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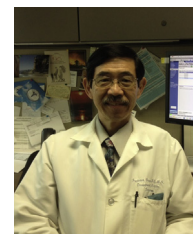
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Review Article

Food safety in the 21st century

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ABSTRACT

Food is essential to life, hence food safety is a basic human right. Billions of people in the world are at risk of unsafe food. Many millions become sick while hundreds of thousand die yearly. The food chain starts from farm to fork/plate while challenges include microbial, chemical, personal and environmental hygiene. Historically, documented human tragedies and economic disasters due to consuming contaminated food occurred as a result of intentional or unintentional personal conduct and governmental failure to safeguard food quality and safety. While earlier incidents were mainly chemical contaminants, more recent outbreaks have been due to microbial agents. The Disability Adjusted Life Years (DALYs) attributed to these agents are most devastating to children younger than 5 years of age, the elderly and the sick. To ensure food safety and to prevent unnecessary foodborne illnesses, rapid and accurate detection of pathogenic agents is essential. Culture-based tests are being substituted by faster and sensitive culture independent diagnostics including antigen-based assays and polymerase chain reaction (PCR) panels. Innovative technology such as Nuclear Magnetic Resonance (NMR) coupled with nanoparticles can detect multiple target microbial pathogens' DNA or proteins using nucleic acids, antibodies and other biomarkers assays analysis. The food producers, distributors, handlers and vendors bear primary responsibility while consumers must remain vigilant and literate. Government agencies must enforce food safety laws to safeguard public and individual health. Medical providers must remain passionate to prevent foodborne illnesses and may consider treating diseases with safe diet therapy under proper medical supervision. The intimate collaboration between all the stakeholders will ultimately ensure food safety in the 21st century.

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Introduction and historical perspective

Food safety is a basic human right

Billions of people in the world are at risk of unsafe food. Many millions become sick while hundreds of thousands die every year because they consume unsafe food. Therefore, safe food saves lives. Safe food enhances individual and population health. Safe food improves economic growth of the region where food safety is practiced and enhanced. Safe food supply depends on both sound science and equitable law enforcement. With technological advances, new regulations must be enacted to protect a continuing supply of food products that are safe and wholesome for the health and wellness of people.

As the standard of living improves, concerns over food safety and potential contaminants will continue to be an important health issue. Consumers demand quality and safety of products they consume because food as energy and nutrient is necessary to sustain life. In general, consumers rely on government to ensure all food products not only are safe but are sold as what they claim to contain. For example, a jar of olive oil labeled as 100% virgin olive oil must contain exactly what the label says except the naturally occurring trace elements that are part of olive oil and which cannot be extracted or eliminated completely without destroying the olive oil.

Challenges and tragedies in food safety include chemical, biological, personal hygiene and environmentally related incidents. Historically, incidents of food products contaminated with industrial pollutants have been well documented. Japan, Iraq, United States and other nations experienced incidents where hundreds and thousands of people fell ill or died.

Most notorious is the Minamata disease (methylmercury poisoning) first discovered in 1956 around Minamata Bay in Kumamoto Prefecture, Japan. A second epidemic occurred in 1965 along the Agano River, in Niigata Prefecture, Japan. Symptoms of this disease included cerebellar ataxia, sensory disturbance, narrowing of the visual field, and hearing and speech disturbances. The discharged methyl mercury accumulated in fishes and shellfishes and caused poisoning on consumption [1,2].

Before 1960, the local population in the Jinzu river basin of Japan suffered an endemic illness called “Itai–Itai” due to the residents in that area consumed rice contaminated with high level of cadmium. An investigation in 1961 determined that the Mitsui Mining and Smelting’s Kamioka Mining Station caused the cadmium pollution and that the worst-affected areas were 30 km downstream of the mine. Not until 1968 the Ministry of Health and Welfare of Japan issued a formal statement about the symptoms of “itai–itai” disease is in fact caused by the cadmium poisoning [3].

In 1968, a mass poisoning by polychlorinated biphenyls (PCBs) occurred in northern Kyushu, Japan where rice oil that had become contaminated by heat-degraded PCBs during processing. These patients suffered a unique skin disease called chloracne. In addition, hepatic, reproductive, endocrine, neurobehavioral and carcinogenic effects have been described. The illness was coined “Yusho” disease (literally oil syndrome). It should be noted that Yusho was not a deliberate contamination of cooking oil [4,5].

In 1971–72, a large outbreak of mercury poisoning caused by the consumption of seed dressed with organomercury compounds occurred in Iraq. The source of organomercury came from seeds are treated with fungicides before planting, mainly to control infection by seed- or soil-borne fungi. Patients who consumed these seeds suffered tremor, confusion, hallucination, delusion and seizure [6].

Similar food contamination incidents have appeared in Taiwan around 1979. It was discovered that cooking oil contaminated with PCBs and dibenzofurans (PCDFs) was sold to the public. The volume of contaminated oil and the nature of oil processing, packaging, labeling, distribution, sales, and usage were extensive that about 2000 people consumed contaminated eating oil. A recent study concludes that exposure to PCBs and PCDFs may increase mortality pattern even 3 decades later [7]. The short and long term health consequences of people consumed contaminated oil during recent (2014–5) oil incidents in Taiwan are yet to be studied.

