

Chemical Food Safety Issues in the United States: Past, Present, and Future

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Considerable advances have been made over the past century in the understanding of the chemical hazards in food and ways for assessing and managing these risks. At the turn of the 20th century, many Americans were exposed to foods adulterated with toxic compounds. In the 1920s the increasing use of insecticides led to concerns of chronic ingestion of heavy metals such as lead and arsenic from residues remaining on crops. By the 1930s, a variety of agrochemicals were commonly used, and food additives were becoming common in processed foods. During the 1940s and 1950s advances were made in toxicology, and more systematic approaches were adopted for evaluating the safety of chemical contaminants in food. Modern gas chromatography and liquid chromatography, both invented in the 1950s and 1960s, were responsible for progress in detecting, quantifying, and assessing the risk of food contaminants and adulterants. In recent decades, chemical food safety issues that have been the center of media attention include the presence of natural toxins, processing-produced toxins (e.g., acrylamide, heterocyclic aromatic amines, and furan), food allergens, heavy metals (e.g., lead, arsenic, mercury, cadmium), industrial chemicals (e.g., benzene, perchlorate), contaminants from packaging materials, and unconventional contaminants (melamine) in food and feed. Due to the global nature of the food supply and advances in analytical capabilities, chemical contaminants will continue to be an area of concern for regulatory agencies, the food industry, and consumers in the future.

KEYWORDS: Adulteration; food safety; chemical contaminants

INTRODUCTION

Over the past year, hundreds of people across the United States have fallen ill from consuming peanut products contaminated with *Salmonella typhimurium* and jalapeno and serrano peppers tainted with *Salmonella Saintpaul* (1, 2). Whereas microbiological food safety issues such as these are the main focus of food companies and regulators, media coverage of chemical food safety issues has steadily been increasing over the past decade (3). Recent newsmakers include the discovery of malachite green, nitrofurantoin, gentian violet, and other banned antimicrobial agents in imported farm-raised seafood, the detection of acrylamide in heat-processed, carbohydrate-rich foods, the deliberate contamination of pet food and milk products with melamine, and the migration of packaging chemicals and contaminants such as bisphenol A into foods.

Although it appears from news articles in the popular press that chemical food safety issues are a new phenomenon, they have been an area of concern throughout the past century. The history of the Agricultural and Food Division (AGFD) of the American Chemical Society (ACS) closely follows the evolution of chemical food safety problems in the United States and history of U.S. food regulations. This paper will summarize some of the history

of chemical food safety issues in the United States over the past century and will discuss the involvement of the AGFD in defining and solving some of these issues.

CHEMICAL FOOD SAFETY ISSUES OF THE PAST

In the latter part of the 19th century to the early 20th century, many Americans were exposed to adulterated foods, dangerous medications, and poisonous substances on a regular basis (4, 5). At that time, there were no national regulations for protecting the consumer from adulterated foods (4). Milk and wine were often diluted with water, bakers added alum and chalk to whiten bread, and calcium sulfate and sawdust were used to increase the weight of bakery products. Although the majority of food adulterants were fairly innocuous, some were poisonous, causing illness or death in those who consumed them. One of the most notorious examples was the use of poisonous lead, copper, or mercury salts to create brightly colored candies that were appealing to children. Copper salts were added to pickles, peas, and green beans to enhance their green color and create the illusion that they were of higher quality (6). Brewers added mixtures of bitter substances, some containing poisons such as strychnine, to improve the taste of beer or to save on the cost of hops (7). Some of the common adulterants in food in the late 19th and early 20th centuries are listed in **Table 1**.

The intent of adulteration is cheapening of products through addition of impure or inferior ingredients or by removal of

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Table 1. Common Adulterants in Food in the 19th and Early 20th Centuries

food	adulterant	refs
pepper, black	mustard husks, pea flour, juniper berries, gravel, leaves, twigs, stalks, linseed meal	Miller (11); Fennema and Tannenbaum (17)
pickles	copper salts	Coley (7)
pepper, cayenne	red lead	Coley (7)
tea	leaves of other plants; spent tea leaves	Fennema and Tannenbaum (17)
canned green beans, peas	copper sulfate	Miller (11)
milk	water, chalk, starch, gums, preservatives, glucose, dextrin, gelatin, formaldehyde	Fennema and Tannenbaum (17); Hart (109)
wine	water	Fennema and Tannenbaum (17); Hart (109)
beer	strychnine; extracts of <i>Cocculus indicus</i>	Fennema and Tannenbaum (17)
vinegar	sulfuric acid; tin and lead from pewter vessels	Fennema and Tannenbaum (17); Coley (7)
bread	alum, flour made from other products than wheat	Fennema and Tannenbaum (17)
butter	borax	Janssen (19)
maple syrup	cane sugar	Hart (109)
candy	lead chromate	Hart (109)
olive oil	cottonseed oil; lead from press	Hart (109); Coley (7)
honey	glucose	Hart (109)

valuable ingredients. Although the practice of adulterating food is probably as old as the bartering and trading of food, the practice scaled to extraordinary levels during the latter part of the 19th century. This was mainly due to the industrial revolution, which increased centralization of food processing and distribution in the United States and the lack of government regulations to protect the consumer (8, 9). In addition, there were advances in analytical chemistry allowing food producers more efficient ways to adulterate on the basis of improved scientific knowledge about food composition (6). However, these improvements in analytical chemistry made it possible to reveal food adulteration that would have been previously impossible to detect and ultimately improved the safety of the food supply (8).

