THE CENTER FOR FOOD SAFETY

Public Citizen

May 14, 2001

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

4552 '01 MAY 16 P1:34

Re: Docket No. 01F-0047, Food Additive Petition 1M4727, Use of ionizing radiation for control of foodborne pathogens in crustaceans and processed crustaceans

Dear Sir/Madam,

The Center for Food Safety (CFS) and Public Citizen are pleased to submit this public comment on the above-referenced food additive petition. CFS is a national, non-profit, membership organization established in 1997 to use science and the law to address increasing concerns over the impacts of the United States food production system on human health, animal welfare, and the environment. Public Citizen is a national, non-profit, membership organization established in 1971 that advocates for consumer protection and for government and corporate accountability.

EXECUTIVE SUMMARY OF COMMENT

CFS and Public Citizen **oppose** the above-referenced food additive petition. CFS and Public Citizen further **oppose** the petition's placement on the list of food additive petitions receiving expedited review. Numerous unresolved concerns remain related to the safety and wholesomeness of irradiation as a food additive. Recently, 26 medical experts endorsed a detailed warning published in a public health journal on the dangers of food irradiation.[1] At least **ten positive *in vivo* published studies** that found mutagenic effects in mammals – including one in humans - were misclassified or ignored in the most recent official report on the subject, the 1999 FAO/IAEA/WHO Technical Report #890. *High-Dose Irradiation: Wholesomeness of Foods Irradiated Above 10 kGy,* WHO, Geneva.[2] These ten positive studies compare to only 17 published *in vivo* studies that were reportedly negative for mutagenicity. Similarly, for published

[1] Epstein, S.S., and W. Hauter. 2001. "Preventing pathogenic food poisoning: Sanitation not irradiation," *Intl. J. of Health Services* 31:187-192.

[2] Mutagenicity is the capacity to cause gene-damage that may result in gene mutations, polyploidy, chromosome aberrations, and dominant lethal mutations. Anderson, D., et al. 1981. Irradiated laboratory animal diets - Dominant lethal studies in the mouse. *Mutation Research* 80:333-345.

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in vitro studies, five mutagenicity studies were positive and 8 were negative. **Overall, more than one-third of published studies indicate mutagenicity of irradiated food substances.** Further, several recent *in vitro* and unpublished *in vivo* studies from the respected Karlsruhe irradiation research facility in Germany have uncovered mutagenic effects in human and animal cells and in lab animals. **The *in vivo* results show that a unique marker substance in irradiated foods has failed standard safety testing using the 100-fold safety margin required by 21 CFR 170.22.** Copies of the key studies are attached.[3]

The above-referenced petition utterly failed to address this new information. Safety has not been shown under the food additive petition standards. An objective, dispassionate, review of the detailed information presented in this comment will lead to the firm conclusion that approving the petition would amount to a serious - potentially scandalous - error in judgment.

APPLICABLE LEGAL STANDARDS

The Federal Food, Drug, and Cosmetic Act (the Act) specifically defined a source of radiation as a food additive, under section 201(s) (21 USC 321(s)). Under section 409(c)(3)(A) of the Act (21 USC 348(c)(3)(A)), a food additive cannot be approved for a particular use unless a fair evaluation of the data establishes that the additive is safe for that use.

Under Title 21—Food and Drugs, Part 170--Food Additives, the following key legal standards apply in deciding the referenced petition:

Sec. 170.20 General principles for evaluating the safety of food additives.

> *(a) In reaching a decision on any petition filed under section 409 of the Act, the Commissioner will give full consideration to the specific biological properties of the compound and the adequacy of the methods employed to demonstrate safety for the proposed use....*

Sec. 170.22 Safety factors to be considered.

> *In accordance with section 409(c)(5)(C) of the Act, the following safety factors will be applied in determining whether the proposed use of a food additive will be safe: Except where evidence is submitted which justifies use of a different safety factor, a safety factor in applying animal experimentation data to man of 100 to 1, will be used; that is, a food additive for use by man will not be granted a tolerance that will exceed 1/100th of the maximum amount demonstrated to be without harm to experimental animals.*

Sec. 170.3 Definitions.

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[3] Studies are tabbed with numbers according to the study number herein. Because of the age and difficulty of obtaining some of these studies (several of which were provided by FDA pursuant to Freedom of Information Act requests), some of the copies are in poor condition.

