IBA

GUARDIAN

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Chip Colonna
President

February 7, 2003

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: FAP 9M4697 – Comments for Docket No. 99F-5522

Dear Sir or Madam,

IBA Food Safety Group designs, builds and operates gamma, X-ray and electron beam irradiation facilities. We operate 17 irradiation facilities in the United States, several to process food. Our company currently irradiates approximately 90 million pounds of food and food ingredients each year in the US. We have been working with USDA to achieve Grant of Inspection for the irradiation of meat and poultry products in our facilities.

IBA supports the view that irradiation of food is safe. With this letter, we are providing additional information to support the safety of the irradiation of ready-to-eat foods as defined in FAP 9M4697 from the Food Irradiation Coalition of the National Food Processors Association.

It is clear that some ready-to-eat foods have been responsible for several, serious outbreaks of foodborne illness and many deaths. In the majority of outbreaks, these foods were not processed by 'bad actors' in the food industry, but by food companies following good processing practices and operating under inspection. Analysis of these outbreaks will result in recommendations for

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processing and/or sanitation improvements, which the food industry will probably implement. However, processing improvements alone will not remove the risk; foods are naturally contaminated with pathogens, pathogens are wily competitors and seem to prevail in the face of our continuing efforts to control them. At the same time, efforts to control microorganisms in foods must be affordable; we cannot use drug production methods for food processing and still provide sufficient and affordable food for our nation. We believe food processors are trying to use all available means to avoid contamination in their products, which is why they are interested in irradiation.

Irradiation should be available and used to make ready-to-eat foods safer. Irradiation should and will be used as part of HACCP processing and as part of government inspection programs to ensure that microbial contamination before irradiation is kept as low as possible. Irradiation will work within HACCP processing to ensure a safe and affordable food supply.

Some groups believe the real food safety benefits of irradiation should be ignored. They highlight imagined or infinitesimally small risks pointing to the very few studies that suggested problems with irradiated foods, ignoring the large body of very positive research. In any large body of research, such has been done to study the safety of irradiated foods, there are bound to be studies that suggest problems. That is why many studies are conducted, reviewed and the entire body of research considered. Several expert scientific groups have conducted reviews of the safety of irradiated foods, and they have found in favor of the safety of irradiated foods. We have included many WHO reports supporting this conclusion.

IBA submits the following assessment of the food chemical and toxicological safety of irradiated foods as further evidence for FDA of the safety of irradiated foods.

Yours sincerely,

Chip Colonna
President

attachment

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Chemistry of Irradiated Foods

The major components of foods are water, proteins, lipids, and carbohydrates. Flesh foods contain primarily water, protein and lipids; fruits and vegetables contain primarily water, carbohydrates, and some protein or lipid; and herbs and spices contain primarily carbohydrates, some water, and small amounts of flavor or color ingredients. The radiolytic products formed from these components follow a generally predictable pattern that is common to foods of similar composition and correspond to only very small concentrations within the irradiated food. This common chemistry forms the basis for the chemiclearance principle (Taub et al., 1980; WHO ref 29).

Moreover, the predictability and low yield aspects of radiation sterilization contrast with thermal sterilization, which leads to a wide spectrum of thermolytic products, often in relatively high concentrations. As stated in the Final Rule on meats, there is a large database regarding the dependence of radiolytic products on the classes of similar foods and on the radiation processing parameters. These parameters include the physical state of the food (frozen or non-frozen), the radiation dose, and the processing atmosphere (air, vacuum, etc.) above the food. The amounts of radiolytic products generated are generally proportional to the dose, strongly influenced by the physical state of the food, and affected by the oxygen content in the processing atmosphere (Carberry, 1995; 62 FR 64107 at 64110).