The ability to detect and quantify the presence of impurities, contaminants, and food adulterants was essential for the development of food protection legislation (10). Although scientists in ancient times were able to detect gross adulteration of foods, they were not able to quantify adulterants or detect their presence in low or moderate levels in food (11, 12). It was not until the 17th and 18th centuries that chemistry began to emerge in its modern form (11, 12). In the late 17th century British chemist Robert Boyle began developing new assays for food adulterants with some based on the principal of specific gravity (8, 10, 11, 13). On the basis of Boyle's work, other chemists made substantial advances in chemical analysis needed to detect food adulterants.

In 1820, Frederick Accum, a German chemist living in Great Britain, published his monumental work *Treatise on Adulteration of Food, and Culinary Poisons*, which was the one of the first to raise the alarm about food adulteration (7). This book describes the numerous types of adulteration at the time and analytical methods for detecting common adulterants of food. His work was an immediate worldwide success and spurred the publication of other books (14, 15) on chemical adulterants in food and methods for detecting and quantifying them (10, 16).

In the 1850s Arthur Hill Hassall, a British physician, began investigating food and drug adulteration in England (10). From 1851 to 1854, Hassall bought samples of food and drink and used microscopy to detect the presence of foreign material and chemical tests to identify alum in bread, iron, lead, and mercury compounds in cayenne pepper, copper salts in bottled fruits and pickles, and alkaloids in beer (7). Hassall's work led to regulations in England for preventing adulteration of food and drugs. Hassall and Accum's works provided the public awareness and stimulus responsible for precipitating the reform movement in the United States and the resulting regulations needed to protect the consumer from food and drug fraud. Once the seriousness of food adulteration in the 1800s was brought to the attention of the

public, corrective forces gradually increased and took the form of new legislation to make adulteration unlawful (17).

Until the mid-19th century, food regulations in the United States were enacted at a state or local level and were targeted toward specific food products (8). In 1862, Congress created the Department of Agriculture, Division of Chemistry, which became the focal point of all food protection activities (16). Commissioner of Agriculture, Isaac Newton, appointed Charles M. Wetherill as the first Chief Chemist of the Division of Chemistry (18). Wetherill and subsequent chemists of the Division of Chemistry began to use existing chemical methods for the detection of food adulteration and began to develop new methods for detecting the presence of chemical adulterants (8). These investigations were expanded under the supervision of Dr. Harvey W. Wiley, when he became Chief Chemist in 1883. Wiley's investigations on the widespread occurrence of food adulteration were documented in Department of Agriculture Bulletin 13, which was published in 10 parts from 1887 to 1902, and Wiley's textbook, *Foods and Their Adulteration* (8, 16, 18, 19). Harvey Wiley served two terms (1893–1894) as ACS President and used his office and its visibility to promote legislation in food and drug regulation.

Prompted by an increasing use of untested chemicals as food preservatives, Harvey Wiley initiated studies in 1902 on the health effects of chemical preservatives (20). Wiley's "Poison Squad" experiments consisted of feeding healthy male volunteers meals containing increasing amounts of commonly used adulterants and preservatives (borax, boric acid, salicylic acid, sulfurous acids, benzoic acid, sodium benzoate, formaldehyde) to determine whether they were injurious to health (4, 20, 21). Although these experiments were scientifically flawed in that they did not have a control group, they represent an important first step in introducing science into policymaking (8). These and other studies influenced scientists, physicians, pharmacists, and several civil groups to ask their congressmen to develop federal oversight for foods (4).

Harvey Wiley's research helped form the technical framework to justify passing of a comprehensive national food and drug law (18). The Pure Food and Drugs Act (PFDA) was signed by President Theodore Roosevelt on June 30, 1906, the same day that he signed the Meat Inspection Act (8, 18). The Meat Inspection Act was legislation passed in response to public outcry following publication of Upton Sinclair's *The Jungle*, a novel documenting the unsanitary conditions and practices in meat-packing plants.

The PFDA prohibited interstate commerce of adulterated food and drugs and banned false and misleading statements on packaging. The law forbade marketing food that was filthy or

decomposed or adding substances to food to conceal inferiority or to make the food injurious to health (18). The administration of the PFDA was assigned to the USDA Bureau of Chemistry, the first federal regulatory agency, later to be known as the Food and Drug Administration (FDA) (8).

The PFDA was an asset for U.S. consumers, making entire industries accountable for their actions for the first time (18). However the 1906 law had some weaknesses. First, ingredient listings on the food were voluntary with the exception of 11 ingredients that were required to be listed. Second, inspection of manufacturing facilities to ensure compliance was not explicitly addressed in the law. Third, although the law explicitly prohibited false and misleading statements about the product, advertising material was not considered part of the labeling (8). Finally, there was no means for preventing a firm from introducing a product on the market (lack of premarket approval) and no requirement of efficacy or safety (18). Although the law was weak in its loopholes, its main outcome was the establishment of a federal agency to establish a role for the federal government in protecting consumers (8).

In 1908, two years after the passing of the PFDA, the first divisions in ACS, including the AGFD, were formed. At the ACS meeting held in Detroit, MI, during the summer of 1909, a paper was presented by Edmund Clarke on the determination of benzoic acid, a commonly used preservative, in food products. This paper was timely because there was controversy over the use of benzoic acid and its salts as food preservatives and there was a need for a rapid method for measuring their levels in food.

