

For the portion of the meeting of the Food Advisory Committee and its Dietary Supplements Subcommittee, oral presentations from the public will be scheduled between approximately 3:30 p.m. and 5 p.m. on June 7, 2004.

For the portion of the meeting of the Food Advisory Committee and its Contaminants and Natural Toxicants subcommittee, oral presentations from the public will be scheduled between approximately 4 p.m. and 5 p.m. on June 8, 2004.

Time allotted for each presentation may be limited. Those desiring to make formal oral presentations should notify the contact person before May 24, 2004, and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, the specific portion of the meeting at which they wish to present, and an indication of the approximate time requested to make their presentation.

Persons attending FDA's advisory committee meetings are advised that the agency is not responsible for providing access to electrical outlets.

FDA welcomes the attendance of the public at its advisory committee meetings and will make every effort to accommodate persons with physical disabilities or special needs. If you require special accommodations due to a disability, please contact Linda Reed at least 7 days in advance of the meeting.

Notice of this meeting is given under the Federal Advisory Committee Act (5 U.S.C. app. 2).

Dated: April 29, 2004.

Jeffrey Shuren,

Assistant Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2004N-0205]

Furan in Food, Thermal Treatment; Request for Data and Information

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; request for data and information.

SUMMARY: The Food and Drug Administration (FDA) is requesting the submission of data and information on furan, a heat treatment related byproduct that has been detected in

certain thermally treated foods. FDA is seeking data on the occurrence of furan in food, on sources of exposure to furan other than food, on mechanisms of formation of furan in food, and on the toxicology of furan, including mechanisms of toxicity. FDA will evaluate the available data and will develop an action plan that will outline FDA's goals and planned activities on the issue of furan in food. Elsewhere in this issue of the **Federal Register**, FDA is announcing a meeting of the agency's Food Advisory Committee (FAC) on June 7 to 8, 2004.

DATES: Submit data, information, and general comments by July 9, 2004. Data and information received by June 1, 2004, may be shared with the FAC before or at that meeting.

ADDRESSES: Submit written comments, data, and information to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments, data, and information to <http://www.fda.gov/dockets/ecomments>.

FOR FURTHER INFORMATION CONTACT:

Lauren Posnick, Center for Food Safety and Applied Nutrition (HFS-306), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20741, 301-436-1639.

SUPPLEMENTARY INFORMATION:

I. Background

A. General

During investigations relating to review of a petition for certain uses of irradiation in food, FDA scientists identified the substance furan in a number of foods that undergo heat treatment, such as canned and jarred foods. Furan is a colorless, volatile liquid used in some segments of the manufacturing industry. The presence of furan is a potential concern because, based on animal tests, furan is listed in the Department of Health and Human Services Report on Carcinogens (Ref. 20) and is considered possibly carcinogenic to humans by the International Agency for Research on Cancer (IARC).

FDA has developed a gas chromatography/mass spectrometry (GC/MS) method that is capable of detecting and quantitating low levels of furan in food (Ref. 1). Although furan had previously been reported in foods, FDA has recently applied this method to a wider variety of food samples than previously reported in the literature. FDA has analyzed approximately 120 food samples for furan (including replicates of the same brand/product) and found furan levels ranging from

nondetectable (within the limits of detection of the method) to approximately 100 parts per billion (ppb). Jarred baby foods and canned infant formulas are among the foods in which FDA has found measurable furan. FDA has recently posted these furan data on the agency's Web site at <http://www.cfsan.fda.gov/~lrd/pestadd.html#furan>, along with a description of its GC/MS method to provide other researchers the opportunity to review and use the method.

FDA is requesting data on the occurrence of furan in food, on sources of exposure to furan other than food, on mechanisms of formation of furan in food, and on the toxicology of furan, including mechanisms of toxicity. This notice summarizes information currently available to FDA about the occurrence of furan in food, consumer exposure to furan, the mechanisms of furan formation in food, and the toxicology of furan, including the mechanism of toxicity. This notice also identifies the areas in which additional data would be helpful to FDA in learning more about furan and evaluating the risk, if any, posed by the presence of furan in food. These areas are outlined in more detail in section II of this document.

