Comment on 99F-5322

THE CENTER FOR FOOD SAFETY

August 11, 2004

Lane A. Highbarger
Office of Food Additive Safety, HFS255
FDA CFSAN
5100 Paint Branch Parkway
College Park, MD 20740-3835

Re: ~~Docket 2003-P0544, petition to~~ modify existing food additive regulation

Dear Mr. Highbarger,

With respect to the above-referenced petition filed in November, 2003, by the Center for Food Safety (CFS) and Public Citizen, when I recently asked you about its status your reply email to me dated Aug. 4 stated:

> "The citizen petition that you submitted consists of material that you have previously submitted as comments to the irradiation petitions that are currently under review. In light of the fact that we are currently reviewing those comments, it would be inappropriate to make a conclusion on the request of the citizen petition prior to completing the review of the other five irradiation petitions."

For the record, not all of the information supporting our irradiated ground beef revocation petition was previously submitted by us in the form of comments on the other five pending irradiation petitions. Our petition itself provides extensive additional information. This includes: flaws in the 1997 FDA approval for irradiated meats (pp. 3-6); new evidence regarding probable consumption of irradiated ground beef especially by vulnerable school children (pp. 12-14), plus additional scientific support and analysis throughout. Thus, your justification for delaying consideration of the ground beef revocation petition appears superficial.

Further, even if the bulk of the supporting information was earlier filed with comments on the other petitions, that is not directly relevant to the issues presented in the CFS and Public Citizen petition. Rather than seeking to expand food irradiation as the other five pending petitions do, ours seeks to reduce it because of unresolved health risks. Our petition covers only irradiated ground beef and ground beef byproducts whereas the other petitions cover a wide variety of other foods. Our petition is more important to resolve first because if FDA determines that it has merit, the agency would need to take follow-up steps to protect the public health and it would be very unlikely that the agency would grant the other petitions.

Also, as further evidence in support of this petition, and in opposition to the other pending petitions,

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enclosed is a peer-reviewed article that is "In Press" in the *International Journal of Hygiene and Environmental Health*, by B.C. Ashley, P.T. Birchfield, *et al.*, entitled, "Health Concerns Regarding Consumption of Irradiated Food". It analyses the toxicity issues surrounding irradiated foods. The article is being sent separately to the Dockets Management Branch by way of additional comment by CFS on all of the pending irradiation petitions. Some key quotes:

> "Although the application of the food irradiation procedure has been heavily promoted and recommended, unresolved health concerns related to the consumption of irradiated food remain." (p. 4)
>
> "[C]onsumption of irradiated food can possibly result in a significant accumulation of 2-ACBs in the adipose tissues of consumers. The long-term health consequences of this observation are unclear at this time." (p. 9)
>
> "[C]ompounds found exclusively in irradiated dietary fats may promote colon carcinogenesis in animals treated with a known carcinogen and identifies a new area of toxicity that the FDA and WHO have yet to examine. The 2-ACB tumor promotion activities should be further investigated, and their effects evaluated systematically." (pp. 9-10)
>
> "In summary, it is quite clear that additional research is needed in order to fully address the issue and concerns of irradiated food. The toxicity of unique radiolytic products should be tested vigorously, especially in regards to the tumor promoting activities. Animal bioassays should be conducted systematically and comprehensively with whole food and with unique radiolytic products to generate a dose-response understanding of the toxicity and safety of irradiated food. It would prove beneficial to establish a dose that does not cause any observable toxic effects in an experimental animal model. The data obtained would better substantiate extrapolation and application in human health risk evaluation. In addition, as of now, there are no extensive human trials available to assess irradiated food safety in human populations. Regulatory agencies in the US and around the world need to be proactive in resolving these health concerns prior to the ubiquitous consumption of irradiated food. It is notable that the European Parliament has halted the addition of new food products for irradiation and has chosen to maintain the 10kGy limit on irradiation." (p. 18)

FDA is urged to follow the authors' recommendations of being proactive in resolving the health concerns. Undertaking the additional research that the authors' say it is "quite clear" is needed would be a good start. Above all, irradiated ground beef should not be fed *en masse* to vulnerable school children, as USDA intends to begin when the school year starts in the next few weeks.

In closing, you are requested to please promptly (in the next few weeks) affirm FDA's intention to respond substantively in the future to the CFS and Public Citizen petition on irradiated ground beef and to state approximately when we should expect your full substantive response. Feel free to contact me if you would like additional information.

Very truly yours,

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CC: FDA Dockets Management Branch for Dockets No. 2003-P0544, 99F-5522; 01F-0047; 99F-4372; 99F-5321; 99F-5322
Laura Tarantino, Ph.D., Director, OFAS, FDA CFSAN
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Enclosure

International Journal of Hygiene and Environmental Health, in press, 2004

Health Concerns Regarding Consumption of Irradiated Food

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Running title: Irradiated food and health

Keywords: Food irradiation, environmental health, public health, mutagenesis, tumor promotion, food safety, food borne illness.