Intentional adulteration of food remained a serious dilemma in the United States until about 1920, when regulatory pressures reduced the frequency and seriousness of this problem (9). However, in the 1930s the numbers and uses of diverse pesticides and additives used in food was increasing (12, 22). Industrialization and urbanization in the United States were dependent on an increasingly sophisticated food industry to ensure an abundant food supply (12). The USDA Bureau of Chemistry enforced the PFDA until 1927, when the Food, Drug, and Insecticide Administration was formed, to be renamed in 1931 the Food and Drug Administration (21). In 1933, the new FDA recommended a complete revision of the PFDA due to the deficiencies in the 1906 law (20).

In 1938, Congress passed the Food Drug and Cosmetic Act (FDCA), which extended regulatory control to cosmetics in response to the dangerous products that were on the market. The new law required premarket approval of new drugs and brought medical devices and cosmetics under regulation. The FDCA was the first law worldwide to require that new drugs be subjected to scientific safety testing before they could be marketed, with the burden of proof placed on the manufacturer (8). It also required implementation of standards of identity for some foods and mandated factory inspections. The FDCA required that colors had to be listed and approved before they were used in foods, drugs, and cosmetics. Colors made from coal tar sources had to be batch certified (20). The law also established tolerances for certain poisonous substances and produced the framework within which the FDA could require good manufacturing practices (18).

The 1940s–1950s saw great developments in science and technologies resulting in proliferation of food chemicals (additives and preservatives) and new food processes (e.g., food irradiation) (12). During this time, the presence of undesirable byproducts of industrialization such as mercury, lead, and pesticides became a public and regulatory concern, and recognition was spreading of the need to monitor and control their presence in food (17, 22). The AGFD of ACS was instrumental in its coverage of some of the key chemical food safety problems occurring in the United States. Timely AGFD symposia

occurring in the 1940s and 1950s included *Insecticides in Food Production; Antibiotics; Methods of Analysis for Microquantities of Pesticides; Current Status of Pesticides; Significance of Pesticide Residues; Systemic Insecticides; Rodenticides; Radiation Sterilization of Food and Pharmaceuticals; Pesticides in Tropical Agriculture; Metabolism of Pesticides in Plants, Mammals and Insects; and Radiation Sterilization; Food Additives; and Deleterious Compounds in Foods and Feeds* (23).

Also occurring in the 1940s and 1950s were advances in the field of toxicology, which enabled more systematic approaches for evaluating the safety of food ingredients and contaminants (11, 12). Before this time, the safety of ingredients and contaminants was assessed in short-term (acute) toxicity tests. However, it became apparent that short-term tests did not provide a complete picture when it came to assessing the safety of food ingredients and contaminants. By 1949, the FDA published a monograph, *Procedures for the Appraisal of the Safety of Chemicals in Foods, Drugs, and Cosmetics*, which effectively mandated the performance of long-term (chronic) toxicity tests for food additives (11). In 1955, FDA issued a monograph that included a separate section on carcinogenicity (11). In 1959, FDA issued a monograph that contained a separate section on carcinogen screening and outlined scientific criteria that should be considered when conducting carcinogenicity tests (11). The “no observable effect level”, or NOEL, became the basic determinant for regulatory decisions (11). Changes in the FDCA that occurred during this time included the Miller Pesticide Amendment (1954), the Food Additives Amendment (1958), and the Color Additive Amendment (1960) (8). The “Delaney clause” in the food and color additive amendments stated that no additive could be deemed safe if it was found to induce cancer when ingested by humans or animals (8).

By the 1970s traditional approaches for establishing “no effect levels” based on chronic toxicity tests was becoming so difficult to interpret that a new approach was needed. The result was the use of statistical risk assessment methods for estimating human hazards to food additives and contaminants (11).

Advances in analytical chemistry were made in the latter half of the 20th century allowing the detection and quantitation of food chemicals at levels far below what was previously possible. Before the 1940s the only instruments of widespread availability for quantitative analysis were the balance and simple spectrophotometers (24). Gas chromatography (GC), first invented in the early 1950s, became the key analytical methodology in the contaminant laboratory (25). High-performance liquid chromatography (HPLC), first invented in the early 1960s and evolving to its current form in the 1970s, allowed the detection and quantitation of food components of low volatility. Mass spectrometers became commercially available as detectors for GC and HPLC in the 1970s and 1980s. They offer specific advantages over other methods of detection because they offer distinctive information about the chemical composition of the analyte and allow detection of contaminants at very low levels (24, 26). More recent advances in instrumentation used in the analytical laboratory that allow real-time detection of food contaminants include MS/direct analysis in real-time (DART) and immunochemical methods. For more information about analytical advances that occurred during the past century, the reader is invited to read the paper written by Dr. Robert McGorran in this issue titled “One Hundred Years of Progress in Food Analysis”.