The radiation phenomena responsible for any discernible physical or chemical changes in the food can be understood by considering the processes by which reactive intermediates are formed, diffuse apart, and react with one another or with the food components. Because of the heterogeneous nature of meats and their muscle structure, the major components constitute distinct phases in which distinctive reactions occur and between which there is essentially no cross reactions, except at interfaces or in emulsified matrices. Accordingly, the phenomena occurring in the aqueous sarcoplasmic phase of the muscle will be generic to the hydrated protein phase of the muscle or to the totally lipoidal phase of the intercellular fat phase and will lead to counterpart intermediates. Exposure to high energy radiation initiates the phenomenological events in each phase associated with energy loss by the radiation and the

resultant chemistry of such intermediates. Exposure to high energy radiation initiates in each phase the phenomenological events associated with energy loss by the radiation and the resultant chemistry of the intermediates formed.

The penetration of the radiation into the food involves interaction with the valence electrons of the molecular constituents. High energy electrons from machine sources or the energetic electrons created by gamma ray scattering through the Compton process will ionize or excite some of the molecules in random and spatially separated events, decreasing the energy of the radiation and creating small clusters (or spurs) of positive, negative, and excited entities. The number of such entities created is fixed by the energy required for ionization, and therefore limits the number of reactive intermediates that can be formed. Using the aqueous phase for illustrative purposes here and in what follows, the required energy is 33 ev per ion pair and the number per 100 ev of absorbed dose is essentially 3, which is the basis for the *G*-values of intermediates or radiolytic products used to quantify yields. These initial entities in the spurs can neutralize, deexcite, transfer protons, and combine, leading to the more stable but still reactive intermediates recognized in water to be the solvated electron, the hydrogen atom, and the hydroxyl radicals. Since all of these have an unpaired electron, they are classified as free radicals. They are not exclusive to irradiation, but are also formed in oxidation-reduction reactions, thermal decomposition reactions, photolysis reactions, electrochemical reactions, and even in physiological reactions (e.g., ascorbic acid, alphatocopherol, NAD, etc.). Their subsequent chemistry, however, does depend on how they are created and on the environment in which they are created.

The fate of these radicals in the spurs is determined by competition between two processes: reaction and diffusion. Reaction with each other, regenerating water and producing dihydrogen or hydrogen peroxide, takes place at the same time as diffusion out of the spur. Ultimately this diffusion leads to a more homogeneous distribution of the water radicals throughout the aqueous phase. The rate of diffusion is related to the size of the radical and is significantly affected by the viscosity or rigidity of the food matrix. In a high moisture and fluid matrix, the diffusion is rapid; in a relatively dry or in a moist but frozen matrix, the diffusion is slow or even prevented. The larger hydroxyl radical is particularly affected by these factors. Its diffusion is essentially prevented in frozen systems, and reactions with it would be confined to constituents in close

proximity. Overall, the net effect of this competition between reaction and diffusion and the influence of physical state on diffusion is to significantly reduce the yield and reactivity of these free radicals that are produced when the food is irradiated while frozen.

The fate of the radicals that do escape the spur is determined by the nature and concentration of the food components and by the reactivity of the radicals towards these food components. Illustrating again with the aqueous and proteinaceous components of muscle tissue, all of the water radicals could react either with the myoglobins or micronutrients in the sarcoplasm or with the actomyosin/myosin proteins of the muscle. The likelihood of any particular reaction occurring is subject to the usual kinetic considerations—reactions with constituents in high concentration and characterized by high rate constants will be favored over constituents in low concentration and characterized by low rate constants—as well as to those discussed above relating to the physical state of the matrix. Consequently, the color of the meats is affected by the reduction of metmyoglobin and their texture is slightly affected by some fragmentation in the myosin chain, both due to respective reactions with solvated electrons. Other reactions with solvated electrons and with the hydrogen atom or the hydroxyl radical can occur leading to the formation of a secondary radical—the peptide backbone radical characterized by the unpaired electron on a carbon in the peptide chain. The major radical can combine with another and results in a cross-linked protein. Since the actomyosin/myosin proteins represent the major constituents in all the flesh foods, the chemistry will be common to all their irradiated products. Moreover, the similar pattern of volatile hydrocarbons from irradiated meat lipids and its dependence on the precursor fatty acids provide a quantitative demonstration of such common chemistry (Merritt and Taub, 1983 WHO ref 59; Kou and Morehouse, 1992, 1993; and Morehouse and Taub, 1999). This commonality is manifested in the chemiclearance principle

These phenomenological considerations provide an insight into the conclusions drawn by FDA regarding the effects of irradiation on the food components.