(i) Safe or safety means that there is a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use. It is impossible in the present state of scientific knowledge to establish with complete certainty the absolute harmlessness of the use of any substance. Safety may be determined by scientific procedures or by general recognition of safety. In determining safety, the following factors shall be considered:

(1) The probable consumption of the substance and of any substance formed in or on food because of its use.

(2) The cumulative effect of the substance in the diet, taking into account any chemically or pharmacologically related substance or substances in such diet.

(3) Safety factors which, in the opinion of experts qualified by scientific training and experience to evaluate the safety of food and food ingredients, are generally recognized as appropriate.

POSITIVE STUDIES MENTIONED BUT MISCHARACTERIZED IN THE 1999 FAO/IAEA/WHO REPORT

The 1999 FAO/IAEA/WHO report is the most detailed recent review of food irradiation safety. CFS anticipates that FDA will seek to rely on it. It is critical that FDA understand the defects in that report before making a determination on the above-referenced additive petition.

That report incorrectly labeled each of the first four published irradiation studies summarized below as "*negative for high-dose irradiation effect, possible effect of nutrition or diet.*" This was a mischaracterization because each of these *in vivo* mammalian studies was plainly in fact "positive," meaning that mutagenic effects were found associated with the irradiated food. In sum, the 1999 FAO/IAEA/WHO report fails to justify its off-hand, non peer-reviewed, but crucial, suggestion that the positive results of these published studies - each conducted by respected laboratories - represented mere artifacts of the nutrition or diet in the experiments.

Studies 1 through 4 were cited frequently in the report and no indication exists of defects in their approaches or methodologies. The studies and discussion of the 1999 FAO/IAEA/WHO report's rationalizations for them are below:[4]

Study 1. Anderson, D., M.J.L. Clapp, M.C.E. Hodge, and T.M. Weight. 1981. Irradiated laboratory animal diets - Dominant lethal studies in the mouse. *Mutation Research* 80:333-345.

Study 1 abstract:

> In 4 separate dominant lethal experiments, groups of mice were fed laboratory diets (Oakes, 41B, PRD, BP nutrition rat and mouse maintenance diet No.1).

[4] The abstracts are virtually verbatim from the published articles, with a few minor edits for readability.

The diets were either untreated (negative control diets) or irradiated at 1, 2.5, and 5 Mrad and were freshly irradiated, or stored.[5] The animals were fed their test diets for a period of 3 weeks prior to mating. Groups of mice given a single intraperitoneal injection of 200 mg cyclophosphamide per kg body weight served as the positive controls. Freshly irradiated PRD diet fed to male mice of both strains caused an increase in early deaths of offspring of females mated to the males in week 7 and to a lesser extent in week 4. The increase due to irradiation was small by comparison with that produced by the positive control compound. The responses for the other irradiated diets showed no significant increases in early deaths of offspring, although some values for Oakes diet were high. The effect of storage was examined with PRD and BPN diet on one occasion and produced conflicting results. Thus there was some evidence that irradiated PRD diet has weak mutagenic activity in the meiotic and/or pre-meiotic phase of the spermatogenic cycle, which appeared to be lessened on storage.

Discussion of Study 1: The 1999 FAO/IAEA/WHO report acknowledged the Anderson et al. study showed "*evidence of weakly mutagenic effect*" with one diet that was irradiated, yet it classified the study as "*negative for high-dose irradiation effect, possible effect of nutrition or diet*" (p. 117). However, no indication exists that the irradiated standard PRD laboratory diet that produced the mutagenic effect was otherwise deficient. Further, the unirradiated control PRD diet did not produce the mutagenic effect. Anderson et al. found irradiation of the diet produced the effect. The 1999 FAO/IAEA/WHO report's classification of the study as "negative" was unfounded.

Study 2. Bugyaki, L., A.R. Deschreider, J. Moutschen, M. Moutschen-Dahmen, A. Thijs, and A. Lafontaine. 1968. Do irradiated foodstuffs have a radiomimetic effect? II. Trials with mice fed wheat meal irradiated at 5 Mrad. *Atompraxis* 14:112-118.