In 1989, the United States Food & Drug Administration (US FDA) issued a “fats and oils” injunction against brokers buying and selling non-feed oils, such as waste industrial oil, and labeled them for animal feed use. One case evolved from findings PCB residue in turkeys marketed for human food. FDA field investigators traced the PCBs to waste oils from a chemical plant’s scum pond, labeled “industrial waste not for animal feed use.” Further investigation showed that merchants “buy and sell” railcars and tankers of oils and invoice the products to feed manufacturers as feed grade regardless of source. The manufacturer might have blended it with other fats and oils so its original identity and any contaminants were greatly diluted. This US incident was not widespread because of the alert FDA field investigators program and state of the art food toxicology laboratory that stopped a major crisis [8].

In the 21st century, food safety issues have not waned. Local outbreaks can turn into international emergencies due to the speed and range of product distribution. Serious food-borne disease outbreaks have occurred on every continent. In China alone, the 2008 contamination of infant formula with melamine affected 300,000 infants and young children, 51,900 were hospitalized and 6 of whom died. In addition to renal damages, complications such as tumorigenesis or growth retardation in the future have been raised [9,10].

In 2011, the *Enteropathogenic Escherichia coli* (EHE coli) outbreak in Germany linked to contaminated fenugreek sprouts, where cases were reported in 8 countries in Europe and North America, leading to 53 deaths. The 2011 *E. coli* outbreak in Germany caused US\$ 1.3 billion in losses for farmers and industries and US\$ 236 million in emergency aid payments to 22 European Union Member States [11].

Unsafe food poses global health threats. The young, the elderly and the sick are particularly vulnerable. If food supplies are unsecured, population shifts to less healthy diets and consume more “unsafe foods” – in which chemical, microbiological and other hazards pose health risks, that in turn costs higher healthcare expenditure and drains national wealth [12]. In light of recurrent food contamination incidents, food safety in the 21st century should expand beyond improving nutritional profile, transparency of ingredients and regulations of unhealthy foods to include regular monitoring,

surveillance and enforcement of food products in furtherance of the general public well-being and prevention of foodborne illnesses [13]. For up to date information, the Center for Science in the Public Interest provides comprehensive tracking and documentation of foodborne illness outbreaks since 1997 [14].

Major challenges of food safety

Challenges of food safety include four major areas

- **Microbiological Safety.** Food by nature is biological. It is capable of supporting the growth of microbials that are potential sources of foodborne diseases. Viruses are more responsible for the majority of foodborne illnesses but hospitalizations and deaths associated with foodborne infections are due to bacterial agents. The illnesses range from mild gastroenteritis to neurologic, hepatic, and renal syndromes caused by either toxin from the disease-causing microbe. Foodborne bacterial agents are the leading cause of severe and fatal foodborne illnesses. Over 90% of food-poisoning illnesses are caused by species of *Staphylococcus*, *Salmonella*, *Clostridium*, *Campylobacter*, *Listeria*, *Vibrio*, *Bacillus*, and *E. coli*. For instance, in the US and France, in the last decade of the 20th century, *Salmonella* was the most frequent cause of bacterial foodborne illness accounting for 5700 to 10,200 cases, followed by *Campylobacter* for 2600 to 3500 cases and *Listeria* for 304 cases [15].
- **Chemical Safety.** Nonfood grade chemical additives, such as colorants and preservatives, and contaminants, such as pesticide residues, have been found in foods. Some food samples had higher levels of heavy metals such as lead, cadmium, arsenic, mercury, and copper than average food samples, suggesting possible leaching from the utensils and inadequate food hygiene.
- **Personal Hygiene.** Poor personal hygiene practices of food handler and preparers pose considerable risks to personal and public health. Simple activities such as thorough hand washing and adequate washing facilities can prevent many foodborne illnesses.
- **Environmental Hygiene.** Inadequate recycling and waste disposal equipment and facilities lead to the accumulation of spoiled and contaminated food. This leads to an increased pest and insect population that can result in risk of food contamination and spoilage. Poor sanitary conditions in the area where foods are processed and prepared contribute to poor food storage and transport as well as selling of unhygienic food.

Why is safe food supply important?

A safe food supply is important because of significant disease burden as well as economic burden to the society and nation. In US alone, foodborne illnesses each year result in 325,000 hospitalizations and 5000 deaths [16]. Worldwide, it has been estimated that more than one billion (1,000,000,000) episodes of food poisoning-related diarrhea occur annually [16]; these

poisonings are responsible for the deaths of about 3 million children a year, mostly in underdeveloped regions.

Foodborne illnesses associated with microbial pathogens or other food contaminants pose serious health threat in developing and developed countries. WHO estimates less than 10% of foodborne illness cases are reported whereas less than 1% of cases are reported in developing nations [17]. In a recent report, WHO estimates 600 million foodborne illnesses and 420,000 deaths in 2010. The most frequent causes of foodborne illness were diarrheal disease agents, particularly norovirus and *Campylobacter* spp. Other major causes of foodborne deaths were *Salmonella typhi*, *Taenia solium*, hepatitis A virus, and mycotoxins especially aflatoxins [18,19].