Acknowledgement: This review is the product of a class project resulting from an Environmental Health and Toxicology course in the Master of Public Health program at the University of Texas Medical Branch (UTMB) in Galveston, Texas. B.C. Ashley, M.D., B. Chamberlain, M.D. and S. Moynahan, M.D. are in the UTMB Aerospace Medicine Residency Program; P.T. Birchfield, D.O., R.S. Kotwal, M.D., S.F. McClellan, M.D., and S.A. Salmon, M.D. are in the Army Aerospace Medicine Residency Program; S.B. Patni, M.D. is in the UTMB Occupational Medicine Residency Program.

Disclaimer: The views, opinions, and/or findings contained in this report are those of the authors and should not be construed as official Department of the Army (DA) or Department of Defense (DOD) position, policy or decision, unless so designated by other official documentation. Additionally, citations of commercial organizations or products in this report do not constitute an official DA or DOD endorsement or approval of the products or services of these organizations.

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Abstract

Food irradiation is being promoted as a simple process that can be used to effectively and significantly reduce food-borne illnesses around the world. However, a thorough review of the literature reveals a paucity of adequate research conducted to specifically address health concerns that may directly result from the consumption of irradiated food. Consequently, there is considerable debate on the issue of health concerns from irradiated food among international agencies and between different nations. This report presents a critical review of scientific data and recommendations from different agencies and consumer groups. The objective of this review is to provide the scientific community and the general public with a balanced discussion on irradiated food from the viewpoint of an environmental or public health professional. As a result of this review, the authors conclude that current evidence does not exist to substantiate the support or unconditional endorsement of irradiation of food for consumption. In addition, consumers are entitled to their right of choice in the consumption of irradiated versus un-irradiated food. Different countries should further evaluate their local and global risks and benefits prior to developing and recommending national and international food irradiation policies.

Introduction

Food safety is a global issue with paramount environmental and public health consequences if inadequately maintained. With the increased globalization of food supply, ensuring the safety of this supply to consumers has become an international collaborative endeavor. The concern for ensuring food safety can be illustrated by the extent of food-borne illnesses around the world. Even with a well-established food inspection and supply system in the US, food-related health problems are estimated to cause 76 million illnesses, 323,000 hospitalizations and 5,000 deaths annually (Mead et al., 1999). A large portion of the health problems is caused by the contamination of food by infectious agents such as *Salmonella*, *E. coli* and *Listeria*. The potential for contamination is inherent at each step along the food supply and preparation processes. Therefore, a variety of procedures have been developed and used to reduce food-borne contamination Since the late 1980's, the World Health Organization and the US Food and Drug Administration have approved the irradiation of food by ionizing radiation at the beginning of the food supply chain as an inexpensive and effective procedure (http://www.cdc.gov/ncidod/dbmd/diseaseinfo/foodirradiation.htm; http://www.who.int/archives/inf-pr-1997/en/pr97-68.html). In a recent conference (First World Conference, 2003), it was estimated that there were approximately 7,000 stores representing more than 50 retail chains that sold irradiated food. Additionally, more than 2,000 restaurants (including major fast food chains) served meals containing irradiated food. Although the application of the food irradiation procedure has been heavily promoted and recommended, unresolved health concerns related to the consumption of irradiated food remain. In this review,

background information and concerns with the use of irradiation for food sterilization are presented followed by recommendations for academic, industry and consumer consideration.

Food irradiation technology typically uses electron beam and ionizing radiation (e.g. X-rays). The energy from the irradiation breaks chemical bonds and produces toxic ions and free radicals that react with cellular constituents in food to form altered products (often classified as radiolytic products). With respect to dose, the amount of radiolytic products increases in proportion to the radiation dose (Federal Register, 1997). It is by breaking the bonds in a microorganism's DNA structure and prohibiting its replication that food irradiation prevents spoiling and food-born illness. However, irradiated food is not radioactive.

The radiation dose and exposure time can affect the taste and consistence of foods in addition to its effect on microorganisms. Odd odors and discoloration have been noted in some irradiated foods in the past, and radiolytic compounds have been implicated. Specifically, radiolytic compounds have been shown to cause oxidation of myoglobin and fat in meat, which in turn is thought to produce foul odors and discoloration. Ozone can be produced from oxygen during irradiation which can also cause discoloration. Irradiating food at appropriate doses and under appropriate conditions such as a reduced oxygen environment and/or a frozen state can minimize these effects (Federal Register, 1997). Perhaps the most important radiolytic products are 2-alkylcyclobutanones (2-ACBs) which are produced from the irradiation of fat in food. This family of cyclobutanones includes 2-dodecylcyclobutanone (2-DCB) from irradiation of palmitic acid, 2-tetradecylcyclobutanone (2-TCB) from stearic acid, and 2-tetradecenylcyclobutanone (2-TDCB) from oleic acid (Delincee et al., 2002). To date there is no evidence that 2-ACBs are found in any non-irradiated foods and concern for cytotoxic and genotoxic effects from these byproducts has been raised (Delincee et al., 2002).