Study 2 abstract:

Two groups of 10 male and 50 female mice were fed diet containing 50% wheat flour, which was either untreated or irradiated with 5Mrad of gamma radiation. The flour was fed within one week of irradiation. Females and males were caged together for mating; when a female became pregnant it was isolated to deliver and raise its litter, after which it was placed with the male again. The procedure was repeated until the mice became too old to reproduce. They were then caged individually until death. The offspring were raised to weaning and sacrificed for chromosomal analysis, examination of the testicles and blood picture determinations. Cytogenic examinations of the developing spermatogonia in 30 mice of each group revealed that cytogenetic abnormalities were significantly

[5] Note that the unit measurement for irradiation doses was formerly Mrads and is currently kGy. One Mrad is equivalent to 10 kGy.

more frequent in the group fed irradiated flour than in the control group. Red cell counts and total and differential white cell counts in the offspring were unchanged. There was no significant effect on fecundity; none of the mice was sterile. In both the test and the control groups, a large number of litters were born in which none of the offspring was viable; the incidence of litters so affected was significantly higher in the group fed irradiated flour. In both groups, there was approximately the same number of young per litter at birth and there was a high death rate between birth and weaning; on the average the losses were about 35% higher in the test group than in the controls. The life span of mice fed irradiated flour was slightly shorter than in the control mice.

Discussion of Study 2:

A thorough discussion of the Bugyaki et al. study in a 1970 FAO/IAEA/WHO Expert Committee report highlighted it as a significant positive finding.[6] That earlier report, at pp. 28 and 29, stated:

> *The Committee took cognizance of certain disturbing effects in mice fed wheat irradiated with 5 Mrad and consideration of these effects is one important reason for the requirement that certain further work should be undertaken to confirm that similar effects on reproduction are demonstrable at the dose levels of practical importance.*

The 1999 FAO/IAEA/WHO report admitted that Bugyaki et al. showed "*chromosomal abnormalities in germ cells due to formation of peroxides and radicals*," but - without explanation - classified the study as "*negative for high-dose irradiation effect, possible effect of nutrition or diet*" (p. 118). That is plain inconsistency; the "peroxides and radicals" resulted from the irradiation (see Bugyaki et al., at p. 118: "*...some of the changes produced by radiation – the free radicals for example – will disappear with time...*" [translated from French]). Further, the same Expert Committee agreed 29 years earlier that Bugyaki et al. demonstrated "*certain disturbing effects*" of high dose irradiation. That Committee did not discount the effects as artifacts of nutrition or diet, as the 1999 Committee did. The 1999 FAO/IAEA/WHO report's classification of this study as "negative" again lacks a rational foundation.

Study 3. Moutschen-Dahmen, M., Moutschen J., and L. Ehrenberg. 1970. Pre-implantation death of mouse eggs caused by irradiated food. *International Journal of Radiation Biology* 18:201-216.

Study 3 abstract:

> Feeding of mice (males and females) for two months before mating with 50% of the standard complete diet (solid cakes) irradiated with 5 Mrads of radiation provokes a significant increase of pre-implantation embryonal deaths, but no

[6] 1970 FAO/IAEA/WHO Technical Report #451. *Wholesomeness of Irradiated Food with Special Reference to Wheat, Potatoes and Onions*, WHO, Geneva.

> increase of post-implantation deaths. The pre-implantation deaths have probably to be interpreted as dominant lethal mutation associated with gross chromosomal aberrations, such as centromeric breaks repeatedly found to be induced by irradiated materials. Other interpretations, such as enhanced ageing, cannot be ruled out, however, on the basis of the present data. The investigation demonstrates disturbances in the fertilization processes as well as in development of eggs.

Discussion of Study 3:

The 1999 FAO/IAEA/WHO report states the study showed "*increased pre-implantation embryonic deaths; not confirmed by cytological analysis*" and classified the study as "*negative for high-dose irradiation effect, possible effect of nutrition or diet*" (p. 115). The suggestion of an effect of nutrition or diet is unsupported. Further, the suggestion that the observed pre-implantation deaths were "not confirmed by cytological analysis" is a non sequitur. There was no question that the pre-implantation deaths occurred, and the study did not include any cytological examination.

Study 4. Johnston-Arthur T., M. Brena-Valle, K. Turanitz, R. Hruby, and G. Stehlik. 1975. Mutagenicity of irradiated food in the host mediated assay system. *Studia Biophysica, Berlin* 50:137-141.

Study 4 abstract:

> Groups of Swiss albino mice (SPF) fed with normal and gamma-irradiated food at doses of 0.75, 1.5, and 3.0 Mrad, were injected intraperitoneally with Salmonella tymphimurium TA 1530 for the host mediated assay test of mutagenesis. The mutation frequency was calculated in terms of the number of mutant colonies per unit number of surviving cells. The results indicate that there is a significant increase in mutation frequency induced by the 3 Mrad sterilized food. No difference was observed in the 0.75 Mrad dose when compared with the control.