CURRENT CHEMICAL FOOD SAFETY ISSUES

Chemical food safety issues have always been of great concern to scientists working in the agriculture and food scientific community. In the past several decades, chemical hazards in food

Table 2. Chemical Hazards in Food

chemical hazard	subcategory of chemical hazard
agrochemical	pesticides fungicides fertilizers herbicides veterinary drugs
environmental and industrial contaminants	heavy metals (lead, cadmium, mercury) PCBs dioxins radionuclides organic chemicals (benzene)
toxins produced during processing and storage	heat-produced chemical hazards (acrylamide, furan, heterocyclic aromatic amines, polycyclic aromatic hydrocarbons, <i>N</i> -nitrosamines, lipid degradation products) chemical hazards produced during nonthermal processing and storage (trans fatty acids, benzene, ethyl carbamate)
packaging-derived hazards	monomers (vinyl chloride, styrene, acrylonitrile) pigments (lead) plasticizers (phthalates) other (BPA, semicarbazide)
allergens	major food allergens (milk, peanut, egg, peanut, tree nut, soy, fin fish, crustacean shellfish)
natural toxins	mycotoxins (aflatoxins, deoxynivalenol, patulin, T-2 toxin, ochratoxin) plant toxins (cyanogenic glycosides, alkaloids, trypsin inhibitor, hydrazine) seafood toxins (paralytic shellfish toxins, okadaic acid, yessotoxins, brevetoxins, azaspiracids)
unconventional chemical hazards	adulterants (melamine) chemical threat agents (ricin, picrotoxin, nicotine, heavy metals)

have been high on the lists of consumer concerns, especially due to their long-term carcinogenic potential (27). In addition, chemical food safety has emerged as a significant global issue with public health and international trade implications (28).

Chemical hazards in food can be multiple (Table 2) and introduced at any point into the food and feed chain, including during production, processing, retail distribution, food preparation, and consumption. In recent decades, chemical food safety issues that have been the center of media attention include the presence of agrochemicals (pesticides, fungicides, veterinary drug residues), natural toxins (mycotoxins and marine toxins), allergens, processing-produced toxins (e.g., acrylamide, heterocyclic aromatic amines, furan, *trans* fats), heavy metals (lead, arsenic, mercury, cadmium), industrial chemicals (benzene, perchlorate), packaging-derived chemicals (bisphenol A, semicarbazide), unconventional contaminants/adulterants (melamine, chemical threat agents), and genetically modified crops in food and feed. The following sections will highlight some of the more recent chemical food safety issues for each class of contaminants and, if possible, review the role of AGFD of ACS in characterizing the hazards and arriving at possible solutions for controlling these hazards.

Contaminants Formed during Processing and Storage. Processed foods are a way of life in the modern world (27). Processing allows for a more consistent supply of foods, increasing consumer convenience and variety and, in general, increasing food safety, quality, and palatability (27). Processing unit operations such as washing, trimming, milling, leaching, and mechanical separation may decrease the natural toxicity of some raw materials by eliminating specific undesirable components (29). However, processing can decrease nutrient levels and bioavailability and produce chemical and physical changes that may render a food hazardous (27). Thermal processing may induce the formation of

harmful compounds such as various mutagens, carcinogenic heterocyclic aromatic amines (HAAs), polycyclic aromatic hydrocarbons (PAHs), furan, acrylamide, and *N*-nitrosamines. Other detrimental changes in food that occur as the result of processing include the formation of *trans* fatty acids during the hydrogenation of fats and the creation of chloropropanols and their fatty acid esters during the production of hydrolyzed vegetable protein (HVP) (30, 31). A comprehensive review of process-induced food toxicants was recently published (32).

Heat-Produced Toxic Compounds. Carcinogens from heated foods have been a health concern since the 1970s, when it was discovered that HAAs were formed in overheated meats, PAHs were produced in barbequed meats, and *N*-nitrosamines were created in fried bacon. Modern science has showed that heating of foods can generate various kinds of potentially hazardous compounds, some of which are carcinogenic and genotoxic. Cooking or heat processing causes free amino acids and sugars to react via the Maillard reaction to form a wide variety of chemical compounds. The Maillard reaction products are important for the sensory properties of foods such as flavor, color, and texture, but some are toxic. Examples of toxic Maillard reaction-derived products include the heterocyclic aromatic amines and acrylamide. Furan, a toxic volatile cyclic ether found in a number of foods that receive heat treatment, is formed by thermal degradation and reactions of carbohydrates, ascorbic acid, and polyunsaturated fatty acids in food (33).

The AGFD of ACS has been one of the leading scientific organizations responsible for publishing groundbreaking articles on the chemistry of formation, mitigation, exposure estimates, and toxicology of the known heat-produced toxins. The AGFD has played an instrumental role in identifying the issue of acrylamide in food as well as improving our understanding of how the compound is formed in food, methods by which it is

detected, approaches for reducing its formation, and the risks and toxic effects caused by its consumption.

The acrylamide issue began in 2002, when researchers at the Swedish National Food Administration and Stockholm University published a paper in the *Journal of Agricultural and Food Chemistry (JAFC)* describing their discovery of up to 3 mg/kg acrylamide in a wide range of potato- and cereal-based products such as potato chips, French fries, roasted and baked potatoes, bread, breakfast cereals, and biscuits (34). The discovery of acrylamide in foods is a concern because acrylamide is a human neurotoxin, a potent rodent carcinogen, and a possible human carcinogen (35).