Results

In vitro toxicological evaluation

The generation of altered cellular substances, e.g. radiolytic products, by radiation has caused concern regarding the mutagenicity of irradiated food. Several in vitro studies have therefore been conducted using bacterial mutagenic assays to address this concern. A summary of these published studies is shown in Table 1. In order to test irradiated foodstuffs, which are complex macromolecules, early *in vitro* tests were conducted utilizing natural juices, extracts or digests from irradiated food. Inherent limitations with these approaches are apparent. For example, it is difficult to extract all compounds from all food types. Chemically altered macromolecules that are different from those found under human study conditions may be formed during the preparation process. Cellular uptake of the mixtures by the bacteria, especially the toxic component, is unknown. Food juices, extracts, and digests may contain compounds that interfere with the essential component of the test, e.g. the presence of histidine will render the Ames assay ineffective (Ames, 1975). In addition, many of the in vitro assays were not conducted in a systematic and comprehensive manner. As shown in Table 1, the majority of the studies using food juice, extracts and digests produce negative results in mutagenic assays.

During the last few years, attention has been focused on evaluating the mutagenic effects of unique radiolytic products from irradiated food, e.g. 2-ACBs. Testing of these products becomes possible because they can be synthesized instead of extracted from irradiated food. As shown in Table 1, one of the 2-ACBs, 2-DCB, was tested in bacterial and mammalian cells for toxic activities (Delincee and Pool-Zobel, 1998; Delincee, 2002; Titeca et al., 2003; Sommers,

2003). These studies did not depict 2-DCB as mutagenic. However, cytotoxic and other biological effects were observed. As shown in the next section, some radiolytic products have been shown to be probable tumor promoters. Since tumor promoters are not mutagenic agents, 2-ACBs are not expected to cause gene mutations. However, testing should still be conducted on 2-ACBs to determine the degree of tumor promotion activity.

In vivo toxicological evaluation

Experimental Animal Studies with whole food

In 1999, the Food and Agriculture Organization (FAO)/International Atomic Energy Agency (IAEA)/World Health Organization (WHO) reviewed the scientific literature on *in vivo* toxicological evaluation of irradiated food and produced the Technical Report #890 that is entitled "*High-Dose Irradiation: Wholesomeness of Foods Irradiated Above 10Kgy*" (FAO/IAEA/WHO, 1999). A summary from the technical report is shown in Table 2. The table includes 27 peer-reviewed publications that mostly report negative results but ignores 5 peer-reviewed publications that illustrate toxicologic effects (Vijayalaxmi, 1975, 1976, 1978; Vijayalaxmi and Sadasivan, 1975; Vijayalazmi and Rao, 1976). The latter publications were disregarded based on the decision that the observed toxicity could have been caused by confounding factors such as nutritional and dietary deficiencies. However, the exclusion of these studies has been criticized (Vijayalaxmi, 1999; Kimbrell and Hauter, 2002; http://www.centerforfoodsafey.org/li.html).

Based on the review by the WHO and FDA (FAO/IAEA/WHO, 1999; Food and Drug Administration, 1986), the wholesomeness of irradiated food is generally considered to be safe to consumers. There are, however, major limitations with regard to published animal studies that

were used in support of this position. There is no documentation to indicate that the experimental animals had in fact consumed the putative hazardous (e.g. radiolytic) products in the food mixture. In addition, the animal bioassays are not designed to show adverse effects from the consumption of a small amount of toxic substances e.g. 2-ACBs in food. Traditionally, pure compounds, not mixtures, are tested in animal bioassays to generate dose-response observations and possibly to document the lowest no adverse effect dose. With the data that is obtained, it is then practical to evaluate the toxicity or safety of the compound and to extrapolate experimental findings to how it may pertain to human consumers. With these major limitations, the current data from animal studies are inadequate for making valid health risk assessment and such assessment has not enjoyed wide-spread acceptance.

Human Studies with whole food

Only two human studies have been reported. In one study, ten children (2 to 5 years old) suffering from severe protein-calorie malnutrition were fed freshly irradiated wheat (N = 5) or stored irradiated wheat (N = 5) for six weeks (Bhaskaram and Sadasivan in 1975). These ten children were compared to a matched control group of five children who were fed unirradiated food during the same time period. The first group of five children developed significantly more polyploid cells (having multiple sets of chromosomes) and other cellular abnormalities in their lymphocytes than the five who were fed the stored irradiated food. In addition, the abnormality persisted for up to two months after the feeding period ended. None of the children fed the un-irradiated diet developed any abnormal cells.

In another study, healthy adults were fed irradiated food for three months (Institute of Radiation Medicine, 1987). They did not display any increase of chromosomal aberrations when

compared to a control group. Upon reanalysis of the data (Louria, 1990), an increase in chromosomal aberrations was demonstrated. Although these results were from small scale investigations, the information is based on human responses and does raise some safety concerns about the health risk of irradiated food.