For proteins, irradiation can involve reactions that result in breaking of polypeptide bonds to form shorter-length polypeptides, cross-linking of polypeptide chains, and changing some amino acids in the protein. FDA has stated that compounds produced by such reactions are similar or

identical to those found in foods that are not irradiated and there is little change in the amino acid composition of flesh foods irradiated at doses below 50 kGy (62 FR 64107 at 64110).

For lipids, FDA stated that many studies have been performed on fats and oils and on the lipid fraction of irradiated foods. Researchers have identified a number of radiolytic products derived from lipid fractions, including fatty acids, esters, aldehydes, ketones, alkanes, alkenes, and others. All of these types of compounds are also found in foods that have not been irradiated, including heated foods (62 FR 64107 at 64110).

Irradiation of aqueous carbohydrate solutions produces a number of sugars, aldehydes, ketones, alcohols, and acids as end-products (Diehl and Scherz, 1975; WHO 1994). The presence of other components in a carbohydrate solution decreases the amount of radiolytic products from carbohydrates (Diehl et al, 1978). FDA has acknowledged that the reaction products resulting from the irradiation of sugar solutions in the presence of oxygen have been shown to cause biological effects *in vitro* as a result of the presence of dicarbonyl sugars produced by reaction of peroxy radicals with sugar molecules. FDA concluded that such studies are unsuitable models for predicting and extrapolating any toxicity of irradiated foods (51 FR 13376 at 13383).

FDA determined that the large numbers of studies on the radiation chemistry of food and food components, taken together, support the chemiclearance principle that irradiated foods of similar composition will yield radiolytic products of similar composition and quantity (Taub et al., 1980). FDA concluded that it was scientifically sound to generalize from the data obtained in specific foods to draw conclusions regarding the foods (i.e., meats/flesh foods) as a class (62 FR 64107 at 64110).

Table (1) Current uses of ionizing radiation greater than 10 kGy

USE	FOOD TYPE	LIMITATION
Microbial disinfection	Dry or dehydrated aromatic vegetable substances when used as ingredients solely for flavoring or aroma	≤ 30 kGy (3 Mrad)
Sterilization	Frozen, packaged, precooked meats used solely in NASA space flight programs	≥ 44 kGy (4.4 Mrad)
Microbial disinfection	Bagged complete diets for laboratory animals	≤ 50 kGy (5 Mrad)
Salmonella negative	Complete poultry diets, poultry feed ingredients	≥ 2.0 kGy, ≤ 25 kGy (0.2 to 2.5 Mrad)

Table (1) lists the foods that can be irradiated to high doses (> 10 kGy). FDA currently permits the use of radiation for the microbial disinfection of 1) spices and seasoning ingredients that are used for flavoring, and 2) frozen, packaged, precooked meats for the NASA space flight programs. Because of the limited use of such meats in the programs, questions regarding acute hazards were considered a more significant concern. NASA stated that it would ensure the sterility of the product and the integrity of the product packaging with strict adherence to a scheduled process that specifies a minimum dose of 44 kGy to ensure sterility of the treated meat (60 FR 12669; March 8, 1995).

FDA also permits the use of radiation for the microbial disinfection of bagged complete diets for laboratory animals to doses not to exceed 50 kGy (21 CFR 579.22; 51 FR 5992, February 19, 1986; 58 FR 18147, April 8, 1993) and for rendering complete poultry diets and poultry feed ingredients *Salmonella* negative using doses between 2 kGy and 25 kGy (21 CR 579.40; 60 FR 50098, September 28, 1995). The Agency was aware that this process does have a minimal effect on the content of some nutrients, such as water soluble vitamins and some amino acids, and allowed such feeds treated by irradiation to be formulated to allow for nutritional loss. FDA also evaluated the safety data in the petitions and other relevant material and concluded that such irradiation treatment of feeds was safe. Such feeds have been used by producers of germ-free

and gnotobiotic animals for many years. The petitioner is unaware of adverse effects in colonies of germ-free and gnotobiotic animals fed a diet of radiation-sterilized feed.

