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HIGHBARGER

DEPARTMENT OF HEALTH & HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Public Health Service

Memorandum

Date: December 21, 2001

From: Division of Petition Review
Toxicology Review Group II

Subject: Evaluation of Ionizing Radiation for the Treatment of Human Foods Consisting of Edible Tissue of Animal Food Sources and Plant Material (Fruit and Vegetable Products)

To: REGULATORY POLICY BRANCH (HFS-206)
ATTENTION: Lane Highbarger, Ph.D.

FAP 9M4697
Vols. 1 & 2

Food Irradiation Coalition
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I. Introduction

The National Food Processors Association, on behalf of the Food Irradiation Coalition, has submitted a petition requesting that 21 CFR part 179 of the food additive regulations be amended to allow the use of approved sources of ionizing radiation as a physical process for treating a variety of human foods. The radiation doses requested are 4.5 kGy for non-frozen and non-dry food products, or 10 kGy for frozen or dried food products. The purpose of irradiation of human foods is to control microorganisms in the food, thus extending shelf life and reducing the incidence of food-borne illness.

Currently, FDA permits manufacturers to use approved sources of irradiation to treat: 1) fresh or frozen poultry products at doses up to 3 kGy (55 FR 18538, May 2, 1990); and 2) fresh (chilled, not frozen) meat at doses of 4.5 kGy and frozen meat at doses of 7 kGy (62 FR 64108, December 3, 1997). FDA also permits manufacturers to use irradiation at doses not to exceed 1 kGy to inhibit the growth and maturation of fresh foods, such as fruits and vegetables, and to disinfect food, such as grains, of arthropod pests (51 FR 13376, April 18, 1986).

This petition requests expanding the use of irradiation so that more types of food products can be irradiated at higher doses than are currently permitted by regulation. To support this request, the petitioner submitted information on the proposed uses and efficacy of radiation. The petitioner also submitted publications from the literature on the microbiological safety and nutritional adequacy of irradiated food products. However, the submission does not include toxicology literature or new toxicological studies.

This memorandum presents the toxicology review of the available information considered as of February 1, 2001. Analysis of radiolysis products in human food products is being conducted in FDA's chemical laboratory. We will address the findings when the experiments are completed.

The microbiological safety and nutritional adequacy of irradiated food products will be discussed in separate memoranda.

II. Review approach

In order to assess the safety of the use of food irradiation as proposed by the petitioner, this toxicology review is based on re-consideration/consideration of:

- Initial FDA and World Health Organization (WHO) reviews of toxicology data on irradiated foods
- FDA decisions on the safety of irradiated poultry and meat and consideration of the use of the petitioned dosage
- FDA decisions on the safety of irradiated carbohydrate-rich foods (up to 1kGy)

Because the existing regulations do not address the irradiation of carbohydrate-rich food at higher doses (greater than 1 kGy), we:

- Re-evaluated toxicity data in animals fed carbohydrate-rich foods irradiated at higher doses
- Considered for the first time, the radiolysis products from carbohydrate-rich foods by chemical analysis
- Considered for the first time, radiolysis products from certain high poundage food additives

Each of these six areas is discussed below (Parts III-VIII). The overall toxicological safety assessment was conducted using a weight-of-the-evidence approach. This approach is discussed in a memorandum that is in the record for supporting the approval of irradiated meat (Hattan memo of 11/20/97).

III. Initial FDA and WHO reviews of toxicology data on irradiated foods

In 1981-82, FDA established a Task Group for the Review of Toxicology Data on Irradiated Foods. This Task Group assembled and evaluated all available toxicology study reports on irradiated foods, including studies with significant deficiencies that reported adverse effects from irradiated foods. In its final report, the Task Group concluded that studies with irradiated foods do not appear to show adverse toxicological effects given the limitations of the available data (Toxicology memo entitled Final Report of the Task Group for the Review of Toxicology Data on Irradiated Foods, from M. VanGemert et al., Food Additives Evaluation Branch, HFF-156, to G. Flamm, HFF-152, memo dated 4/9/82).