Children are disproportionately bearing this burden - accounting for an estimated half of foodborne illness cases annually. Children are also among those most at risk of associated death and serious lifelong health complications from foodborne diseases. They are at high risk for foodborne illness for a number of reasons. Children have developing immune systems that are not always well equipped to fight infection; they are often smaller in size than adults, reducing the amount of pathogen needed to make them sick; and children have limited control over their diets and lack the developmental maturity necessary to carefully judge food safety risks.

From economic perspective, access to sufficient amounts of safe and nutritious food is crucial to sustaining life, promoting good health and economic growth. According to one study, the average cost per case of foodborne illness (in US dollars) was \$1626 for the enhanced cost-of-illness model and \$1068 for the basic model. The resulting aggregated annual cost of illness was \$77.7 billion and \$51.0 billion for the enhanced and basic models, respectively. The study defines basic cost-of-illness model to include economic estimates for medical costs, productivity losses, and illness-related mortality. The enhanced cost-of-illness model replaces the productivity loss estimates with a more inclusive pain, suffering, and functional disability measure based on monetized quality-adjusted life year estimates [20].

Major foodborne illnesses and burden

According to US Centers for Disease Control, foodborne diseases cause an estimated 48 million illnesses each year in the United States, including 9.4 million caused by known pathogens. The pathogen-commodity pairs most commonly responsible for outbreaks were scombroid toxin/histamine and fish (317 outbreaks), ciguatera and fish (172 outbreaks), *Salmonella* and poultry (145 outbreaks), and norovirus and leafy vegetables (141 outbreaks). The pathogen-commodity pairs most commonly responsible for outbreak-related illnesses were norovirus and leafy vegetables (4011 illnesses), *Clostridium perfringens* and poultry (3452 illnesses), *Salmonella* and vine-stalk vegetables (3216 illnesses), and *C. perfringens* and beef (2963 illnesses) [21,22]. Examples of unsafe food that commonly contain these hazards include uncooked foods of animal origin, fruits and vegetables contaminated with feces, raw shellfish and industrial pollution.

In a comprehensive estimation, the 2015 WHO report not only provides numbers of foodborne illnesses in terms of incidence but also number of deaths and Disability Adjusted Life Years (DALYs) as a measure of burden due to foodborne related morbidity and mortality. The DALYs data are based on the metrics established by WHO and are consistent with the Global Burden of Disease project [18]. Together, these foodborne hazards caused an enormous human burden of 33 millions DALYs with 40% among children younger than 5 year-old. With substantial global burden of foodborne diseases and deaths, the impact is most significant among young children living in low income regions where food hygiene and water sanitation are below optimal standards. Therefore, improving microbial, personal, chemical and environmental health will improve overall health of children and adults alike. It should be noted that antimicrobial overuse and misuse in veterinary and human medicine has been linked to the emergence and spread of resistant bacteria, rendering the treatment of infectious diseases ineffective in animals and humans [24].

From a global perspective, most foodborne pathogens and toxins, along with morbidity, mortality and health burden are summarized in Table 1. Commonly encountered microbial pathogens and toxins include the following categories. A brief description of their illnesses is provided below for a quick reference.

- **Bacteria:** *Salmonella*, *Campylobacter*, and *Enterohemorrhagic Escherichia coli* (EHE coli) are among the most common foodborne pathogens. Symptoms include fever, headache, nausea, vomiting, abdominal pain and diarrhea. Sources of salmonellosis include eggs, poultry and other products of animal origin. Foodborne *Campylobacter* is caused by raw milk, raw or undercooked poultry and drinking water. EHE coli are associated with unpasteurized milk, undercooked meat and fresh fruits and vegetables. *Listeria* infection increases the risk of spontaneous abortions and stillbirths. *Listeria* is found in unpasteurized dairy products and various ready-to-eat foods and can grow at refrigeration temperatures. *Vibrio cholerae* infects people through contaminated water or food. Symptoms include abdominal pain, vomiting and profuse watery diarrhea, which may lead to severe dehydration and possibly death. Rice,

vegetables, millet gruel and various types of seafood have been implicated in cholera outbreaks.