In 1981, FDA initiated its rulemaking process with an advance notice of proposed procedures for the regulation of irradiated foods for human consumption that announced the availability of the Bureau of Foods' Irradiated Food Committee (BFIFC) Report and requested comments on the overall approach (46 FR 18992; March 27, 1981). Based on its review of toxicological studies available at that time, FDA issued regulations to permit the use of irradiation on foods to doses below 1 kGy and on dry flavoring ingredients to doses no greater than 30 kGy in 1986 (51 FR 13376; April 18, 1986). FDA also stated that it could not permit the use of irradiation for other uses because the agency had not assessed the nutritional, microbiological, and toxicological effects of irradiating major dietary components to doses above 1 kGy, due to limitations in the design and conduct of individual studies. This conclusion was based on recommendations of the Irradiated Food Task Group established by FDA to review the toxicology data available at that time.

Since that time, FDA has issued regulations permitting the irradiation of poultry (55 FR 18538; May 2, 1990) and meat products (62 FR 64102; December 3, 1997) to control foodborne pathogens. In the Federal Register of May 2, 1990 (55 FR 18537), FDA cites the Raltech Scientific Services (Raltech) study of radiation sterilized chicken and states: "The Agency fund no evidence in any of the Raltech studies of adverse effects that could be attributed to irradiation of chicken at doses up to 59 kGy." In the Federal Register of December 3, 1997 (62 FR 64102), FDA reexamined the toxicological database reviewed earlier (51 FR 13376; April 18, 1986) and found that:

> while many of these studies cannot individually establish safety, they still provide important information that, evaluated collectively, supports a conclusion that there is no reason to believe that irradiation of flesh foods presents a toxicological hazard.

FDA's analysis focused on the types of studies that provide the greatest opportunity for detecting a treatment-related effect. These include chronic feeding studies, reproduction and teratology studies, and genotoxicity studies. FDA considered all studies and data in its files regarding the radiolytic chemical changes in foods and the toxicological effects of consuming irradiated foods. The December 3, 1997 Final Rule focused on flesh foods, including meat, chicken, and fish.

Animal Feeding Studies

FDA summarized the status of its toxicological review of irradiated foods, in general, in its Final Rule permitting the use of a source of radiation to treat refrigerated or frozen uncooked meat products (62 FR 64107, December 3, 1997). FDA stated that based on all available information from the results of chemical analyses, there is no reason to suspect a toxicological hazard due to consumption of irradiated foods. This conclusion drew upon a reexamination of the studies previously reviewed by FDA and is included in the review by the WHO. Further, based on a review of available data from toxicological studies relevant to the irradiation of foods, FDA concluded that consuming irradiated flesh foods poses no toxicological hazard, because no toxicologically significant adverse effects attributable to consumption of irradiated flesh foods were observed in any of the studies (62 FR 64107 at 64112).

The above conclusion is striking because many foods were irradiated under worst-case conditions and only the optimal irradiation processes developed by the U.S. Army's Natick Laboratories will be used commercially. Wholesomeness studies by Raltech used the Natick process of vacuum packing enzyme-inactivated (by heat) chicken and then treating by irradiation at subfreezing temperatures. The majority of other studies using foods irradiated under various conditions above 10 kGy was conducted by the Army in the 1950's and 1960's.

