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THE CENTER FOR  
FOOD SAFETY

September 12, 2005

Division of Dockets Management  
Food and Drug Administration  
HFA-305  
5630 Fishers Lane – Room 1061  
Rockville, MD 20852

**Re: Docket No. 1999F-4372– Irradiation in the Production, Processing and Handling of Food; Final Rule; Molluscan shellfish - OBJECTIONS, HEARING AND STAY REQUEST**

To whom it may concern:

Under the provisions of 21 CFR §12.24, the Center for Food Safety and Public Citizen are requesting a stay of action and a formal evidentiary public hearing for the purposes of revoking the Food and Drug Administration's above-referenced Final Rule, published in the Federal Register at 70 FR 48057-48073 (Aug. 16, 2005).

The Center for Food Safety (CFS) is a national, non-profit, membership organization established in 1997 that uses 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 (PC) is a national, non-profit, membership organization established in 1971 that advocates for consumer protection, and for government and corporate accountability.

We seek to present at a public hearing **new, reliable, and specifically identified evidence that raises genuine and substantial issues of fact** and that questions in a material way the rationale of FDA's Final Rule. Our ten well-documented objections submitted herein plainly satisfy the standard for providing a formal hearing under the criteria in 21 CFR §12.24(b)(1) through (b)(6). The regulatory change FDA has promulgated is based on numerous arbitrary and capricious analytical failures and must be revoked.

Due to massive shortcomings and factual misrepresentations in the Final Rule, potential risks that FDA's decision poses to public health have not been sufficiently examined. Additionally, the vast majority of public comments in the docket that we have reviewed – by a margin of greater than 100

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to 1 – opposed the granting of the underlying Petition by the National Fisheries Institute and the Louisiana Department of Agriculture and Forestry (“the Petition”), which reinforces the justification for a hearing.

Our ten objections follow. The Docket file already includes, as attachments to the CFS and PC comments, copies of most of the documents cited herein with the exception of the seven tabbed additional documents attached hereto, and further except for FDA’s own documents or references to which the agency already has referred.

### **OBJECTION 1. FAILURE TO CONSIDER CRITICAL TOXICOLOGY STUDIES**

We object to the amendment of 21 CFR §179.26 as proposed to allow for the irradiation of molluscan shellfish.

#### **Grounds for Hearing Request: Description and Analysis of Facts In Support of Objection**

It is inconceivable that neither the Final Rule nor the underlying Petition considered the published toxicological evidence detailing harmful effects in animal feeding studies from irradiated molluscan shellfish. As stated in the Final Rule, at p. 48068:

“The petitioner did not submit copies of toxicological data specific to irradiated shellfish.”

That omission amounts to misrepresentation of the science on the topic, as **at least two such studies have made such findings** (attached hereto). They are:

- (1) A 1976 published study (**Tab 1**) in which irradiated soft-shell clams were fed to chickens for two years. The clams were irradiated at 4 kGy and 8 kGy. The 4 kGy level is well within the 5.5 kGy level approved in the current Rule, while the 8 kGy level is not significantly higher as to dismiss the results. Numerous negative health effects were observed in the animals fed irradiated clams:
  - The reduction of the percentage of chicks in the F<sub>2</sub> generation that survived 30 days was “aggravated” by irradiation;
  - “A significant decrease in fertility of eggs” was observed in the F<sub>2</sub> generation;
  - Embryonic viability in the F<sub>2</sub> generation was reduced. This effect was “intensified” by the addition of 8 kGy-irradiated clams;
  - The hatchability of eggs in the F<sub>2</sub> generation was reduced. This effect was “intensified” by the addition of 8 kGy-irradiated clams;
  - The gonads of males in the F<sub>1</sub> generation were smaller in size and weight;
  - Males in the F<sub>1</sub> generation had “significantly higher” hemoglobin levels;

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<sup>1</sup> CFS reviewed all of the public comments in the FDA docket for the Petition. The “pro” comments numbered 6 and the “con” numbered 948. Thus, 99.4 % of commenters were opposed and only 0.6 % supported it.

- Females in the F<sub>2</sub> generation “weighed significantly less;” and
- Females had “significantly larger” kidneys, and the effect increased with radiation dose.<sup>2</sup>

This study was published in the journal of the International Project in the Field of Food Irradiation (IFIP) in Karlsruhe, Germany. Then the world’s leading food irradiation research institute, IFIP was supported by 23 nations – including the U.S. – and by the World Health Organization, the UN’s Food and Agriculture Organization, the Organization for Economic Cooperation and Development, and the International Atomic Energy Agency.

Inexplicably, this study is not listed in the FDA’s Sept 15, 1982 master bibliography of more than 400 studies on the safety of irradiated foods. As a result, the study was not assessed by the Task Group for the Review of Toxicology Data on Irradiated Food, which the FDA impaneled in 1981 for the purpose of “compiling, summarizing and writing the final report on the toxicology data pertaining to irradiated foods.” The Task Group’s leader wrote that “there is a need for the FDA to look carefully at the open literature...before issuing a final regulation on irradiated foods.”<sup>3</sup>

The Task Group’s assessment of these 400-plus studies has formed the foundation of every FDA Ruling on food irradiation since the “Omnibus Rule” of 1986, which legalized irradiation for fruit and vegetables, and increased the maximum dose for spices. Building upon the Omnibus Rule, the FDA has subsequently legalized irradiation for poultry (1990), red meat (1997), fresh shell eggs (2000), sprouting seeds (2000), and fruit and vegetable juice (2000). **The FDA’s failure to assess this study – or even acknowledge its existence – not only calls into question the molluscan shellfish Rule, but every prior Rule on food irradiation.**

- (2) A 1976 study, (**Tab 2**) conducted by the same researchers and also published in the IFIP journal, in which irradiated soft-shell clams were fed to beagle dogs for two years. Like the study on chickens, the clams were irradiated at 4 kGy and 8 kGy. The researchers wrote: “It was observed...that there was a significant inverse correlation between the irradiation dose applied to the clams and the blood urea nitrogen level of male dogs fed on them.”<sup>4</sup> Though the researchers did not speculate, low blood urea nitrogen levels are usually a symptom of liver damage.

**This exemplifies the arbitrary fashion in which the FDA chooses which research to ignore and which to embrace.** The Task Group assessed this study and classified it “Accept with reservation.”<sup>5</sup> Internal FDA documents on the Task Group’s work and findings are silent on why the agency

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2 Fegley, H.C. and Edmonds, R.E. 1976. “To Examine the Wholesomeness of Irradiated Soft-Shell Clams (*Mya arenaria*) in White Leghorn Chickens.” *Food Irradiation Information*, International Project in the Field of Food Irradiation, Karlsruhe, Germany, No. 6 (Supplement), 113-115, June.

3 FDA Memorandum from Marcia van Gemert, Food Additives Evaluation Branch, to W. Gary Flamm, Acting Associate Director for Regulatory Affairs, Nov. 25, 1981.

4 Fegley, H.C. and Edmonds, R.E. 1976. “To Examine the Wholesomeness of Irradiated Soft-Shell Clams (*Mya arenaria*) in Dogs.” *Food Irradiation Information*, International Project in the Field of Food Irradiation, Karlsruhe, Germany, No. 6 (Supplement), 111-112, June.