Finally, FDA will evaluate the available data and will develop an action plan that will outline FDA's goals and planned activities on the issue of furan in food. Possible elements of the action plan include an expanded survey of furan levels in food; studies to address mechanisms of furan formation in food; possible strategies to reduce furan levels (if a risk assessment indicates this is necessary); and toxicology studies to address such issues as mechanisms of furan toxicity and dose-response. Elsewhere in this issue of the **Federal Register**, FDA is announcing plans to seek, from its Food Advisory Committee at a meeting scheduled for June 7 to 8, 2004, advice about what data are needed to assess fully the risk to consumers, if any, posed by furan.

B. Occurrence of Furan in Foods

Furan is the parent compound of a class of derivative compounds collectively known as "furans." These compounds are found in a wide assortment of foods and may contribute to food's sensory characteristics (Ref. 2). The nonderivatized furan (i.e., furan) has been identified previously in a small number of heat-treated foods, including coffee, canned meat, baked bread, cooked chicken, sodium caseinate, filberts (hazelnuts), soy

protein isolate, hydrolyzed soy protein, rapeseed protein, fish protein concentrate, and caramel (Refs. 2, 3, 4, and 5). FDA has identified very little published quantitative information on furan levels in food.

C. Mechanisms of Formation

Maga reviewed the formation of furan and furan derivatives (furans) in food (Ref. 2). The primary source of furans in food is thermal degradation and rearrangement of organic compounds, particularly carbohydrates (Ref. 2). A variety of experimental systems, including heating of sugars (e.g., glucose, lactose, fructose, xylose, rhamnose), heating sugars in the presence of amino acids or protein (e.g., alanine, cysteine, casein), and thermal degradation of vitamins (ascorbic acid, dehydroascorbic acid, thiamin), have been used to produce, isolate, and identify furans in food. In the studies reviewed by Maga, the nonderivatized furan was found in the following systems: Thermal degradation of glucose; thermal degradation of glyceraldehydes, D-Erythrose, pentosans, hexoses, and polysaccharide; and a lactose-casein browning system (Ref. 2). FDA has not identified any specific mechanism or mechanisms that produce furan in the samples the agency has tested to date.

D. Toxicology

1. Carcinogenic and cytotoxic effects.

Furan is classified by IARC as possibly carcinogenic to humans (Ref. 6). Furan is both carcinogenic and cytotoxic in rodents. In a bioassay conducted by the National Toxicology Program (NTP), furan administered by gavage to Fisher 344 rats (2, 4, or 8 milligram per kilogram per body weight (mg/kg/bw)) and B6C3F1 mice (8 or 15 mg/kg per kg/bw) 5 days a week for up to 2 years produced hepatic cholangiocarcinoma, hepatocellular adenoma and carcinoma, and mononuclear cell leukemia in rats, and hepatocellular adenoma and carcinoma and benign pheochromocytoma of the adrenal gland in mice (Ref. 7). In both the 2-year NTP bioassay and a 13-week NTP study, furan also caused cell proliferation, inflammation, biliary tract fibrosis, hyperplasia, hepatocellular cytomegaly, degeneration, necrosis, and vacuolization in rats and mice (Ref. 7). A preliminary report from a second 2-year bioassay in female mice found increased incidence and multiplicity of hepatic tumors and decreased tumor latency in mice dosed with 4 or 8 mg/kg bw furan, but not in mice dosed with 0.5, 1.0, or 2.0 mg/kg bw furan (Ref. 8). Furan has also been shown to induce

apoptosis in mice at hepatocarcinogenic doses (8 and 15 mg/kg bw), perhaps in response to an increased number of DNA (deoxyribonucleic acid)-altered cells (Ref. 9). In addition, cytotoxic doses of furan were shown in vivo and in vitro to cause irreversible uncoupling of hepatic mitochondrial oxidative phosphorylation, leading to adenosine triphosphate (ATP) depletion (Ref. 10).