Details of the approach taken by this Task Group were provided in a subsequent memorandum (Memo for the Administrative File from the Toxicology Data on Irradiated Foods, by M.Van Gemert, dated 12/28/82), and studies with adverse findings were listed and discussed in an attachment to that memorandum (attachment to the VanGemert memo dated of 9/15/82). Certain effects were reported in some of the toxicology studies evaluated by the Task Group. For example, in one of the irradiated beef studies (Malhotra & Reber, 1965) hemorrhagic diathesis of male rats was related to inadequate dietary level of vitamin K (FAP 9M4125 Irausquin memo of 4/10/89). In another study, polyploidy chromosomal changes in humans (Bhaskaram & Sadasivan, 1975) fed irradiated wheat in India were discounted by a committee of Indian scientists because of contradictions and variability in the data. In no case could adverse effects be attributed to the consumption of irradiated foods. The Agency has addressed these potential concerns and others in *Irradiation in the Production, Processing, and Handling of Food* in 51 FR 13385, April 18, 1986 and 53 FR 53185, December 30, 1988.

In 1992, the World Health Organization (WHO) appointed an Expert Panel to review and evaluate all of the studies available at that time related to food irradiation, including older studies previously considered by international and national expert committees, including FDA. The WHO evaluation was published in a report titled *Safety and Nutritional Adequacy of Irradiated Food* (1994). In this report, the WHO Expert Panel concluded that overall no adverse effects of feeding irradiated foods to animals have been observed and that the irradiation of foods in accordance with established good manufacturing practices raised no unresolved question of safety.

IV. FDA decisions on the safety of irradiated poultry and meat and consideration of the use of the petitioned dosage

According to the meat regulation (21 CFR 179.26), fresh refrigerated meat may be irradiated at doses of 4.5 kGy and frozen meat at doses of 7 kGy (62 FR 64108, December 3, 1997). Later, the Food Safety and Inspection Service (FSIS) of the U.S. Department of Agriculture (USDA) petitioned FDA to amend the meat regulations to allow for the safe use of ionizing radiation at a maximum dose of 4.5 kGy to treat unrefrigerated meat (known as "hot-boned" meat), as well as refrigerated, uncooked meat, meat products, and certain meat food products. FDA concluded that irradiation of meat under the conditions proposed by FSIS will not result in adverse toxicological effects or nutritional impact (FAP 9M4695, 3/2/00 memo of meeting between A. Mattia, K. Morehouse, E. Jensen, and R. Alrefai). Both of these evaluations were based on the previous evaluations of relevant toxicological studies and also on a careful review of the radiolysis products of both meat and poultry.

The conditions under which irradiation may be safely used to treat poultry are also listed under 21 CFR 179.26. In 1999, FSIS/USDA petitioned FDA to amend the poultry regulation to increase the permissible irradiation dose from 3 kGy to 4.5 kGy for non-frozen poultry and 7.0 kGy for frozen poultry products. FDA concluded that irradiation of poultry under the conditions proposed by FSIS will not result in adverse toxicological effects or nutritional impact (FAP 9M4696, Chen memo of 1/19/00).

The permissible irradiation doses in the poultry and meat regulations and the doses proposed in amendments to these regulations are listed in Table 1.

Table 1. Irradiation Doses in the Poultry and Meat Regulations and their Proposed Amendments

Date	Regulations/Amendment	Unrefrigerated	Fresh chilled	Frozen
1990	Poultry	—	3.0 kGy	3.0 kGy
2000	Proposed Amendment to the Poultry Regulation	—	4.5 kGy	7.0 kGy
1997	Meat Regulation	—	4.5 kGy	7.0 kGy
2000	Proposed Amendment to the Meat Regulation (hot boned)	4.5 kGy	—	—

In the meat regulation, fresh chilled meat may be irradiated at doses of 4.5 kGy and frozen meat at doses of 7 kGy. This petition proposes an irradiation dosage level of 4.5 kGy for non-frozen and non-dry food products, which does not exceed the currently approved dose for meat. However, in this petition, the proposed dose level of 10 kGy for frozen or dried products is somewhat higher than the currently approved maximum dosage of 7 kGy for the irradiation of frozen meat. Below, we re-considered the animal toxicological studies and the potential toxicity of the radiolysis products produced in poultry and meat in order to assess the safety of the proposed higher dosage of irradiation.

