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Division of Dockets Management
HFA-305
U.S. Food and Drug Administration
5630 Fishers Lane
Rm. 1061
Rockville, MD 20852

Re: Docket No. 1999F-4372

To whom it may concern:

Under the provisions of 21 CFR §12.24, I object to amending 21 CFR §179.26 to allow for the irradiation of molluscan shellfish, and request a stay of action and a formal evidentiary public hearing to revoke the Final Rule – "Irradiation in the Production, Processing, and Handling of Food." (70 FR 48057, 8/16/2005).

I have identified and seek to present at a public hearing genuine and substantial issues containing new evidence that raises material issues of fact and that questions in a material way the rationale of the Rule.

As will be document herein, the FDA has ignored every key safety measure required by federal law, demonstrating an utter abdication of the agency's mandate to protect the American public from unsafe and unwholesome foods.

Many of my concerns have been outlined an article published in the *International Journal of Health Services*, which was endorsed by 45 medical and public health professionals.[1]

OBJECTION 1

It is inconceivable that neither the Rule nor the Petition consider the published toxicological evidence detailing harmful effects in animal feeding studies from irradiated molluscan shellfish. The Rule itself states: "The petitioner did not submit copies of toxicological data specific to irradiated shellfish." (p. 48068)

This omission amounts to misrepresentation of the science on the topic, as at least two such studies exist:

(1) A 1976 published study 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, including: the reduction of the percentage of chicks in the F_2 generation that survived 30 days was "aggravated" by irradiation; "a significant decrease in fertility of eggs" was observed in the F_2 generation; and embryonic viability and hatchability of eggs in the F_2 generation were reduced, which was "intensified" by the addition of 8 kGy-irradiated clams.[2]

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."[3]

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, 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."[4] Though the researchers did not speculate, low blood urea nitrogen levels are usually a symptom of liver damage.

This is a stark example of the arbitrary and capricious 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."[5] Internal FDA documents on the Task Group's work and findings, however, are silent on why the agency ignored this positive study but has embraced negative studies that were also classified "Accept with reservation."

FDA either intentionally or ignorantly passes these studies and seeks to demonstrate safety by analogy from studies of <u>other</u> food types. The agency 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 – which the agency has also done without scientific rationale. **This is a monumental double-standard.**

We are requesting a formal evidentiary public hearing on this issue.

OBJECTION 2

The Rule dismisses – without supporting evidence – the need to study the toxicity of new chemicals formed in irradiated foods by stating that some natural food components already have toxic properties. This ignores the fact that irradiation can dramatically increase the concentration of many potentially toxic chemicals. This has been shown in numerous studies dating to the 1950s, and as recently as this year.

These chemicals include benzene, an unequivocal human carcinogen and teratogen, and toluene, a suspected human teratogen. D.U. Ahn of Iowa State University, who has published numerous journal articles about the chemical byproducts of irradiation, wrote: [B]enzene and toluene…could be formed from amino acids upon irradiation… Benzene has deleterious effects on human health."[6]

Additionally, the FDA makes this blanket statement, which the agency fails to explain further: "FDA and food scientists worldwide have long agreed that the evaluation of the safety of irradiated foods requires consideration of the whole food, not the testing of each component." Ironically, the agency acknowledges that "identification of major radiolysis products will aid in the interpretation of data."

This admission begs the obvious question: What *are* "major radiolysis products," and how will identifying them help analyze the safety of irradiated foods? The Rule leaves these questions – upon which the health of people who consumer irradiated foods may hinge – unanswered.

We are requesting a formal evidentiary public hearing on this issue.

OBJECTION 3

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, 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*."[7] (emphasis added)

Contrary to the agency's assertion, nowhere does the Raltech study state that the health effects could not 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."[8] (emphasis added)

We are requesting a formal evidentiary public hearing on this issue.

OBJECTION 4

The Rule and the Petition are silent on whether irradiating mollusk shells could form chemical byproducts; whether any byproducts could migrate into the meat; and whether any byproducts could have toxic properties. 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 *Vibro, Listeria, Salmonella* and other harmful bacteria.

The Petition cites a 1996 Ph.D. dissertation by a University of Florida student. The student wrote that shell weights and shell-to-meat ratios differ widely for oysters from Florida, Louisiana and Texas. He underlined the importance of dealing with this problem: "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."[9] The Rule and Petition offer no solution to a problem that is almost certain to arise if and when mollusks are irradiated commercially.

We are requesting a formal evidentiary public hearing on this issue.

OBJECTION 5

21 CFR §170.22 states: "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."

The Rule states that molluscan shellfish flesh is distinct from other meat and fish flesh, yet

without adequately characterizing that distinctness, the Rule goes on to repeatedly rely on toxicity studies for other types of meat.

For example, the Rule relies on the Raltech study (which, ironically, revealed adverse health effects; see Objection 3, above) to discount concerns about 2-alkylcyclobutanones (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.

When irradiated, stearic acid 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-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."[10] (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 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 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 conjecture akin to "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.[11] These assertions are facile at best, negligent at worst.

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.

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."[12]
>
> – "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."[13]
>
> – "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."[14]

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 Rule is utterly inadequate to protect public health.

Thus, the FDA's rejection of the 100-fold safety factor is arbitrary and capricious.

We are requesting a formal evidentiary public hearing on this issue.

OBJECTION 6

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 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 mollusks are exempt from safety reviews prescribed by the agency's "Redbook" because they are "processed foods." **FDA cannot use its rulemaking authority to re-write federal law.**

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 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 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.

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 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 Rule's factual support.

Based on the above, FDA's 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.

FDA's complete failure to abide by federal law, federal regulations, and the agency's own internal policies places the public at serious risk. This failure necessitates the prompt convening of formal evidentiary public hearing and the immediate staying of the Final Rule until the hearing is held.

Respectfully,

<electronically submitted>

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[1] Epstein, Samuel S. and Hauter, Wenonah. "Preventing Pathogenic Food Poisoning: Sanitation Not Irradiation." *International Journal of Health Services*, 31(1):187-192, 2001.

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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).

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[7] 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. 44.

[8] "Gamma Irradiation Safety Questions Raised by USDA Chicken Studies," *Food Chemical News*, April 16, 1984.

[9] Dixon, Dustin 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.

[10] Burnouf, D. et al. (Eds.) "Etude toxicologique transfrontalière destinée à évaleur 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.

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[12] 62 Federal Register 64102, Dec. 3, 1997.

[13] 52 Federal Register 5450, Feb. 23, 1987.

[14] 51 Federal Register 13376, April 18, 1986.