5 Data Summary Form for Irradiated Foods, FDA Task Group for the Review of Toxicology Data on Irradiated Food, Ref. #121, reviewed by Francis Lin (1/4/82) and Marcia van Gemert (1/7/82).

ignored this positive study but has embraced negative studies that were also classified “Accept with reservation.”

Thus, **one study that the FDA has never reviewed, and another that the agency did not reject in its earlier internal evaluations of irradiation studies**, found serious toxicity concerns associated with irradiated molluscan shellfish. FDA’s Final Rule either intentionally or ignorantly passes over the omission of these studies from the underlying Petition and seeks to demonstrate safety by analogy from studies of other food types. Further, none of the internal FDA memos cited by FDA in support of the Final Rule include any mention, discussion, or reference to those two studies. **This is simple scientific negligence that underlines the arbitrary and capricious nature of FDA’s decision.**

**Based on FDA’s failure to consider this critical toxicity data on irradiated molluscan shellfish, we are requesting a formal evidentiary public hearing on the issue of lack of reasonable certainty of safety.**

## **OBJECTION 2. FAILURE TO CONSIDER THE LEADING PAPER IN THE FIELD OF MICROBIOLOGICAL SAFETY AND EFFECTIVENESS**

We object to the amendment of 21 CFR §179.26 as proposed to allow for the irradiation of molluscan shellfish.

### Grounds for Hearing Request: Description and Analysis of Facts In Support of Objection

A document the Petitioners use to support their contention that irradiation is a safe and effective treatment for molluscan shellfish is, in reality, a treatise in opposition. In his 1996 Ph.D. dissertation from the University of Florida (**Tab 3**), Dustin W. Dixon researched the use of gamma irradiation to eradicate *V. vulnificus* in shellstock oysters harvested in Florida and Texas.<sup>6</sup> Among his key findings were that “minimal research has been conducted on oysters and clams” (p. 38); that earlier safety researchers (Gardner and Watts) concluded “radiation would not be effective in oyster meat preservation” (p. 38); that internal dosimetry indicated that the shells blocked about 50% of the radiation dose.

Further, Dixon observed that the *V. vulnificus* count in oysters irradiated at 1.0 kGy and 3.0 kGy rose nearly to the level of *unirradiated* oysters after two and nine days of storage, respectively (p. 62).

Given the number and depth of Dixon’s concerns regarding irradiation, his conclusion is quoted at length (emphasis added):

“It is apparent that there is a serious decrease in shelf life associated with the

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<sup>6</sup> Dixon, D. W. “The Influence of Gamma Radiation upon Shellstock Oysters, and Culturable and Viable but Nonculturable *Vibrio vulnificus*.” A dissertation presented to the Graduate School of the University of Florida, 1996.

irradiated oyster and that a serious product loss can be expected with irradiating summer oysters. However **if the microbial levels are reduced to undetectable or very low levels, then the benefit of clean oysters may outweigh the rapid product loss. However, this is not the case.**" (p. 104)....

**"In conclusion, irradiation processing cannot be considered as a method to sterilize shellstock oysters, and provide a shelf stable product.** Irradiation can reduce some pathogens and viruses, perhaps below their infective dose, but not rid the shellstock oyster completely of all contaminants. The shellstock oyster poses many challenges to irradiation and food processing technology. These problems include uneven dose distribution, different shell to meat ratios for oysters from different geographic locations and the potential for growback of organisms in the irradiated product over time. Furthermore, oysters are live animals with their own inherent radiation sensitivity, and thus radiation D value... [T]he conundrum of deciding on the dose that will give the best shelf life and maximum bacterial reduction will continue. **The survival of organisms is a great concern because when competition is altered between the flora, the result could be the rapid outgrowth of a potentially dangerous microbe.**

[I]n a complex system like shellstock oysters, there is a protective effect by the shell itself and [*V. vulnificus*] can survive. More importantly it can grow and divide in dry cold storage, or even worse enter the viable but nonculturable [VBNC] state. The VBNC forms of *V. vulnificus* are 3X more resistant to radiation than the corresponding culturable forms and this too could be a potential problem in winter harvest oysters that have VBNC cells. **There is evidence from this research for the presence of resuscitation of VBNC *V. vulnificus* cells post-irradiation.**" (p. 108-110)

Incredibly, neither the Final Rule nor the critical FDA internal Memorandum of Jan. 2, 2003 (Merker to Highbarger. Ref. 25) mention Dixon's 1996 dissertation. The latter memo cites to Dixon's 1992 Master's thesis only, and relies only on assumed temperature controls to rebut the concerns Dixon expressed then, and ignores the much more detailed and persuasive Ph.D. dissertation on these fundamental problems underlined in bold, above.

The Final Rule states that *Vibrio* "are usually eliminated" by 0.5 kGy (p. 48061), and the Petition states that 0.5 kGy "should be adequate to eliminate" the bacteria. The vague nature of these statements is troubling enough – particularly in light of Dixon's findings that even 3.0 kGy may not be sufficient, and that this dangerous bacteria will re-infest oysters that unsuspecting consumers think are sterilized. These statements are even more alarming considering that the main supporting document cited by Petitioners includes nothing about recommended irradiation doses.<sup>7</sup> Additionally, the final rule includes no additional requirements for irradiated oysters related to minimum

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<sup>7</sup> Tamplin, Mark L. "The Seasonal Occurrence of *Vibrio vulnificus* in Shellfish, Seawater and Sediment of United States Coastal Waters and the Influence of Environmental Factors on Survival and Virulence." Final Report to the Salstonstall-Kennedy [sic] Program, 1994.

temperature or maximum time of storage of treated oysters, despite the fact that the underlying Petition proposed such conditions. This is verified in FDA's internal memo of Jan. 2, 2003 (Merker to Highbarger. Ref. 25), at pp. 1-3, which emphasizes that the Petition urged that required temperatures be included in the actual regulatory language, and Dr. Merker stresses that "irradiation would remain effective for transient short term reduction of the number of vibrios,...however, temperatures must be controlled."

By dropping any mention of temperatures or storage times in the Rule – without explanation other than FDA's assumption that poorly-enforced and largely non-mandatory HACCP plans will ensure consistent and adequate temperature control (at p. 48601) – FDA has utterly failed to show how its Rule will assure the microbiological safety of fresh oysters.

**The glaring omissions in the Final Rule for the *V. vulnificus* problem are reckless – given that the Rule itself states that the bacteria is associated with 95 percent of all seafood-related deaths in the United States (p. 48061). We are requesting a formal evidentiary public hearing on the issue of the microbiological hazards of irradiated molluscan shellfish. At this hearing we will seek to introduce testimony from Dr. Dixon himself or an equally qualified expert on the dangers of the proposal.**

### **OBJECTION 3. LACK OF REASONABLE CERTAINTY OF SAFETY IN THE MINDS OF COMPETENT SCIENTISTS**

We object to the amendment of 21 CFR §179.26 as proposed to allow for the irradiation of molluscan shellfish.