Discussion of Study 4:

The 1999 FAO/IAEA/WHO report admits the study showed "*significant increase in the mutation frequency induced by the high dose irradiated foods,*" but nevertheless classified the study as "*negative for high-dose irradiation effect, possible effect of nutrition or diet*" (p. 115). This is patently contradictory; the "negative" classification again lacks explanation.

The following positive *in vitro* human cell study, and the companion positive *in vivo* mammal study discussed after it, resulted in a lengthy text rationalization in the 1999 FAO/IAEA/WHO report:

Study 5 (*in vitro*). Delincée, H., and B.L. Pool-Zobel. 1998. Genotoxic properties of 2-dodecylcyclobutanone, a compound formed on irradiation of food containing fat. *Radiation Physics and Chemistry* 52:39-42.

Study 5 abstract:

When food containing fat is treated by ionizing radiation, 2-dodecylcyclobutanone (2-DCB) is formed. To date there is no evidence of this compound in unirradiated food, that is, it is unique to irradiated foods. Therefore it cannot be considered inherent in food and it is advisable to determine whether it is toxic. Measurements of DNA damage in cells exposed to 2-DCB were carried out. *In vitro* experiments using rat and human colon cells indicate that 2-DCB in the concentration range of about 0.30 - 1.25 mg/ml induces DNA strand breaks in the cells. To what extent these *in vitro* findings are relevant for the *in vivo* human exposure situation needs to be further investigated.

Study 6 (unpublished): Delincée, H., B.L. Pool-Zobel, and G. Rechkemmer. 1998. Genotoxicity of 2-dodecylcyclobutanone. *Food Irradiation: Fifth German Conference*, Report BFE-R-99-01, Federal Nutrition Research Institute, Karlsruhe, Germany.

Study 6 abstract:

In the treatment of foods containing fat with ionizing radiation - for example, the irradiation of chicken or hamburger to kill pathogens such as *Salmonella spp. or E. coli* O157:H7 - a range of lipolytic digestion products are generated, among them the group of 2-alkylcyclobutanones. These compounds contain the same number (n) of carbon atoms as their precursor fatty acids, whereby a hydrocarbon chain with n-4 carbon atoms is attached to ring position 2 of the cyclobutanone. In this way, 2-dodecylcyclobutanone (2-DCB) is generated from palmitic acid. Up to the present day, cyclobutanones have not been found in non-irradiated foods. Therefore, it is important to examine the toxic or genotoxic potential of cyclobutanones in the context of discussions about the safety of irradiated foods.

In this study, *in vivo* experiments were conducted on rats, which received two different doses of 2-DCB by way of pharyngeal probe. After 16 hours, colon cells were isolated from the rat and analyzed for DNA damage by means of the comet assay. No cytotoxic effects were detected in the trypan blue vitality test. When the "% tail intensity" or the "tail moment" was used in the comet assay for quantitative analysis, the values obtained with an experimental group that received a low concentration of 2-DCB (1.12 mg/kg body weight) were similar to those of the control group, which was administered 2% dimethyl sulfoxide. Slight but significant DNA damage was observed in the experimental group that received the higher concentration of 2-DCB (14.9 mg/kg body weight). Further studies are needed to clarify the relevance of these results to an evaluation of risk from the consumption of irradiated foods.

Discussion of Studies 5 and 6:

The 1999 FAO/IAEA/WHO report properly labeled Study 5 as demonstrating a "*possible effect of high-dose irradiation.*"[7] But, it rationalized this by saying the level of the lipid present in the experiment was three orders of magnitude greater than the normal lipid level in chicken meat.

In the discussion of Study 5 in the report text, a late note added in the manuscript proof by the WHO Secretariat states:

> *In a subsequent* in vivo *study,* [Study 6, here] *as yet unpublished, the researchers claim to have found a small positive effect when six rats were administered an extremely high level of the synthetically-prepared 2-DCB.* (fn. 1, p. 124)

But, Study 6 did not, in fact, use an "*extremely high level*" of 2-DCB as claimed in the WHO Secretariat's proof note. The level of 2-DCB, according to the researchers, was carefully calibrated and multiplied by the appropriate toxicological safety factor, to determine the safety of chicken irradiated for shelf sterilization. Delincée et al. conclude that applying the standard toxicological safety factor of 100 below the "no-effect level" means that 2-DCB failed the standard safety test. The WHO Secretariat's allegation that the level was "extremely high" begs the question of why an experienced irradiation researcher would use an incorrect level of the substance for toxicological testing?[8] **The real point is that *in vivo* results show that a unique marker substance in irradiated foods has failed standard safety testing using the 100 fold safety margin required by 21 CFR 170.22.**