The U.S. Army Quartermaster Corps became interested in the feasibility of preserving foods using ionizing radiation from radioisotopes and radioactive by-products from nuclear reactors in the early 1950's (Raica et al. 1963; WHO ref 423). As part of the Army's overall program, the Medical Research Branch of the Surgeon General's Office was assigned the task of determining the wholesomeness of radiation-sterilized foods in 1953. This program supported studies in academic and research institutions as well as in military research institutions and resulted in many of the feeding studies listed in the tables on feeding studies with rats, mice, dogs, and monkeys. The Army initially had 49 foods under investigation with short-term studies, but chose 21 for long-term toxicity studies. The foods included ground beef, pork loin, bacon, shrimp, cod, chicken, tuna, beef stew, chicken stew, carrots, cole slaw, corn, green beans, potatoes, sweet potatoes, flour, fruit compote, evaporated milk, peaches, oranges, and jam. In general, the food

was irradiated to 27.9 and 55.8 kGy with spent fuel rods in Idaho Falls, Idaho, Dugway, Utah, or in Aiken, South Carolina. Potatoes, flour and oranges were treated with low-dose irradiation (0.1-1.5 kGy). Some batches were irradiated in local academic or private facilities.

To maximize any potential toxicity, the doses applied for some foods were greater than would normally be applied, and the quantities of test foods consumed by the animals were greater than would normally be consumed. The large group of foods used for the studies reflected the Army's concern that each food item, or a combination of irradiated foods, might respond to irradiation in a unique way (Read et al. 1958 WHO ref 320; Read et al. 1961 WHO ref 76 and WHO ref 314). The Army also tried to correct the problem of low palatability of diets containing high levels of the irradiated food item by including caloric consumption in the statistical evaluation of the results (Read et al. 1958; WHO ref 320). One reason for the palatability problem was the absence of a scheduled process for preparing and handling the food. The enzymes in the food were not heat-inactivated during the preparation, and storage conditions prior to and during irradiation were not standardized, resulting in unpalatable food. In spite of these deficiencies, the studies provide information on the safety of foods processed under extreme conditions.

Because of the large number of studies in the database, FDA focused on the types of studies that provide the greatest opportunity for detecting a treatment-related effect. Summaries of specific scientific evaluations of toxicological studies with flesh foods irradiated at high doses (> 10 kGy) are presented below.

Chronic Feeding Studies

Both FDA and WHO evaluated a large number of chronic studies conducted in rats, mice, and dogs fed foods at a maximum of 35% of the diet irradiated to doses between 28 and 74 kGy (Tables (1), (2) and (3)). In these studies, no toxic effects that can be attributed to radiation treatment were consistently observed. The three effects listed in the tables were considered incidental (62 FR 64107 at 64113; Irasquin, 1995; Trotter 1997a; these tables were condensed from a FDA memorandum).

In one study, FDA concluded that the observed decrease in alkaline phosphatase levels in weanling rats is not of toxicological significance, because (1) the effect observed in weanling rats was not observed in rats maintained on the same diet into adulthood, (2) the effect was not reproduced when either of the two irradiated foods was fed individually, and (3) no other reported observations indicate a toxic effect (Phillips, et al., 1961 WHO ref 325 and 331); 62 FR 64107 at 64113).

In another study where rats were fed a composite of irradiated foods, the authors reported a decreased weight gain for third generation females, but not for males. FDA concluded that this effect is indicative of overall dietary deficiencies unrelated to radiation treatment and cannot be attributed to irradiation because it was accompanied by breeding problems that significantly reduced the sizes of the groups of rats fed the control diet as well as the irradiated diet (Reed et al., 1961 WHO ref 76 and WHO ref 314); 62 FR 64107 at 64113).

In the third study, mice fed irradiated pork and chicken were reported to have a significant increase in heart lesions (Monsen 1960 WHO ref 351; 62 FR 64107 at 64113). Additional testing by the author suggested that the lesions could have been due to a mineral deficiency (Monsen 1963 WHO ref 352, 1965 WHO ref 353). A replicate study with more than 4,000 mice of the same strains showed no such lesions, demonstrating that irradiation was not responsible for the heart lesions originally reported (Thompson et al. WHO ref 354, 1965; WHO 1994).