Potentially Harmful Radiolytic Products

In the modern era, a new concern has arisen in regard to some of the radiolytic products formed uniquely in irradiated food. Of particular interest is 2-ACB, a radiolytic derivative of triglycerides. In one report (Horvatovich et al., 2002), laboratory rats were fed a low concentration of 2-ACBs in drinking water, and the absorption and excretion of the chemicals were monitored. The study showed that a substantial portion of the chemical crossed the intestinal barrier, entered the blood stream, and accumulated in adipose tissue. Therefore, consumption of irradiated food can possibly result in a significant accumulation of 2-ACBs in the adipose tissues of consumers. The long-term health consequences of this observation are unclear at this time.

In another study (Raul et al in 2002), Wistar rats received a daily solution of 2-tDCB or 2-tDeCB (while controls received ethanol) solution daily in combination with an intraperitoneal injection of a known carcinogen (azoxymethane [AOM]). Observations were made at two distinct intervals. At three months after initiation of the exposure, no significant changes in the number of pre-neoplastic colonic lesions were observed among the rats (all were exposed to AOM). At six months, however, the total number and the overall size of tumors were markedly increased in the 2-ACB-AOM treated rats as compared to the ethanol-AOM control rats. This demonstrates that compounds found exclusively in irradiated dietary fats may promote colon carcinogenesis in animals treated with a known carcinogen and identifies a new area of toxicity

that the FDA and WHO have yet to examine. The 2-ACB tumor promotion activities should be further investigated, and their effects evaluated systematically.

Recommendations from regulating agencies

Various agencies from around the world have made recommendations regarding the safety of irradiated food consumption. The recommendations from major agencies that will be discussed in this review are the World Health Organization, the European Parliament, the US Food and Drug Administration, and the US Department of Agriculture.

World Health Organization (WHO)

The WHO has been an advocate of food irradiation since their appraisal of the technology. Based on a review of scientific evidence, their expert panel concluded that food irradiated at an appropriate dose was safe to consume and nutritionally adequate. The panel also concluded that an upper dose limit did not need to be imposed; stating "irradiated foods are deemed wholesome throughout the technologically useful dose range from below 10 kGy to envisioned doses above 10 kGy" (FAO/IAEA/WHO, 1999). In addition, they also stated that the limit could be set as based on the deterioration on the quality of the irradiated food. However, such decision that is based on vigorous scientific evaluation of public health impact should be more reliable.

Recently the Joint FAO/IAEA/WHO Food Standards Program (2003) under the United Nations promoted irradiation doses beyond the 10 kGy limit. During the deliberations, Germany objected to the absence of a 10 kGy limit and the United States argued for a 30 kGy limit to kill micro-organisms on spices. In the end the Commission adopted a revised standard over the objections of Austria, Denmark, Germany, Greece, Hungary, Italy, Mexico, Poland, Spain and

Sudan. The Commission argued that the higher levels of irradiation (30 kGy) were justified to eliminate bacterial spores. The Codex Alimentarius (Food Code) is a compilation of Standards, Codes of Practice, Guidelines and Recommendations of the 169 countries represented in the Codex Alimentarius Commission, a subsidiary body of FAO and WHO. This commission previously recommended a minimum of 1 kGy and a limit of 10 kGy.

The European Parliament

The European community has provided funding for some of the recent studies on the safety of irradiated food (e.g. Horvatovich et al., 2002; Raul et al., 2002). Based on the observed adverse effects resulting from these investigations, the European Parliament has retained the 10 kGy limit and has issued a moratorium on the addition of food items for irradiation:

> "In adopting this resolution, a majority of MEPs took the view that the current list of food ingredients authorized for irradiation treatment should not be extended at this stage. An amendment was adopted in favor of the third Commission option, the most restrictive one. The current list should be regarded as complete, which would mean that only dried aromatic herbs, spices and vegetable seasonings are permitted for irradiation in the European Union as and when scientific knowledge suggested that it was safe and efficacious to do so." (Breyer, 2002)

The Food and Drug Administration (FDA)

The regulations from the FDA are codified in CFR 21 Part 179 (1986) and the recommended irradiation conditions are listed in Table 3. Since the regulation does not supercede the authority of the U.S. Department of Agriculture (USDA), anyone irradiating food needs to comply with regulations set forth by the Food Safety and Inspection Service.

Under general labeling requirements, the FDA requires that the label bear the radura symbol and a prominent phrase "treated with radiation" or "treated by irradiation." However, if irradiated ingredients are additives to foods that are not irradiated they do not require any special labeling. Labeling is also not needed for irradiated food items once that are prepared and served in restaurants. To ensure foods are not irradiated multiple times, pre-retail labeling is required for any food that may need further processing. The FDA encourages other truthful statements about food irradiation on labels to educate consumers.