One of the arguments formerly made by FDA and others in support of the safety of irradiated foods went like this:

> *The difficulty of detecting characteristic differences between irradiated and unirradiated foods is part of the evidence that irradiated foods are as safe as unirradiated foods.*[9]

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[7] The 1999 FAO/IAEA/WHO report shows bias not only in its misclassification of certain studies, but also in the basic classifications it uses. See keys for Table 31, at p. 113, and Table 32, at p. 118. Negative studies are classified unqualifiedly as "negative for high-dose irradiation effect." But, positive studies are classified conditionally, as "possible effect of high-dose irradiation" (emphasis added). This facially unequal treatment is not explained.

[8] While the simulation of the 60 kGy concentration of 2-DCB, representing sterilized chicken, was clearly genotoxic in the 6 rats tested, the more alarming result may have been from the lower concentration of 2-DCB. According to the study, "The low concentration was meant to model radiation pasteurization (e.g., with 3 kGy)." This represents the level commonly used now when irradiating chicken. Even at that ordinary level, 2 of the 6 rats in the experiment indicated a genotoxic response. However, when the responses of all 6 rats were combined, the difference was not statistically significant relative to the control group.

[9] Swallow, A.J. 1991. Wholesomeness and safety of irradiated foods. In M. Friedman, ed., *Nutritional and Toxicological Consequences of Food Processing.* Plenum Press, NY, at p. 17; see also the FDA 1986 Omnibus rule, 51 FR, at p. 13378.

Now researchers have identified a unique marker for irradiated foods **and the marker happens to be genotoxic, causing DNA strandbreaks in human and rat cells, in both *in vitro* and *in vivo* testing**. In addition to his calls for further research in Study 6, Dr. Delincée has made the following points to an author of this comment (pers. comm. to Peter T. Jenkins):

> *Since we would like to know whether in case of cyclobutanones these DNA strandbreaks have any significance, we concluded that further experiments are required. Thus, a large database with results from both* in vitro *and* in vivo *testing is needed, combined with the results of appropriately designed multilaboratory international validation studies.*

The recommended further tests have yet to be completed and published. However, a preliminary, unpublished example of the ongoing studies by Dr. Delincée and his associates has produced further disturbing results. (Delincée, H., C. Soika, and E. Marchioni. 2001. "Genotoxicity of 2-alkylcyclobutanones, markers for an irradiation treatment in fat-containing food," *12th International Meeting on Radiation Processing, Conference Abstracts, 25-30 March 2001,* Avignon, France, pp. 148-149.) According to that study, further "*in vivo tests with rat colon cells are planned to supplement these results.*"

The FDA must ensure that the needed further studies are completed and published in peer-reviewed journals before considering the several pending petitions to irradiate a much greater portion of the food supply, including foods containing substances found to be genotoxic in the Karlsruhe studies. Proceeding otherwise would be contrary to science.

Discussion of 2-DCB and Palmitic Acid:

Numerous studies conducted since 1990 have identified 2-DCB as a unique irradiation byproduct of palmitic acid at doses as low as 0.5 kGy.[10] This chemical, which has never been found in any non-irradiated food,[11] is so readily identifiable as a unique irradiation byproduct of palmitic acid that it is commonly used as a marker for irradiated food — a byproduct that has been shown to persist in food up to 13 years.[12] As explained above, 2-DCB has been shown to be cytotoxic and/or genotoxic in recent *in vivo* and *in vitro* experiments.

Palmitic acid appears in crustacean shellfish in appreciable quantities, representing 16 percent of the fatty acids in Alaskan shrimp, 14 percent of the fatty acids in queen crab, and 9.2 percent of the fatty acids in king crab.[13]

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[10] Stevenson, M.H. Identification of irradiated foods. *Food Technology*, 48: 141-144, 1994.

[11] Ibid.

[12] Crone, A.V.J. et al. Detection of 2-dodecylcyclobutanone in radiation-sterilized chicken meat stored for several years. *International Journal of Food Science and Technology*, 27: 691-696, 1992.