Animal toxicity studies

In most of the long-term toxicological studies in rats, mice, and dogs that have been evaluated previously, the animals were fed chicken or beef irradiated at doses much higher than the requested irradiation dosage. In fact, the irradiation dosage exceeded 50 kGy in many animal feeding toxicity studies with no adverse effects reported (toxicology memo, FAP 4M4428, Irausquin to Hansen, dated 4/20/95). We conclude that the earlier reviews on the toxicological safety of irradiated food products apply to the conditions of use currently requested in this petition (FAP 9M4697).

Chemical analysis of radiolysis products

The radiolysis products formed in irradiated poultry and meat are mainly from lipids and proteins because poultry and meat contain only trace amounts of carbohydrates. Based on Chemistry's review, the radiolysis products of irradiated lipids and proteins are either the same as, or structurally very similar to, compounds found in foods that have not been irradiated (Memorandum from the Division of Product Manufacture and Use (DPMU), Morehouse to Highbarger, dated 8/10/01). Additionally, DPMU stated that heating food produces the same types of chemical products as irradiation, when the irradiation dosage applied is below 50 kGy. In fact the amounts of chemical products in thermally processed foods are far greater than the trace amounts present in irradiated foods.

Based on the animal toxicological studies discussed above and the radiolysis products produced in poultry and meat (DPMU Morehouse to Highbarger, dated 8/10/01), a toxicological hazard due to consumption of meat and poultry irradiated at the proposed dose level of 10 kGy for frozen or dried products is highly unlikely.

V. FDA decisions on the safety of irradiated carbohydrate-rich foods

As noted, FDA currently permits manufacturers to use irradiation at doses not to exceed 1 kGy to inhibit the growth and maturation of whole fresh fruits and vegetables and to disinfect food, such as grains, of arthropod pests (51 FR 13376, April 18, 1986). This is the only regulated use of food irradiation for carbohydrate-rich foods. For the purpose of increasing shelf life and reducing pathogens, the current petition proposes to permit the irradiation of carbohydrate-rich foods not previously permitted (e.g. pre-processed vegetables, fruits, and other agricultural products of plant origin, certain multi-ingredient food products, etc.). For pathogen reduction in the relevant products, doses higher than 1 kGy are required. Therefore, toxicology studies that address the irradiation of a variety of carbohydrate-rich foods at higher doses are re-evaluated below.

VI. Re-evaluation of toxicity data in animals fed carbohydrate-rich foods irradiated at higher doses

In the WHO 1994 report entitled *Safety and Nutritional Adequacy of Irradiated Food*, many studies were discussed in which irradiated vegetables, fruits, grains and whole diet were fed to mice, rats, dogs, pigs, and monkeys at levels typically around 35% of the diet for up to two years in length. FDA has previously reviewed the toxicology studies, which included subchronic, chronic, reproduction, and genotoxicity studies. Overall, no consistent trends or adverse effects were reported in animal feeding studies, which are listed in Tables 1-5 (attached). In case an effect was reported, this is indicated in the table and the findings are re-evaluated and discussed below.

Subchronic or chronic toxicity studies with effects reported in rats

In attachment Table 1, subchronic and chronic toxicity studies in rats fed irradiated carbohydrate-rich foods are listed. Most studies did not show adverse effects in rats. However, Verschuuren (1966) reported decreased growth after male rats were fed strawberry powder irradiated at 50 kGy. In this study, rats were fed strawberry juice (6 ml/100g body weight/day) or strawberry powder (5% of the diet) irradiated at 5 or 50 kGy. The average daily intake of strawberry per kg body weight was about 22 g and 39 g for the strawberry-juice and strawberry-powder groups, respectively. Because the quantity of strawberry-powder was limited, the rats in this group were fed restricted diet for 12 weeks. Under the experimental conditions, body weight in high dose strawberry powder treated males was a significantly decrease. The authors stated,…"There appears to be no reasonable explanation for this effect on body weight. The corresponding female rats receiving the same powder and rats of both sexes receiving the juice irradiated with 5000 Krad [50 kGy] showed no significant effects." It is possible that the combined effects of food restriction and inadequate nutrition further underlie the decreased body weight observed in male rats given the high dose irradiated strawberry powder.