U.S. Department of Agriculture (USDA)

In May of 2003, the U.S. Department of Agriculture (USDA) released specifications to guide the National School Lunch Program in purchasing irradiated ground beef. Under the 2002 Farm Bill, the USDA may not prohibit approved food safety technologies on foods purchased for the National School Lunch Program. In California, the legislature is making recommendation that the local school boards provide consumer educational materials on irradiated food and decide on how to serve irradiated food (Legislative Session in Sacramento, California, June – July, 2004).

Meat and poultry establishments that use irradiation must meet sanitation and Hazard Analysis and Critical Control Point (HACCP) regulations. Additionally, the USDA conducts microbial testing to ensure processing plants are producing wholesome products.

Concerned Citizen Groups Positions on Irradiated Food

Citizen groups, like citizens themselves, have widely varying opinions on the safety of irradiated food. For the context of this review, the consumer groups will be classified broadly into those who oppose food irradiation, those that are neutral, and those who support it. In addition, only positions from representative citizen groups that are not observably funded by industry or whose opinions are not obviously based on financial or political interest are presented.

Groups that are against food irradiation, e.g. Public Citizen and The Center for Food Safety, base their concerns on peer-reviewed journal articles that state that the safety of consuming these foods has not been established (Is Irradiated Food Safe, 2003; Kimbrell and Hauter, 2002; http://www.centerforfoodsafety.org/li.html). They believe there are unique by-products of irradiated fat that can potentially cause cancer. They also believe that these products, 2-ACBs, have not been tested properly in the traditional toxicological manner. Another argument of the anti-irradiation food groups is the concept of sterilized filth. These groups contend that the food industry will use irradiation as a substitute for normal precautions when handling food, thus leaving the entrails, feces, blood, pus, tumors and other contaminates on the meat (Kimbrell and Hauter, 2002). Providing credence to this statement, the European Parliament has cited examples of illegal use of irradiation at European facilities to clean up contaminated seafood (Breyer, 2002). The consumer groups also contend that food irradiation would lead to a false sense of security in consumers. Consequently, consumers of irradiated foods may believe these foods cannot ever become contaminated, and would thus minimize traditional precautions instituted to ensure sanitary and safe food preparation, ultimately leading to more food-borne illness.

Another category of consumer groups is comprised of organizations that maintain a neutral position (e.g. Consumer Reports, Safe Tables Our Priority, The American Council on Science and Health, and the Center for Science in the Public Interest). These groups are well aware of the dangers of food-borne pathogens and see a need to improve the process of food handling overall. Some of them, such as STOP (Safe Tables Our Priority) are groups of concerned citizens which have themselves, or have a relative, that has been a victim of food borne illness. In general, these groups have no official policy stance on food irradiation, but they can see its potential benefit in protecting the general public from food-borne pathogens such as *Eschericia coli, Salmonella* and *Campylobacter*. These groups do emphasize the need to maintain normal safety precautions when handling food, and recommend that food be irradiated in its final packaging to reduce the chances of recontamination (Donley, 1999; Consumer Union, 2003). They feel that the irradiated products should be clearly labeled and the words "treated by irradiation" be used, as opposed to "cold pasteurized or electric pasteurized" (Donley, 1999; Mitchell, 1999). As long as the proper labeling (which includes the radura symbol) is present, and the public is educated about the possibility of recontamination, these groups contend that consumers can vote with their pocketbooks, thus choosing for themselves whether or not they want irradiated food products. These groups believe that the benefits of a safer food supply protected from bacterial and viral pathogens may outweigh any risks.

The last category of citizen groups, including the Hudson Institute's Center for Global Food Issues and the Competitive Enterprise Institute, endorse food irradiation. They contend irradiation defeats well-known and potentially deadly food-borne pathogens, and will save lives. These groups cite the fact that food irradiation has been used for decades by the military and NASA to prepare long shelf-life food products for soldiers and astronauts (CEI

Staff, 1999; Avery, 2003). They also referenced estimates from the USDA that the American consumer would receive approximately $2 in benefits from reduced spoilage and less illness for each $1 spent on food irradiation (Loaharanu, 2003).

Whether citizen groups are for or against food irradiation, nearly all groups agree the consumers should be informed of any food that has been irradiated. However, the groups that are most in favor of irradiation do not usually mention the issue of labeling.

Other methods for food sterilization and sanitation.

In addition to destroying, inhibiting, or removing micro-organisms from food products, other goals of food processing are to retard or prevent deleterious biochemical, chemical and physiochemical changes, to maintain and generate acceptable organoleptic (taste, texture, color and aroma) properties, and to preserve and enhance the nutritive value. Examples of bacteriostatic food processing methods include drying, freezing, pickling, salting, smoking and fermenting. Bacteriocidal procedures include thermal processing, electric energy, high pressure processing, and electromagnetic microwave technology.

