FOOD, COSMETICS AND NUTRACEUTICALS

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NOTE FROM THE CHAIRS

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The FDA's War on Pathogens: How Unknowingly Selling Unsafe Food Can Land You in Prison

By Shawn Stevens, Esq.

Over the course of the past decade, there has been an alarming increase in the number and types of food product recalls. No food, it seems, is immune. The products appearing in recent recall notices include a broadening range of unsuspecting foods such as caramel apples, ice cream, sunflower kernels, strawberries, frozen vegetables, hummus, and flour. Indeed, last year alone, over 500 food products were recalled by processors.[1] Many of these recalls were triggered because of foodborne illness outbreaks.

While the United States Department of Agriculture (USDA) regulates the safety of all meat and poultry products, the Food and Drug Administration (FDA) is responsible for ensuring the safety of all other food. Following the passage of the Food Safety Modernization Act (FSMA) in 2011, the FDA was tasked with the responsibility of overhauling the safety of this segment of the U.S. food supply. Virtually overnight, the FDA found itself in the unenviable position of needing to draft, adopt, and eventually enforce sweeping new regulations aimed at the safety of virtually all imported and domestic foods. In the years that followed, the FDA worked tirelessly to finalize new FSMA regulations requiring food processors to develop and implement comprehensive

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Nanotechnology and Food Safety

By A. Wallace Hayes, PhD,
and Michael Holsapple, PhD

Introduction

New science and new technology are the products of human dreams and imagination. Albert Einstein, the author of the theory of relativity, believed that "[i]magination is more important than knowledge." Is it too much to speculate that the history of nanotechnology began with our earliest ancestors, who used naturally occurring nanoscale materials for cave drawings, resulting in their integration into the porous surface of the cave walls, thus allowing these drawings to remain for thousands of years? Let us also not forget that the appreciation of miniaturization, the principle of nanotechnology, is not new to industries such as the electronic industry.

Thomas Jefferson, the third President of the United States, once said, "I like the dreams of the future better than the history of the past." Modern nanotechnology can certainly be attributed to the dreams and imagination of Richard Feynman, the 1965 Nobel Prize-winning American physicist. Feynman speculated that because cells were capable of manufacturing processes, humans should be able to manufacture things at the same level. And he further asked why humans couldn't manufacture at the atomic level. In 1974, Tokyo Science University professor Norio Taniguchi coined the term "nanotechnology." Subsequently, nanotechnology was off and running as a "new" technology that engaged scientists, physicists, and engineers to develop and study a broad range of nanotechnology applications.

Nanotechnology is defined as "the understanding and control of matter at dimensions between 1 and 100 nm, where unique phenomena enable novel applications."[1] "Nano" is equal to one-billionth; therefore, a nanometer (nm) is one-billionth of a meter, an extremely small unit of measurement. Nanomaterials are, indeed, very small in size. For example, a water molecule is less than one nanometer; a strand of human DNA is approximately two nanometers thick; and a typical bacterium is approximately 1,000 nanometers. Because of their extremely small size, nanomaterials may have unique physicochemical properties and, therefore, novel applications. For example, their small size leads to high surface area, and they may have greater strength, stability, and chemical and biological activities. Nanotechnology enables the development of novel materials with a wide range of potential applications that can be used in a variety of consumer, medical, commercial, and industrial products.[2] Because nanotechnology is an emerging and rapidly developing technology, information about the safety of such materials is currently limited.

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FOOD IRRADIATION

A Technology That Is Moving Away from Photons Towards Electrons

By Suresh D. Pillai, PhD

Food irradiation is one of the most extensively studied food processing technologies, but unfortunately remains one of the least understood food processing technologies by the general public.[1, 2] All around the world, foods and spices are pasteurized and decontaminated using food irradiation. The technology is not new. British scientists patented this technology for the preservation of foods in 1905. By 1921, scientists with the United States Department of Agriculture (USDA) were recommending its use to control the protozoan pathogen trichinae in pork.[3]

"Electromagnetic spectrum" is a term used for the collection of non-ionizing and ionizing electromagnetic radiation **(Figure 1)**. Radio waves, infrared, visible light, and ultraviolet (UV) are examples of non-ionizing radiation, while X-rays, gamma rays, and cosmic radiation are examples of ionizing radiation. They are termed "ionizing radiation" because these types of radiation have enough energy in them to ionize (i.e., remove electrons) from atoms that they encounter. This energy is capable of creating extensive amounts of nicks and breaks in the DNA that is in the path of such ionizing radiation. This is the reason why sunlight or radio waves are not dangerous to humans, while we need extra protection when dental offices use X-rays, or why astronauts need extra protection from the harmful effects of cosmic radiation during space walks. When microbes and insects are exposed to gamma rays or X-rays, the DNA is "shredded" to such an extent that they can no longer multiply, and they then become inactivated. Ionizing radiation, therefore, has the ability to render harmful microbial pathogens, spoilage bacteria, and harmful plant insects and pests inactive.[4, 5, 6] The food and agricultural industries leverage this ability of ionizing radiation under the collective technology term "food irradiation." The food industry can use this technology to prevent the sprouting of potatoes, reduce spoilage (extend the shelf life) of fresh produce, pasteurize foods (i.e., eliminate harmful foodborne pathogens), pasteurize or decontaminate spices (i.e., eliminate or reduce microbial pathogens) and, in unique instances, sterilize foods (e.g., food for astronauts). The different applications are based on the dose that is delivered to the different food types. Dose is measured in grays (Gy) or kilograys (kGy). **Table 1** shows the dose ranges that are typically used for the different food irradiation applications.

TABLE 1. Typical dose ranges used in food irradiation.

