter into force in 2003 at the latest. The labelling provisions in respect of food and feed will be reviewed after two years of operation."

"Traceability" here means the ability to trace and follow a food, feed, or food-producing animal or substance through all stages from rearing or growing of primary products, through production, manufacture, and distribution up to and including its sale or supply to the final consumer and, in the case of a food containing a GMO, or a food, food ingredient, additive, or flavoring derived from a GMO, an unique code identifier following it from "farm to fork," provision to the authorities of information facilitating the detection and identification of a particular GM product including lodging of a sample of the GMO or its genetic material.

Of course, traceability is highly important for all aspects of product food safety. But for any scheme that wants an effective system for authorization of specific GMOs and labeling distinction between GM and non-GM products, not only analysis but also traceability is a must. However, this is the first time that a proposal has been made to establish mandatory traceability measures. Moreover, it would seem that the new approach will place more emphasis on traceability of heritage than on analysis. The statement includes the explanatory comment

> "In comparison with the labelling system in place today, the proposal on GM food and feed will add the labelling of:
>
> All foods produced from GMOs irrespectively of whether there is DNA or protein of GM origin in the final product
>
> All genetically modified feed."

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CHAPTER 38

FAO/WHO FOOD STANDARDS PROGRAM: CODEX ALIMENTARIUS

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BACKGROUND AND HISTORICAL SIGNIFICANCE

During the mid-1800s, the first attempt to standardize food and food products appeared in Austria and was called the Codex Alimentarius Europeus. The idea behind this attempt was to have a system that could harmonize the food laws existing in Europe. After some time this effort ended, but many years later the idea of creating an international system of food standards was revisited and discussed in many forums. In 1943, during a United Nations conference on food and agriculture held in Hot Springs, Virginia, 44 nations joined together to create an organization that would give governments assistance to develop and review existing standards with three goals in mind. These were to (1) improve the nutritional value of food that had importance in the international market as well as the national market, (2) create systems that would facilitate commerce, and (3) protect the health of the consumer. These discussions were based on concerns raised by escalating international food trade after World War II. Such concerns included the increased use of food additives to preserve food, new pesticide compounds that were being used in agriculture and food storage, and differing food standards in various countries affecting basic food composition and nutritional value. Other basic problems included accurate food labeling, promotion of good food hygiene to reduce or eliminate contamination of foods with insect, rodent, and bird filth, and pathogenic microorganisms.

This conference created an Interim Commission to carry out the conference recommendations, which, in turn, led to the creation of a Food and Agriculture Organization within the United Nations (UN) on October 16, 1945. This organization was the precursor to the Organization for Food and Agriculture (FAO). The UN General Assembly was created one month later; the World

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Health Organization (WHO) was formed several years later. In the early years, FAO and WHO concentrated on general problems of food production and malnutrition, but in the 1950s joint FAO/WHO discussions and activities on food standards, additives, and other aspects of food quality and safety were initiated. During these discussions, member countries emphasized the need for international scientific evaluation mechanisms that could provide them with the best possible science-based advice, with periodic updating to ensure that the new scientific information was always taken into account in their recommendations.

In the 1950s and the 1960s, the member nations of FAO and WHO held extensive discussions about international mechanisms to assist all member countries in improving the quality and safety of domestic food supplies and all food in international commerce.

After an FAO/WHO conference on food additives in the mid-1950s, the joint FAO/WHO Expert Committee of Food Additives (JECFA) was established. The purpose of JECFA was to utilize the services of internationally recognized scientists serving in their individual capacities in expert meetings to evaluate available data on food additives, animal drug residues in foods, and other food contaminants such as mycotoxins, heavy metals, and industrial chemicals. JEFCA makes recommendations regarding chemical contaminants in food (e.g., food additives, animal drug residues, and other contaminants) as well as considering specifications and analytical test methods, acceptable daily intakes, and/or tolerable weekly intakes. JEFCA recommendations have, for many years, been of great value in setting science-based national rules for such compounds in both developing and developed countries. The work of JEFCA has continued unabated over the past 45 years and continues to be a mainstay for member countries and for the Codex Alimentarius Commission (Codex).

In the 1960s, FAO and WHO carried out similar discussions about the use of pesticides in agriculture and health programs and about pesticide residues in foods. From these discussions came another expert assessment body, the joint FAO/WHO Meeting on Pesticide Residues (JMPR), which is a joint meeting of the FAO Panel of Experts on Pesticide Residues in Foods and the Environment and the WHO Core Assessment Group. As with JEFCA, the recommendations of JMPR—on the use of pesticides in agriculture and public health programs, residues in foods, specification and test methods for pesticides and their residues, and acceptable daily intake levels for various pesticides—have been invaluable to member countries and to Codex in setting science-based recommendations for pesticide residues in foods.