#### Grounds for Hearing Request: Description and Analysis of Facts In Support of Objection

Under Title 21 CFR, Food and Drugs, Part 170--Food Additives, the following key legal standards apply in deciding the 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. 170.3 Definitions.*

*(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.*

CFS and PC have filed eight sets of public comments in the above-referenced docket. In addition to citations to numerous individual studies indicating safety concerns, those comments have attached a total of eleven mostly Ph.D. or MD-authored peer-reviewed papers or other publications stating safety concerns associated with irradiated foods.<sup>8</sup> They also have referenced at least 25 other highly “competent” Ph.D.s or MDs who have stated that they have safety concerns in published literature.<sup>9</sup> FDA’s Final Rule did not respond to these authorities, whose statements demonstrate an obvious lack of “reasonable certainty” in the minds of competent scientists on the safety issue. Still more qualified scientists are referenced expressing similar concerns in the other Objections herein.

While, except for those studies listed under Objection 1 and 2, above, the past scientific statements of concern did not focus on the risks of irradiated molluscan shellfish, *per se*, they did focus on other analogous irradiated foods. This is important because neither FDA’s Final Rule nor the underlying Petition on irradiating molluscan shellfish actually contain any data from, or references to, any toxicity studies on irradiated molluscs. FDA has demonstrated a willingness to consider statements regarding analogous foods that support safety, which it has done without scientific rationale, but has demonstrated bias in refusing to consider statements regarding analogous foods that indicate safety concerns. A double-standard is apparent.

In an unbiased assessment, a lack of reasonable certainty of safety in the minds of competent scientists would be found here.

Further, FDA has misstated what is contained in its literature reference numbered as “Ref. 20,” which relates to this point and FDA’s reasoning. At p. 48060 of the Final Rule, FDA assumes that irradiated molluscan shellfish are safe, reasoning by analogy from irradiated fish. It states:

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8 Ashley, B.C., P.T. Birchfield, B.V. Chamberlain, R.S. Kotwal, S.F. McClellan, S. Moynihan, S.B. Patni, S.A. Salmon, and W.W. Au. 2004. Health concerns regarding consumption of irradiated food. *International Journal of Hygiene and Environmental Health* 207:1-12; Epstein, S.S., and W. Hauter. 2001. Preventing pathogenic food poisoning: Sanitation not irradiation. *Intl. J. of Health Services* 31:187-192; Louria, D.B. 1993. Food irradiation: Perceptions of a qualified opponent. *Infectious Diseases in Clinical Practice* 2:313-316; Louria, D.B. 2001. Food irradiation: Unresolved issues. *Clinical Infectious Diseases* 33:378-380; Kesavan, P.C., and M.S. Swaminathan. 1971. Cytotoxic and mutagenic effects of irradiated substrates and food material. *Radiation Botany* 253:-281; Murray, D.R. 1990. *Biology of Food Irradiation*. Research Studies Press Ltd. Staunton, UK.; Organization for Economic Cooperation and Development (OECD), Steering Committee for Nuclear Energy, Study Group on Food Irradiation. 1965. Genetic effects produced by irradiated food and food components. SEN/IR (65)15. Unpublished report by G.T. Scarascia-Mugnozza, A.T. Najaran, and L. Ehrenberg. Paris, France; Rao, C.V. 2003. Do irradiated foods cause or promote colon cancer? *Nutrition and Cancer* 46(2):107-109; Schubert, J. 1969. Mutagenicity and cytotoxicity of irradiated foods and food components. *Bulletin of the World Health Organization* 41:873-904; Tritsch, G.L. 2000. Food irradiation. *Nutrition* 16:698-701; and Webb, T., T. Lang, and K. Tucker. 1987. *Food Irradiation - Who Wants It?* Thorsons Publishing, Wellingborough, England.

9 Some examples of prominent MD and Ph.D. expressing concern: 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.

“In addition, a study summarized in an International Consultative Group on Food Irradiation monograph compared the fatty acid composition of unirradiated and irradiated herring oil(Ref. 20).”

Yet, Ref. 20, which we reviewed in the docket, is not a monograph on irradiated herring, it is actually a global status report on food irradiation in 1998, containing no such scientific conclusions. FDA’s reliance on it is inexplicable.

Additionally, the Rule falsely states that the “Raltech” study, in which 300,000 pounds of irradiated chicken were fed to various types of animals during the late 1970s and early 1980s, found “no adverse toxicological effects that could be attributed to the consumption of irradiated chicken.” In reality, the study found several negative health effects, including a significant dose-related decrease in the offspring of *Drosophila melanogaster*, and a “high incidence of testicular” tumors and “significantly reduced” survival in CD-1 mice.

In the mice study (Tab 4), researchers wrote: “While no single finding from the study is highly illuminating, a collective assessment of study results **argues against a definitive conclusion that the...test material was free of toxic properties...** [W]hile there is no evidence of a highly toxic effect,...the preponderance of evidence suggests **some degree of toxicity was present.**”<sup>10</sup> (emphasis added)

Contrary to the agency’s assertion, nowhere does the Raltech study state that the health effects could not be attributed to the consumption of irradiated chicken.

Shortly after the study was completed, lead researcher Donald Thayer of the USDA was publicly quoted as saying that the studies “strongly support the safety and efficacy of the process, but nevertheless, raise some questions which are *potentially serious*, and must be evaluated...before it can be said that [irradiated foods are] safe for the user.”<sup>11</sup> (Tab 5; emphasis added)

**Based on the absence of any toxicity data underlying FDA’s decision on irradiated molluscan shellfish, *per se*; based on published research explicitly revealing toxic properties of irradiated molluscan shellfish that FDA has ignored; and based on the extensive concerns expressed by a large number of scientists regarding analogous irradiated foods, there is no “reasonable certainty in the minds of competent scientists” that the irradiation is not harmful as applied to molluscan shellfish. We are requesting a formal evidentiary public hearing on the issue of lack of reasonable certainty of safety.**

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10 Thayer, Donald W. “Summary of Supporting Documents for Wholesomeness Studies of Precooked (Enzyme Inactivated) Chicken Products in Vacuum Sealed Containers Exposed to Doses of Ionizing Radiation Sufficient to Achieve ‘Commercial Sterility.’” U.S. Department of Agriculture, Food Safety Laboratory, Eastern Regional Research Center, Philadelphia, Aug. 23, 1983, p. ix. (000044).

11 “Gamma Irradiation Safety Questions Raised by USDA Chicken Studies,” *Food Chemical News*, April 16, 1984, p. 50.

**OBJECTION 4. FAILURE TO ASSESS IRRADIATION SAFETY FACTORS UNIQUE TO MOLLUSCAN SHELLFISH**

We object to the amendment of 21 CFR §179.26 as proposed to allow for the irradiation of molluscan shellfish.

**Grounds for Hearing Request: Description and Analysis of Facts In Support of Objection:**

Irradiating molluscan shellfish for *Vibrio* and other pathogens will most foreseeably be used for fresh oysters, which will primarily need to be irradiated while live and in their shells. These differ substantially from other meat and fish in that they contain extensive salt water, large shells relative to the flesh mass, and they are eaten whole thus their undigested stomach contents will be irradiated and eaten. Neither FDA's Final Rule nor the underlying Petition actually contain any evidence on the effects of 5.5 kGy of irradiation on salt water, molluscan shells, and the chemicals that they "off-gas" which may be absorbed in the meat, or undigested stomach contents such as plankton and algae.

The Rule and the Petition also leave unanswered a question that the Petitioners themselves raise: whether varying shell thickness would require varying radiation doses necessary to eliminate *Vibrio*, *Listeria*, *Salmonella* and other harmful bacteria.