Acrylamide forms in carbohydrate-rich foods that are subjected to high-temperature (>120 °C) processes such as frying, baking, and extrusion. Acrylamide can be found in processed foods as well as foods prepared by consumers. It is not present in uncooked food or in foods that are cooked at lower temperatures (e.g., boiled foods). Rather than being a food contaminant, acrylamide is generated from certain food products during heat treatment as a result of the Maillard reaction between certain amino acids (primarily asparagine) and reducing sugars such as glucose and fructose (36). Many of the groundbreaking studies that elucidated the mechanisms of acrylamide formation in food were published in *JAFC* (36–39).

Acrylamide is ubiquitous in the human diet; it has been estimated that more than one-third of the calories that are consumed by the U.S. and European populations are derived from foods that contain acrylamide (40). The relatively high level of exposure to acrylamide from dietary components and the possibility of human cancer risk demonstrated the need for developing a better understanding of its formation and distribution in food and its effect on human health (41). To catalyze this effort, Dr. Donald Mottram and Dr. Mendel Friedman organized an AGFD-sponsored symposium on the *Chemistry and Safety of Acrylamide* held at the March 2004 ACS National Meeting in Anaheim, CA. This groundbreaking symposium brought together 34 speakers from 8 countries and covered such diverse topics as the mechanisms of formation of acrylamide in food, distribution of acrylamide and its precursors in food, toxicology, pharmacology, and metabolism, epidemiology, and risk assessment (42). The proceedings of the symposium were published as one of the first comprehensive volumes on the topic of acrylamide in food (42).

Since the initial ACS symposium in 2004, considerable progress has been made in understanding the chemistry and toxicology of acrylamide. As a result, a second AGFD-sponsored symposium was held at the August 2007 ACS National Meeting in Boston, MA. The symposium was titled *Chemistry and Toxicology of Acrylamide* and organized by Drs. Mottram and Friedman. The proceedings of the symposium were published as 27 papers in *JAFC* (Vol. 56, No. 15 (August 13, 2008)).

Until expert scientific committees and regulatory agencies understand the mechanisms of formation and the toxicology of acrylamide more clearly, it will be difficult to set the appropriate limits for acrylamide (43, 44). The FDA National Center for Toxicological Research (NCTR) has recently completed a two-year chronic carcinogenicity study in rats and mice. The results of this chronic study will be summarized and disseminated in the next year. It is likely that the outcome of this study will shape the future for acrylamide regulation and risk management (44).

Toxic Compounds Formed during Nonthermal Processing and during Storage. Although many of the processing-produced toxicants are formed during heating of foods, there are several that are formed through nonthermal processes or during storage. Two such chemical hazards that have been in the public and

scientific media recently include *trans* fatty acids in hydrogenated fats and oils and benzene in soft drinks.

In recent years there has been scrutiny of the health implications associated with *trans* fatty acids in foods. *trans* fatty acids are commercially produced by partial hydrogenation of edible oils, mainly to impart desirable stability and physical properties to edible oils. They are found in foods such as margarines, spreads, shortenings, frying fats, and specialty fats and occur naturally in foods such as milk, butter, and tallow (30). Until fairly recently, the fats used in the manufacture of retail margarines and spreads contained an average of 15–25% *trans* fatty acids (30, 45).

Reports in the scientific literature have indicated that diets containing high levels of *trans* fatty acids have resulted in increases in total cholesterol and low-density lipoproteins (LDL) and a decrease in high-density lipoproteins (HDL) in the blood (45). In response, health professionals have recommended reducing consumption of foods containing *trans* fatty acids. By January 1, 2006, the FDA issued regulations requiring the labeling of *trans* fatty acids on packaged foods. In addition, many food manufacturers have developed food products containing no or lower amounts of *trans* fats (30, 46).

Benzene is a common environmental/industrial contaminant that has been found to contaminate foods at trace amounts (47). However, in the early 1990s, the FDA learned that benzene could form in some beverages from the reaction of benzoate salts and ascorbic or erythorbic acid under certain conditions of storage, shelf life, and handling (48–50). Levels of benzene detected in some soft drink products were higher than the regulatory limit of 5 ppb established by FDA for bottled water, and in one product levels were as high as 87.9 ppb (49, 51, 52). Concern over benzene stems from its ability to cause tumors in rodents and leukemia in humans (53). In response to the finding of benzene at levels over 5 ppb in some beverage products, soft drink manufacturers have reformulated their beverages to minimize or eliminate benzene formation. Risk assessments on the potential human health risks posed by benzene in beverages indicate that they do not pose a safety concern to consumers (49, 51, 54). The discovery of benzene in some soft drink products suggests a need to monitor levels of the compound in new beverage products to ensure that benzene levels are minimized (50).

Packaging Contaminants. Packaging is an essential element of the food manufacturing process (55). Plastics and other synthetic polymers are the preferential materials used for packaging foods because they have properties that prevent detrimental changes to food during storage. A variety of materials can be used in packaging as long as they have the desirable functional properties and do not pose health hazards after coming into contact with food. Most packaging materials are of high molecular weight and are inert toward food. However, lower molecular weight components such as residual plastic monomers or oligomers and additives (slip agents, antioxidants, plasticizers, stabilizers, and pigments) may transfer into food and result in the potential for human exposure (56).

Over the past 30 years there have been concerns and much controversy over the safety of packaging contaminants in food. Increasingly, these substances are becoming subject to control and regulation (56). The safety concerns stem from the lack of information on the effects of prolonged exposure to these contaminants in humans (56). Recently, bisphenol A (BPA) has attracted much public attention because this compound is suspected of possessing endocrine-disrupting properties (57).