In 1962, during a joint meeting between the FAO Conference and the WHO World Health Assembly on food standards and food, Codex was created. It was to be the goal of the Codex to develop worldwide food standards, with the main objectives of protecting the health of the consumer and facilitating international commerce in food.

In 1963, the first meeting of this commission took place; to date, 25 addi-

tional sessions have been held. At present, 165 countries belong to this program, representing about 99% of the world's population. This gives an idea of the importance of the impact of the decisions made there, and it is a fact that many countries have benefited from the recommendations that have been advocated by this group of experts. It is important to note that 70% of the countries that belong to the Commission are developing; it is in these developing countries that the biggest impact of this commission is seen, because these are the countries with the highest production and export levels of raw materials. Thus their participation is encouraged and reinforced, in recognition of the fact that it is necessary to obtain the best benefits for the available resources.

SCIENTIFIC BASIS AND IMPLICATIONS

Unlike JEFCA and JMPR, which were bodies of individual experts serving in their own individual capacities to provide FAO, WHO, and the member countries with recommendations based on current scientific data, Codex was created as an international commission. This means that the members of Codex are governments and they participate in Codex activities representing their own national interests.

The Statues of Codex delineate the purposes of Codex, which are:

- To protect the health of consumers and ensure fair practice in food trade.
- To promote coordination of all food standards work undertaken by international governmental and nongovernmental organizations.
- To prioritize, initiate, and prepare draft standards, finalize these standards, amend standards when necessary, and publish final recommended international standards.

Over the past 40 years, Codex has served as a very effective mechanism for obtaining consensus among its member countries on a wide range of standards for individual food products, food labeling, recommendations on pesticide residue, food additives and food contaminant levels, codes of hygienic practice, and other recommendations.

In carrying out the Codex work for the commission, a number of subcommittees were established to work on general and specific aspects of Codex work. These committees are generally referred as "vertical committees" when they are set to deal with commodity standards—for example, milk and milk products, processed foods and vegetables, cereals, pulses, and legumes. "Horizontal committees" deal with matters such as food labeling, food hygiene, pesticide residues, food additives and contaminants, and Codex general principles. There are also Codex Regional Coordinating Committees that discuss regional food standards issues and work toward more effective utilization of Codex in developing and developed countries.

FAO and WHO have organized several international conferences of member countries to review Codex and related work from time to time. The most recent of these conferences was held in Melbourne, Australia in October, 1999 and reviewed and endorsed ongoing science-based Codex JEFCA and JMPR work. It also strongly supported Codex work with WTO to provide all member countries, especially developing countries, with equal opportunities to compete in international trade of good-quality and safe foods.

Codex member countries have understood from the outset that effective implementation of food legislation requires science-based systems to ensure the best consumer protection and to enable justification of actions taken by courts, policymakers, and consumers. It is clear that all matters related to the control of quality or safety of foods, such as net weight, volume, ingredient lists, claims, additives, pesticide or animal drug residues, control of contaminants, or food hygiene, must be based on good science. Additional information on the names and addresses of food manufacturers or distributors must also be accurate, but this is perhaps the only information about foods in the general system of food quality control and safety that could be considered not based in science. However, it is clear that government food control authorities must use the best possible science-based judgment in food control decisions. Taking action on the basis of the uninformed and non-science-based opinions of individuals or groups with hidden agendas can only lead to chaos.

A recent problem that has arisen in Codex work relates to new foods and food ingredients derived from techniques such as cloning and genetically modified foods. National and international evaluation of genetically modified foods has shown that these products are not significantly different from other more "traditional" foods, which themselves have been genetically modified over many centuries and generations. Despite the reassurance from the U.S. FDA and other national or international bodies (such as FAO and WHO) that genetically modified foods are safe and present no more problems to consumers than other foods on the market, pressure continues from some groups to require specific labeling for genetically modified foods and ingredients. According to the best available science, this is not justified and is more likely to cause unnecessary confusion among consumers and additional regulatory problems for food producers and for government regulators. Codex discussions are continuing on this point, and it is hoped that science-based information will be used in making a final Codex decision.

One additional point about Codex work is its value to developing countries in carrying out overall developmental plans. Most developing countries rely on the agriculture industry as a mainstay of overall development. Codex work provides a basis for national regulations that improve the quality and safety of domestic or imported foods and promote export trade possibilities. At present, many developing countries have problems in international trade because of poor food hygiene, pesticide residues in export crops, microbial contamination, and food labeling. Codex activities can help to resolve some of these problems.