The Petition makes only a casual reference to this "shell" problem: "[A]ttention should be drawn to this phenomenon due to the special nature of the products." The Petition cites Dixon (1996), the dissertation cited above. Dixon found that shell weights and shell-to-meat ratios differ widely for oysters from Florida, Louisiana and Texas. While he did not address toxicity concerns of shell irradiation, he underlined the importance of addressing shells: "An oyster shell with a higher density may actually attenuate the radiation dose delivered, and thus, 'thicker' shells may need a higher dose of irradiation for the same effect in 'thinner' shells." (Tab 3, above) The Rule and Petition offer no solution to a problem that is almost certain to arise if oysters are irradiated commercially.

Further, the agency has failed to consider whether the potential carcinogen furan is produced from irradiating oyster shells, in that the internal memo cited in the Final Rule (Ref. 7) that purports to assess furan in oysters examined only irradiated shucked oysters, not shellstock. We seek to submit an expert affidavit from a qualified toxicologist at the requested hearing regarding potentially significant safety concerns for consumers of irradiated shellstock oysters.

**Based on the absence of evidence of safety regarding irradiated salt water, "off-gassing" from irradiated oyster shells, or irradiated undigested oyster stomach contents; the problem of blockage of irradiation by the shells; and the lack of data on furan creation from the shells, there can be no reasonable certainty that the irradiation is not harmful as applied to fresh shellstock oysters. We are requesting a formal evidentiary public hearing on these topics.**

## **OBJECTION 5. ARBITRARY AND CAPRICIOUS REJECTION OF 100-FOLD SAFETY MARGIN FOR 2-ALKYLCYCLOBUTANONES**

We object to the amendment of 21 CFR §179.26 as proposed to allow for the irradiation of molluscan shellfish.

### **Grounds for Hearing Request: Description and Analysis of Facts In Support of Objection**

Under Title 21 CFR 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.*

FDA's Final Rule, at p. 48059, indicates that molluscan shellfish flesh is distinct from other meat and fish flesh, yet without adequately characterizing that distinctness, the ruling goes on to repeatedly rely on toxicity studies for meat and fish. Oysters and other mollusks contain a unique combination of fatty acids compared to other foods; these fatty acids when irradiated produce a unique combination of 2-alkylcyclobutanones (2-ACBs).<sup>12</sup>

For example, the Rule relies on the Raltech study (which, ironically, revealed adverse health effects; see Objection 3, above) to discount concerns about 2-ACBs in irradiated molluscan shellfish. This comparison is invalid. The Raltech study used chicken comprised of breast and leg meat, which have stearic acid contents of 0.44 and 1.55 mg/g of meat, respectively. The stearic acid content for oysters, however, is approximately 4 times higher – 4.44 mg/g of meat.

These 2-ACBs are found only in irradiated foods and they are known to be potentially toxic at certain concentrations, and to promote tumor formation in the presence of known carcinogenic substances.

For example, stearic acid when irradiated forms 2-tetradecylcyclobutanone (2-tDCB), which the study by Burnouf et al. found to have the most toxic properties of the five types of 2-ACBs they studied. These include: promotion of colon tumors in rats; cyto- and genotoxicity to human cells; cytotoxic and oxidative DNA damage to human cells; and cytotoxicity to bacteria. In addition, 2-

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12 Marchioni, E., P. Horvatovich and D. Werner. Chapt. 2.5 on "Determination of the Levels of 2-Alkylcyclobutanones in Irradiated Foods." in D. Burnouf, H. Delincée, A. Hartwig, E. Marchioni, M. Miesch, F. Raul, D. Werner (2001), Etude toxicologique transfrontalière destinée à évaluer le risque encouru lors de la consommation d'aliments gras ionisés - Toxikologische Untersuchung zur Risikobewertung beim Verzehr von bestrahlten fetthaltigen Lebensmitteln – Eine französisch-deutsche Studie im Grenzraum Oberrhein, Rapport final d'étude Interreg II, projet NE 3.171. BFE-R--02-02, Federal Research Centre for Nutrition, Karlsruhe, Germany.

tDCB was found in the adipose tissue and feces of rats, leading the researchers to state: “To characterize the potential risk, hazards need to be identified, the exposure, the exact dose-response and *particularly the kinetics and metabolism of 2-ACB* in the living organism should be elucidated. All these studies are deemed necessary to gain insight into the mechanisms of the toxic effects.”<sup>13</sup> (emphasis added) Inexplicably, the Rule ignores this recommendation, which is perhaps the most significant of the study’s many recommendations.

The techniques to do the necessary 2-ACB level testing, as Burnouf et al. call for, are readily available, having been done repeatedly for other foods, but they have not been conducted for irradiated molluscan shellfish. Indeed, FDA’s Final Rule contains not one iota of information on the 2-ACB type or levels in this food.

Despite the known toxicity of 2-ACBs to rats in concentration, no “maximum amount demonstrated to be without harm to experimental animals” has been determined. The toxicological research simply has not been undertaken and published. Additionally, no “tolerance” has been granted nor has an alternative safety margin been set. The Final Rule admits that there are “no adequate animal feeding studies in existence to determine no-observed-adverse-effect levels (NOAELs) for various alkylcyclobutanones.” (p. 48065).

Instead of basing its safety assessment of 2-ACBs on actual data, the agency relies on the concept that “the solution to pollution is dilution.” The Rule states that because people would not consume pure irradiated fat when they eat irradiated molluscan shellfish, any 2-ACBs would be “diluted substantially by the major components in shellfish and further by other components being consumed simultaneously.” (p. 48066). The Rule does not indicate what these “other components” are. The Rule states, without supporting evidence, that human colon cells would therefore “be in contact with concentrations more than a thousand times lower than those used” in a 1998 published study that detected genetic damage in human and rat cells exposed to 2-ACBs.<sup>14</sup> These assertions are facile at best.

Further, there are no adequate long-term safety studies that assist in assessing the overall health hazards that consuming 2-ACBs could pose, including likely variations in sensitivities to 2-ACBs among the human consumer population. It is unconscionable that FDA has rejected the 100-fold safety margin, given the need to protect children and other vulnerable consumers, for whose benefit the margin exists. PC and CFS have submitted expert information into the docket in an Affidavit from toxicologist William Au, Ph.D., on the higher sensitivity of children, which FDA’s Final Rule ignored. Attached hereto (**Tab 6**) is a peer-reviewed, published article based on that Affidavit.<sup>15</sup>

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13 Burnouf, D. et al. (Eds.) “Étude toxicologique transfrontalière destinée à évaluer le risque encouru lors de la consommation d’aliments gras ionisés – Toxikologische Untersuchung zur Risikobewertung beim Verzehr von bestrahlten fetthaltigen Lebensmitteln – Eine französisch-deutsch Studies im Grenzraum Oberrhein. Rapport Final d’étude Interreg II, Projet N° 3.171, 2002.”

14 Delincée, H. and Pool-Zobel, B. “Genotoxic Properties of 2-dodecylcyclobutanone, a Compound Formed on Irradiation of Food Containing Fat.” *Radiation Physics and Chemistry*, 52:39-42, 1998.