- **Viruses:** Norovirus infections are characterized by nausea, explosive vomiting, watery diarrhea and abdominal pain. Food handlers infected with Hepatitis A virus are common source of contamination and spreads typically through raw or undercooked seafood or contaminated raw produce.
- **Parasites:** Some parasites, such as fish-borne trematodes, are only transmitted through food. Others, for example *Echinococcus* spp, may infect people through food or direct contact with animals. Other parasites, such as *Ascaris*, *Cryptosporidium*, *Entamoeba histolytica* or *Giardia*, enter the food chain via water or soil and can contaminate fresh produce.
- **Worms:** Cestodes, nematodes, trematodes and helminths are worms most prevalent in regions where food preparation and storage, personal hygiene, water sanitation and environmental health are not routinely practiced. Even though worm related foodborne illness are not as fatal as virus and bacteria, they account for a substantial burden to foodborne disability.
- **Chemicals:** Naturally occurring toxins and environmental pollutants have caused many outbreaks. In addition, chemical residues used to eradicate or control pests and worms can be an independent risk of foodborne hazard. Mycotoxins, marine biotoxins, cyanogenic glycosides and poisonous mushrooms are all natural toxins. Staple foods like corn or cereals can contain high levels of mycotoxins, such as aflatoxin and ochratoxin. A long-term exposure can affect the immune system and normal development, or cause cancer. Environmental pollutants are becoming major concerns for pediatricians and public health practitioners. Persistent organic pollutants (POPs) are compounds that accumulate in the environment and human body. Dioxins and polychlorinated biphenyls (PCBs) are byproducts of industrial processes and waste incineration. They are found in the environment and accumulate in animal food chains. Dioxins are highly toxic and can cause reproductive and developmental problems, damage the immune system, interfere with hormones and cause cancer. Finally, heavy metals such as lead, cadmium and mercury can cause neurological and kidney damage. Contamination by heavy metals in food occurs mainly through environmental pollution of air, water and soil.

Table 1 Common foodborne pathogens and their medical and economic impacts.

Foodborne hazards	Common Infectious or toxic agents	Incidence of foodborne illness	Death due foodborne illness	Total DALYs
Bacteria	<i>Salmonella</i> , <i>Vibrio</i> , <i>E. coli</i> , <i>Shigella</i> , <i>Listeria</i> , <i>Brucella</i> , <i>Listeria</i> , <i>Campylobacter</i>	359,747,420	272,554	20,188,792
Virus	Noro virus, Hepatitis A	138,513,782	120,814	3,849,845
Protozoa	<i>Entamoeba</i> , <i>Giardia</i> , <i>Cryptococcus</i> , <i>Toxoplasma</i>	77,462,734	6242	1,311,435
Worms	Cestodes (tapeworms), Nematodes (round worms), Trematodes (flatworms); helminths (parasites)	26,063,664	90,261	11,599,735
Chemicals	Aflatoxins, Cyanogenics, Dioxins, Heavy Metals	217,632	19,712	908,356

The Uncertainty Intervals (UI) are not shown

Source: Extracted and compiled from Ref. [18]

Diagnostic advances to ensure food safety

Due to the globalization of the world's food trade, food has become a major pathway for human exposure to pathogenic microbials responsible for foodborne illness entering at many points along the value chain [23]. Thus, tracking and detecting microbials especially pathogenic bacteria in foods back to their sources pose challenges to producer, processor, distributor, and consumer of food alike. In addition, clinicians and epidemiologists are frequently confronted with diagnostic and treatment uncertainty of patients with potential foodborne infectious diseases at the point of care.

Rapid and accurate detection of foodborne pathogens is essential for public health bio-surveillance to prevent foodborne infections and ensure the safety of foods. Detection methods of microbials have improved over time [25–27]. Generally speaking, culture-based tests are being substituted by faster and more sensitive culture-independent diagnostic tests such as antigen-based assays and PCR panels [28]. However, these tests are used mainly in the public health laboratories not readily available for practitioners in the industry and clinical fields.

Non-culture based applications are gaining importance mainly because of their relatively quick results when compared with culture based methodologies. There are several diagnostic technologies to detecting pathogenic microbes such as *Salmonella* and *Vibrio* spp in animals and food. Ideally, microbial pathogens and contaminants can be detected at relatively low cost in the field because of assay and instrument simplicity. This will ensure higher sampling efficiency of analyte of interest as a result of higher sample measurement volume, detects with near 100% specificity and accuracy as a result of orthogonal measurement [29] of biomarkers with flexibility in sample type such as soil, feces, animal tissue, fruits, water and blood. The goals are savings in time due to higher speed of detection and savings to overhead expenses. However, Point of Need Test (PONT) devices for field diagnostics do not exist for many of the pathogens of interest in agriculture, animal farming, aquaculture, wild caught animals, and food safety in general.

- NMR-nanotechnology

Nuclear Magnetic Resonance (NMR) nanotechnology platform detects multiple target microbials hybridizing to pathogen's DNA or protein in same the device chamber that runs

assays using nucleic acid, antibodies, and other biomarkers [30]. Orthogonal confirmatory tests can be achieved via multiple biomarkers of single microbial in same detection device. This raises specificity and accuracy thus serving as both screening and confirming tool at the same time. It has a dynamic range of 8 log before saturation, more sensitive than other systems due to standard amplification process plus signal amplification through the nanoparticles. Hence, this technology increases the sensitivity and specificity of detecting target microbial. End point PCR can be applied on DNA amplification while antibody ligands method can be used for protein structure amplification. Multiplexing with large sample volume enables multiple biomarker measurements to be analyzed thus further increases specificity of the detection method.