Application	eBeam dose
Sprouting Inhibition	0.1 kGy – 0.2 kGy
Insect Disinfestation	0.1 kGy – 0.4 kGy
Protozoan Control	0.3 kGy – 0.5 kGy
Delay of Ripening	0.5 kGy – 1.0 kGy
Controlling Fungi	1.5 kGy – 3.0 kGy
Bacterial Pathogen Control in Foods	1.5 kGy – 3 kGy
Viral Pathogen Control in Foods	3 kGy – 10 kGy

Ionizing radiation inactivates microbial cells by two main mechanisms: 1) It can cause direct effects (breaks) in the nucleic acid (DNA and RNA) of a cell; or 2) it can ionize the water molecules present within the cells. Because water makes up about 70% of any cell, the ionization of water molecules generates a large concentration of highly reactive,

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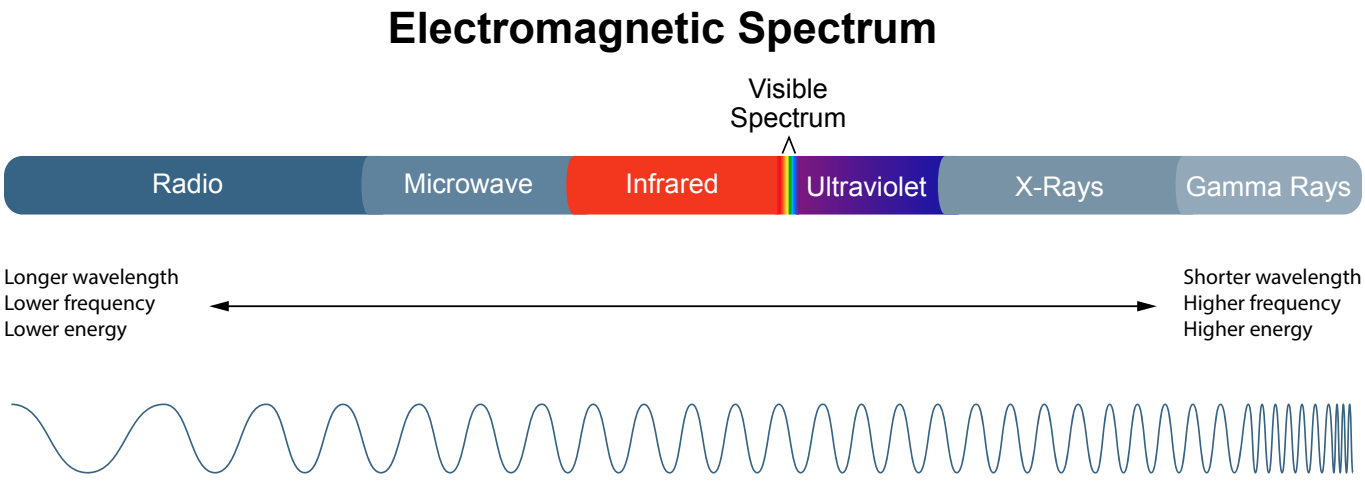
FIGURE 1. Schematic representation of the electromagnetic spectrum showing the high-energy "ionizing radiation" region on the extreme right.



written food safety and related programs to enhance the overall safety of food.

Although requiring food companies to develop and implement written food safety plans will likely have a positive impact on the safety of food in the long run, the FDA recognizes that simply requiring food companies to author new programs will not improve food safety overnight. Indeed, motivated by the 1993 Jack in the Box *E. coli* O157:H7 undercooked hamburger outbreak which sickened 600 and killed four, the USDA mandated in 1998 that all meat processors adopt written food safety plans. Notwithstanding this mandate, it took nearly 15 years before the meat industry achieved any significant decreases in the number of foodborne illnesses or recalls associated with meat products. The year 2007, for example, was known as the "Year of the Recall," during which 22 recalls involving approximately 35 million pounds of ground beef were announced because of *E. coli* O157:H7 contamination.[2] Many of those recalls were triggered because the products at issue were causing foodborne illness outbreaks. In turn, by 2012, the significant regulatory changes mandated by the USDA in 1998 began to show progress, and the number of recalls (for *E. coli*) decreased to only four, involving a mere 25,000 pounds of beef.[3]

Aware that merely enacting new regulations will have little immediate effect on food safety, the FDA has made some startling and significant policy shifts to help facilitate its mandate to overhaul the safety of the U.S. food supply. The most significant maneuver has been to threaten the use of criminal sanctions against food companies which process and sell food products that make people sick. Thus, if a company's products are linked to human illness, the Department of Justice (DOJ) has announced that it will likely initiate a criminal probe in cooperation with the FDA to determine whether there is a sufficient basis to bring criminal charges. In doing so, the FDA is, in effect, moving toward a zero-tolerance standard for foodborne illness.

This new policy represents a major departure from the policies of the past. Following the Jack in the Box *E. coli* O157:H7 outbreak in 1993, both industry and the USDA shared a general "tolerance" for foodborne illness outbreaks. At that time, *E. coli* O157:H7 was not an adulterant in ground beef. With the exception of irradiation or cooking, there was really no way to guarantee the elimination of pathogens from raw animal products. Indeed, many argued that the USDA's efforts to prevent foodborne illness by declaring *E. coli* O157:H7 to be an adulterant in ground beef (which it eventually did) would be no different than Congress trying to prevent airline crashes by repealing the laws of gravity.

As industry worked ineffectively to control pathogens in raw animal products, the government and the American consumer became resigned to the fact that foodborne illness outbreaks were likely here to stay.

In tandem with those efforts, the USDA also began mandating that beef processors affix safe handling labels to all raw animal products they sold, warning that, although "inspected and passed" by the USDA, ***raw animal products might nevertheless contain bacteria that could cause illness*** if improperly handled or cooked.[4] By virtue of these warnings, the USDA was, in essence, telling industry and consumers that raw animal products could, and should be expected to, cause foodborne illness.

As a result, in the decades which followed, and as a seemingly endless parade of *E. coli* O157:H7 outbreaks and recalls were reported, neither the beef industry nor the agency responsible for regulating the industry seemed surprised. And they weren't. Instead, following the announcement of each recall, the USDA would simply visit the facility at issue, carefully critique its programs, identify some arguable regulatory failures (even if there were arguably none), and mandate that certain corrective actions be implemented. Once those corrective actions were put into motion, business would resume as usual.

For about 20 years, this reflected the standard approach that the USDA took to outbreak response. As industry worked ineffectively to control pathogens in raw animal products, the government and the American consumer became resigned to the fact that foodborne illness outbreaks were likely here to stay.

With respect to non-meat and non-poultry products, the FDA appeared to share the same philosophy. As the government's ability to detect emerging foodborne illness outbreaks continued to improve between 2000 and 2010, an increasing number of outbreaks were being linked to FDA-regulated products. As these outbreaks were investigated, the FDA approached outbreak response in the same way as the USDA. The FDA would visit the facility involved, critique its operations, record any observations of regulatory failures, demand that changes be made and, once implemented, allow business to resume.