In another study, Metwalli (1977) reported a significant decease in serum aspartate aminotransferase (AST) activity in female rats only when the whole diet was irradiated at 25 or 45 kGy. An increase in AST activity may suggest an adverse effect on the liver. However, a decrease in AST activity was reported and this decrease occurred in one sex only without evidence of a dose-response relationship. Consequently, the effect cannot be considered a treatment-related toxicological effect.

Phillips et al. (1961) reported reduced alkaline phosphatase in rat duodenal tissue. FDA previously concluded that the observed effect was not of toxicological significance because the effect was not observed in weanling rats maintained on the same diet into adulthood. The effect was also not reproduced when either of the two irradiated foods (chicken stew or cabbage) was fed individually (see 62 FR 64108, December 3, 1997).

Chronic toxicity studies with effects reported in mice

In Table 2 (see attachment), chronic toxicity studies in mice fed irradiated carbohydrate-rich foods are listed. Most studies did not show adverse effects. However, decreased growth and fertility in mice fed whole diet irradiated at 60 kGy was reported by Biagini et al. (1967). The reduction in growth was less than 10% and there was a palatability problem with the diet. The fertility problems appeared to be related to inadequate nutrition and the investigators' failure to rotate the males to non-pregnant females (Administrative File from the Toxicology Data on Irradiated Foods, M. Van Gemert memo of 12/28/82).

Bugyaki (1968) reported that mice fed a diet for 538-605 days of freshly irradiated wheat flour (50 kGy) showed increased incidences of tumors and produced litters with increased numbers of dead mice. The incidence of tumors was 32% in the treated groups and 22% of the controls. The proportion of litters with nonviable young (dead) was 34% in the treated group versus 26% in the controls. The author reported that physical and chemical changes were obvious in wheat meal freshly irradiated (50 kGy) and increased concentrations of peroxides were observed even before the wheat meal was fed to the animals. This peroxide-rich diet might be responsible for the adverse effects reported in the test animals. The author stated that…"it is important to draw a distinction between freshly irradiated foods such as those used in our experiments and foods irradiated some time before use, … Some of the changes produced by radiation - the free radicals for example - will disappear with time and/or further processing." Consequently, this experimental situation does not represent real conditions in the market place. Furthermore if a food had undergone physical and chemical changes as observed by the author, it would not likely be sold.

Subchronic or chronic toxicity studies with effects reported in dogs

In Table 3, subchronic and chronic toxicity studies in dogs fed irradiated carbohydrate-rich foods are listed. Most studies did not show adverse effects. However, Gabriel et al. (1976) reported that dogs fed a diet containing 10% irradiated (0.25 kGy) onions (dry weight basis) for 90 days developed anemia. Control dogs fed non-irradiated onions also developed anemia but at a slower rate. Since anemia was reported in both control and experimental animals, the observed stated that the results suggest an effect due to the diets rather than the sterilization methods that were employed (i.e., irradiation or autoclave).

Genotoxicity studies

There were no effects in most of the genotoxicity studies on carbohydrate-rich foods considered by WHO in 1994 (see WHO report, *Safety and Nutritional Adequacy of Irradiated Food*, Chapter 6, Table 13). However, a few positive genotoxicity studies were reported. For example, polyploidy (chromosomal changes) was reported in humans and rodents fed irradiated wheat (Bhaskaram et al., 1975; Vijayalaxmi et al., 1975) and dominant lethal mutations were reported in mice fed irradiated wheat (Vijayalaxmi et al., 1976). FDA has previously addressed the potential concerns raised by these reports in its previous decisions (51 FR 13385, April 18, 1986 and 53 FR 53190, December 30, 1988). In addition, we also consider the genotoxicity data to be of limited value because long-term animal test results are available.