15 Au, W. 2002. Susceptibility of Children to Environmental Toxic Substances. *Intl. J. Hygiene and Envtl. Health*, 205:1-3

The Rule marks the first time the FDA has ever publicly acknowledged the presence of 2-ACBs in irradiated foods. In doing so, the agency – in the face of incontrovertible evidence – has finally reversed a position it had held for nearly 20 years: that chemical by-products formed by irradiation are identical or similar to natural food components, that irradiated foods contain no unique chemicals that could have toxic properties, and that even if such chemicals existed, detecting any toxic properties would not be possible.

The agency has stated this position in several *Federal Register* notices dating to 1986:

- “[R]adiolytic products are typically identical to substances that occur naturally in foods.”<sup>16</sup>
- “There is no evidence, or any reason to believe, that the toxicity or carcinogenicity of any unique radiolytic products is different from that of other food components.”<sup>17</sup>
- “Because any [radiolytic products] are likely to be toxicologically similar to other food components, it would be virtually impossible to detect potential toxicological properties of these substances.”<sup>18</sup>

Now that this position has been invalidated by vast scientific evidence – and abandoned by the FDA itself – the agency’s response to the 2-ACB issue in the Final Rule is utterly inadequate to protect public health.

**Based on the above, FDA’s rejection of the 100-fold safety factor in 21 CFR Sec. 170.22 for food additives is arbitrary and capricious, in particular with respect to consumption of irradiated molluscan shellfish by children. We are requesting a formal evidentiary public hearing to challenge the factual basis for FDA’s rejection.**

#### **OBJECTION 6. ARBITRARY AND CAPRICIOUS WEIGHING AND REJECTION OF PUBLISHED EVIDENCE**

We object to the amendment of 21 CFR §179.26 as proposed to allow for the irradiation of molluscan shellfish.

#### **Grounds for Hearing Request: Description and Analysis of Facts In Support of Objection**

With respect to other toxicity studies, the peer-reviewed, published, positive mutagenic studies cited in PC and CFS’s earlier comments, (at p. 12 of our comment on this Docket of May 14, 2001, with

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16 62 Federal Register 64102, Dec. 3, 1997.

17 52 Federal Register 5450, Feb. 23, 1987.

18 51 Federal Register 13376, April 18, 1986.

full explanations in footnotes 17 and 18 therein), can be summarized as: in vivo: 12 (1 human); - in vitro: 6.

FDA's Final Rule either ignores or improperly discounts these results - with no clear rationale or standard for doing so - rather than addressing their cumulative significance. Further, at pp. 48067-48068, FDA flatly rejects all of the five peer-reviewed published studies below, which found mutagenic effects in feeding experiments with human children, mice, rats, and monkeys. They were published in reputable scientific journals:

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

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

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

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

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

The FDA also neglected to consider the following Australian genotoxicity expert's testimony to a government commission examining food irradiation backed the malnourished children 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 cytogenetics 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."<sup>19</sup>

FDA's Final Rule, at p. 48067, falls back on verbiage in its 1986 Omnibus irradiation rule for its rejection of those NIN studies:

"The comment implies that FDA has not considered the cited studies despite the fact that FDA previously discussed the reason why some of the study reports could not be

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<sup>19</sup> 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.

used to support a decision on irradiated foods (51 FR 13376 at 13385 and 13387). In 1986 FDA addressed the studies performed at the NIN (Ref. 54) and stated:

A committee of Indian scientists critically examined the techniques, the appropriateness of experimental design, the data collected, and the interpretations of NIN scientists who claimed that ingestion of irradiated wheat caused polyploidy in rats, mice, and malnourished children. After careful deliberation, this committee concluded that the bulk of these data are not only mutually contradictory, but are also at variance with well-established facts of biology.”

However, the Indian scientists upon whom FDA relied were discredited nearly 20 years ago in a hearing before the U.S. Congress. In testimony before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, dated June 19, 1987, S.G. Srikantia, the former Director of the NIN testified to FDA’s lack of wisdom in accepting that report (**Tab 7**):

“The Committee of Indian Scientists referred to here, is a two-man committee which consisted of Dr. P.C. Kesavan and Dr. P.V. Sukhatme, whose report, according to the federal register's citation, was submitted to the Joint FAO/WHO/LAEA Expert Committee on the Wholesomeness of Irradiated Food, held at Geneva in 1976.

This statement [ in 1986 by the U.S. FDA ] leaves the reader with the impression that the [ Kesavan-Sukhatme ] report was discussed by the Joint Expert Group and that the findings in the report were endorsed by it. This would be at variance with the facts because the report was NOT submitted to the Joint Expert Group and therefore was never discussed. I can vouch for this since I was a member of that Expert Group. At that meeting, the [ earlier ] findings of the National Institute of Nutrition were accepted, as is reflected in the published reports of the Proceedings....

The FDA has now accepted that it was indeed incorrect to have cited that the Kesavan-Sukhatme report had been submitted to the Expert Group in 1976. It is unfortunate that many of the original readers of the Federal Register may not get to know the truth....

The [Kesavan-Sukhatme ] report was a confidential document. After receiving the report, the government of India sent it to the Director, National Institute of Nutrition, for his views and comments. The Institute's Director sent his comments to the government, which was also a confidential document. As of today, to the best of my knowledge neither of these documents has been made public. It was therefore surprising to learn that the FDA has a copy of the confidential Kesavan-Sukhatme report, and that it has accepted its findings without being aware that the conclusions of that report had been questioned. In his comments the Director, National Institute of Nutrition, has not only refuted some of the statements made

in the report, but also provided additional evidence to back up the Institute's conclusions....

The FDA has committed a serious error of judgment. Had it seen the Institute's rejoinder to the Kesavan-Sukhatme report, surely, it would have been in a better position to evaluate that report....

It is indeed very strange that aspersions should have been cast on the scientific honesty and integrity of the Institute's workers a full ten years after the work was published. It is even stranger that the two scientists who allegedly made these statements have denied having made them when they were approached by me.....

I wish to reiterate that the Institute has NOT withdrawn anything which it said earlier on this subject and stands fully behind all that it has published. Indeed, its stand has received support from the publications of both Renner and Anderson and coworkers. The Institute also does not agree with the Kesavan-Sukhatme report.”

The results of the NIN studies were further supported, and the criticisms further rebutted, in two later-published defenses, which, along with the Srikantia testimony, above, the FDA has utterly failed to consider in its Final Rule, instead simply parroting its 1986 reasoning.:

Vijayalaxmi 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.

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

Further, in a 1977 letter to Hubert Blumenthal, then-Acting Director of the FDA's Division of Toxicology, Srikantia stated that the NIN's results were mirrored in a study on hamsters.<sup>20</sup> Among the findings: polyploid cells occurred five times more frequently in animals fed irradiated diets, and the incidence of polyploidy was related to irradiation dose. The researcher wrote: “[T]here is doubtless a clear effect upon the polyploidy incidence.”<sup>21</sup>

This study was classified “Accept” by the FDA's Task Group for the Review of Toxicology Data on Irradiated Food.<sup>22</sup> It is noteworthy that the Task Group also classified four other studies by the same

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20 Letter from S.G. Srikantia, Director, National Institute of Nutrition, Indian Council of Medical Research, Hyderabad, India, to H. Blumenthal, Acting Director, Division of Toxicology, Bureau of Foods, FDA, Sept. 17, 1977.

21 Renner, H.W. “Chromosome studies on bone marrow cells of Chinese hamsters fed a radiosterilized diet.” *Toxicology*, 8:213-222, 1977.