2. *Metabolism.* Experiments in rats with [¹⁴C] furan show that furan is rapidly absorbed and extensively metabolized and eliminated after ingestion; the highest concentration of the absorbed dose was retained in the liver (Ref. 11). A number of urinary metabolites of furan have been observed but not identified (Ref. 11). *cis*-2-butene-1,4-dial has been identified as a key reactive and cytotoxic metabolite of furan (Ref. 12), which has been found to bind to protein (Ref. 11) and nucleosides (Ref. 13). Both in vitro and in vivo studies show that metabolic activation by cytochrome P450 enzymes is involved in furan-induced toxicity. Glutathione inhibited the covalent binding of reactive furan metabolites to microsomal protein in vitro (Ref. 14), presumably by forming less reactive, water-soluble conjugates with the activated furans.

3. Mutagenicity and genotoxicity.

Furan tested negative for mutagenicity in the Ames Salmonella test (with and without S9 activation) in the NTP study (Ref. 7), but was weakly positive in one test strain (TA100) in another study (Ref. 15). The furan metabolite *cis*-2-butene-1,4-dial was mutagenic at nontoxic levels in Ames assay strain TA104, but was not mutagenic in strains TA97, TA98, TA100, and TA102 (Ref. 16). Furan also tested negative for mutagenicity in germ cells of male *Drosophila melanogaster* (Ref. 17). Furan is positive in mammalian systems in vitro, such as in mouse lymphoma cells, and caused sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells, with and without S9 activation (Ref. 7). Furan also induced DNA double-strand breaks in isolated rat hepatocytes at doses of 100 micromolar (Ref. 18). In in vivo mammalian systems, furan induced chromosomal aberrations, but not sister chromatid exchanges, in mice bone marrow cells and in hepatocytes in mice and rats (Ref. 19). It did not cause unscheduled DNA synthesis in mouse or rat hepatocytes (Ref. 19).

4. *Mechanism of action of carcinogenesis.* As noted previously, *cis*-2-butene-1,4-dial is believed to be a key metabolite involved in furan toxicity and carcinogenesis. *cis*-2-butene-1,4-dial has been shown to form

both protein and nucleoside adducts (Refs. 11 and 13); it acts as a mutagen in the Ames assay, and its acute toxic and genotoxic effects are mitigated by glutathione in vitro (Ref. 16). One hypothesis for furan carcinogenicity is that *cis*-2-butene-1,4-dial stimulates cell proliferation, increasing the likelihood of tumor induction (Ref. 20). Another hypothesis is that *cis*-2-butene-1,4-dial activity uncouples mitochondrial oxidative phosphorylation, thereby depleting ATP supplies, and leading to activation of DNA double-strand endonucleases, with the DNA double-strand breaks in surviving cells ultimately resulting in mutagenesis (Ref. 21).

5. Additional toxicology information.

No human studies are available on the effects of furan. No data were found on the reproductive and developmental toxicology of furan.

II. Request for Data and Information

FDA has identified a number of areas in which additional data and information would be helpful to the agency in evaluating the risk, if any, posed by the presence of furan in food. These areas are outlined in more detail below. Accordingly, FDA invites all interested persons to submit data and information on the topics identified.

Interested persons should submit comments on the information in this notice and responsive data and information to the Division of Dockets Management (see **ADDRESSES**) by July 9, 2004. Three copies of all comments, data, and information are to be submitted. Individuals submitting written information or anyone submitting electronic comments may submit a single copy. Submissions should be identified with the docket number found in brackets in the heading of this document. Received submissions may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

FDA requests data and other information that responds to the following questions:

A. *Concerning the occurrence of furan in foods and consumer exposure to furan, FDA has identified the following data needs:*

1. Data and information on the particular foods in which furan occurs.
2. Data on levels of furan in these foods.
3. Data on the formation and occurrence of furan in home-prepared foods, as opposed to manufactured foods.
4. Data on environmental sources of furan to which a typical consumer is likely to be exposed.