- PCR-based

Polymerase chain reaction (PCR) based assay enzyme linked immuno-sorbent assay (ELISA) and instruments rely on extensive enrichment (up to 24 h) to produce enough cells for detection. Following enrichment, the assay requires DNA amplification and detection. The entire process from enrichment through detection may take several hours to days. Because of sample preparation processes and ancillary lab equipment (shakers, incubators, microplate readers) such detection system may not be practical as PONT devices. Another commonly utilized technology is based on either standard or real-time PCR (qPCR) depending on the instrument and takes up to 3.5 h for detection. The system is limited to using PCR method thus unable to perform multiple biomarkers detection. Table 2 provides an example of comparing two non-culture based detection systems for *Salmonella* [31,32]. The commercial testing brand names are not mentioned in this analysis.

Medical provider's role in food therapy

Most medical professionals have focused on the treatment of diseases without seeking which are caused by long-term exposure to problematic food and food products. Some dietitians tend to keep counting the calories of macronutrients without considering chemicals adding in the food and food product that have no nutrient values. The food industry for business reasons may look mainly for continuous profit over the health of general population. Many diseases could be

Table 2 Provides an example of comparing two non-culture based detection systems for *Salmonella*.

Non-culture based microbial detection	NMR Nanotech (microbes, nucleic acids, proteins)	PCR (<i>Salmonella</i>)
Detection method	PCR-NMR	Isothermal PCR
Sample-to-answer time	<1 h	10–26 h
Sample type	Food, tissue, water, soil, feces	Fish tissue
Sample size	1–325 g (food); 0.1 g (eg. shrimp tissue)	25–325 g
Limits of detection (LOD)	103 colony forming unit (CFU)/mL post-enrichment; 1–10 CFU/analytical unit	104 CFU/mL post-enrichment; 1 CFU/analytical unit
Sensitivity	>98%	98.7%
Specificity	Near 100%	98.3%

Source: Ref. [31,32] Commercial testing brand names not mentioned

prevented or treated with appropriate and safe food under proper medical supervision. Ketogenic diet therapy for epilepsy is a good example. This medical food therapy began at least 100 years ago, but was abandoned gradually over the next five decades because of the appearance of antiepileptic drugs [33,34]. This approach has been revived about 20 years ago because 40% of epileptic patients are resistant to antiepileptic medications. As a result of medically promising indications of the ketogenic diet, it is expanding its therapeutic efficacy from epilepsy to diabetes mellitus, malignancies, and many selective neurodegenerative disorders [35–37]. Therefore, the important role of medical providers in food therapy cannot be over emphasized. The late Professor Ja-Liang Lin, aka Lin Chieh-liang [38], renowned toxicologist–nephrologist left behind an important legacy that serves as a role model [39] for medical professionals to exercise the duty to improve and safeguard food quality and safety of Taiwan and international community for many years to come.

Government's role to regulate and enforce food safety

Safe food supply depends on both sound science and equitable law enforcement. Periodically, new laws and regulations must be enacted to further protect a continuing supply of food products that are safe and wholesome for the health and wellness of people.

In most countries, the overarching goal of having Food and Drug Administration (FDA) or similar agency is to take responsibility for compliance of food safety law to ensure a three-fold aim in protecting public health and safety: (1) inform citizens of nutrition and components of important food products; (2) enforce existing laws and regulations on food industry to ensure supply of safe food products; and (3) investigate and eliminate potential toxic contaminants and prosecute economic fraud via regular monitoring and surveillance on chain of food supply.

Once the laws are enacted, they must be enforced to ensure compliance by the entire food industry including industries that are directly or indirectly connected with the food source, labeling, packaging, transportation, distribution down to retail sales. The FDA is given resources and authority to write rules and regulations, assemble experts both as agency employees or consultants so to fulfill the three-prong aim of informing, enforcing and eliminating any food related safety and risk.

All governmental agencies involved in potential food chain supply must be given resources and authorities to discharge the 3-fold duty of (1) inform, (2) enforce, and (3) eliminate as described above. In addition to FDA, other governmental agencies collaborations are required. For example, US Environmental Protection Agency (EPA) is in charge of safe drinking water, clean air, and nontoxic natural resources such as soil and land; the US Department of Agriculture (USDA) is in charge of ensuring animal and plant health, as well as food and nutrition services; and Immigration and Customs Enforcement of US Department of Justice are all involved in stopping illegal and contaminated toxic substances. Therefore, to enforce food safety, inter-agency sharing of

information and database is necessary [40]. Some have proposed to expand FDA's discretionary authority as part of the anti-terrorism in the post-9/11 period, particularly with respect to FDA's authority to monitor and publicize potential health risks linked to food, dietary supplements, nonprescription drugs, and other consumer health products [41].

To equitably enforce food safety laws, sound science must be the basis of setting the regulations and protocols to inform, enforce and eliminate unsafe foods. Risk assessment is a scientific process that puts the concern about food contaminations in proper perspective. As the purpose of scientific risk calculation is to get the best estimate of the true risk using available and current information.

