

Coughlin & Associates

Consultants in Food/Chemical/Environmental Toxicology and Safety
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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. 2004N-0205: Furan in Food, Thermal Treatment; Request for Data and Information

Dear Sirs:

I am responding to your May 10, 2004 *Federal Register* notice (69FR 25911-25913) on “Furan in Food, Thermal Treatment; Request for Data and Information.” I understand that your Food Advisory Committee (FAC) and its Contaminants and Natural Toxicants Subcommittee will address this issue at its meeting on the afternoon of June 8, 2004 in Bethesda, MD. I am not sure if I will be able to attend that meeting to present oral testimony, but I would appreciate if my comments could be placed before FAC and Subcommittee members for their preliminary evaluation during the meeting.

To assist the Committee and Subcommittee members in properly evaluating the current scientific information database on furan in thermally treated foods and beverages, I am submitting these brief comments on some significant studies demonstrating beneficial antioxidant properties of furan (and related heat-produced compounds) that may not have yet come to FDA’s attention in your literature review. My comments do not fall under any of the questions or data needs posed in the notice; they do, however, address what I feel is a very important aspect of heat-induced reactions in foods, one that does not receive enough evaluation or consideration when assessing the potential risks of compounds produced by heating.

My comments actually hold equally well for FDA’s consideration of the corresponding Action Plan and risk assessment for acrylamide, since furan and acrylamide are just two of the thousands of compounds produced in foods and beverages by the action of heat. The scientific

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literature on heat-induced food components is certainly replete with information on the potential carcinogenic/mutagenic/other toxic effects of such compounds, but a growing literature also demonstrates that heating of foods produces many compounds that may have health-protective effects in humans as well. In fact, in the case of furan, it has been demonstrated that the compound is a potent food antioxidant as well as a rodent carcinogen. In its antioxidant role, it may be able to protect foods from producing damaging oxidants during heating, processing and storage and it may also add a beneficial antioxidant to the human diet.

I. Historical Background.

I became involved in the study of heat-induced mutagens and carcinogens in foods in the mid-1970's while pursuing my Ph.D. dissertation research in Agricultural and Environmental Chemistry and my postdoctoral research in Environmental Toxicology at the University of California at Davis. My focus was the chemical production and health evaluation of potentially carcinogenic N-nitroso compounds formed during the Maillard browning reaction (among sugars and amino acids/proteins) in foods in the presence of sodium nitrite. A colleague in the laboratory at that time was Dr. Takayuki Shibamoto, then doing his postdoctoral studies on the Maillard reaction as well. He has since spent his career as a professor in the Department of Environmental Toxicology at UC Davis and has devoted his career to the study of this reaction, with over 230 published papers on its chemistry and toxicology. Shibamoto and I, along with one or two other scientists, were the first researchers to characterize and report potential carcinogens formed in the Maillard reaction in 1978-1979.

In May and October, 2003 Dr. Shibamoto and I submitted both written and oral testimony to the State of California's Office of Environmental Health Hazard Assessment (OEHHA, within the California Environmental Protection Agency) during the development of the *Work Plan on Acrylamide* (OEHHA, 2003a, b). We jointly addressed the chemistry and beneficial health effects of compounds produced during the Maillard browning reaction. Dr. Shibamoto presented his body of research on these beneficial compounds, particularly his more recent studies on antioxidants produced during the heating of foods. Although many researchers have focused on the polyphenolic antioxidants typically found in many foods, Shibamoto has pioneered the discovery of various heat-induced heterocyclic compounds as antioxidants, including furan itself (Eiserich and Shibamoto, 1994; Eiserich et al., 1995).

The antioxidative activity of Maillard Reaction Products (MRPs) was first observed in the early 1950's (Franzke and Ivanisky, 1954), although the exact chemical nature of the antioxidants formed has only recently been investigated carefully. However, since the preliminary antioxidant studies by Lingnert and Eriksson (1980, 1981), much research has been done on the antioxidative properties of MRPs (reviewed in Manzocco et al., 2001).