B. Concerning the mechanisms of the formation of furan in food, FDA has identified the following data needs:

1. Data and information on possible mechanisms of furan formation.
2. Data and information on variables that enhance or mitigate furan formation in foods.
3. Data on the stability or dissipation of furan in foods.
4. Data about the effect of post-production practices, such as consumer heating of canned foods, on furan levels in foods.

C. Concerning the toxicology of furan, FDA has identified the following data needs:

1. Data and information on mechanism(s) of furan toxicity, mutagenicity, and carcinogenesis.
2. Data and information on the reproductive and developmental toxicology of furan.
3. Data and information on the metabolism of furan in vivo, including characterization of any reactive furan metabolites in addition to *cis*-2-butene-1,4-dial, and data on the role of such metabolites in producing furan's adverse effects, including carcinogenesis.
4. Data and information on the diversity of furan pharmacokinetics in humans or the alteration of furan metabolism as a result of dietary, medical, or environmental interactions.
5. Data and information on whether sub-cytotoxic furan doses produce any adverse effect, such as a change in enzyme activities or ATP levels.
6. In the NTP furan study, Cytotoxic and carcinogenic effects were seen at all doses, and a no adverse effect level (NOAEL) was not identified. A preliminary report by Goldsworthy et al. showed a NOAEL dose of 2.0 mg/kg bw in female mice, but data from this study are not yet available (Ref. 12). FDA would like to acquire data on the effects of furan doses lower than those used in the NTP study in order to accomplish the following objectives: (a) Establish a dose-response curve for the various toxicological endpoints, (b) Determine whether furan toxicity, including carcinogenesis, is a threshold-dependent event; and (c) determine whether the carcinogenic activity of furan is secondary to its hepatotoxic effects.
7. Additional data on the mutagenicity of furan in the TA100 strain in the Ames test, given the two existing contradictory reports.
8. Additional data and information on the behavior of furan in other in vivo assays for mutagenicity or toxicity.