With the passage of the FSMA, however, the FDA was commanded by Congress to make foodborne illness stop. What followed has been a near-immediate shift by the FDA away from tolerating foodborne illness to demanding that outbreaks cease and

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aggressively penalizing companies when they occur. Indeed, FDA and DOJ criminal investigations are now a real possibility when food products make people sick.

In 2016, the DOJ acknowledged its partnership with the FDA and the agencies' cooperative policy of initiating criminal investigations against any company (or its employees) that sells a product that makes people sick. In prepared remarks, Benjamin C. Mizer, Principal Deputy Assistant Attorney General, explained that "one of the government's highest obligations is to protect citizens when they cannot protect themselves."[5] According to the agency, and the development of recent policy, the FDA and DOJ view any human illness caused by a food product as a potential violation of the law. Mizer explained, "In deciding whether to use our civil or our criminal enforcement tools, . . . prosecutors [will] evaluate the nature and seriousness of the offense, the deterrent effect of the prosecution and the culpability of the individuals or entities involved."

Under this new "Human Illness Standard," a food company executive, manager, or employee can be charged with a crime even if he or she didn't know that the company was selling product that was contaminated or making people sick. According to Mizer, "Congress has made the prohibition on introducing adulterated food into interstate commerce a strict liability offense, meaning that a company or individual violates the law and can face misdemeanor charges whether or not it intended to distribute adulterated food." Mizer continued, "Make no mistake: misdemeanor violations can mean serious penalties." A single misdemeanor violation can result in a fine of up to $250,000 and as much as a year in prison. The executives of an Iowa egg company accused by the FDA and DOJ of causing a *Salmonella* outbreak in 2014, for instance, eventually pleaded guilty to a misdemeanor violation of the Food, Drug, and Cosmetic Act and were each sentenced to "three months in prison, one year of supervised release and a $100,000 fine." Following the Jensen Farms *Listeria monocytogenes* cantaloupe outbreak, company owners were investigated by the FDA, criminally charged, and then sentenced to six months of home detention and individual fines of $150,000.

The tools the FDA has at its disposal to effectuate its new policy have been around for some time. The FDA's power to bring criminal charges against corporate executives and employees originates from a 1975 Supreme Court case. In *United States v. Park*, 421 U.S. 658 (1975), the Supreme Court upheld the misdemeanor conviction of the president of a major grocery chain.[6] In that case, the president was found to be criminally liable for failing to eliminate rodent activity in a warehouse notwithstanding his argument that he had delegated the responsibility for correcting the condition to his subordinates.

Under this new "Human Illness Standard," a food company executive, manager, or employee can be charged with a crime even if he or she didn't know that the company was selling product that was contaminated or making people sick.

The Supreme Court concluded that if a company ships adulterated food, the executives or managers of that company can be charged with a misdemeanor, even if they had no direct knowledge that they were selling adulterated food. Rather, under this standard, now known as the "Park Doctrine," a company executive or QA manager can be charged simply if he or she is aware of a condition within his or her facility that could possibly lead to product contamination, and then fails to take action to correct it. In each case, the FDA will consider the individual's position within the company and his or her relationship to the violation. Following the Supreme Court's 1975 decision, the Park Doctrine was rarely used by the FDA, lying dormant for decades.

Because of the exponential increase in the number of outbreaks and recalls in recent years, coupled with the FDA's new command to overhaul the safety of the U.S. food supply, the doctrine has been resurrected. In turn, the FDA and DOJ have proved they are neither hesitant nor shy about launching criminal investigations against food companies, as demonstrated in a series of recent high-profile examples.

In addition to resurrecting the Park Doctrine, the FDA has shown its willingness to use other available tools to solve foodborne illness outbreaks and hold companies accountable. Indeed, the new adulteration standards and safe handling labels were not the only changes the government mandated following the 1993 Jack in the Box outbreak. In an effort to enhance the federal government's national outbreak detection capabilities, the government implemented a system of mandatory reporting for

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FDA'S WAR ON PATHOGENS

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healthcare providers whenever a U.S. consumer was cultured positive for a foodborne illness.

Thus, for nearly two decades, in each of these cases, the government has conducted testing to identify the specific genetic DNA strain of the microorganism making people sick, and then uploaded the DNA signature into a national database called PulseNet. While this system has allowed the government to solve many high-profile outbreaks over the last 20 years (linking consumers sickened by a pathogen sharing a common DNA strain to a single food product), the vast majority of foodborne illnesses uploaded into the PulseNet database remain unsolved. What this means is that there are likely a large number of food companies that are unknowingly processing and distributing food products that are contaminated at low levels with pathogens and which are making American consumers sick.

In turn, within the coming years, the FDA will visit and inspect every food facility in the nation. To facilitate its goal of overhauling the safety of the U.S. food supply, the FDA has adopted stunning new policies designed to solve past outbreaks and prevent new ones from occurring. As part of its routine inspections, the FDA is now conducting extensive microbiological profiling inside of all U.S. food processing facilities. While conducting these visits, the agency will execute microbiological swab-a-thons, collecting more than 100 samples from each food facility and then testing those samples for pathogens such as *Listeria monocytogenes* or *Salmonella*. If the FDA finds a positive sample, the agency will immediately compare the DNA from that sample against the PulseNet database. If the DNA matches a strain that made someone sick in the preceding years, the FDA will presume that the illness or illnesses were caused by a product distributed from that facility. Once that occurs, the company will be forced to initiate a recall and likely cease operations until any contamination is isolated and eliminated. In addition, because the company's products caused illness, the company may find itself the target of a criminal investigation.

Recent examples demonstrate how the FDA's new policies are impacting the food industry. In 2015, Blue Bell ice cream was linked to an outbreak of *Listeria monocytogenes*. Following an inspection of the Blue Bell facilities, the FDA linked positive samples from Blue Bell's processing environment to 10 case patients in the PulseNet database who carried the same strain of the bacteria. No one within the company knew that their products had caused illness. Nevertheless, in addition to forcing the company to recall all products it had ever produced, the FDA and DOJ launched a criminal investigation against the company.