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Table (2) Long Term Studies in Rats

Food	Duration Days	Dose kGy	Effect	Reference
Beef	730	55.8	None	Bone (1963: WHO ref 321)
Pork, Peach, Flour, Carrots	730	55.8	None	Bone (1963: WHO ref 321)
Tuna Fish , Corn	728	55.8	None	Paynter (1959; WHO ref 322)
Chicken Stew, Cabbage	730	56	Alkaline phosphatase in duodenum, decrease	Phillips et al. (1961; WHO ref 325)
Beef Stew, Milk Powder	730	55.8	None	Radomski et al. (1965b; WHO ref 326)
Bacon, Ham, Fish	721	55.8	Weight gain decrease in 3rd generation	Read et al. (1961 WHO ref 76 and WHO ref 314)
Beef, Pork, Fish	365	27.9	None	Teply & Kline (1959; WHO ref

				313)
Pork Brain, Beef	365	93	None	Teply & Kline (1959; WHO ref 313)
Bacon, Beef, Fish	960	58	None	Teply & Kline (1959; WHO ref 313)
Pork	900	74	None	Van Logten et al. (1983; WHO ref 341)

Table (3) Long Term Studies in Mice

Food	Duration Days	Dose kGy	Effect	Reference
Chicken	730	59	None	Raltech Scientific Services (1983 XXX)
Bacon	750	55.8	None	Dixon et al. (1961; WHO ref 347)
Bacon Fat	500	55.8	None	McKee et al. (1959; WHO ref 346)
Pork, Chicken	800	55.8	Auricular dilation	Monsen (1960; WHO ref 351)
Tuna Fish, Beef	730	55.8	None	Radomski et al. (1965a; WHO ref 349)
Beef, Pork, Fish	365	27.9	None	Teply & Kline (1959; WHO ref 313)
Pork Brain, Beef	265	93	None	Teply & Kline (1959;

				WHO ref 313)
Pork, Chicken	600	55.8	None	Thompson et al. (1963; WHO ref 355)

Table (4) Long Term Studies in Dogs

Food	Duration days	Dose kGY	Effect	Reference
Chicken	999	59	None	Raltech Scientific Services (1982; WHO ref 372)
Chicken, Beef, Jam	730	55.8	None	Blood et al. (1966; WHO ref 367)
Bacon, Cabbage	730	55.8	None	Hale et al. (1960; WHO ref 1960)
Beef	728	55.8	None	Reber et al. (1962; WHO ref 364)

Reproduction and Teratology Studies

FDA reviewed reproduction/teratology studies in laboratory animals where the food was irradiated to doses of 6 kGy or higher and concluded that the available studies of irradiated flesh foods show no adverse effects on reproductive or developmental endpoints that can be attributed

to radiation treatment. Tables (5) and (6) list studies in which diets irradiated to doses greater than 10 kGy were fed to rats, mice, and dogs (Trotter 1997b; these tables were condensed from a FDA memorandum). There were no adverse effects reported for studies where animals were fed irradiated food at doses greater than 10 kGy.

Table (5) Reproduction and Teratology Studies in Rats

Food	Dose (kGy)	Effect	Reference
Pork	55.8	None	Bubl & Butts (1960; WHO ref 328)
Chicken, green beans	59	None	Richardson (1960; WHO ref 322 or WHO ref 323)

Table (6) Reproduction and Teratology Studies in Mice

Food	Dose (kGy)	Effect	Reference
Chicken	59	None	Christopher, Ronning et al. (1983 XXX)
Chicken	45	None	Thompson et al. (1977 XXX)

Table (7) Reproduction and Teratology Studies in Dogs, Hamsters, and Rabbits

Food	Dose (kGy)	Effect	Species	Reference
Beef	56	None	Dog	Clarkson & Pick (1964; WHO ref 365)
Chicken	45	None	Hamster	Dahlgren et al. (1977 XXX)
Chicken	45	None	Rabbit	Dahlgren (1978 XXX)
Beef	56	None	Dog	Loosli et al. (1964; WHO ref 375)