Generally, to assure the public safety, regulatory agencies go beyond scientific risk. To calculate regulatory risk, agencies first start with the scientific risk level. Then, the maximum consumption is estimated as if that item is consumed daily for a person's entire lifetime. This risk is multiplied by a factor of 100 or 1000 [42,46] as additional safety factor for the vulnerable individuals. Animal toxicology studies and any available human reports and studies are extensively reviewed and analyzed for relevancy and validity. The sponsor (usually the food manufacturer) must establish scientifically that the substance is safe and free from contamination. The sponsor must also demonstrate that any residues remaining in a food product pose no threat to human health, both acutely and chronically. If toxicological studies raise the suspicion that a contaminant may cause cancer, the agency may require the sponsor to conduct chronic feeding studies in animals. If the results show that the chemical causes cancer, the FDA uses a conservative risk assessment procedure to determine how much contaminant presents the consumer with no significant risk of cancer. Under this procedure the FDA allows the upper limit of lifetime risk of cancer to be one in one million (that is, if one million consumers ingested the contaminant for their entire lifetime of 70 years, one of them might get cancer from the drug/chemical residue). Such a risk is approximately 10 times less than the risk of being struck by lightning [42–47].

Programs and tools to ensure the safety of food supply

In general, periodic food monitoring provides a 95% assurance that microbial or chemical contaminant of any targeted food is detected if it occurs in more than 1% of product lots. Food surveillance is used to investigate and control the movement of potentially contaminated products. The field inspectors are granted the power of the agency vested by the executive branch of the government. Anonymous tips may trigger some food products for surveillance testing if they appear reasonably suspicious of foul play such as unclear labeling, or coming from questionable sources. Contaminants above legal limits are to be re-tested in split samples given to two separate laboratories to ensure fairness. Food safety inspector has responsibility to inspect foods during packaging, labeling, processing and distribution and storage. Similarly, inspector of different training may assume responsibility when the food products are in the grocery store or in retails.

The voluntary report of “accidental” exposure program has worked well in many countries. Food products may accidentally be exposed to contaminants without any deliberate or knowingly use contaminated products such as microbial, pesticides, industrial chemicals or natural toxicants. In such event, the merchant or manufacturer may voluntarily report such contamination to FDA. FDA may then send specially trained consultant to provide regulatory and scientific assistance to the food industry. Depending on the nature and extent of consultation, consultant or laboratory fees may be assessed to be paid by the company owner or corporation [48].

In the US, programs such as the Food Safety and Inspection Service (FSIS) ensure safety of current and future food supply must be implemented. Regular monitoring, surveillance and voluntary report or recall are all part of risk management that will minimize mishaps and ensure safe food supply [50]. The Pathogen Reduction/Hazard Analysis & Critical Control Points System has been implemented by US FDA so that food safety risks are addressed more adequately and the allocation of inspection resources is improved further [48–50].

The future food safety

Safe food provides basic human necessity. It supports national economy, trade and tourism, contributes to nutrition security, and underpins sustainable development. Globalization has triggered growing consumer demand for a wider variety of foods, resulting in an increasingly complex and longer global food chain. As the world's population grows, the intensification and industrialization of agriculture and animal production to meet increasing demand for food creates both opportunities and challenges for food safety. The food producers, distributors, handlers and vendors must bear the primary responsibility to ensure food safety. Consumers should remain vigilant and literate on food safety issues. Government agencies such as FDA and EPA are the legal enforcers to protect public health and safety. They must enforce the law equitably and with fairness.

The legal professionals appear to be more active in advocating food safety in the global market. The medical and healthcare professionals should be equally passionate to take the lead in addressing food safety. After all, safe and nutritious food implies healthier population. Regardless of who is taking the lead in food safety, in the end, a close collaboration between all the stakeholders should be the goal in achieving a meaningful food safety for every person in a global perspective [51–55].

In summary, food safety and nutrition are closely connected. Unsafe food creates a vicious cycle of disease and malnutrition affecting infants, young children, elderly and the sick. Because food supply chains cross multiple national and regional borders, collaboration between governments, producers, suppliers, distributors and consumers will ultimately ensure food safety in the 21st century.

Conflicts of interest

The authors declare no conflict of interest.