More recently, Dole prepackaged salads were linked by the FDA to a *Listeria monocytogenes* outbreak that lasted seven months and caused 18 illnesses and one death. Reportedly, the FDA cultured *Listeria* from Dole's processing facility that matched the outbreak strain. Here too, although neither Dole nor its employees knew they were making people sick, the company remains the target of a criminal probe.

Chipotle, the national restaurant chain, struggled for months in 2015 to contain and manage numerous foodborne illness outbreaks allegedly linked to food served at its restaurants. Although the source of many of the illnesses remains uncertain, Chipotle reported in public statements that it was served with a grand jury subpoena by the DOJ requiring it to produce documents related to company-wide food safety matters dating back to January 1, 2013.[7] The criminal investigation is ongoing.

Long past are the days when the FDA reached its conclusions regarding the sanitary conditions of a processing facility based upon visual observations alone. Today, during routine inspections, the FDA is now basing its conclusions regarding the sanitary conditions of a processing facility upon the results of the agency's expansive and intensive microbiological sampling of its ingredients, food production areas, and finished products. Work now with your food safety teams and, where necessary, your lawyers to identify and eliminate any hidden problems that may exist. When the FDA arrives, if any of the agency's samples are positive, the government may expect or require the company to announce a recall. If any of those samples match a human illness, the government may expect or require someone to go to jail. ■

Shawn K. Stevens, Esq., *Food Industry Council LLC.*

NANOTECHNOLOGY AND FOOD SAFETY

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What food technologists and engineers are doing to improve our food supply seems limited only by one's imagination, and nanotechnology opens the doors to a whole new array of applications and products. Fresh fruits, vegetables, meat, and poultry products are potential vehicles for the transmission of human pathogens leading to foodborne disease outbreaks,[3] which draw public attention to food safety. Therefore, there is a need to develop new antimicrobials to ensure food safety. Because of the antimicrobial properties of nanomaterials, nanotechnology offers great potential for novel antimicrobial agents for the food and food-related industries. The use of nano-antimicrobial agents added directly to food or through antimicrobial packaging is an effective approach. As a result, the use of nanotechnology by the food and food-related industries is expected to increase, impacting the food system at all stages, from food production to processing, packaging, transportation, storage, security, safety, and quality.[4, 5]

Food Ingredients for Color, Texture, and Flavor

The food industry uses nanotechnology to develop nanoscale ingredients to improve the color, texture, and flavor of food.[6, 7] The nanoparticles titanium dioxide (TiO_2) and silicon dioxide (SiO_2)[8, 9] and amorphous silica[9, 10] are used as food additives; TiO_2 is a common whitener in many processed foods and as a coloring agent in the powdered sugar coating on doughnuts. In response to pressure from the advocacy group As You Sow, Dunkin' Brands has announced that it will remove allegedly "nano" titanium dioxide from Dunkin' Donuts' powdered sugar donuts [http://www.huffingtonpost.com/2015/03/09/dunkin-donuts-titanium-dioxide-whitening-agent_n_6833364.html].

Food Production and Packaging

Nanomaterials used for food packaging provide many benefits, such as improved mechanical barriers, detection of microbial contamination, and potentially enhanced bioavailability of nutrients. Enhanced bioavailability of nutrients is perhaps the most far-reaching application of nanotechnology in food and food-related industries.[10] A number of nanocomposites, such as polymers containing nanoparticles, are used by the food industry for food packaging and

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food contact materials.[11] The use of zinc oxide (ZnO) and magnesium oxide (MgO) nanoparticles for food packaging has been reported.[8] Amorphous silica is used in food and in food containers and other packaging.[6, 9, 10] Engineered water nanostructures generated as aerosols are very effective at killing foodborne pathogens such as *E. coli*, *Listeria*, and *Salmonella* on steel food production surfaces.[12] This novel environmentally friendly intervention holds promise for application in the food industry as a green alternative to existing disinfection methods. Such food contact substances containing nanomaterials may have the potential to migrate from food packaging into food, so the safety of this technology must be demonstrated before it gains widespread acceptance in the industry.

Nutrients and Dietary Supplements

Nanotechnology has emerged as a "promising" method of delivering bioactive materials to humans through skin-care products and dietary supplements. Nanomaterials can be used as ingredients and additives (e.g., vitamins, antimicrobials, antioxidants) in nutrients and health supplements for enhanced absorption and bioavailability.[13] One product reports using Microcluster® Technology to make silica spheres as small as 5 nm. According to the manufacturer, when the liquid is consumed, the nanospheres enter the cells of the body, release their nutrients, and pick up waste compounds, thus bringing health and vitality. However, the only evidence provided to support these claims is anecdotal (https://www.aquatechnology.net/Microcluster_water.html). In another product, the extract of an herb is enclosed within nanosomes, which are said to be more efficiently absorbed by the skin. However, once again, not only does the safety of such usage need to be more rigorously evaluated, but the claims need to be carefully examined.

Food Storage

The antimicrobial properties of nanomaterials enable them to preserve food during storage and transport.[6, 14, 15] One example is bottles made with nanocomposites that minimize the leakage of carbon dioxide out of the bottle; this increases the shelf life of carbonated beverages without having to use heavier glass bottles or more expensive cans. Another example is food storage bins with silver nanoparticles embedded in the plastic. The silver nanoparticles kill bacteria from any food previously stored in the bins, minimizing harmful bacteria. Once again, the use of nanomaterials seems to have no limit.

Food Nanosensors

Nanomaterials are beginning to be used as sensors to detect contamination in the food environment. Potential applications of bioanalytical nanosensors include the detection of pathogens, contaminants, nutrients, environmental characteristics (light/dark, hot/cold, wet/dry), heavy metals, particulates, and allergens. Commercial uses have been reported as a means to check storage conditions, including temperature and moisture[14] and during food transport in refrigerated trucks for temperature control.[15] Sensors have been reported to detect nutrient deficiency in edible plants and in dispensers containing nutrients used to deliver nutrients to plants. Nanosensors in plastic packaging can detect gases given off by food when it spoils, and the packaging itself changes color to alert when food has gone bad. Plastic films are being developed that will allow food to stay fresher longer. These films are packed with silicate nanoparticles to reduce the flow of oxygen into the package and the leaking of moisture out of the package. Nanomaterials are being investigated as nanosensors and nanotracers with almost unlimited potential by the food industry.[16]

Nanomaterials as Double-Edged Swords

Nanoscience and nanotechnology are exciting emerging technologies. With all the benefits of nanotechnology, in the words of Charles Percy Snow, the British scientist, a new "[t]echnology is a queer thing. It brings you great gifts with one hand, and it stabs you in the back with the other." Therefore, the question comes to mind, is nanotechnology a double-edged sword?