In summary, we re-evaluated certain toxicology studies in which carbohydrate-rich foods, irradiation doses up to 60 kGy, were fed to animals for periods of 90 to 999 days. While there are sporadic indications of effects in the studies re-evaluated; there is an absence of toxicological effects attributable to irradiation. This conclusion is consistent with FDA's previous reviews of these studies in the attached Tables (1-5).

VII. Consideration of the radiolysis products from carbohydrate-rich foods by chemical analysis

Radiolysis products from carbohydrate-rich foods

Most vegetables, fruits and grains are rich in carbohydrate, but contain only small amounts of fat and protein. The DPMU has assessed the possible chemical changes in irradiated vegetables, fruits, and other agricultural products of plant origin that are the subject of this petition (Morehouse memo of 8/10/01 reviews data up to 2/1/01). In the memorandum, DPMU noted that the main effects of ionizing radiation upon carbohydrates are reported to be hydrolysis and oxidative degradation. These effects result in shortening of polysaccharide chains, degradation of starch and cellulose into simple sugars and the formation of sugar acids, ketones and other sugar monosaccharides. The effects of irradiation are basically the same as those caused by cooking or heat-treatment.

The nature and concentration of the main irradiation-induced products show no marked differences among the carbohydrates. Regardless of their origin, all of the starch varieties analyzed behaved similarly. The nature and concentration of the juice irradiated at 7.8 kGy. According to DPMU, of the radiolysis products found in the irradiated high water content fruits and vegetables, only acetaldehyde, malonaldehyde, and methanol are formed in any appreciable amount. The agency has previously addressed the safety issue of exposure to methanol in foods (49 FR 6675, February 22, 1984).

Acetaldehyde is present naturally in many foods, including fruits, vegetables, dairy products, alcoholic beverages and breads. Analysis of various foods shows that acetaldehyde concentration varies over a wide range (from 0.0001 to 400 ppm) in foods because of natural variations in plant metabolism and growth conditions. Its volatility makes its concentration in both processed and unprocessed foods strongly time- and processing-dependent. Acetaldehyde is metabolized to acetic acid through aldehyde dehydrogenase. Acetaldehyde was reported to induce tumors of the oral and upper respiratory tract epithelium in long-term inhalation studies in rats and hamsters. However, Dr. F. Hines (Office of Scientific Analysis and support, Division of General Scientific Support, Pathology Branch, PB Hines memo of 9/14/98) has noted that acetaldehyde is unlikely to induce tumors in rodent by an oral route. According to the DPMU's assessment, a concentration of 1.5ppm acetaldehyde has been reported in juice irradiated at a dose of 19 kGy that is more than four times higher than the dose requested in this petition. However, the concentrations of acetaldehyde occurring naturally in some food of up to 400 ppm is far higher than that in irradiated juice. We have no safety concerns due to the negligible increase of acetaldehyde that is possible due to the consumption of irradiated high water content fruits and vegetables.

Malonaldehyde (MA), also known as malondialdehyde, is produced in irradiated carbohydrates. Additionally, MA is a natural metabolic byproduct of prostaglandin biosynthesis and the end product of polyunsaturated fatty acids peroxidation. It can be found in cooked and raw beef and poultry. The National Toxicology Program (see Technical Report Series No.331) reported that MA is a carcinogen for male and female F344/N rats (100 mg/kg bw/5 day/week) based on the increased incidences of follicular cell adenomas or carcinomas (combined) of the thyroid gland. There was no evidence for the carcinogenicity of MA in B6C3F1 male and female mice. In order to assess whether consuming irradiated carbohydrate-rich foods will increase the dietary exposure to MA, we asked the Chemistry Review Team (CRT) for information on exposure to MA in the diet.