Emerging electromagnetic microwave technology has some highly desirable features (http://www.pubit.it/sunti/euc0301q.html; http://www.techmonitor.net/techmon/03sep_oct/fpr/fpr_preserve.htm). The process has the potential to extend shelf life of food for a minimum of nine months, eliminate the need for refrigeration and offer the convenience of ready-to-eat food while maintaining organoleptic qualities and more than 90% of the nutritional value. In addition, the process uses a patented electromagnetic microwave (non-ionizing radiation) that has not been shown to generate unique

radiolytic products. Nevertheless, the overall quality and safety of the application needs to be determined scientifically and systematically.

Regardless of the ultimate technology applied, emphasis on sanitary processing of food prior to the sterilization phase and also at the time of food preparation by the consumer, should not be undermined. To prevent food-borne illnesses, it would be prudent to practice the four Cs of food safety: Clean well, Cook thoroughly, Combat Cross Contamination (Separate), and Chill (Refrigerate).

Discussion

Improvement of food safety and prevention of food-borne illness are fundamental and crucial public health objectives. The use of radiation on food has been heavily promoted as the approach to achieve these stated objectives. However, less emphasis has been placed on determining the potential health consequences that can result from this process. The justification used for approving food irradiation is based mainly on early studies which demonstrate that (1) the process did not generate substances that are not also generated by other food preservation procedures and (2) the wholesomeness of irradiated food is safe based on animal bioassays. However, recent studies have propagated uncertainty with regard to the safety of irradiated food that is to be provided to the consumer.

The *in vitro* and *in vivo* research outlined in this review clearly depict the formation of radiolytic products, e.g. 2-ACBs, in irradiated food that are not found in food items prepared by using other food processing technologies. Preliminary studies demonstrate that 2-ACBs accumulate in fatty tissues in experimental animals, exhibit toxicity, and possess tumor promoting activities. Testing for toxicity using wholesome irradiated food in animal bioassays is

not entirely appropriate because these assays are not designed to show the adverse effects of exposure to small concentrations of toxic substances such as 2-ACBs in food. These assays are traditionally used to test pure compounds, not mixtures, in order to demonstrate a dose-response effect for toxicity evaluation. Up to this point in time, there have been no comprehensive and systematic studies to assess human toxic effects resulting from irradiated food. Given the history of use of this technology thus far, one could argue that if it were unsafe then we should have seen some specific adverse health effects. However, if the toxic by-products are acting as promoters we may only recognize a small increase in cancer in the population (in terms of percentages but not in terms of number of affected individuals) and it would be very difficult to prove that irradiated food was in fact the direct cause of increased cancer morbidity and mortality. Any argument would have to be made inferentially based on the data presented.

The greatest concern expressed by mainstream consumer advocacy groups is the use of the technology without first informing the consumer. Even the names used are confusing. The proposed labeling statements "cold pasteurization" and "electronic pasteurization" instead of radiation are misleading to consumers.

There are many differing opinions on the use of radiation in food processing. However, there appears to be universal support for sanitary processing as being one of the most important considerations. Irradiation of poorly processed food only sterilizes something that should not be consumed in the first place. In addition, other useful procedures that do not generate health concerns should not be precipitately discarded without due consideration. The other major consideration is that evolving technology may replace the need to use radiation as a means to process food.

Recommendations

In summary, it is quite clear that additional research is needed in order to fully address the issue and concerns of irradiated food. The toxicity of unique radiolytic products should be tested vigorously, especially in regards to the tumor promoting activities. Animal bioassays should be conducted systematically and comprehensively with whole food and with unique radiolytic products to generate a dose-response understanding of the toxicity and safety of irradiated food. It would prove beneficial to establish a dose that does not cause any observable toxic effects in an experimental animal model. The data obtained would better substantiate extrapolation and application in human health risk evaluation. In addition, as of now, there are no extensive human trials available to assess irradiated food safety in human populations. Regulatory agencies in the US and around the world need to be proactive in resolving these health concerns prior to the ubiquitous consumption of irradiated food. It is notable that the European Parliament has halted the addition of new food products for irradiation and has chosen to maintain the 10kGy limit on irradiation.

In a global perspective, prevention of food-borne illness is a critically important practice. Third world countries with malnutrition, widespread famine and limited hygiene resources may view the concept of irradiated food differently from developed countries. Nevertheless, considerations for the approval of irradiated food for consumption need to be based on realistic and informed evaluation of the risk and benefits to the populations.

This illustrates the core issue in processing food with radiation. One can argue their respective position based on sound reasoning and with a convincing tone. Therefore, the decision to consume irradiated food should be made through knowledgeable risk assessment,

using all available scientific evidence-based data, and involving all stakeholders prior to achieving an informed decision.