II. Furan as an Antioxidant.

As FDA has learned from its review of the literature, furan does not require the presence of a source of nitrogen to be formed, i.e., the furan molecule does not contain a nitrogen atom and is therefore not a classic initial product of the sugar-amino acid Maillard reaction. It is formed

during the heating of carbohydrates (and perhaps lipids) in the absence of amino acids and proteins, but in most foods this happens concurrently along with the Maillard reaction. It is also possible that furan could form from fragments of classic MRPs being further degraded by heat. As noted above, furan itself has been shown by Shibamoto's group to be an antioxidant in two separate assay systems (Eiserich and Shibamoto, 1994).

More recent work by Shibamoto's group has focused on assessing the antioxidative activities of furan and other heterocyclic compounds in brewed coffees (Fuster et al., 2000; Yanagimoto et al., 2002, 2004), noting that furan and its derivatives are sugar degradation products that are the most abundant volatile compounds in roasted coffee. They first examined many heterocyclic compounds found in coffee and showed that furan (at a concentration of 500 $\mu\text{g/mL}$) exhibited antioxidative activity comparable to that of the synthetic antioxidant butylated hydroxytoluene (BHT, at a concentration of 50 $\mu\text{g/mL}$) (Fuster et al., 2000). In Yanagimoto et al. (2002), Shibamoto's group showed that all furans exhibited dose-dependent antioxidative activity, and that unsubstituted furan showed the greatest antioxidant activity among all the furans, inhibiting hexanal oxidation by 80% at a concentration of 500 $\mu\text{g/mL}$ over a 40-day storage period.

Among the heterocyclic compounds found in coffee volatiles, Shibamoto reported in the two papers above that both pyrroles and furans showed the strongest antioxidative activity, which was almost equal to that of α -tocopherol. Shibamoto and his colleagues noted that it is nearly impossible to test the possible antioxidant synergism among the >1000 compounds identified in brewed coffee, but that the combined antioxidant activity may explain the known improvement in stability following heating. Most recently, in a paper published this year on the antioxidative activities of various organic and aqueous fractions extracted from brewed coffee, his group found some furan derivatives among the active antioxidant fractions (Yanagimoto et al., 2004). The paper concluded with the following statements:

“The results from the present study indicate that brewed coffee contains many antioxidants including some heterocyclic compounds. Although the activity of each component is not as strong as the known antioxidant BHT, a total activity of numerous compounds in brewed coffee might be comparable to those of known antioxidants. Therefore, consumption of antioxidant-rich brewed coffee may prevent diseases caused by oxidative damage.”

III. Other Health-Protective Compounds Formed in Heated Foods along with Furan.

One of the challenges in considering the public health implications of the presence of furan in various heated/cooked foods and beverages is that the same chemical processes that create furan also produce the chemicals that make food palatable and desirable (i.e., the aroma, color, texture, and flavor of food) as sources of nutritive value. Additionally, many beneficial substances are created by these heat-driven reactions, including antioxidants, anti-carcinogens, anti-mutagens, and other health-protective compounds (reviewed by Lee and Shibamoto, 2002).

These authors and other researchers have concluded that such compounds, including the oxygen-heterocyclic compound furan and its derivatives, may help to prevent *in vivo* oxidative damage such as lipid peroxidation, which is associated with many diseases including cancer, arteriosclerosis, diabetes and immune deficiency as well as pathological conditions such as aging. Although living organisms are known to be protected from active oxidants by enzymatic systems, natural antioxidants (a-tocopherol, carotenoids and ascorbic acid in fruits and vegetables) are also known to protect cells from oxidation and humans from various diseases. In addition, it is clear that humans consume some quantity of additional antioxidants, including furan, formed during the heat-treatment of foods. Therefore, this entire compliment of mixed antioxidants (the natural vitamins and heat-induced compounds) may play an important role in protecting humans from oxidative damage associated with the diseases described above.

IV. Conclusion.

I urge the Committee and Subcommittee to consider the beneficial, health-protective effects of the compounds described above, including furan's now well-known antioxidative effects, in evaluating the safety of this compound. I would be happy to provide further information regarding these areas of study if the Committee/Subcommittee believes it would be helpful.

Thank you for this opportunity to submit these comments on furan for your review and consideration. Should the Committee or Subcommittee have any questions regarding the scientific issues addressed, please do not hesitate to contact me.

Sincerely,

James R. Coughlin, Ph.D.

References

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