22 Data Summary Form for Irradiated Foods, FDA Task Group for the Review of Toxicology Data on Irradiated Food, Ref. # 304, reviewed by V.C. Dunkel, (1/15/82).

researcher (from Germany's Federal Research Center for Nutrition) as "Accept" or "Accept with reservation." None of these studies revealed adverse health effects.<sup>23</sup> One of these, in fact (which was conducted on rats<sup>24</sup>), is among the seven key studies upon which the FDA based its precedent-setting "Omnibus Rule" of 1986,<sup>25</sup> which paved the way for six subsequent Rules – including the current one.

**This is yet another example of the arbitrary fashion in which the FDA chooses which research to ignore and which to embrace.** Internal FDA documents on the Task Group's work and findings are silent on why the agency ignored the positive hamster study but embraced the negative rat study – which were conducted by the same researcher, and both of which the Task Group classified "Accept."

**FDA's refusal to consider the above peer-reviewed published evidence and other commentaries supporting them on the mutagenic effects of analogous irradiated foods, including the only published study on effects of freshly irradiated food on children, and FDA's unqualified reliance on the "Indian Committee" report as an excuse to disregard this evidence, were arbitrary and capricious. Based on the high number of positive peer-reviewed published studies on the mutagenicity of irradiated foods, a consistent potential for harm has been observed and no reasonable certainty of safety exists. We are requesting a formal evidentiary public hearing on this matter.**

## **OBJECTION 7. MISREPRESENTATION OF EXPERT WARNINGS ON POTENTIAL RISKS**

We object to the amendment of 21 CFR §179.26 as proposed to allow for the irradiation of molluscan shellfish.

### Grounds for Hearing Request: Description and Analysis of Facts In Support of Objection

FDA has misrepresented the warnings of the leading recent researchers on the toxicity of 2-ACBs. At pp. 48066 and 48068 of the Final Rule, FDA suggests that various authors have not issued warnings on the uncertain status of irradiated foods with respect to potential safety concerns for long-term consumption. FDA improperly seeks to show that CFS and PC have misrepresented those warnings, particularly by focusing on one comment that is hostile to PC and CFS from one researcher, Henri Delincee, at p. 48068, and which largely related to a draft report by PC and CFS that was changed before publication to accommodate Dr. Delincee's suggested edits. In contrast to

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23 Data Summary Forms for Irradiated Foods, FDA Task Group for the Review of Toxicology Data on Irradiated Food, Refs. #303, 305, 306 and 307.

24 Renner, H.W. and Reichelt, D. 1973. "Zur Frage der gesundheitlichen Unbedenklichkeit hoher Konzentrationen von freien Radikalen in bestrahlten Lebensmitteln." ("On the Wholesomeness of High Concentrations of Free Radicals in Irradiated Foods") *Zentralblatt fur Veterinaermedizin*, Reihe B, 20:648-660, July.

25 51 Federal Register 13384, April 18, 1986.

Dr. Delincee, the numerous varied warnings from qualified scientists – including Delincee’s many co-authors – speak clearly to the potential risks and are documented in detail in the PC and CFS comments:

- ...further studies are absolutely necessary in order to elucidate the metabolism of 2-ACBs

- [S]ince our results point to toxic, genotoxic and even tumor-promoting activity of several 2-ACBs, we consider it necessary that further research, including confirmation of our results by other laboratories, be conducted to permit an assessment of the possible risks associated with consumption of irradiated, fat-containing foods.

- [O]ur new data which will be published in peer-reviewed journals, raise some doubts or at least suggest that caution should be exercised before any risk to consumers by exposure to these compounds is denied.... It needs to be shown that despite the presence of potentially cyto- and genotoxic radiation-induced agents, the consumption of irradiated fat-containing food is safe for consumers.<sup>26</sup>

- A thorough investigation of the effect of 2-alkylcyclobutanones at levels consumed by human populations in models (in vitro and in vivo) of various types of cancers is warranted before proposing that irradiated foods do not increase the risk of colon cancer in human population.<sup>27</sup>

- In summary, it is quite clear that additional research is needed in order to fully address the issue and concerns of irradiated food. The toxicity of unique radiolytic products should be tested vigorously, especially in regards to the tumor promoting activities. Animal bioassays should be conducted systematically and comprehensively with whole food and with unique radiolytic products to generate a dose response understanding of the toxicity and safety of irradiated food. It would prove beneficial to establish a dose that does not cause any observable toxic effects in an experimental animal model. The data obtained would better substantiate extrapolation and application in human health risk evaluation.<sup>28</sup>

- It is perhaps too early to start irradiating beef to give to children.<sup>29</sup>

FDA has misrepresented these warnings. While the scientists generally do say that current

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26 Passages are from Burnouf et al. cited above, fn 13, and from an unpublished Comment submitted to the Scientific Committee on Food in July, 2002

27 Rao, C.V. 2003. Do irradiated foods cause or promote colon cancer? *Nutrition and Cancer* 46(2):107-109.

28 Ashley et al., cited above, fn. 7.

29 A statement of the lead scientist on the 2-ACB colon tumor promotion study, Dr. Francis Raul, Research Director of the French National Institute of Health, as reported in: Burros, M. 2003. "Questions on Irradiated Food." *The New York Times*. Oct. 15, p. D-6.

information is not adequate to fully characterize any possible risk from 2-ACB consumption, they plainly state that additional research is needed before the safety of irradiated foods that contain fatty acids can be assured. In rejecting these warnings before ruling on the molluscan shellfish petition, FDA has chosen ignorance over consumer safety.

**Based on the above, FDA's Final Rule misrepresents important published and unpublished warnings from qualified scientists calling for additional research on 2-ACBs. We are requesting a formal evidentiary public hearing to challenge FDA's Final Rule on this issue.**

### **OBJECTION 8. OVERALL FAILURE TO FOLLOW CRITICAL GUIDELINES FOR FOOD ADDITIVES**

We object to the amendment of 21 CFR §179.26 as proposed to allow for the irradiation of molluscan shellfish.

#### Grounds for Hearing Request: Description and Analysis of Facts In Support of Objection

The Federal Food, Drug and Cosmetic Act, at 21 U.S.C. §321(s), explicitly defines use of an irradiation source as a "food additive." Yet the Final Rule **falsely states** that irradiated molluscan shellfish are "processed foods." (p. 48069) Whether the agency did this intentionally or not, this is a very serious error – as food processes generally undergo safety reviews far less stringent than those for food additives. The FDA says as much in the Rule itself, stating that irradiated molluscan shellfish are exempt from safety reviews prescribed by the agency's "Redbook".

At 21 CFR §170.20(a), FDA's regulations indicate that FDA "will be guided by the principles and procedures...stated in current publications of the National Academy of Science-National Research Council." The regulations states that the agency can follow other procedures, but only if based on "available evidence...the procedures used give results as reliable as, or more reliable than, those reasonable expected from the use of the outlined procedures."

The Rule presents no such evidence to support the agency's decision to ignore the current NAS-NRC publication – "Risk Assessment/Safety Evaluation of Food Chemicals." The Rule does not present alternative procedures. If the agency did use alternative procedures, the Rule does not demonstrate whether they are as reliable as the NAS-NRC procedures. The CFR also states the agency "will give due weight to the anticipated levels and patterns of consumption of the additive." The Rule presents no evidence that this review was conducted.