III. References

The following references are on display in the Division of Dockets Management (see **ADDRESSES**) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. FDA, "Determination of Furan in Foods," 2004, <http://www.cfsan.fda.gov/~lrd/pestadd.html#furan>.
2. Maga, J. A., *CRC Critical Reviews in Food Science and Nutrition*, "Furans in foods," pp. 355–400, 1979.
3. NRC (National Research Council), *Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants*, vol. 4., appendix B14, "Furan," pp. 307–329, National Academy Press, Washington, DC, 1994.
4. Persson, T. and E. von Sydow, "Aroma of canned beef: Gas chromatographic and mass spectrometric analysis of the volatiles," *Journal of Food Science*, 38: 377–385, 1973.
5. Stoffelsma, J., G. Sipma, D. K. Kettenes, and J. Pypker, "Volatile components of roasted coffee," *Journal of Agricultural Food Chemistry*, 16(6): 1000–1004, 1968.
6. IARC, *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Volume 63: "Dry Cleaning, Some Chlorinated Solvents and Other Industrial Chemicals," pp. 394–407, Lyon, France, 1995.
7. NTP, "Toxicology and carcinogenesis studies of furan (CAS No. 110–00–9) in F344/N rats and B6C3F₁ mice (gavage studies)," NTP Technical Report No. 402., U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC, 1993.
8. Goldsworthy, T. L., R. Goodwin, R. M. Burnett, P. King, H. El-Sourady, G. Moser, J. Foley, and R. R. Maronpot, "Dose Response Relationships Between Furan Induced Cytotoxicity and Liver Cancer," Society of Toxicologic Pathology Annual Conference, Orlando, FL, 2001.
9. Fransson-Steen, R., T. L. Goldsworthy, G. L. Kedderis, and R. R. Maronpot, "Furan-induced liver cell proliferation and apoptosis in female B6C3F₁ mice," *Toxicology*, 118(2–3): 195–204, 1997.
10. Mugford, C. A., M. A. Carfagna, and G. L. Kedderis, "Furan-mediated uncoupling of hepatic oxidative phosphorylation in Fischer-344 rats—an early event in cell death," *Toxicology Applied Pharmacology*, 144(1):1–11, 1997.
11. Burka, L. T., K. D. Washburn, and R. D. Irwin, "Disposition of [¹⁴C]furan in the male F344 rat," *Journal of Toxicology and Environmental Health*, 34(2): 245–257, 1991.
12. Chen L.-J., S. S. Hecht, and L. A. Peterson, "Identification of *cis*-2-butene-1,4-dial as a microsomal metabolite of furan," *Chemical Research in Toxicology* 8(7): 903–906, 1995.
13. Byrns, M. C., D. P. Predecki, and L. A. Peterson, "Characterization of nucleoside adducts of *cis*-2-butene-1,4-dial, a reactive metabolite of furan," *Chemical Research in Toxicology* 15(3):373–9, 2002.
14. Parmar, D. and L. T. Burka, "Studies on the interaction of furan with hepatic cytochrome P-450," *Journal of Biochemical Toxicology*, 8: 1–9, 1993.
15. Lee, H., S. S. Bian, and Y. L. Chen, "Genotoxicity of 1,3-dithiane and 1,4-dithiane in the CHO/SCE assay and the *Salmonella*/microsomal test," *Mutation Research*, 321(4): 213–218, 1994.
16. Peterson, L. A., K. C. Naruko, and D. P. Predercki, "A reactive metabolite of furan, *cis*-2-butene-1,4-dial, is mutagenic in the Ames assay," *Chemical Research in Toxicology*, 13(7): 531–534, 2000.
17. Fourman, P., J. M. Mason, R. Valencia, and S. Zimmering, "Chemical mutagenesis testing in *Drosophila*, IX. Results of 50 coded compounds tested for the National Toxicology Program," *Environmental and Molecular Mutagenesis*, 23(1): 51–63, 1994.
18. Mugford, C.A. and G. L. Kedderis, "Furan-mediated DNA double strand breaks in isolated rat hepatocytes," *Fundamental Applied Toxicology*, 30(1, Part 2):128, 1996.
19. Wilson, D. M., T. L. Goldsworthy, J. A. Popp, and B. E. Butterworth, "Evaluation of genotoxicity, pathological lesions, and cell proliferation in livers of rats and mice treated with furan," *Environmental and Molecular Mutagenesis*, 19(3): 209–222, 1992.
20. National Toxicology Program (NTP), Report on Carcinogens, 10th ed., U.S. Department of Health and Human Services, Public Health Service, 2002.
21. Kedderis G. L. and S. A. Ploch, "The Biochemical Toxicology of Furan," *CIIT Activities* 19(12), 1999.

Dated: May 4, 2004.

Jeffrey Shuren,

Assistant Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Government-Owned Inventions; Availability for Licensing

AGENCY: National Institutes of Health, Public Health Service, DHHS.

ACTION: Notice.

SUMMARY: The inventions listed below are owned by an agency of the U.S. Government and are available for licensing in the U.S. in accordance with 35 U.S.C. 207 to achieve expeditious commercialization of results of federally-funded research and development. Foreign patent applications are filed on selected inventions to extend market coverage for companies and may also be available for licensing.

ADDRESSES: Licensing information and copies of the U.S. patent applications listed below may be obtained by writing to the indicated licensing contact at the Office of Technology Transfer, National Institutes of Health, 6011 Executive Boulevard, Suite 325, Rockville, Maryland 20852–3804; telephone: 301/