[13] Chow, C.K. ed. *Fatty Acids in Foods and Their Health Implications*. New York: Marcel Dekker, 2000.

Because palmitic acid appears in crustacean shellfish in varying quantities and high percentages, the FDA should refrain from considering the petition until the potential cytotoxicity and genotoxicity of 2-DCB in each type of shellfish covered by the petition is thoroughly studied.

POSITIVE STUDIES IGNORED IN THE 1999 FAO/IAEA/WHO REPORT

Studies 1 through 6 at least received mention in the 1999 FAO/IAEA/WHO report, upon which it is anticipated FDA will rely in considering the above-referenced petition. But, it outright ignored the studies below, numbered 7 through 12, which found mutagenic effects in feeding experiments with human children, mice, rats, and monkeys. They were published in four reputable, peer-reviewed, scientific journals, including the American Journal of Clinical Nutrition.

Study 7: Bhaskaram, C., and G. Sadasivan. 1975. Effects of feeding irradiated wheat to malnourished children. *American J. of Clinical Nutrition* 28:130-135.

Study 8: Vijayalaxmi. 1975. Cytogenetic studies in rats fed irradiated wheat. *Int. J. Radiat. Biol.* 7:283-285.

Study 9: Vijayalaxmi. 1976. Genetic effects of feeding irradiated wheat to mice. *Canadian Journal of Genetics and Cytology* 18:231-238.

Study 10: Vijayalaxmi. 1978. Cytogenetic studies in monkeys fed irradiated wheat. *Toxicology* 9:181-4.

Study 11: Vijayalaxmi and G. Sadasivan. 1975. Chromosomal aberrations in rats fed irradiated wheat. *Int. J. Radiat. Biol.* 27:135-142.

Study 12: Vijayalaxmi and K.V. Rao. 1976. Dominant lethal mutations in rats fed on irradiated wheat. *Int. J. Radiat. Biol.* 29:93-98.

Discussion of Studies 7 through 12

The FDA must give full consideration to these studies (copies attached), before deciding on the safety of further food irradiation. The FDA should consider an expert cancer researcher's commentary on these Indian National Institute of Nutrition (NIN) studies:

> *These experiments have been strongly criticised but have been confirmed by some independent experiments although not by others. Nevertheless, further well-*

> *conducted work would seem to be required if the question of the safety of freshly-irradiated wheat is to be resolved.*[14]

Most noted has been Study 7, the NIN study involving children. It is unfathomable for the 1999 FAO/IAEA/WHO report to have disregarded it, the only published, controlled, human study using freshly-irradiated food. The following Australian genotoxicity expert's testimony to a government commission examining food irradiation backed the study's validity:

> *The [NIN children] study itself I guess could be criticized in some ways, although, given that it was carried out in 1975, when perhaps not so much was known about cytogenics as today, it is a reasonable study. It is fairly small but they looked at quite a number of cells and the findings seemed reasonable.*[15]

The results of the NIN studies were further supported, and the criticisms rebutted, by the researchers themselves in two later-published defenses, which the FDA should consider before approving the petition at issue here:

Study 13: Vijayalxmi and S.G. Srikantia. 1989. A review of the studies on the wholesomeness of irradiated wheat, conducted at the National Institute of Nutrition [NIN], India. *Radiation Phys. Chem.* 34:941-952.

Study 14: Vijayalaxmi. 1999. Comparison of studies on the wholesomeness of irradiated wheat: A review. *Nutrition Research* 19:1113-1120.

Neither these follow-up papers nor the original NIN studies by Vijayalaxmi and others have been adequately addressed by their critics in any published article. Again, the 1999 FAO/IAEE/WHO report authors omitted studies 7 through 14 altogether – despite compiling and citing 495 other irradiation studies - although they did see fit to include the one study by Dr. Vijayalaxmi in which no mutagenic effect of irradiation was found.[16] Bias is apparent.

THE NUMBER OF POSITIVE MUTAGENICITY STUDIES COMPARES FAVORABLY WITH THE NUMBER OF NEGATIVE STUDIES

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[14] Swallow, A.J. 1991. Wholesomeness and safety of irradiated foods. In M. Friedman, ed., *Nutritional and Toxicological Consequences of Food Processing.* Plenum Press, NY, at p. 20.