REFERENCES

- [1] Eto K. Minamata disease. *Neuropathology* 2000;20:S14–9.
- [2] Shimohata T, Hirota K, Takahashi H, Nishizawa M. Clinical aspects of the Niigata Minamata disease. *Brain Nerve* 2015;67:31–8.
- [3] Ikeda M, Ezaki T, Tsukahara T, Moriguchi J. Dietary cadmium intake in polluted and non-polluted areas in Japan in the past and in the present. *Int Arch Occup Health* 2004;77:227–34.
- [4] Umeda G. PCB poisoning in Japan. *Ambio* 1972;1:132–4.
- [5] CDC. Polychlorinated Biphenyls (PCBs) toxicity - What are adverse health effects of PCB exposure?. <http://www.atsdr.cdc.gov/csem/csem.asp?csem=30&po=10>. [Accessed 5 November 2017].
- [6] Skerfving SB, Copplestone JF. Poisoning caused by the consumption of organomercury-dressed seed in Iraq. *Bull World Health Organ* 1976;54:101–12.
- [7] Li MC, Tsai PC, Chen PC, Hsieh CJ, Leon Guo YL, Rogan WJ. Mortality after exposure to polychlorinated biphenyls and dibenzofurans: 30 years after the “Yucheng accident”. *Environ Res* 2013;120:71–5.
- [8] Miksch D, Means W, Johns J. Food Safety: Residues in Animal-Derived Foods. Issued: 8–90. University of Kentucky Agricultural Communication Services. <http://www2.ca.uky.edu/agcomm/pubs/ip/ip11/ip11.htm>. [Accessed 5 November 2017].
- [9] El-Nezami H, Tam PK, Chan Y, Lau AS, Leung FC, Chen SF, et al. Impact of melamine-tainted milk on foetal kidneys and disease development later in life. *Hong Kong Med J* 2013;19:S34–8.
- [10] US FDA 2009. <http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm179005.htm>. [Accessed 5 November 2017].
- [11] Yeni F, Yavaş S, Alpas H, Soyer Y. Most common foodborne pathogens and mycotoxins on fresh produce: a review of recent outbreaks. *Crit Rev Food Sci Nutr* 2015;56:1532–44.
- [12] CDC. Questions about the 2011 E. Coli outbreak in Germany. 2011. <http://www.cdc.gov/ecoli/general/germany.html>. [Accessed 5 November 2017].
- [13] Silver L, Bassett M. Food safety for the 21st century. *JAMA* 2008;300:957–9.
- [14] Center for science in the public interest Accessed 11/20/2017. http://www.cspinet.org/foodsafety/outbreak_report.html. [Accessed 5 November 2017].
- [15] Vaillant V, de Valk H, Baron E, Ancelle T, Colin P, Delmas MC, et al. Foodborne infections in France. *Foodb Pathog Dis* 2005;2:221–32.
- [16] Mead PS, Slutsker L, Dietz V, McCaig LF, Bresee JS, Shapiro C, et al. Food-related illness and death in the United States. *Emerg Infect Dis* 1999;5:607–25.
- [17] Satcher D. Food safety: a growing global health problem. *JAMA* 2000;283:1817.
- [18] WHO. WHO estimates of the global burden of foodborne diseases Foodborne diseases burden epidemiology reference group 2007–2015. 2015. http://www.who.int/foodsafety/publications/foodborne_disease/fergreport/en/. [Accessed 5 November 2017].
- [19] Fung F, Clark R. Health effects of mycotoxins: a toxicological review. *Clin Toxicol* 2004;42:217–34.
- [20] Scharff RL. Economic burden from health losses due to foodborne illness in the United States. *J Food Protect* 2012;75:123–31.
- [21] Painter JA, Hoekstra RM, Ayers T, Tauxe RV, Braden CR, Angulo FJ, et al. Attribution of foodborne illnesses, hospitalizations, and deaths to food commodities by using outbreak data, United States, 1998–2008. *Emerg Infect Dis* 2013;19:407–15.