Human Clinical Studies

In a series of studies involving young male human volunteers, the U. S. Army evaluated the wholesomeness and potential toxicity of foods treated with high-doses of ionizing radiation. (Levy et al. 1957 (WHO ref 428); Plough et al. 1957 (WHO ref 310); Bierman et al. 1958 (; WHO ref 429)). This series of clinical studies was designed to detect toxic effects of high-dose food irradiation after short latency periods with up to one-year follow-ups; it was not designed to detect long-term nutritional deficiencies or the potential for carcinogenic effects after consumption of diets treated with high-dose irradiation. As discussed earlier, there was a problem of palatability of diets with high levels of irradiated foods because they were not prepared, stored and processed like commercially processed foods. Nevertheless, these studies provide information on the short-term toxicological effects of these foods processed under extreme conditions.

Subjects consumed irradiated foods for periods of 15 days separated by control and washout intervals. Generally, the experimental protocol called for a variety of foods (54 items) to be sealed in cans, frozen, and treated with 25 to 40 kGy of gamma irradiation from spent fuel rods in Dugway, Utah, and Arco, Idaho. Non-irradiated control items were processed and stored similarly, except where freezing was required in lieu of storage at room temperature. Irradiated

foods were tested for sterility and the presence of bacterial exotoxins prior to human consumption. Individuals and groups served as their own controls during the series of experimental periods. Controlled housing in a metabolic ward was provided during testing and subsequent follow-up evaluations. Particular attention was paid to clinical examinations, cardiac performance, and hematological, hepatic, and renal functions.

Ideally, human safety studies require double-blind experimental designs to prevent placebo or unintentional experimenter bias. Volunteer participants in these studies reported in journal entries and interviews that control foods and foods treated with high dose irradiation could be readily distinguished by flavor, odor, and texture.

Volunteers reported no adverse clinical experiences or reactions associated with the consumption of irradiated foods. Clinicians detected no adverse findings during physical evaluations or in clinical laboratory values during either consumption of irradiated diets or in follow-ups after these short-term exposures.

Spices and Seasoning

FDA initiated a regulatory review of food irradiation in the early 1980's and conducted a review of all toxicological studies of irradiated foods that were available at that time. The agency's review was limited to whether individual studies could stand alone to support a safety decision and to whether the studies showed any evidence of toxicity attributable to irradiation. The agency concluded that there was sufficient evidence to authorize the use of radiation on minor dry ingredients at doses no greater than 30 kGy and on foods at low doses (no greater than 1 kGy) (51 FR 13376 at 13378, April 18, 1986). The years following that approval have seen a steady adoption of irradiation as a disinfection treatment method for spices, herbs and vegetable seasonings worldwide. It is difficult to find data, but informal information from the petitioner and other radiation processing companies indicates the volume of spices irradiated in North America is approximately 100 million pounds/year. In addition, irradiation is the treatment of choice for spices in Europe and other world regions.

Foods for the Space Flight Program

FDA concluded that the radiation-sterilized meats would be at least as nutritious as those sterilized by conventional means. FDA also found that the total amount of radiolytic products produced in the irradiated meats and consumed by individuals in space, including those that might be formed in packaging material and might migrate into the meats, is too small to be of any toxicological significance. NASA continues to incorporate irradiated meats in their space programs , (Loveridge, 1998; US ARMY SBCCom, 2002).

Genotoxicity Studies

Genotoxicity tests are generally used to screen for possible carcinogenic and mutagenic effects. FDA reviewed a large variety of such studies with irradiated chicken, ham, beef, or fish and agreed that these studies demonstrate that irradiated flesh foods are not genotoxic (62 FR 64107 at 64114; Irasquin 1995 XXX; Trotter 1997c XXX). In addition, the irradiation conditions for food tested for genotoxicity can be considered as worst-case conditions, and are not the conditions considered for commercial irradiation.

WHO stated that studies conducted to determine the potential of irradiated foods to induce dominant lethal mutations in rats and mice were negative except for several that reported polyploidy due to feeding wheat irradiated at 0.75 kGy to a small number of malnourished youngsters. WHO concluded that it seems unlikely that the effect was due to feeding wheat because other studies using much higher doses were negative.