[15] Sutherland, G.R. 1988. *Official Hansard Report of the House of Representatives Standing Committee on Environment, Recreation and the Arts, Australia.* Evidence given to the Committee on the 26th Sept., 1988, Australian Govt. Publ. Serv., Canberra, p. 3842. Dr. Sutherland is Director of the Department of Cytogenetics and Molecular Genetics at the Women's and Children's Hospital, Adelaide, Australia. He pioneered investigation into fragile sites on chromosomes. He was President of the Human Genome Organization in 1996 and 1997, and a co-recipient of the 1998 Australia Prize.

[16] Reference number 385 in the 1999 FAO/IAEE/WHO report; Vijayalaxmi. 1980. Sister chromatid exchanges in human peripheral blood lymphocytes grown in irradiated medium. *Intl. J. of Irradiation Biology* 37:581-583.

In sum, ten published *in vivo* mammal studies cited herein, including one human study, have found mutagenic effects from eating irradiated diets. In several instances these results have replicated and reinforced one another. No credible argument has surfaced that all ten of these were defective or spurious.

Remarkably, this total compares favorably with the number of published *in vivo* mammalian and human studies reportedly with negative findings for mutagenicity. The detailed 1999 FAO/IAEA/WHO report lists 17 *in vivo* studies of mammals published in scientific journals with negative findings for mutagenicity (after subtracting its misclassification of Studies 1 through 4, above.) (Table 1, below.[17]) For comparison, Table 1 also shows the proportion of published positive *in vitro* studies on mutagenic effects of irradiated foods in relation to the published negative studies, both as listed in the 1999 FAO/IAEA/WHO report.[18] The comparisons are very consistent; **more than one-third of both *in vivo* and *in vitro* studies are positive.**

Table 1. Summary results of published studies on mutagenic effects of irradiated foods.

	Positive for mutagenicity	**Negative for mutagenicity**
***In vivo* mammal (including human) studies**	10 (37 %)	17 (63 %)
***In vitro* studies**	5 (38 %)	8 (62 %)

[17] The negative study numbers are the reportedly negative studies from the 1999 FAO/IAEA/WHO report, Table 32, pp. 114-118; studies are only included if they were published in a scientific journal (i.e., studies numbered: 387, 389, 390, 393, 398, 400, 401, 404, 405, 406, 407, 411, 412, 415, 416, 418, and 421); studies 388, 397, 413, and 414, are excluded because they were not journal-published. Studies 1 through 4 herein (respectively, studies numbered 408, 361, 402, and 407 in the 1999 FAO/IAEA/WHO report) are not considered negative studies in Table 1 because of misclassification; other than these four, the numbers of other negative studies are provided without any review of the actual studies to determine whether they received proper classification. Non-mammal studies are excluded. The positive studies are Studies 1-4 and 7-12 discussed herein. Study 6 herein is not included because it was not journal-published.

[18] The numbers of reportedly negative and positive *in vitro* studies are from the 1999 FAO/IAEA/WHO report, Table 31, pp. 112-113. The numbers are provided without any review of the actual studies to determine whether they received proper classification. Studies are only included if they were published in a scientific journal (i.e., negative studies numbered: 382, 384, 385, 386, 387, 389, 390, and 394; 388 is excluded because it was not journal-published; and positive studies numbered 383, 391, 392, 393, and 427). For the record, the positive studies are, in order: Niemand, J.G., et al. 1983. A study of the mutagenicity of irradiated sugar solutions: implications for the radiation preservation of subtropical fruits. *J. of Agric. and Food Chem.* 31:1016-1020; Shaw, M.W., and E. Hayes. 1966. Effects of irradiated sucrose on the chromosomes of human lymphocytes *in vitro*. *Nature* 211:1254-1256; Bradley, M.V., L.L. Hall, and S.J. Trebicock. 1968. Low pH of irradiated sucrose in induction of chromosome aberrations. *Nature* 217:1182-1183; Aiyar, A.S., and S. Rao. 1977. Studies on mutagenicity of irradiated solutions in *Salmonella typhimurium*. *Mutation Research* 48:17-28; and Delincée et al., Study 5 cited above.

Official suggestions in the past that positive mutagenicity findings have not been duplicated ring false, apparently resulting from bias. Vijayalaxmi and Srikantia, in Study 13, above, describe bias in the official posture in support of the safety of irradiation:

> *It is difficult to escape from the feeling that all findings which are in favour of the wholesomeness of irradiated foods are readily accepted, while observations which raise doubts and question this stand are either viewed with suspicion, either covertly or overtly, or outrightly rejected.* (p. 950)

As shown above, the 1999 FAO/IAEA/WHO report either mischaracterizes or ignores the large percentage of positive studies, bolstering Vijayalaxmi and Srikantia's contention. Perhaps the bias has resulted from a "groupthink" mentality among a small number of officials working in an esoteric field. These officials apparently believe they can rationalize, or "explain away," the positive results, but they have failed to do so adequately. The small number of officials pushing food irradiation safety needs to be compared with the large number of scientists who have stated its risks remain unresolved.