BPA is a chemical of high product volume that is used as an intermediate in the production of polycarbonate (PC) bottles and epoxy resins (58). PC is used in food storage containers such as

water and baby bottles, and epoxy resins are used to coat the interior of metal food and beverage containers (58). Various studies have shown that BPA can migrate from packaging material into a variety of canned vegetables and fruits, meats, fish, beverages, and liquid infant formulas (58–60). Concern over BPA stems mainly from its possible estrogenic effects (61), but additional reports have shown the chemical to have other possible toxic effects such as inducing liver damage (62, 63), disrupting pancreatic β cell function (64), and thyroid hormone disruption (65, 66).

Debate about the health effects of BPA in humans has resulted in manufacturers of infant formula and baby bottles to phase out BPA from their packaging. The European Food Safety Authority (EFSA) and the U.S. EPA have set a tolerable daily intake (TDI) for BPA of 50 $\mu\text{g}/\text{kg}$ of body weight/day (67). Health Canada has established the provisional TDI for BPA at 25 $\mu\text{g}/\text{kg}$ of body weight/day (58). Recently, the Canadian government has placed a ban on baby bottles containing BPA. Debate about the health effects of BPA in humans has been hindered by the lack of epidemiological data of sufficient statistical power to detect low-dose effects (66). Research is currently being conducted on the long-term health effects of exposure to BPA from contaminated foods.

BPA is only one of a myriad of packaging contaminants (semicarbazide, monomers, etc.) that have been found to migrate into foods during processing or storage. Research aimed at understanding factors that affect migration of these contaminants as well as evaluating consumer exposure to packaging-derived substances is increasing worldwide. It is important to understand that packaging itself is a major contributor to food safety and that the risks and benefits need to be determined when the risks of exposure to packaging-derived compounds are assessed (56).

Natural Toxins. Chemical hazards from natural sources are found in most staple foods in the human diet (68). These natural toxins include antinutritional factors (e.g., lectins, phytic acid, and trypsin inhibitor), seafood toxins (tetrodotoxin, ciguatera toxins, paralytic shellfish poisoning toxins, neurotoxic shellfish poisoning toxins, etc.), plant toxins (e.g., alkaloids, cyanogenic glycosides, goitrogenic glycosides, and hydrazines), and mycotoxins (aflatoxins, fumonisins, patulin, ochratoxins, and trichothecenes). Recent research has increased awareness of chemical residues and natural toxins in food. At an international level, this has resulted in more stringent imposition of new, legislative limits for a range of natural toxins that can contaminate raw food ingredients and enter the food chain.

Some of the most potent natural toxins responsible for human health risks are the mycotoxins (68). Mycotoxins are toxic secondary metabolites produced by fungi. Despite efforts to control fungus contamination of food, fungi are ubiquitous in the environment and are found in many agricultural products including grains, fruits, and vegetables (69). Of the toxigenic fungi found in food, those in the genera *Penicillium*, *Fusarium*, and *Aspergillus* have the greatest consequence to food safety. Of the over 1000 mycotoxins that are known to form, those having the most public health and economic significance include the aflatoxins, ochratoxins, trichothecenes, zearalenone, and fumonisins (69, 70). When present in foods in sufficiently high levels, these mycotoxins can have toxic effects ranging from acute to chronic (69). Chronic exposure to mycotoxins is a worldwide concern. In countries where contaminated crops serve as dietary staples, exposure can be frequent and at a high level (27). Although the consumption of mycotoxin-contaminated foods has been linked to the occurrence of human diseases in populations in India, Africa, and China, information is lacking on human mycotoxin toxicities in the United States (70).

The AGFD has played an instrumental role in its dissemination of information on the fumonisins, a recently discovered family of mycotoxins found in food. Fumonisins are mycotoxins produced by a variety of fungi of the *Fusarium* genus. These toxins are ubiquitous contaminants of cereal grains and are found predominantly in corn and corn-based foods (71). Fumonisins were first isolated in 1988 from cultures of *Fusarium verticillioides* strain MRS 826 by Gelderblom et al. (72). The isolation and chemical characterization of fumonisins in 1988 came after 18 years of research into the causal agent(s) for equine leukoencephalomalacia (ELEM), a fatal disease in horses, and human esophageal cancer in some populations in the Transkei region of South Africa. In 1989, shortly after the discovery of the fumonisins, there were widespread, large-scale outbreaks of ELEM and other animal diseases in the United States, resulting in the death of large numbers of horses and pigs fed fumonisin-contaminated corn. This chain of events set the stage for the proliferation of research programs throughout the world aimed at measuring the occurrence and levels of fumonisins in corn-based foods, understanding factors affecting the formation of the toxin, developing analytical methods for fumonisins, determining the toxicological properties of the toxin, and identifying methods for reducing fumonisin levels in foods. In 1995, the AGFD sponsored a three-day symposium on *Fumonisins in Food*, which brought together over 30 scientists from all over the world to report on research efforts that were underway at the time. The proceedings for this symposium (73) represented one of the first and most comprehensive volumes published on the topic of fumonisins in food.