Food Safety

Consumers are potentially exposed to nanomaterials by consumption of food and beverages containing these extremely small particles of large reactive surface area. Safety concerns with nanoparticles are not well known, but their potential for harm is evident due to the high surface area to volume ratio, which can make certain nanoparticles very reactive. For nanoparticles, the situation is different than their larger counterpart, as their extremely small size opens the potential for crossing various biological barriers within the body that may be useful for the delivery of drugs but may also increase toxicity. The absorbed species will also influence toxicity, depending on whether the particles remain nano in size or if they agglomerate to form larger particles. Nanoparticles may be able to pass through cell membranes and thus have the potential to interact with receptors and other biological end points. Once absorbed in the gastrointestinal system, they

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may bioaccumulate in various organs of the body, leading to potentially adverse effects.

As with so many issues, public acceptance of food and food products containing nanomaterials depends both on actual safety and on perceived safety. Therefore, the safety evaluation of innovative nanomaterials for consumer use in products such as food and food packaging is necessary prior to their marketing.

The European Food Safety Authority

The Scientific Committee of the European Food Safety Authority (EFSA) published an opinion on nanoscience and nanotechnology regarding food and animal feed safety in 2009.[17] A guidance document on how to assess potential risks related to certain food-related uses of nanotechnology followed in 2011, providing practical recommendations to regulators on how to assess applications from industry to use engineered nanomaterials in food additives, enzymes, flavorings, food contact materials, novel foods, food supplements, feed additives, and pesticides (http://nanotech.lawbc.com/2011/05/efsa-publishes-guidance-for-assessing-engineered-nanomaterial-applications-in-food-and-feed/). The guidance covers risk assessments for food and feed applications. It stipulates the additional data needed for the physical and chemical characterization of the nanomaterial in comparison with conventional applications and outlines different toxicity testing approaches to be followed by applicants. This report was followed in 2016 by the latest report from the EFSA [Network 2015 Annual Report (http://nanotech.lawbc.com/2016/01/efsa-publishes-nano-network-2015-annual-report/)].

Food Contact Substance Notification Program

Food packaging is used for convenience in handling, transporting, and storage. Because packaging may come into direct contact with the food, the potential migration of chemicals from packaging into the food is a possible safety issue and of public concern. The U.S. Food and Drug Administration (FDA) considers food packaging ingredients indirect food additives and approves all food packaging materials. The FDA uses the Food Contact Substance Notification Program[18] to regulate the safe use of a food contact substance (FCS). In addition, packaged liquid solutions are often marketed in plastic containers or polymer-coated metal cans. In case of thermal treatment in containers or in extended storage conditions, there is potential for the migration of FCSs from the container to the food. The FDA recommends FCS migration testing for articles in contact with packaged foods and allows the use of information on formulation or residual levels of the FCS in the food-contact article, assuming 100% migration of the FCS to food unless the rate of migration is known experimentally. Nanomaterials, because of their potential to possibly migrate more readily from packaging materials, may create new and interesting issues for the FDA.

Food Contact Materials for Meat and Poultry

Packaging for the meat and poultry industry is an extremely important issue because once again, the food touches the packaging materials containing potentially migrating chemicals, including nanomaterials. The potential for nanoparticles to migrate from the packaging materials to food is largely unknown but may be more prevalent than their larger counterpart chemicals. The responsibility for the safety evaluation of these materials falls to the Food Safety and Inspection Service (FSIS) of the U.S. Department of Agriculture, which has not issued any special guidance for industry regarding nanomaterials in meat and poultry packaging.

Nanomaterials in Animal Feed

Nanomaterials also are used in animal feed as additives for a variety of purposes. For example, nanocapsules are used to carry essential oils, antioxidants, vitamins, and minerals for improved bioavailability. They are used in feed processing to increase the absorption of nutrients.

Titanium dioxide nanoparticles are used as a UV protection barrier in feed packaging. Nanosilver is used as an antimicrobial agent in feed packaging materials and storage boxes. In August 2015, the FDA issued a draft guidance for industry use of nanomaterials in animal feed, entitled "Use of Nanomaterials in Food for Animals," available at https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM401508.pdf.

Safety Assessment of Nanomaterials in Food and Food-Related Products

Toxicity testing is essential for safety assessment. Safety assessment of nanomaterials in food and food-related products has yet to be fully resolved. In general, when considering whether an FDA-regulated product involves the application of nanotechnology, the FDA asks: (1) whether a material or end product is engineered to have at least one external dimension, or an internal or surface structure, in the nanoscale range (approximately 1 nm to 100 nm); and (2) whether a material or end product is engineered to exhibit properties or phenomena, including physical or chemical properties or biological effects, that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to one micrometer (1,000 nm). These considerations apply broadly to all FDA-regulated products. At present, the FDA appears to be handling the safety of nanoscale materials no differently than their larger counterparts.

More research is needed to determine the impact on human health of nanomaterials in food to ensure public safety and, of equal importance, to improve public discourse about the safe use of such materials in our food supply. Some test methods for nanomaterial safety assessment have been reported.[19, 20] Safety assessment of nanomaterials in foods requires data from all sources, including *in vitro* and *in vivo* models. Extrapolation of toxicity data obtained by the oral route of exposure from animal models to humans is required for the risk assessment of nanomaterials in food. However, no internationally accepted standard protocols for toxicity testing of nanomaterials in food or feed are currently available. Such protocols are in the development stage by organizations such as the International Alliance for Nano Environment, Human Health and Safety Harmonization,[21] and the U.S. National Research Council.[22] A uniform international regulatory framework for the evaluation of nanotechnology is a necessity for both food and animal feed. The role of 21st-century toxicity testing by relevant *in vitro* models needs to be accepted internationally with a better understanding of their benefits, challenges, and applications as related to nanomaterials in the food arena. New predictive approaches for toxicity testing of food-related nanomaterials are needed for better understanding of nanotoxicity and the underlying mechanisms involved in such toxicities. Recently, the role of the gastrointestinal microbiota in human health has attracted much attention in the toxicology community because of the interaction between the additive and the gut microbiota, often resulting in changes in the nanomaterial potentially into more toxic