Furthermore, Codex provides additional technical assistance to strengthen government and food industry food control activities. The FAO website has additional information on a wide range of food control guidance documents and expert reports used by all countries in setting up improved food control systems.

REGULATORY AND INTERNATIONAL IMPLICATIONS

The General Agreement on Tariffs and Trade (GATT) was established in 1947 as an attempt to carry out harmonization of tariffs and to promote better international trade in all products. At the outset, agriculture and food were not included in GATT, but in 1970 a recognition of Codex standards produced a nonbinding text on nontariff barriers to trade. Later, in 1986, countries belonging to GATT decided to start a new round of trade negotiations that included, for the first time, agriculture and agriculture products. These discussions were called the Uruguay Round of Multilateral Trade Negotiations and were concluded in mid-1994.

During the period from 1970 to 1988, the relationship between Codex and GATT was quite weak. However, during the latter part of 1988, GATT was invited to participate in an executive committee meeting of Codex that took place at WHO headquarters in Geneva, Switzerland. From then on, the continued participation of GATT was noticeable.

On January 1, 1995, the World Trade Organization (WTO) was created as a continuation and preemption of the GATT program. The WTO included:

- Agreements on Agriculture—designed to reduce and harmonize support levels for agricultural commodities;
- Sanitary Phytosanitary (SPS) Measures—designed to harmonize or promote equivalents in food standards and food contamination problems related to human health; and
- Technical Barriers to Trade (TBT)—designed to prevent restrictions on free and fair access of foods and other products to national markets of other countries through controlling issues such as labeling, basic food composition or other nonhealth food issues in national standards.

The SPS agreement specifically recognizes the work of Codex as benchmark standards, the recommendations and guidelines for judging foods in international trade. The TBT agreement recognizes all international standards work such as Codex as authoritative in examining technical barriers to trade issues involving food standards.

The WTO has been authorized to examine trade complaints from its member countries in a tribunal system and to make binding decisions about such

complaints. One of the first complaints to come before the WTO involved the ban of beef imports by the European Union (EU) if the beef came from cattle that had been produced using growth-promoting hormones. Before the creation of WTO, JEFCA had on several occasions reviewed growth-promoting hormones and the safety of residues in meat and had set acceptable daily intake levels for these. The Codex Committee on veterinary drug residues in food had reviewed JEFCA recommendations and other relevant information and the recommended residue limits for these hormonal substances to Codex. Despite strong opposition by the EU member countries, Codex formally approved the recommended residue limits, leading to the eventual WTO complaint.

The WTO considered the U.S. complaint that the EU ban was too restrictive and was not based on sound scientific evidence. This WTO tribunal, in examining the relevant JEFCA and Codex decisions, ruled against the EU, agreeing that its ban was not based on adequate scientific information. The EU, however, has in effect ignored this decision and maintained its ban, invoking among other things the "precautionary principle," consumer demands, and other non-science-based factors. Although there has been no explicit statement as to the reasons for the EU ban, it would appear that current support systems for EU farmers are an important factor. At present, for example, between the EU and the French government, payments to farmers raising large animals in France represent about 80% of all farmers' overall income. Given the political influence of farm groups in all countries, and the lower prices of meat imports into the EU, if allowed, it is easy to understand some of the reasons for the EU ban. One can hope that the more general aspects of the WTO Agreement on Agriculture will eventually reduce or eliminate or some of these non-science-based factors.

Despite government and food industry efforts, in many countries consumers have doubts about the quality and safety of the foods they buy and consume. Codex and WTO have concentrated on improving risk analysis procedures, including (1) basic risk assessment that is carried out by JEFCA, JMPR, and national government counterparts, (2) risk management of food problems through appropriate government regulatory, inspection, and analysis systems, (3) industry quality and safety management procedures, and (4) improvements in risk communication information. In the last area, scientists from government, industry, and academia have considerable room for improvement in preparing and presenting science-based information about food quality and safety in an understandable manner to help consumers and policy makers accept assurances that food supplies are both of good quality and safe.

CONCLUSIONS

This chapter presents information about the Codex Program—its commission, activities, and current Codex considerations. At present, the main concerns that

are being studied are genetically modified organisms (GMOs), food additives, traceability, equivalence, and labeling.

It is clear that food standards work, and the control of food quality and safety must be based on the best available scientific information and judgment to ensure a constant supply of food quality and safe foods for all. It is also evident that this goal will be met more easily by following the recommendations of the Codex System.