Further, 21 CFR §170.20(b) states that the agency will advise a food additive petitioner whether it believes "the experiments planned will yield data adequate for an evaluation of the safety of the additive." The Rule fails to state whether the Petitioners here provided the agency with any information about such experiments.

As indicated 21 CFR §170.22 requires the FDA to establish a 100-fold safety factor for food additives – “Except where evidence is submitted which justifies use of a different safety factor.” The Final Rule does not present a different safety factor, nor does it document evidence to justify using one if it did. Instead, FDA makes unsupported statements that using a 100-fold safety factor for irradiated foods is “neither feasible nor rational,” that testing each food component separately is “impossible;” and that there are “too many components to test them all.”

Additionally, the agency failed to comply with the testing protocols set forth in the Redbook (a.k.a. *Toxicological Principles for the Safety Assessment of Food Ingredients*). The publication states it “does not operate to bind FDA or the public. You can use an alternative approach if such an approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach contact the FDA staff responsible for implementing this guidance.” However, the Final Rule does not present an alternative approach or indicate whether the Petitioner discussed an alternative approach with the agency. Again, if the agency used an alternative approach, neither the Rule nor the Petition demonstrates that it satisfied the requirements of the applicable statutes and regulations.

The Rule misrepresents the Redbook to dismiss arguments by the CFS and PC that the Petition should be denied because more one third of *in vivo* and *in vitro* mutagenicity studies have reported positive results. The Rule cites – but does not directly quote – the Redbook when it states: “Animal feeding studies are more reliable for determining the true mutagenic potential of a compound that is consumed in food.”

In reality, the Redbook states: “When long-term animal feeding studies are available for the evaluation of carcinogenicity, **genetic toxicity data may assist** in the interpretation of the results of such studies... We consider it **essential** that chemicals be evaluated for their ability to **induce both gene mutations and chromosomal aberrations**... Tests for chemicals that induce gene mutations can...be performed in mammalian cells grown *in vitro*. Tests that detect the induction of chromosomal aberrations are performed using cells exposed to chemicals *in vitro* or *in vivo*. [A]ll available data relating to such endpoints in any test system should be submitted.” (emphasis added)

Evidence previously submitted by the Center for Food Safety and Public Citizen meets this standard precisely. Positive *in vivo* and *in vitro* mutagenicity studies submitted to the agency were conducted in a wide variety of tests systems – including children, human cells (2 studies), monkeys, mice (4 studies), rats (3 studies), rat cells and bacteria.

Moreover, FDA has ignored the recommendations of the Irradiated Food Committee, which prepared the report, “Recommendations for Evaluating the Safety of Irradiated Foods,” for the agency’s Bureau of Foods in July 1980. In its recommendations on testing, the report states:

– that “it is apparent that any toxicological testing must...be predicated on the amounts of new chemical constituents generated by the irradiation process (URPs)”;

- that four mutagenicity tests to assess carcinogenicity represent “the minimum battery;”
- that the mutagenicity tests “must be performed on extracts in which the concentration of radiolytic products is maximized” (emphasis in original); and
- that two 90-day feeding studies “must” be conducted.

While it is true that the Committee’s recommendations are non-mandatory, the Final Rule’s outright failure to adequately explain its noncompliance with the recommendations, in combination with all of its other defects discussed above, severely compromises the Final Rule’s factual support.

**Based on the above, FDA’s Final Rule failed to follow critical guidelines. As the agency clearly failed to abide by safety procedures at the very core of its mandate – most of which are prescribed by regulations and formal guidelines – what regulations and guidelines *did* the agency follow to conclude that irradiated molluscan shellfish are safe for human consumption? We are requesting a formal evidentiary public hearing on this issue.**

## **OBJECTION 9. FAILURE TO ADDRESS WHOLESOMENESS ISSUES**

We object to the amendment of 21 CFR §179.26 as proposed to allow for the irradiation of molluscan shellfish.

### **Grounds for Hearing Request: Description and Analysis of Facts In Support of Objection**

FDA’s Final Rule fails to address recent studies in its possession indicating that irradiation at low dose levels in oysters may cause unpleasant – perhaps unwholesome – byproducts. In FDA’s recently-issued “Quantitative Risk Assessment on the Public Health Impact of Pathogenic *Vibrio Parahaemolyticus* in Raw Oysters”<sup>30</sup> (Risk Analysis), the only study cited for demonstrating irradiation’s effectiveness also finds that irradiation doses at levels of 2 kGy or greater, as proposed here, produced an unpleasant yellow exudate.<sup>31</sup> The researcher never investigated the nature of the substance, but she later describing it as resembling “saliva.”<sup>32</sup> FDA surely is aware of this exudate, yet there is no discussion of it in FDA’s Final Rule and the agency has provided no follow-up analysis of its safety or wholesomeness.

Additionally, FDA failed to address the several references in Dixon’s 1996 Dissertation on the organoleptic damage to irradiated oysters, including “grassy” and “oxidized” odors in fresh irradiated

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30 70 Fed. Reg. 41772-41773 (July 20, 2005)

31 Andrews, L. S. 2002. “Gamma Irradiation Processing to Reduce the Risk of *Vibrio* Infections from Raw Oysters.” (unpublished presentation at the Institute for Food Technologists 2002 Annual Meeting), abstract available at [http://ift.confex.com/ift/2002/techprogram/paper\\_11111.htm](http://ift.confex.com/ift/2002/techprogram/paper_11111.htm)

32 Linda S. Andrews, pers. comm., Aug. 24, 2005.

shellstock oysters (p. 38 therein).

**Based on the above, FDA's Final Rule failed to address key wholesomeness issues. We are requesting a formal evidentiary public hearing on these issues.**

**OBJECTION 10. THE FINAL RULE IS BASED ON INTERNAL MEMORANDA THAT CONTAIN SERIOUS INACCURACIES AND MISREPRESENTATIONS**

We object to the amendment of 21 CFR §179.26 as proposed to allow for the irradiation of molluscan shellfish.

Grounds for Hearing Request: Description and Analysis of Facts In Support of Objection

(A) FDA significantly misrepresents published research on the tumor-promoting qualities of 2-ACBs. The FDA Memo associated with Ref. 52 in the Rule (Twaroski to Highbarger, 7/14/05) states:

- [T]he data showed no significant difference in tumor incidence between treatment groups.” In reality, Raul et al (2002) detected 14 tumors in the 2-tDCB group and 13 in the tDeCB group – as compared to 4 in the AOM group. Further, multiple medium and large tumors were observed *only* in 2-ACB-treated animals.
- “2-tDeCB...is the only ACB tested that possibly shows any increase in the promotion of AOM-initiated colon tumors.” In reality, Raul et al detected an increase for both 2-tDCB- and 2-tDeCB-treated animals.<sup>33</sup>
- “ACBs are products that appear to be derived in very small amounts from irradiation of fatty acids.” In reality, it is a certainty that 2-ACBs are formed when fats are irradiated – to the point that 2-ACBs are recognized internationally as a marker for determining whether certain foods have been irradiated.<sup>34</sup> Further, there has been no determination of what “very small amounts” of 2-ACBs are.

These mischaracterizations severely bias the agency's analysis of 2-ACBs.