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metabolites. The gastrointestinal microbiota may play an important role in the safety and/or the toxicity of food-related nanomaterials. An editorial published in 2010 entitled "Nanofood for Thought" in the journal *Nature Nanotechnology* stated, "The food industry will only reap the benefits of nanotechnology if issues related to safety are addressed and companies are more open about what they are doing."[23]

Conclusions

The benefits of nanotechnology for the food industry are numerous and are expected to grow. This relatively new, rapidly developing, and exciting technology has the potential to impact every aspect of the food system, from production to processing, packaging, transportation, storage, shelf life, bioavailability and, ultimately, consumption. Commercial applications of nanomaterials in the food industry will grow because of their unique and novel properties and their potential to offer desirable characteristics for food and food packaging. Human exposure to nanomaterials is increasing and will continue to increase. Therefore, the health impact of nanomaterials in food is of prime public concern. The ability to quantify the nanomaterial throughout the food life cycle is critical for manufacturing consistency, safety, and potential benefits of the consumer product. A uniform international regulatory framework for nanotechnology in food is essential. Public acceptance of food and food-related products containing nanomaterials will depend on their safety and the transparency of the industry in sharing information with the consuming public. ■

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extremely short-lived species such as hydroxyl radicals (OH^-), hydrated electrons (H^-), hydrogen peroxide (H_2O_2), hydrogen (H_2), and hydrated protons (H_3O^+). These reactive species formed during ionizing radiation of food will cause indirect effects (breaks) in the DNA and RNA of the contaminating microorganisms. Ionizing radiation does not discriminate between harmful pathogens and desirable microorganisms, nor does it discriminate between the nucleic acids of the microbial population and the nucleic acids in the foods. The key to utilizing this technology is to identify the optimal dose that will eliminate the harmful pathogens or insects without affecting the nutritional or sensory attributes of the foods. There are decades of research on this particular focus area.[7, 8]

In 1958, the United States Food and Drug Administration (FDA) amended the Food, Drug, and Cosmetic Act (FD&C) to designate food irradiation as a food additive and not a food processing technology. This was a pivotal regulatory decision because designation of this technology as a food additive requires all foods (human and pet food) in the U.S. that are treated with ionizing radiation to be specifically labeled as such. The FDA, however, has not yet permitted the use of ionizing radiation technology on cooked foods. The current list authorizes irradiation for a select number of fresh, frozen, and dried (low-moisture) foods. Foods that are treated with ionizing radiation either for food preservation, food pasteurization, or decontamination have to be specifically labeled with the "radura" symbol and with the phrase "treated with radiation" or "treated by radiation." Though there is no empirical data to prove that the labeling requirement is responsible for the negative connotations associated with food irradiation technologies, there is enough anecdotal information that the labeling requirement is a key impediment in the wider acceptance of this technology by the food industry.[9] Whatever the reason behind the reluctance by the U.S. food industry to adopt this technology, the net result is that in the U.S., consumers do not have choice in the marketplace to purchase high-quality, preservative-free foods that are microbiologically safe and wholesome. However, there are only a few retailers selling irradiated meat in the U.S. Irradiated spices, food ingredients, and irradiated tropical fruits and vegetables are widely available in the U.S. In fact, the volume of tropical fruits and vegetables treated with this technology to eliminate agriculturally harmful insects and pests continues to increase significantly in the U.S. **(Figure 2)**. A number of studies have shown that U.S. consumers are willing to purchase irradiated foods.[1] Not only are they willing to purchase irradiated foods, their willingness to pay a premium for irradiated foods also increases when provided with relevant, accurate information highlighting the purpose of food irradiation.[10, 11, 12, 13]

The FDA, USDA Animal and Plant Health Inspection Service (APHIS), and the USDA Food Safety and Inspection Service (FSIS) are the regulatory agencies that oversee food irradiation applications in the U.S. Because food irradiation is legally a "food

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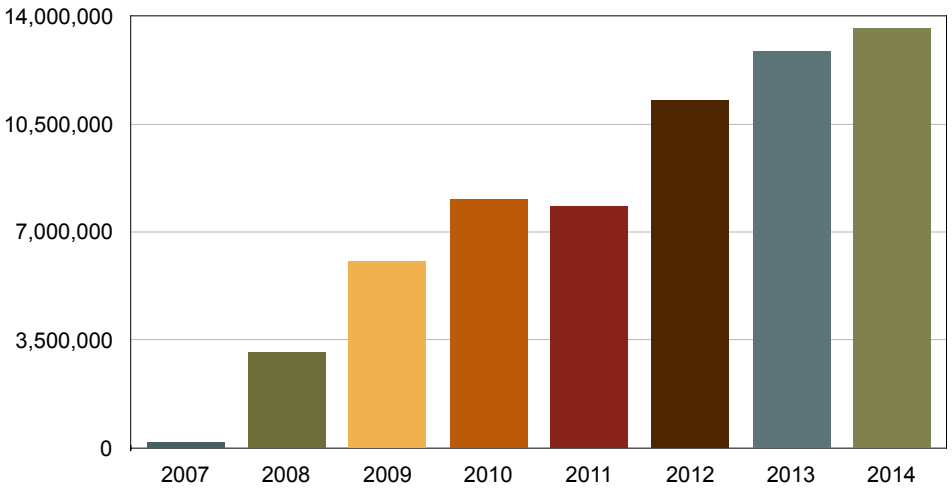
FIGURE 2. Volumes (kg) of irradiated fresh produce entering the United States.[10]



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additive," there are specific regulations governing the specific application, types of foods, maximum irradiation doses, and approved packaging materials. Cooked foods, however, cannot be irradiated **(Table 2)**. The FDA, as part of Title 21, Part 579, does allow the use of ionizing radiation for treating bagged animal and poultry diets including packaged feeds, feed ingredients, bulk feeds, and animal treats and chews. However, for poultry feed and feed ingredients, the dose cannot be below 2 kGy and no more than 25 kGy. The dose cannot exceed 50 kGy for other animal feed and treats.[14] There is little published data available from the FDA on the amount of food that is irradiated in the United States. However, it is thought that approximately 175 million pounds of spices and 18 million pounds of ground beef are irradiated in the U.S. annually. There is verifiable data from the USDA APHIS on the volumes and specific commodities that are treated by irradiation for phytosanitary purposes. An increasing volume of tropical fruits and vegetables is now irradiated overseas and entering the U.S. **(Figure 2)**. In this case, the technology is used to prevent the accidental introduction of insects and pests that are harmful to U.S. agriculture.