Based on the published literature, the CRT estimated that the MA found in non-irradiated raw or cooked food is at levels in the 0.1- 1.0 mg/kg range (see Jensen note to Chen of 9/7/00, FAP 9M 4697). The amount of MA formed from the irradiation of carbohydrate depends on the water content of the food and the presence of other food constituents (mutual protection). The self-limiting nature of irradiation will also serve to limit exposure to MA since high concentrations of MA are likely to be perceived as indication of spoilage and rancidity. Dr. Jensen concluded that, when compared to the background MA level, the additional exposure to MA from irradiated carbohydrate-rich foods would be negligible. Thus, we have no safety concerns with regard to an increase of MA in irradiated foods.

VIII. Radiolysis products from certain high poundage food additives

According to the CRT (see Jensen memo of 7/25/00) many of the most heavily consumed food additives and ingredients can be classified as food-like because they contain the structural components of carbohydrates, lipids, or proteins. For example, the carbohydrate sweeteners such as mannitol, sorbitol, and xylitol would be expected to exhibit the same reaction chemistry as fructose or sucrose. Enzymes, which are proteins, characterized by a specific reactivity toward selected substrates, undergo the same chemistry as other proteins. Because many food additives and ingredients are food-like, their chemistry is similar to that of basic food components (carbohydrates, lipids, or proteins) and they produce the same kinds of radiolysis products. Because the radiolysis products from carbohydrates, proteins or lipids have previously been considered (K. Morehouse memo of 8/10/01), and because intake of food-like additives and ingredients is considerably less than the intake of carbohydrates, lipids, and proteins from foods *per se*, consuming irradiated food-like additives raises no issues of concern.

The non-food-like additives include antioxidants (e.g., phenolic antioxidants such as BHA, BHT and propyl gallate), antimicrobial agents, preservatives, high-intensity sweeteners (e.g., aspartame, acesulfame-K and saccharin) and other small organic compounds (e.g. adipic acid and annato extract). The radiolysis products from these compounds have not previously been considered in agency reviews.

The CRT (see Jensen memo of 7/25/00) used the food entries data from SRI International and the 1987 report of poundages compiled by the National Academy of Sciences to assess the potential exposure to radiolysis products from the use of non-food-like additives. Based on the top 200 additives in food in order of poundage, the CRT estimated a *per capita* daily intake of 0.31 g/person/day for the most heavily consumed non food-like additives and ingredients. Based on this calculation, CRT estimated that the total cumulative exposure to radiolysis products from the irradiation of all non-food-like food additives and ingredients is on the order of 30 ug/person/day equivalent to a total dietary concentration of 10 ppb (see CRT Jensen memo of 7/25/00). This estimate excludes food-like additives and ingredients in the list of the top 200 additives. It also excludes certain non food-like additives and ingredients, including minerals, processing aids or coating agents. Minerals are not affected by irradiation, and processing aids or coating agents are not likely to be present in irradiated foods when consumed. In addition, the contribution of flavors was not included because added flavoring compounds typically are the same as, or similar to, those that occur naturally.

In summary, any increased exposure to individual radiolysis products from irradiation of food additives and ingredients that are food-like or non-food-like will be trivially small and no unusual types of radiolysis products are expected to be formed. Thus, we have no toxicological concerns regarding radiolysis products produced from the high poundage food additives that are considered above.

IX. Conclusion

In order to assess the safety of the use of food irradiation as proposed by the petitioner, this toxicology review re-considered both new and previously available data and information. We reconsidered the initial FDA and WHO reviews of toxicology data on irradiated foods, as well as FDA decisions on the safety of irradiated poultry and meat (see doses in Table 1) and carbohydrate-rich foods (up to 1kGy). We also considered the use of the petitioned dosage of up to 10 kGy for frozen meat and poultry based on animal data and chemical analysis for radiolysis products. Because the existing regulations do not address the irradiation of carbohydrate-rich food at higher doses (greater than 1 kGy), we re-evaluated toxicity data in animals fed carbohydrate-rich foods irradiated at higher doses (up to about 55 kGy). For the first time, we considered the radiolysis products from carbohydrate-rich foods and certain high poundage food additives that were determined by chemical analysis. Based on the totality of the available data and information up to the present time, we conclude that a toxicological hazard due to consumption of processed poultry, meat, vegetables, and fruits and certain multi-ingredient food products irradiated at the petitioned doses is highly unlikely.