EXPERT CALLS FOR FURTHER RESEARCH

Again, Delincée et al. of the respected Karlsruhe research facility, in Study 6, above, stated: "*...the results urge caution and should provide impetus for further studies.*" If established irradiation researchers are urging caution and more studies, then "reasonable certainty," as required by 21 CFR 170.3(i), is missing. Numerous other experts have also called for, at least, more research on irradiation safety.[19] Notably, 26 medical experts and many other prominent individuals recently endorsed a detailed warning in a health journal on the dangers of irradiation of foods generally.[20] The list of endorsers is impressive.[21] The FDA cannot prudently ignore such explicit caution signals.

THE PETITION CONTAINS NO SPECIFIC DATA ABOUT THE POTENTIAL TOXICITY OF IRRADIATED CRUSTACEAN SHELLFISH

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[19] See, e.g., Louria, D.B. 1993. Food irradiation: Perceptions of a qualified opponent. *Infectious Diseases in Clinical Practice* 2:313-316; Tritsch, G.L. 2000. Food irradiation. *Nutrition* 16:698-701; Steinberg, J., quoted in R. Papazian 1992. Food irradiation - A hot issue, *Harvard Health Letter,* vol. 17, no. 10, p. 3.

[20] Epstein, S.S., and W. Hauter, cited in fn. 1, above.

[21] Some examples of prominent MD and Ph.D. endorsers of the warning: Neal Barnard, President, Physicians Committee for Responsible Medicine; Donald Dahlsten, Professor and Associate Dean, Univ. of California, Berkeley; Robert Elder, Senior Microbiologist, Neogen Co.; Samuel Epstein, Emeritus Professor of Environmental Medicine, Univ. of Illinois School of Public Health, and Chairman of the Cancer Prevention Coalition; Jay M. Gould, Director, Radiation and Public Health Project; William Lijinsky, past Director of Chemical Carcinogenesis, Frederick Cancer Research Center; Donald Louria, Chairman, Department of Preventive Medicine, New Jersey Medical School; Vincente Navarro, Professor, The Johns Hopkins Univ. and Univ. of Pompeu Fabra, Spain; and Dr. Quentin Young, past President, American Public Health Association.

The petitioners submitted no toxicology data on irradiated crustacean shellfish, according to petition co-author Michelle Marcotte.[22] Clearly, the FDA cannot credibly assess the safety and wholesomeness of foods covered by the petition if no toxicology data were included in the petition — particularly in light of the recent revelations concerning the potential toxicity of 2-DCB.

CONCLUSION

Past official reviews have whitewashed potentially serious and pervasive human health concerns that would become more serious if FDA approves the pending petitions to irradiate a much larger portion of the human food supply. Is it conceivable that FDA would approve expanded use of a technology when the studies demonstrating mutagenic effects actually amount to more than one-third of all the published mutagenicity studies, both *in vitro* and *in vivo*? Would the FDA approve any other additive if such a large proportion of the published studies demonstrated a real potential to cause gene damage to consumers and their offspring? Obviously the answer is no.

In sum, the numerous positive studies, together with the warnings from competent irradiation and mutagenicity experts, indicate a lack of adequate proof of safety for food irradiation generally. The petition does not present adequate information to meet the legal standards for safety, quoted above, in Title 21 - Food and Drugs, Pt. 170 - Food Additives. Therefore, the Center for Food Safety and Public Citizen strongly urge the FDA to:

a) **Remove the above-referenced petition from the list of food additive petitions receiving expedited review.**

b) **Deny the above-referenced petition.**

c) **Review the existing regulations on food irradiation at 21 CFR Pt. 179 to determine whether they adequately protect public health based on the best available scientific information.**

Thank you for your attention to this comment. For further information about issues raised herein, please contact Peter T. Jenkins, Attorney/Policy Analyst at CFS, at 202.547.9359 ext. 23, or Mark Worth, Researcher at Public Citizen at 202.454.5123

Sincerely,

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[22] Personal communication, 3/01.

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Enclosures

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To: Docket No:

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