- [22] Gould LH, Walsh KA, Vieira AR, Herman K, Williams IT, Hall AJ, et al. Surveillance for foodborne disease outbreaks - United States, 1998-2008. *MMWR Surveill Summ* 2013;62:1–34.
- [23] Godfray HC, Beddington JR, Crute IR, Haddad L, Lawrence D, Muir JF, et al. Food security: the challenge of feeding 9 billion people. *Science* 2010;327:812–8.
- [24] Cabello FC, Godfrey HP, Buschmann AH, Dölz HJ. Aquaculture as yet another environmental gateway to the development and globalization of antimicrobial resistance. *Lancet* 2016;16:e127–33.
- [25] Collignon P. Superbugs in food: a severe public health concern. *Lancet* 2013;13:641–3.
- [26] Devaraj NK, Weissleder R. Biomedical applications of tetrazine cycloadditions. *Acc Chem Res* 2011;44:816–27.
- [27] Mangal M, Sangita B, Satish SK, Ram GK. Molecular detection of foodborne pathogens: a rapid and accurate answer to food safety. *Crit Rev Food Sci Nutr* 2016;56:1568–84.
- [28] Huang JY, Henaol OL, Griffin PM, Vugia DJ, Cronquist AB, Hurd S, et al. Infection with pathogens transmitted commonly through food and the effect of increasing use of culture-independent diagnostic tests on surveillance — foodborne diseases active surveillance network, 10 U.S. Sites, 2012–2015. *MMWR Morb Mortal Wkly Rep* 2016;65:368–71.
- [29] FDA. Acceptance Criteria for Confirmation of Identity of Chemical Residues using Exact Mass Data within the Office of Foods and Veterinary Medicine. September 2015. Palmer Orlandi Jr., Ph.D., Chair FDA FVM Science and Research Steering Committee, Acting OFVM Chief Science Officer/ Research Director, <https://www.fda.gov/downloads/ScienceResearch/FieldScience/UCM491328.pdf>. [Accessed 5 November 2017].
- [30] Yang P, Hash S, Park K, Wong C, Doraisamy L, Petterson J, et al. Application of nuclear magnetic resonance to detect toxigenic *Clostridium difficile* from stool specimens: a proof of concept. *J Mol Diagn* 2017;19:230–5.
- [31] Yang P, Wong C, Hash S, Fung F, Menon S. Rapid detection of *Salmonella* spp using magnetic resonance. *J Food Saf* 2018;e12473.
- [32] Ferguson BA. Look at the microbiology testing market. *Food Safety Magazine*; February/March 2017. <https://www.foodsafetymagazine.com/magazine-archive1/februarymarch-2017/a-look-at-the-microbiology-testing-market/>. [Accessed 5 November 2017].
- [33] Wilder RM. The effect of ketonemia on the course of epilepsy. *Mayo Clin Bull* 1921;2:307–8.
- [34] Kossoff EH, Wang HS. Dietary therapies for epilepsy. *Biomed J* 2013;36:2–8.
- [35] Yancy WS, Foy M, Chalecki AM, Vernon MC, Westman EC. A low-carbohydrate, ketogenic diet to treat type 2 diabetes. *Nutr Metab* 2005;2:34.
- [36] Smyl C. Ketogenic diet and cancer—a perspective. *Recent Results Canc Res* 2016;207:233–40.
- [37] Paoli A, Bianco A, Damiani E, Bosco G. Ketogenic diet in neuromuscular and neurodegenerative diseases. *BioMed Res Int* 2014;2014:474296.
- [38] Toxicologist Lin Chieh-liang leaves behind important legacy. <http://englishnews.ftv.com.tw/Read.aspx?sno=18B34EB3C0C1716FA011354FAB3C3F13>. [2013/08/05 News, Accessed 5 November 2017].
- [39] Yen TH, Lin-Tan DT, Lin JL. Food safety involving ingestion of foods and beverages prepared with phthalate-plasticizer-containing clouding agents. *J Formos Med Assoc* 2011;110:671–84.
- [40] Johnson Renée. The federal food safety system: a primer. In: Congressional research service; 2015. <http://nationalaglawcenter.org/wp-content/uploads/assets/crs/RS22600.pdf>. [Accessed 5 November 2017].
- [41] Roller ST, Pippins RR, Ngai JW. FDA's expanding postmarket authority to monitor and publicize food and consumer health product risks: the need for procedural safeguards to reduce "transparency" policy harms in the post-9/11 regulatory environment. *Food Drug Law J* 2009;64:577–98.
- [42] Phillips L, Moya J. EPA's exposure factors handbook. *J Expo Sci Environ Epidemiol* 2013;23:13–21.
- [43] Sischo WM. Symposium: drug residue avoidance: the issue of testing. Quality milk and tests for antibiotic residues. *J Dairy Sci* 1996;79:1065–73.
- [44] Report of a Joint FAO/WHO Consultation Rome, Italy, 27 to 31 January 1997. Risk management and food safety. <http://www.fao.org/docrep/W4982E/w4982e00.htm> [Accessed 5 November 2017].
- [45] Center for Drug Evaluation and Research Food and Drug Administration. Guidance for industry Q9 quality risk management. U.S. Department of health and human services. Food and Drug Administration, Center for Drug Evaluation and Research (CDER); Center for Biologics Evaluation and Research (CBER); June 2006. <https://www.fda.gov/downloads/Drugs/.../Guidances/ucm073511.pdf>. [Accessed 5 November 2017].
- [46] Bars R, Fegert I, Gross M, Lewis D, Weltje L, Weyers L, et al. Risk assessment of endocrine active chemicals: identifying chemicals of regulatory concern. *Regul Toxicol Pharmacol* 2012;64:143–54.
- [47] EMPRES Food Safety Emergency Prevention System for Food Safety Strategic Plan. Viale delle Terme di Caracalla; 00153 Rome, Italy: Food and Agriculture Organization of the United Nations; May 2010. <http://www.fao.org/docrep/012/i1646e/i1646e.pdf>. [Accessed 5 November 2017].
- [48] Billy TJ, Wachsmuth IK. Hazard analysis and critical control point systems in the United States Department of Agriculture regulatory policy. *Rev Sci Tech* 1997;16:342–8.
- [49] United States Code of Federal Regulations. PR/HACCP final rule, (9 CFR chapter III). July 1996.
- [50] FDA Recalls, Outbreaks & Emergencies. <https://www.fda.gov/Food/RecallsOutbreaksEmergencies/default.htm>. [Accessed 5 November 2017].
- [51] Strauss D. An analysis of the FDA food safety modernization act: protection for consumers and boon for business. *Food Drug Law J* 2011;66:353–76.
- [52] Plunkett D, Smith DeWaal C. Who is responsible for the safety of food in a global market? Government certification v. importer accountability as models for assuring the safety of internationally traded foods. *Food Drug Law J* 2008;63:657–64.
- [53] Chyau J. Casting a global safety net—a framework for food safety in the age of globalization. *Food Drug Law J* 2009;64:313–34.
- [54] Burke JR. Warning: the imported food you are about to consume may (or may not) be harmful to your health. *J Contemp Health Law Pol* 1998;15:183–205.
- [55] Taylor MR. Lead or react? A game plan for modernizing the food safety system in the United States. *Food Drug Law J* 2004;59:399–403.