By some estimates, over 60 countries employ food irradiation technologies, and irradiated foods are involved in transboundary shipments. Estimates made by Kume and Furuta in 2009 were that approximately 405,000 tons of food was being irradiated annually around the world at that time.[15] China (36%) and the U.S. (23%) lead the countries in terms of irradiated food volumes. The specific Codex Alimentarius standard governing irradiated foods is CODEX-STAN 106-1983.[16] Because this food processing technology is included within the Codex standards, a relatively large volume of irradiated foods is involved in transboundary shipments. The European Union has also approved food irradiation. According to 2015 estimates, the EU processes approximately 12.5 million pounds of food with this technology across the EU.[17] The major food item irradiated in the EU is frozen frog legs, followed by herbs, spices, vegetable seasonings, and poultry. Belgium, the Netherlands, France, Spain, and Germany are the main European countries using this technology. According to most estimates, China is the leader among countries in terms of the volume of food processed with this technology. Most estimates place this volume between 150,000 and 250,000 tons per year.[15] Similar data about the volume of food treated with this technology in India is not available publicly, although spices seem to be the most widely treated commodity in India. A small volume of Indian mangoes gets treated with this technology for export to the United States. In terms of regulations, Brazil has the most liberal food irradiation regulations. In Brazil, consumer preference is the benchmark for the regulatory threshold; that is, as long as there is a consumer need, any food can be irradiated at any dose.

Gamma Radiation Technology

Gamma radiation from cobalt-60 has been the technology of choice for food irradiation. The gamma source is stored within a deep pool of water, and for the irradiation process, the gamma source is raised out of the water and the cases of food are conveyed using product-handling systems around the gamma source. The gamma source is placed under water when not in use because the source cannot be switched off. The packages of food are conveyed around the gamma source for defined periods and positioned so that they receive the minimum required dose, and ensuring that the product receives as uniform a dose as possible. Because the gamma source cannot be switched off, there are obvious challenges associated with possible occu-

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TABLE 2. FDA-approved list of foods and food items permitted for eBeam, X-ray, and gamma processing in the United States. (FDA, CFR 179.26)

Food/Food-Related Item	Specific Application	Maximum Allowable Dose
Fresh, non-heated processed pork	Pathogen control	0.3 – 1.0 kGy
Fresh/frozen uncooked poultry products	Pathogen control	3 kGy
Refrigerated, uncooked meat products (sheep, cattle, swine, and goat)	Pathogen control	4.5 kGy
Frozen uncooked meat products (sheep, cattle, swine, and goat)	Pathogen control	7 kGy
Fresh/frozen molluscan shellfish	Pathogen control	5.5 kGy
Fresh shell eggs	Pathogen control	3.0 kGy
Dry or dehydrated spices and food seasonings	Microbial disinfection	30 kGy
Fresh produce	Growth and maturation inhibition	1 kGy
Fresh produce	Insect disinfestation	1 kGy
Fresh iceberg lettuce and fresh spinach	Pathogen control	4.0 kGy
Seeds for sprouting	Pathogen control	8.0 kGy
Dry/dehydrated spices and food seasonings	Microbial disinfestation	30 kGy
Dry/dehydrated enzyme preparations	Microbial disinfestation	10 kGy
Wheat flour	Mold control	0.5 kGy
White potatoes	Inhibit sprouting	0.15 kGy

pational exposure, radioactive source theft, storage of spent sources, and disposal of spent sources. These challenges have become more acute, especially due to the potential dangers posed by terrorism. Gamma sources have a 12% loss in specific activity each year. Gamma sources are priced on a per-curie basis. The cost of gamma sources has increased substantially over the past decade, especially since there are only a limited number of cobalt-60 suppliers around the world and because of the cost associated with the production of cobalt-60 gamma sources. The current estimate for 1 curie of cobalt-60 is around $5.00. A typical food irradiation facility will require around 0.5 million curies; the cobalt-60 cost alone (not including shipping, installation, disposal) will be around $2.5 million. In addition to these monetary costs, the legal and environmental costs associated with maintaining and operating a cobalt-60 facility can be very high. Because of the myriad of security challenges, the International Atomic Energy Agency (IAEA), the U.S. National Nuclear Security Administration (NNSA), and the U.S. Defense Threat Reduction Agency (DTRA) are promoting the use of alternate technologies to cobalt-60 for commercial applications, especially food irradiation.

Electron Beam Technology

The alternate technology to cobalt-60-based gamma irradiation is electron beam (eBeam) technology. This technology is gaining widespread attention and commercial interest primarily because the cost of acquisition of eBeam technology is less than cobalt-60. Most important, however, is that the security challenges associated with cobalt-60 are non-existent for eBeam technology. The U.S. National Academy of Sciences proposed that alternate irradiation technologies be adopted or developed to avoid the use of radioactive material in food irradiation and other commercial applications involving ionizing radiation.[18]

Electron beam technology relies on the use of pulsed linear accelerator (linac) or Rhodotron technology to generate a dense stream of highly energetic electrons from regular electricity. The linacs accelerate the electrons >99.999 percentage the speed of light. Electrons at this energy and speed cause the same direct and indirect effects on microbial pathogens and insects as gamma radiation. Unlike cobalt-60, eBeam technology utilizes commercial electricity. Briefly, the electrons are produced in a constant and consistent pulse by an electron gun and an accelerating structure (consisting of multiple cavities) that then accelerates these electrons to high speeds and energies. A scanning magnet then scans the highly energetic electrons over the entire case of food or other product that needs to be treated. The product conveyor system and the pulsed linac are computerized and integrated so that consistent and reproducible eBeam doses are delivered.[8, 19]