Isabel S. Chen

Isabel S. Chen, Ph.D.

Attachments (6)
References and Tables 1-5

INIT:A. Mattia A. Mattia

cc:HFS-200, HFS-207 (Harris, Keefe, Mattia, Pauli, Tarantino); HFS-225 (Biddle, Chang, Edwards)
HFS-207:ISChen 202-418-3036:Doc:FAP9M4697

References Cited in the Text*

Bugyaki (1968) To study the effect of feeding irradiated wheat flour to mice Food Irradiation Information (2), FAO/IAEA Suppl, page 7-8. (Translation: Do irradiated foodstuffs have a radiomimetic effect? II. Trial with mice fed on wheat meal irradiated at 5 Mrad. Atompraxis Heft 3: 112-118

Gabriel KL & RS Edmonds (1976) To study the effect of radurized onions when fed to beagle dogs. Food Irradiation Information, 6 (Supplp): 116-117.

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Metwalli OM (1977). Study on the effect of food irradiation on some blood serum enzymes in rats. Z. Ernabrungswiss 16:18-21.

Porter G & M Festing (1970) A comparison between irradiated and autoclaved diets for breeding mice, with observations on palatability. Laboratory Animals 4:203-213.

Reber EF, OP Malhotra, J Simon, JP Kreier, PD Beamer and HW Norton (1961) The effect of feeding irradiated flour to dogs. Tox and Applied Pharm 3:568-573.

The National Toxicology Program (1988), Technical Report Series No.331: Malonaldehyde, sodium salt in F344/N rats and B6C3F1 mice (gavage studies).

World Health Organization (1994) *Safety and Nutritional Adequacy of Irradiated Food.* Geneva

Verschuuren HG, & Van Kooy (1966) Ninety-day rat feeding study on irradiated strawberries. Food Irradiation, 7(1-2): A17-A21.

* References in Table 1-5 are not included in this list

Table 1. Subchronic or Chronic Toxicity Studies in Rats Fed Irradiated Carbohydrate-Rich Foods

Food	Duration(days)	Dose(kGy)	Effect Reported	References[1]
Black beans, coffee	84	1	None	Bernardes (1980)
Bread,beans,pork,shrimp	84	55.8	None	Brin et al. (1961)
Strawberries	84	50	↓ growth[1]	Verschuuren (1966)
Carrots	90	1	None	Coquet et al (1980)
Mangoes	90	0.8	None	Raltech (1979)
Onions	90	0.25	None	Gabriel et al. (1976)
Potatoes	90	2	None	Jaarma et al. (1964)
Mushrooms	90	5	None	Van Logten (1971)
Hole diet	90	50	None	Van Logten (1978)
Cocoa beans	126	0.5	None	Takyi et al. (1981)
Wheat	105	2	None	Vakil (1975)
Whole diet	120	45	↓serum AST*[2]	Metwalli (1977)
Bananas	730	0.4	None	Anon (1976)
Whole diet	728	25	None	Aravindakshan(1978)
Peach,flour,carrots,pork	730	55.6	None	Bone (1963)
Potatoes	730	0.4	None	Brownell et al.(1959)
Mangoes	730	0.8	None	Raltech (1981)
Wheat	750	2	None	Hickman (1975)
Wheat	730	2	None	Ikeda et al. (1969)
Potatoes	730	0.6	None	Ikeda (1971)
Potatoes	455	2	None	Jaarma et al. (1966)
Potatoes	728	0.15	None	Huntingdon (1975)
Potatoes	800	0.3	None	Shillinger (1973)
Strawberries	730	3	None	Nees (1970)
Corn, tuna fish	728	55.8	None	Paynter (1959)
Milk powder, beef stew	730	55.8	None	Radomski *et al.*(1965)
Stew/cabbage, chicken	730	56	↓ALKP**[2] in duodenal tissue	Phillips et al. (1961)
Milk powder	400	45	None	Renner et al (1973)
Starch	742	6	None	Truhaut et al. (1978)
Wheat flour	999	2	None	Vakil (1975)
Mushroom, powder	800	50	None	Vlielander (1968)

*AST (aspartate aminotransferase)
**ALKP (alkaline phosphatase)

[1] The references in this Table are listed in the 1994 World Health Organization publication entitled *Safety and Nutritional Adequacy of Irradiated Food* Geneva.
[2] See text for a discussion of these effects (Section VI, Subchronic or chronic toxicity studies with effects reported in rats).