Industrial and Agricultural Contaminants. Chemical contaminants in food may result from pollution arising from industrial and human activities (heavy metals, polychlorinated biphenyls, dioxins, and PAHs) and from agricultural practices (pesticides, fungicides, fertilizers, and veterinary drug residues) (74). These contaminants may be detrimental to human health if exposure is not controlled.

Industrial contaminants are a group of substances of diverse chemical structures and properties. The majority of industrial contaminants are complex organic compounds, whereas some are organometallic or inorganic substances (74). They tend to be stable and persist in the environment and thus tend to bioaccumulate in the food chain (74). More recent incidences of contamination of food with industrial chemicals includes dioxin contamination of chicken, eggs, and catfish in the southern United States in 1997 and dioxin contamination of chicken, beef, pork, eggs, and milk in Belgium in 1999 (75, 76).

Agricultural chemicals that can contaminate the food supply include pesticides, fungicides, fertilizers, and veterinary drug residues. An area that has gained much media attention over the past several years is the detection of banned antimicrobial agents and antibiotics (fluoroquinolones) in farm-raised seafood obtained from China. These antimicrobial/antifungal agents (nitrofurans, malachite green, gentian violet, and chloramphenicol) have been shown to be carcinogenic in long-term animal studies (77). The use of fluoroquinolones is a concern because they may increase microbial antibiotic resistance (77). The ban has stimulated significant interest in the development of analytical methods for detecting trace levels of these substances in food (78).

Food Allergens. Food allergies affect an estimated 10–12 million people in the United States including about 2% of adults and up to 6% of infants and children. Food allergies are hypersensitivities to food proteins mediated by immunoglobulin E (IgE) antibodies. Each year, an estimated 30000 individuals require emergency treatment and 150 individuals die because of allergic reactions to food (79, 80). Over 160 foods have been

shown to cause allergic reactions, with 8 major foods accounting for 90% of food allergies (81). These most common allergenic foods, known as “the Big 8” or “major food allergens”, are milk, eggs, fish, crustacean shellfish, tree nuts (i.e., almonds, cashews, walnuts, and hazelnuts), peanuts, wheat, and soybeans.

Celiac disease is an immunological hypersensitivity to specific proteins (gluten) in several cereal species (wheat, barley, and rye) that results in damage to the small intestine and malabsorption of nutrients from food (82). Unlike food allergies, in which the hypersensitivities are IgE-mediated, celiac disease is not IgE-mediated. The prevalence of celiac disease in the United States is growing, and currently it is believed to affect 1 in 133 people in the United States (83).

As prophylactic treatment does not exist for individuals with food allergies or celiac disease, strict avoidance of the foods containing the offending proteins is the only current means to avoid reactions. At present, there is no consensus on the minimum level of allergenic protein or allergenic food that can cause a reaction in a sensitive consumer (84). Trace amounts of protein from allergenic foods have been shown to cause allergic reactions in some allergic individuals (85).

Despite the current laws that mandate labeling of foods for the presence of the major food allergens, allergens can still inadvertently appear in a product through a number of avenues, such as incorrect labeling, changes to product formulation without commensurate label changes, production sequence, scheduling, improper handling of rework, in-process and postprocess cross-contamination (cross-contact), and insufficient or ineffective equipment cleaning/sanitization procedures when there is a change-over from one product to the next (86).

Over the past 20 years, food allergies have evolved from a problem for food allergic individuals to one of a significant public health importance (87). The increase in incidence of food allergies in industrialized countries (79) combined with increased consumer awareness on the seriousness of the problem of food allergies have prompted research throughout the world on the identification and characterization of food allergens, development of rapid methods for detecting allergens, and determination of the minimum levels of allergenic protein or food (thresholds) that trigger allergic reactions. The AGFD has sponsored several exceptional symposia on food allergens in the past 15 years including *Chemistry and Biology of Food Allergens* (Boston, MA, 1998), *Allergens in Food* (New Orleans, LA, 2003), and *Mycotoxins and Food Allergens* (San Francisco, CA, 2006) (88).

Unconventional Chemical Contaminants in Food. Unconventional contaminants can be introduced into foods through accidental or intentional means. Of those contaminants added intentionally, some are added as economic adulterants, whereas some are added for malicious intent. The events of September 11, 2001, gave rise to concerns about the safety of the U.S. food supply (89). Those events also increased international awareness that food could be compromised in a terrorist attack by being the vector for delivering a biological or chemical weapon (90–92). Research characterizing possible chemical agents (natural toxins, agrochemicals, heavy metals, nonmetallic ions, etc.) that could be used as weapons and developing rapid methods for detecting them in food matrices has increased in the United States and internationally (92, 93).

Over the past several years, substantial attention has given to the presence of chemical contaminants in imported foods. Of these contaminants, the presence of melamine in human foods and animal feeds has caused considerable consumer anxiety and desire to control the presence of these compounds. Melamine is a nitrogen-based industrial chemical used in the production of melamine resins, which are used in the production of dishes,

furniture, flooring, and adhesives (94). In March 2007, a pet food manufacturer in the United States alerted the FDA to 14 animal deaths in the United States that appeared to be linked to pet food. In the following months, consumers and veterinarians reported more animal illnesses and deaths associated with the consumption of the pet food (95). Analysis of the suspected pet food resulted in the finding of melamine and melamine-related compounds (cyanuric acid, ammeline, and ammelide) (94–96). Although melamine is not approved for use in foods or feeds, it was discovered that some wheat gluten and other protein ingredients imported from China were contaminated with the compound. In these incidents, melamine and its related compounds were added to the ingredients to boost the apparent protein content. It was later discovered that melamine was found in feeds of animals raised for human consumption (hogs, chickens, and fish) (97).