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TABLE I

IN VITRO MUTAGENICITY STUDIES

STUDY	FOOD	CELL TYPE	DOSE (kGy)	HIGH DOSE IRRADIATION MUTAGENIC EFFECT	AUTHOR
1	Glucose, Peptone	E. Coli	50	Negative	Bugyaki et al., 1963
2	Sucrose	Human Lymphocytes	20	**Possible*** Chromosomal breaks in human lymphocytes	Shaw & Hayes, 1966
3	Sucrose	Vicia faba	20	**Possible*** Chromosome changes	Bradley et al., 1968
4	Strawberry	Salmonella, Human	15	Negative	Schubert, et al., 1973
5	Paprika	Salmonella	50	Negative	Central Food Research Institute, 1977
6	Sucrose, Ribose	Salmonella	20	**Possible***	Aiyar & Rao, 1977
7	Cod	Salmonella	12	Negative	Joner et al., 1978
8	Growth Medium	Human Lymphocytes	10, 20	Negative	Vijayalazmi, 1980
9	Herring	Salmonella	12	Negative Possible effect of nutrition or diet	Joner & Underdal, 1980
10	Dates, Fish, Chicken	Salmonella, CHO cells	10	Negative	Phillips et al., 1980
11	Dates, Fish, Chicken	CHO Cells	10	Negative	Phillips et al., 1980
12	Onion Powder	Salmonella	13.6	Negative	Mönzer & Renner, 1981
13	Spice Mix	Salmonella	14, 45	Negative	Farkas et al., 1981

14	Beef, Pork, Veal	Salmonella	50	Negative	Münzer, 1983
15	Sucrose, Fructose, Glucose, Maltose, Mango	Salmonella	50	**Possible*** Simple sugar mutagenic in one of five strains. Negative in Mango	Niemand, et al., 1983
16	2-DCBs	Rat and Human Colon Cells	N/A	**Possible** DNA strand breaks and oxidative damage Cytotoxic, Genotoxic	Delincée & Pool-Zobel, 1998
17	2-DCBs	Human Colon Cells	N/A	**Possible** Cytotoxic, Genotoxic	Delincée, et al., 2002
18	2-DCBs	Salmonella	N/A	**Possible** Cytotoxic	Titeca et al., 2003
19	2-DCBs	E. Coli	N/A	Negative	Sommers, 2003

*May have this mutagenic effect as a result of radiation-induced chemistry of simple carbohydrate solutions
Table adapted from FAO/IAEA/WHO 1999.

TABLE 2
IN VIVO MAMMALIAN MUTAGENICITY STUDIES

Study#	Food Type (% in diet)	Species Type	Irradiation Dose (kGy)	Notations	Reference
1	Black Beans	Mouse Swiss-55	15, 20	NHDIR. Dominant lethal test. No difference in pregnancy rates, total implants, live and dead implants, sex distribution, or abnormalities.	Bernardes et al. (1981)
2	Chicken (35%)	Mouse	59	NHDIR. Dominant lethal test. Feeding of radiation-sterilized chicken meat did not induce dominant lethal events. Positive control produced negative results, unsuitable for supporting safety.	Raltech Scientific Services (1978)
3	Glucose Powder	Mouse Swiss	20, 50	NHDIR. Dominant lethal test. No mutagenic effects.	Varma et al. (1982)
4	Glucose Powder	Mouse Swiss	20, 50	NHDIR. Micronucleus test in bone marrow cells and chromosomal aberration assay. No evidence of mutagenic effects in somatic or germ cells.	Varma et al. (1986)
5	**Laboratory diet: Solid cakes**	**Mouse C57BL**	**50**	NHDIR/PEND. Dominant lethal test. Increased pre-implementation embryonic deaths; not confirmed by cytological analysis.	**Moutschen-Dahmen et al., (1970)**

TABLE 2
(Cont'd)
IN VIVO MAMMALIAN MUTAGENICITY STUDIES

6	Laboratory diet: Pellets, enriched with amino acids and vitamins	Rat SPF Wistar	50	NHDIR. Dominant lethal test. No evidence of mutation.	Eriksen & Emborg (1972)
7	**Laboratory diet: Food pellets**	**Mouse Swiss SPF**	**0, 7.5, 15, 30**	NHDIR/PEND. Host-mediated assay. Significant increase in the mutation frequency induced by the high-dose irradiated food.	**Johnson-Arthur et al. (1979)**
8	Laboratory diet: pellets	Mouse	0, 7.5, 15, 30	NHDIR/PEND. Host-mediated assay for 3 commercial food pellets. Irradiation increased mutation frequency between 10 and 60 fold for the 3 products compared to controls. Subsequent extraction study found mutagenic agent extracted by alcohol. Water extract had a lower effect and ether extract had no effect.	Johnson-Arthur et al. (1975)
9	Laboratory diet 10% moisture	Rat Wistar	25	NHDIR. Dominant lethal test. No evidence of mutagenic effects.	Chauhan et al. (1975a)