Table 2. Chronic Toxicity Studies in Mice Fed Irradiated Carbohydrate-Rich Food

Food	Duration (days)	Dose (kGy)	Effects Reported	References[1]
Whole diet	730	60	↓ growth & fertility[2]	Biagini et al. (1967)
Wheat flour	605	50	Tumor, reduced viability[2]	Bugyaki (1968)
Potatoes	730	0.6	None	Ikeda (1971)
Starch	742	6	None	Truhaut et al. (1978)
Wheat flour	999	2	None	Vakil (1975)

[1] The references in this Table are listed in the 1994 World Health Organization publication entitled *Safety and Nutritional Adequacy of Irradiated Food* Geneva.
[2] See text for a discussion of these effects (Section VI, Chronic toxicity studies with effects reported in mice).

Table 3. Subchronic or Chronic Toxicity Studies in Dogs Fed Irradiated Carbohydrate-Rich Foods

Food	Duration (days)	Dose (kGy)	Effect reported	References[1]
Onions	90	0.25	Anemia[2]	Gabriel et al. (1976)
Fruits, cherries	90	4	None	Gabriel et al. (1976)
Wheat flour	90	0.74	None	Reber et al. (1959)
Potatoes	90	2	None	Jaarma et al. (1964)
Bananas	730	0.4	None	Anon (1976)
Bacon, cabbage	730	55.8	None	Hale et al. (1961)
Onions	540	0.2	None	Hilliard et al. (1966)
Onions	540	1	None	Hilliard (1974)
Strawberries	730	3	None	Nees (1970)
Wheat flour	730	0.74	Thyroiditis[2]	Reber et al. (1961)

[1] The references in this Table are listed in the 1994 World Health Organization publication entitled *Safety and Nutritional Adequacy of Irradiated Food* Geneva.
[2] See text for a discussion of these effects (Section VI, Chronic toxicity studies with effects reported in mice).

Table 4. Chronic Toxicity Studies in Monkeys or Pigs Fed Irradiated Carbohydrate-Rich Foods

Food	Duration(days)	Dose(kGy)	Effect Reported	Species	References[1]
Potatoes	300	0.15	None	Pig	Jaarma et al. (1971)
Rice	730	1	None	Monkey	Tobe et al. (1980)

[1]The references in this Table are listed in the 1994 World Health Organization publication entitled *Safety and Nutritional Adequacy of Irradiated Food* Geneva.

Table 5. Reproduction Studies in Animals Fed Irradiated Carbohydrate-Rich Foods

Food	Duration/days	Dose (kGy)	Species	Effect Reported	References[1]
Potatoes	730	0.4	Rat	None	Burns et al.(1961)
Wheat flour	160	2	Rat	None	Hickman et al. (1964)
Oranges	160	2.79	Rat	↓weight gain & ↓reproductive performance [2]	Phillips et al. (1961)
Onions	120	1	Rat	None	Van Petten et al. (1966)
Maize, nuts & prunes	240	2	Mouse	None	Baev (1980)
Potatoes	Duration varies	0.15	Dog	None	McCay et al. (1961)
Whole diet	200	25	Mouse	↓ number of litters [2]	Porter et al. (1970)
Chicken & Green beans	120	59	Rat	None	Richardson (1960)

[1] The references in this Table are listed in the 1994 World Health Organization publication entitled *Safety and Nutritional Adequacy of Irradiated Food* Geneva.
[2] See text for a discussion of these effects (Section VI, Chronic toxicity studies with effects reported in mice).