(B) The FDA cites no evidence – published or otherwise – to dismiss the Comet assay as a valid technique to test genetic toxicity (p. 48065). In reality, the technique has broad support within the scientific community:

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33 Raul, F. et al. “Food-borne Radiolytic Compounds (2-Alkylcyclobutanes) May Promote Experimental Colon Carcinogenesis.” *Nutrition and Cancer*, 44(2):188-191, 2002.

34 “Detection of Irradiated Food Containing Fat – Gas Chromatographic Analysis of 2-Alkylcyclobutanones.” European Committee for Standardization, EN 1785: 1996.

– At the Fall 1998 meeting of the Genetic Toxicology Association – conducted with the Association of Government Toxicologists – officials from five agencies, **including the FDA and EPA** wrote: “Most [attendees] said that Comet data generated and submitted to regulatory agencies would be accepted and used along with data from assays in the standard test battery, but would not replace standard tests. Much of the success of this assay is due to its simplicity, versatility, reliability, and speed... [I]t is becoming a well used tool for pre-screening of potential DNA damaging activity.”<sup>35</sup>

– “The *in vivo* Comet assay... is being increasingly used in genotoxicity testing of substances such as industrial chemicals, biocides, agrochemicals, **food additives** and pharmaceuticals... A positive result in an appropriately performed *in vivo* comet assay indicates genotoxicity of the test compound in the tissue tested and **gains particular significance when a mutagenic potential of the test compound has already been demonstrated in vitro**.... Such findings will have practical consequences in the risk assessment processes and further development of substances.”<sup>36</sup> (emphasis added) (Note: Delincée followed this protocol precisely. Prior to his *in vivo* Comet assay test, in which he detected “slight but significant DNA damage,”<sup>37</sup> he conducted an *in vitro* test, in which he stated that the “results clearly demonstrate a genotoxic effect of 2-DCB.”<sup>38</sup>)

– “[T]he aggregated data from the publications included in this thesis, and other publications encompassing the Comet assay, indicate that the Comet assay is a reliable method for detection of DNA damage in tissues of experimental animals.”<sup>39</sup>

– “The comet assay is a relatively simple, but sensitive and well-validated tool for measuring strand breaks in DNA in single cells.”<sup>40</sup>

– “To date, the Comet assay has been used for a variety of applications, including toxicological studies, exercise-induced damage, and measuring cell growth and DNA repair mechanisms. More recently, the Comet assay has been used to study the effects

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35 Benz, R.D. and Dearfield, K.L. 1998. “Can the New Genetic Toxicology Tests be Used for Regulatory Safety Decisions?” Genetic Toxicology Association, Fall 1998 Meeting Report, Oct. 29. <[www.ems-us.org/gta/fallr98.html](http://www.ems-us.org/gta/fallr98.html)>

36 Brendler-Schwab S. et al. 2005. “The *in vivo* Comet Assay: Use and Status in Genotoxicity Testing.” *Mutagenesis*, 20(4):245-54.

37 Delincée, H. et al. 1998. “Genotoxicity of 2-dodecylcyclobutanone.” Food Irradiation: Fifth German Conference, Karlsruhe, Nov. 11-13.

38 Delincée, H. and Pool-Zobel, B. 1998. “Genotoxic properties of 2-dodecylcyclobutanone, a compound formed on irradiation of food containing fat.” *Radiation Physics and Chemistry*, 52: 39-42.

39 Moller, P. 2005. “Genotoxicity of Environmental Agents Assessed by the Alkaline Comet Assay.” *Basic Clin Pharmacol Toxicol*. 96 Suppl 1:1-42.

40 Wong, Vincy W.C. et al. 2005. “The COMET Assay: A Biomonitoring Tool for Nutraceutical Research.” *Current Topics in Nutraceutical Research*, 3(1):1-15.

of diet on DNA damage.”<sup>41</sup>

(C) FDA produced a Memo related to the current Rule (Chen to Highbarger, 12/21/01) – though not cited in the Rule – that actually concerns the “ready-to-eat foods” Petition (FAP 9M4697). Beyond the fact that it is irrelevant to the mollusk Rule, the Memo several inaccuracies and misrepresentations, including:

– “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.” Numerous published articles show – and the FDA now admits – that 2-ACBs are fundamentally unique from any naturally occurring food component;

– “we consider...genotoxicity data to be of limited value because long-term animal test results are available.” The FDA Redbook, however, states that genotoxicity tests can contribute significantly to safety assessments (see Objection 8).

FDA produced another Memo (Morehouse to Highbarger, 6/15/05) that concerns the “ready-to-eat” Petition. This Memo is also irrelevant to the mollusk Rule.

Further, the FDA Memo associated with Ref. 8 in the Rule (Chen to Highbarger, 4/7/03) actually refers to the “certain meat food products” Petition (FAP 9M4695). This Memo also is irrelevant to the mollusk Rule.

(D) The FDA Memo associated with Ref. 4 (Folmer/Jensen to Highbarger, 8/2/02) contains a misconception the agency has had for many years. The Memo states that other food processing techniques can also reduce the vitamin content of foods. What the FDA neglects is that irradiation does not necessarily **replace** other processes, but that it can be used **in addition** to other techniques – further compounding nutrient loss already caused by processes such as freezing, canning and drying.

There is evidence indicating that irradiation and cooking have a synergistic effect. The USDA’s Agriculture Research Service found a “highly significant interaction” between irradiation and cooking, when studying the thiamin content in bacon. “The two processes...produced degradation, but when the product was cooked after it had been irradiated the overall effect was greater than the sum of the processes applied individually.”<sup>42</sup>

On what basis was it determined that a 3 percent contribution of thiamine, niacin and B6 from fish and shellfish represents an insignificant contribution to the nutritional needs of Americans? (p. 48062; Ref. 20) What is the threshold for significance? According to Agenda Item 4 of the ICGFI document (Ref. 20, p. 59-60), two studies showed the thiamine level in cod was 47 percent and 86

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41 Heaton, Paul R. et al. 2002. “Application of Single-Cell Gel Electrophoresis (Comet) Assay for Assessing Levels of DNA Damage in Canine and Feline Leukocytes.” *J. Nutr.*, 132:1598S-1603S, June.

42 *Food Chemical News*, Nov. 10, 1986.

percent lower than the controls when irradiated at 6 kGy (just slightly higher than the dose approved in the Rule).

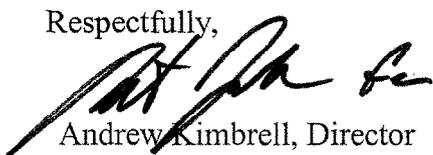
**Official FDA memoranda are riddled with serious flaws that call into question the adequacy of the agency's internal processes to address the regulatory requirements for determining food additive safety as applied to irradiation in this case. We are requesting a formal evidentiary public hearing on these issues.**

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Taken together, the flaws in the FDA's Final Rule raise vital issues of fact and greatly undermine the rationale of the new regulation. Due to these material flaws potential risks to public health have not been sufficiently examined. We request that a formal evidentiary public hearing on each of the above ten objections be held at the earliest possible date and the Final Rule be stayed until the hearing is held and a new decision issued.

For additional information please contact: Peter T. Jenkins, CFS Attorney, at the contact information below or email: [peterjenkins@icta.org](mailto:peterjenkins@icta.org) .

Respectfully,



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Enclosures (7 tabs)

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