TABLE 2
(Cont'd)
IN VIVO MAMMALIAN MUTAGENICITY STUDIES

Study#	Food Type (% in diet)	Species Type	Irradiation Dose (kGy)	Notations	Reference
10	Laboratory diet 10% moisture	Mouse Swiss	25	NHDIR. Dominant lethal test. No evidence of mutagenic effects.	Chauhan et al. (1975b)
11	Laboratory diet: pellets	Mouse	45	NHDIR. Host-mediated assay. No mutagenic effects.	Munzer & Renner (1975)
12	Laboratory diet	Mouse BALB/c	28.5	NHDIR. Bone marrow and male germ cells examined for chromosome aberrations. No mutagenic effects.	Leonard et al., (1977)
13	Laboratory diet: pellets	Chinese hamster	45	NHDIR/PEND. No increase in chromosomal aberrations; slightly increased incidence of polyploidy.	Renner (1977)
14	**Laboratory diet**	**Mouse CD1**	**10, 25, 50**	NHDIR/PEND. Dominant lethal test. Used 4 diets on 2 strains. Some evidence of weakly mutagenic effect with one diet.	**Anderson et al. (1981)**
15	Laboratory feed	Mouse, SPF Ha/ICR (Swiss)	30	NHDIR. Host-mediated assay. No mutagenic effects.	Munzer & Renner (1976)

TABLE 2
(Cont'd)
IN VIVO MAMMALIAN MUTAGENICITY STUDIES

16	Milk powder (35%)	Mouse: NMRI/Han, Rat, Sprague-Dawley	45	NHDIR. Dominant lethal test, reproduction. High content of radicals in the irradiated food. No harmful effects.	Renner et al. (1976)
17	Onion powder (10%)	Chinese hamster, Mouse	13.6	NHDIR. Sister chromatid exchange tests negative in hamsters and 3 strains of mice.	Munzer & Renner (1981)
18	Paprika	Mouse	50	NHDIR. Host-mediated assay. No increase in number of revertants.	Central Food Research Institute (1977)
19	Paprika (20%) 8.6% moisture	Mouse Swiss	30	NHDIR. Micronucleus test. No differences in the incidence of erythrocytes with micronuclei, and polychromatic:normal ratio comparable among all groups.	Chaubey et al. (1979)
20	Spice mix Pepper	Rat CFY	15	NHDIR. E. Coli inductest on blood of rats. No induction of lysogenic bacteria.	Farkas & Andrassy (1981)
21	Spice mix	Rat CFY	15, 45	NHDIR. Negative Ames test on irradiated spice extracts and on urine of rats fed irradiated spices.	Farkas et al., (1981)

TABLE 2
(Cont'd)
IN VIVO MAMMALIAN MUTAGENICITY STUDIES

Study#	Food Type (% in diet)	Species Type	Irradiation Dose (kGy)	Notations	Reference
22	Spice mix (25%)	Rat Sprague-Dawley	15	NHDIR. Dominant lethal test. No significant difference between irradiated spice groups and controls.	Barna (1986)
23	Strawberry	Mouse	15	NHDIR. No clastogenic effects.	Schubert et al. (1973)
24	Sucrose, ribose solutions	Mouse	50	NHDIR. Host-mediated assay. No increase in number of revertants.	Aiyar & Rao (1977)
25	**Wheat (50%)**	**Mouse**	**0, 50**	NHDIR/PEND. Chromosomal abnormalities in germ cells presumed due to formation of peroxides and radicals (see reference 33) with subsequent loss of lipids and carotenoid fractions in irradiated diet.	**Bugyaki et al. (1968)**
26	Wheat (freshly irradiated)	Chinese hamster	0, 15, 30	NHDIR. No difference in polyploids in bone marrow cells or micronuclei in reticulocytes 72h after diets irradiated in N2 or air. Analyses of micronuclei in peripheral blood of rat fed wheat flour irradiated at 0.75kGy done at 6 and 12 weeks.	Tanaka et al. (1992)

NHDIR = negative for high-dose irradiation effect (>10kGy); PEND = possible effect of nutrition or diet; % in diet based on dry weight unless otherwise specified indicated. Information presented in bold font indicates positive findings.
Table modified from FAO/IAEA/WHO, 1999.

Table 3:

Approval date	Food/Product Dose (kGy)*	Purpose
1964, 1965	Potatoes, 0.05 - 0.15	Inhibit sprouting (and extend shelf life)
1983	Spices and dry seasonings, < 30	Disinfestation and decontamination
1985	Pork, 0.3 - 1.0	Control of *Trichinella spiralis*
1985, 1986	Dry or dehydrated enzymes, < 10	Control of insects and microorganisms
1986	Fruit, < 1	Delay maturation and disinfestation
1986	Fresh vegetables, < 1	Disinfestation
1986	Herbs, spices & seasoning, < 30	Control of microorganisms
1990	Poultry, fresh or frozen, < 3	Control of microorganisms
1995	Meat, frozen and packaged (solely for use in NASA), > 44	Sterilization
1995	Animal feed and pet food, 2 - 25	Control of *Salmonella*
1997, 1999	Red meat, meat products (uncooked)	
	• chilled (refrigerated), < 4.5	
	• frozen, < 7.0	Control of microorganisms