With respect to eBeam technology, two parameters need to be considered in addition to the dose that is applied. The two parameters are electron energy, measured in million electron volts (MeV), and the linac power, measured in kilowatts (kW). The electron energy determines the penetrating power of the electrons, while the linac power determines the product throughput.[20] In most commercial food irradiation systems, the ability to penetrate the cases of food on the processing line is critical. Therefore, eBeam systems in the 10 MeV are preferred for large commercial-scale facilities. The U.S. and international regulations governing the eBeam system stipulate the upper limit for eBeam systems not to exceed 10 MeV. In terms of linac power, commercial eBeam systems can vary anywhere between 15 kW and 20 kW for pulsed linacs to as much as 500 kW for Rhodotron-style accelerators.[21] Commercial food irradiation uses either the pulsed linear accelerators or the Rhodotron-style accelerators.[1, 21] A schematic representation of the pulsed eBeam linear accelerator, along with actual images within a commercial-scale eBeam irradiation facility, is presented in **Figure 3 (below) and Figures 4A and 4B (next page)**. The pulsed linear accelerators are characterized by compactness (small footprint) and significantly lower capital and operating costs than the Rhodotron-style accelerators. However, as mentioned above, pulsed accelerators are limited to around 20 kW of beam power while the Rhodotron-style eBeam system is capable of generating as much as 500 kW of beam power. However, it is important to bear in mind that in most commercial-scale food processing facilities, a pulsed linear accelerator would be more than sufficient for a financially sustainable operation. A 20 kW pulsed linac system operating at 90% efficiency, designed to deliver a minimum dose of 2 kGy, can process as much as 9kg of food per second. In eBeam food irradiation facilities, the linac power is rarely the rate-limiting step. It is very often the ability of the product-handling systems to move products on and off the product conveyance system.

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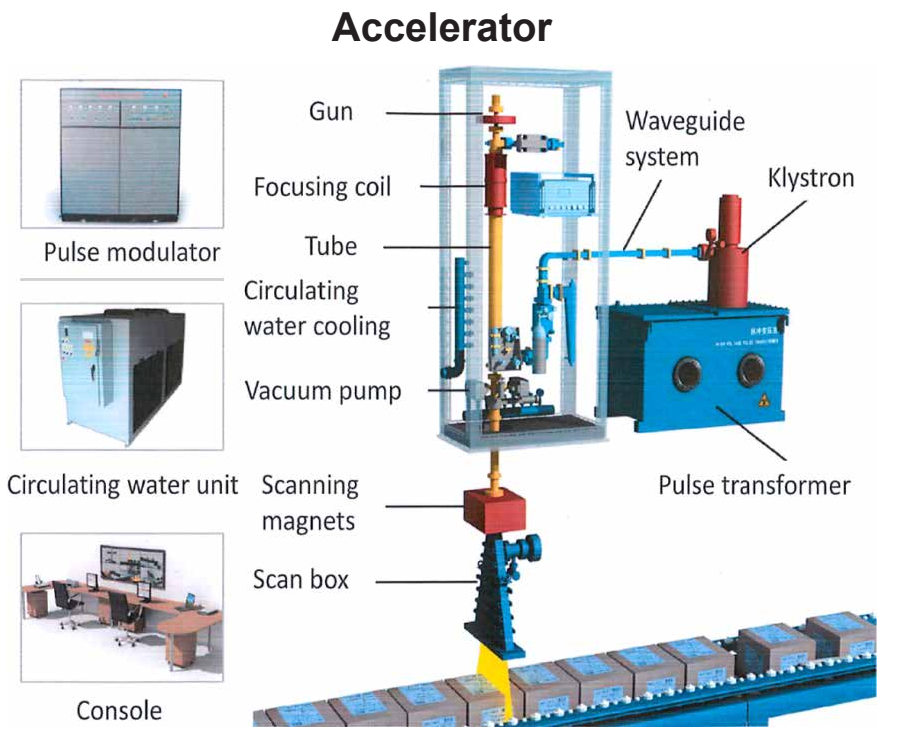
FIGURE 3. Schematic representation of a pulsed electron beam linear accelerator. *(Image courtesy Yang Bin, Tianjin, China)*



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Future Outlook

The ability to dial in a dose to either decontaminate, pasteurize, or sterilize foods to any target level by eBeam technology by irradiation (eBeam) is unparalleled by any other technology other than traditional heat treatment (not usable for many food products because of degradation of food quality). The ability to deliver pasteurizing or sterilizing doses without any addition of heat makes eBeam technology extremely attractive to the fresh fruit and vegetable industries. Electron beam technology is today's technology of choice for food irradiation around the world. The compactness and the rapidly declining capital costs for linacs are making eBeam technology an extremely attractive option for the food industry. However, the food industry needs to make decisions at the corporate level about its willingness to adopt a proven technology that can achieve significant reductions in infection risks to the public. Presently, only a handful of retailers, distributors, and food processors have made the decision to widely employ irradiation to eliminate pathogens both in food and on packaging materials that are in contact with food. In addition to the food industry making such decisions, both the FDA and USDA have key roles in finalizing responses to petitions related to food irradiation that have been under consideration, in certain cases, within the agency for a number of decades.[22] Consumer groups must also communicate to the public that foods sold in retail grocery stores can be made increasingly free of pathogens through use of available and safe irradiation technology. Consumer groups and the food industry also need to be proactive in seeking necessary regulatory approvals for high pathogen risk foods such as fresh produce and ready-to-eat meats and seafood. The legal profession can play a pivotal role in ensuring that FDA and USDA regulations related to food irradiation are consistent and appropriate vis-à-vis other food processing technologies. The insurance industry can also play a major role to incentivize the food industry to adopt eBeam-based food processing to reduce costly recalls. ■

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FIGURE 4A.
View of the inside of an eBeam irradiation chamber showing the "eBeam horn" on the top from which the high-energy electrons emerge. *(Image courtesy National Center for Electron Beam Research, Texas A&M University)*

FIGURE 4B.
View of an actual 10 MeV pulsed electron beam linear accelerator. *(Image courtesy National Center for Electron Beam Research, Texas A&M University)*

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THE FDA'S WAR ON PATHOGENS: HOW UNKNOWINGLY SELLING UNSAFE FOOD CAN LAND YOU IN PRISON

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