Although melamine has a low oral acute toxicity, high and continuous dietary exposure to melamine in combination with cyanuric acid has been shown to result in the deposition of insoluble melamine cyanurate crystals in the kidneys of cats and dogs, causing renal failure (97, 98). The melamine contamination issue resulted in a recall of some brands of pet food, which had an enormous economic impact on the pet food industry and caused concern about the potential risk to humans from consuming meats containing the compound (96).

In September 2008, news stories began emerging about the contamination of milk-based products in China (98). By December 2008, the Chinese authorities reported that over 50000 children in China that had been fed melamine-adulterated infant formula had been treated for renal complications and that 6 children had died as a result (98, 99). Because China is a major exporter of milk products and ingredients, there have been reports of melamine-contaminated foods manufactured in the United States and other countries (99). These melamine contamination incidences have prompted the FDA and other regulatory agencies to develop analytical tools such as infrared spectroscopy, liquid and gas chromatography, mass spectrometry, and gas chromatography–mass spectrometry to monitor food ingredients for melamine and cyanuric acid (94, 97). The FDA has broadened its domestic and import sampling and testing of milk-derived ingredients and finished food products containing milk or milk-derived ingredients from Chinese sources and has recommended that consumers not consume certain products because of possible contamination with melamine (100).

Use of Genetically Modified (GM) Crops. Developments in plant breeding have led to an increased interest in breeding cultivars that are desirable to the consumer (101). Scientific advances over the past 30 years have led to the ability of crop improvement through the use of biotechnology and genetic engineering. Conventional crops have been genetically modified to increase shelf life, to improve nutritional value, enhance disease, insect, and herbicide resistance, and to improve tolerance to a variety of environmental stresses (102). In 1996, GM crops were first introduced into the commercial market in the United States and were rapidly adopted by farmers (102). At present, approximately 140 million hectares worldwide are being cultivated with GM crops including soybean, corn, cotton, canola, potatoes, and tomatoes (103, 104).

Similar to classical breeding methods, genetic modification aims to alter metabolic routes to render the resulting plant varieties more favorable characteristics than their traditional counterparts (101). GM crops contain artificially inserted gene(s) or “transgenes” from another plant or from another totally different species by genetic engineering techniques (102). The process allows desirable alterations to be introduced into

the plant genome in a more specific and controlled manner than can be achieved through traditional breeding techniques (104).

Along with the potential benefits of genetic modification of crops, there are known and unknown risks (105). The risks of GM crops deal with the toxicology of GM crops upon release and use (102, 106). Major food safety concerns stem from the possible presence of newly expressed proteins and other constituents and the possible changes in the level of natural constituents beyond normal variation. For example, genetic engineering is capable of introducing allergenic proteins into recipient plants or altering metabolic pathways that enhance production of toxic compounds (101, 102). An environmental risk includes the possibility of transgenic crops expressing insecticidal transgenes to control agricultural pests that may also affect other nontarget organisms (101). Finally, there is a fear that GM crops are a threat to crop diversity (102, 105).

Approaches to the regulation and safety assessment of GM crops have been developed in a proactive manner (104). The first international and national provisions for the safety assessment and regulation of GM organisms (including crops) were drafted in the mid-1980s, a decade before the first regulation approval of a GM crop in 1995 (104). The Codex Alimentarius Commission has adopted the Principles for the Risk Analysis of Foods Derived from Modern Biotechnology and the Draft Guidelines for the Conduct of Food Safety of Foods Derived from Recombinant-DNA Plants and Microorganisms (106, 107). The safety assessment of GM plant-derived foods and feeds follows a comparative approach in that the food and feed are compared with their non-GM counterparts to identify intended and unintended differences. These differences are subsequently assessed with respect to their potential impact on the environment, safety to humans and animals, and nutritional quality (105). Elements of the assessment procedure are molecular, compositional, phenotypic, and agronomic analyses to identify similarities and differences between the GM crop and its conventional counterpart (105). An integrated view on GM organisms including crops may create greater consumer confidence in the technology (106).

FUTURE OF CHEMICAL FOOD SAFETY

Although the emphasis over the past decade has been on microbial food safety issues, chemical food safety has made the headlines of the news over the past several years. Due to the global nature of the food supply and advances in analytical capabilities, chemical contaminants will continue to be an area of concern for regulatory agencies, the food industry, and consumers in the future. The development of new and increasingly sophisticated techniques for the authentication and analysis of foods will enable detection of chemical hazards both more rapidly and at levels lower than previously possible.

Although it is impossible to predict the next chemical food safety crisis such as acrylamide or melamine, some general predictions can be made. First, new, undiscovered heat-produced toxins and mycotoxins will likely be found in foods. Second, as the number and volume of imported ingredients increase, there will likely be more occurrences of both intentional and unintentional chemical contamination events. Finally, new food packaging materials are being designed with engineered nanoscience materials (nanoparticles) for the purpose of increasing barrier properties or strength (108). Whereas the nanoparticles produce new functional attributes, they also may have toxicological properties different from those of conventionally sized particles of the same material (108). Research is needed to establish the safety of these new food packaging materials.

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