The FDA conclusions regarding the relevance of certain biological effects of irradiating simple sugar solutions in the presence of oxygen also support the overall evidence against any genotoxicity in the irradiated flesh foods, especially because the processing conditions for producing shelf-stable foods will be in the absence of oxygen at – 40°C.

Recent Genotoxicity Studies

The radiolytic product 2-dodecylcyclobutanone (2-DCB) derived from the palmitic acid and other cyclobutanones in food have been shown to be ideal markers for the detection of irradiated foods (Stevenson, 1996).. Preliminary in vitro studies (Delincée and Zobel, 1998) in which rat cells from the bowel were incubated with high concentrations of synthetic 2-DCB indicated some cytotoxity and an associated weak effect on DNA, based on the comet assay technique. The concentrations used were about three orders of magnitude higher than the 17 μg/g lipid actually analyzed in chicken meat irradiated to 59 kGy (Crone et al., 1992 XXX). A subsequent *in vivo* study by the same authors in which six rats were subjected again to high concentrations of synthetic 2-DCB indicated some DNA strand breaks, based again on the comet assay. These strand breaks were observed only when the highest 2-DCB was used and seemed by statistically inconsistent.

As noted in a footnote in the 1999 WHO Report, there were many limitations in these studies, including the use of the unvetted comet assay technique, that call into question the significance to be attached to these findings. In a Conference Room Document prepared for delegates to the 33rd Codex Committee on Food Additives (CCFAC) meeting in March 2001 in connection with the agenda item on revision to the Codex Standard on Irradiated Food, Dr. Henry Delincée is quoted as follows:

> The experiments have several limitations: only a very limited number of animals has been used, and only one genotoxcity test, i.e., the comet assay, which hitherto has not been validated for regulatory purposes, has been applied. Whether the observed DNA strand-breaks have any significance or later on will be repaired, has not been investigated. For this reason, it would at present be premature to draw the conclusion that 2-alkylcyclobutanous are a health hazard.

In the interest of resolving this issue, a new EU-sponsored two phase study was undertaken by Delincée in which the first phase involves a screening test and the more definitive second phase would be used only for a positive screening test. Verbal reports given subsequently at the

CCFAC meeting (and elsewhere) unequivocally indicated that the Phase 1 screening test for 2-DCB was negative.

This recent negative finding for the possible genotoxicity of 2-DCB is consistent with the results of animal feeding studies and separate mutagenicity tests. The long term, multigenerational Raltech study on irradiated chicken meat, which contained 1.7 □g of 2-DCB per gram of lipid showed no treatment-related toxicological effects. The Ames mutagenicity test using synthetic 2-DCB and *Salmonella typhimurium* strain TA100 (Meester, 1992) were also negative. Taken altogether, these results demonstrate that the 2-DCB in the irradiated product poses no risk and should not be an issue.

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References

IBA submits a CD of references cited by WHO (1999) High Dose Irradiation: Wholesomeness of Food Irradiated with Doses Above 10 kGy. Several of the cited references are on that CD, where indicated. References other than US government documents are attached.

1. Bierman EL et al. Short-term human feeding studies of foods sterilized by gamma radiation and stored at room temperature. Denver, CO, United States Army Medical Nutrition Laboratory, 1958 (Report No. 224).(WHO429)
2. Blood FR et al. Long-term monkey feeding experiment on irradiated peaches, whole oranges and peeled oranges. Nashville, TN, Departments of Biochemistry and Pathology, Vanderbilt University School of Medicine, 1963 (United States Army Contract No. DA-49-007-MD-779 and DA-49-193-MD-2286).(WHO376)
3. Blood FR et al. Feeding of irradiated beef to rats. Toxicology and applied pharmacology, 1966, 8:235–240.(WHO318)
4. Blood FR et al. Feeding of irradiated chicken, beef, and pineapple jam to dogs. Toxicology and applied pharmacology, 1966, 8:241–246.(WHO367)
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