Minutes of the
FOOD ADVISORY COMMITTEE
CONTAMINANTS AND NATURAL TOXICANTS SUBCOMMITTEE[1]

FURAN MEETING

June 8, 2004

Bethesda Marriott
Bethesda, MD

Members present—Full Advisory Committee
Douglas L. Archer, Ph.D.; Patrick S. Callery, Ph.D.; Annette Dickinson, Ph.D.; Goulda A. Downer, Ph.D.; Johanna Dwyer, D.Sc, RD; Jean M. Halloran; Norman I. Krinsky, Ph.D.; Daryl B. Lund, Ph.D.; Margaret C. McBride, M.D.; Sanford A. Miller, Ph.D.; Mark F. Nelson, Ph.D.; Robert M. Russell, M.D.; Carolyn I. Waslien, Ph.D., RD.

Members present—Contaminants and Natural Toxicants Subcommittee
Alex D.W. Acholonu, Ph.D.; Marion F. Aller, D.V.M., DABT; George M. Gray, Ph.D.; Ken Lee, Ph.D.; Henry B. Chin, Ph.D.

Temporary voting member present:
P. Joan Chesney, M.D.

Food and Drug Administration representatives:
Dr. Nega Beru, Jeremy Mihalov, Dr. Kim Morehouse, Linda Reed, Dr. Terry C. Troxell.

Guest speakers:
Dr. Don S. Forsyth, Research Scientist, Health Products & Food Branch, Health Canada; Dr. Glenda Moser, Director of Toxicology, Integrated Laboratory Systems, Research Triangle Park, NC.

Background
Charge:
The Food Advisory Committee and Contaminants and Natural Toxicants Subcommittee are being asked to provide input on data that would be helpful for further evaluation of potential risks posed by the presence of furan in food.

Question:
Taking into consideration the data needs already identified in the May 10, 2004 Federal Register notice requesting data on furan, and the presentations at this meeting, are there any additional data that are needed to fully assess the risk of furan in food?

Meeting Summary

The meeting was convened on Tuesday, June 8, at 2 p.m.

Dr. Sanford Miller, Chairman of the Food Advisory Committee, welcomed the committee and introduced the members.

Linda Reed, Acting Executive Secretary for the Food Advisory Committee, read and explained the conflict of interest statement.

Opening Remarks:
Background on Furan in Foods
Nega Beru, Ph.D., Director,
Division of Plant Product Safety
Office of Plant and Dairy Foods, CFSAN, FDA

Dr. Beru provided an overview of what furan is and how it is formed in foods. He noted that it is listed in the DHHS report on carcinogens because it has been found to cause cancer in rodents and that it is formed in food during traditional heat processing techniques such as cooking and canning. The mechanisms of formation, he said, are beginning to be elucidated. Dr. Beru also cited FDA development of a quantitative method for measuring furan in foods and reviewed what foods are being tested for furan and the rationales for choosing those foods.

Dr. Beru then reviewed FDA actions on furan on May 7, 2004, including release on FDA's website of the method for detecting furan, data collected through April 28, 2004, and Qs & As, as well as publication in the Federal Register of an announcement of a Food Advisory Committee meeting and a request for data on furan. The principle points from May 7 action noted that:

- Finding furan in foods is a concern because, based on studies in rodents, furan is a potential carcinogen in humans
- Furan has been reported in food before; what is new is its discovery in a variety of foods, including baby foods
- It is not an immediate pubic health concern and consumers should not change their eating habits.

In addition, FDA noted that they are conducting an expanded survey of different foods and foods as eaten to determine exposure and risk to consumers and they are assessing what additional studies are needed to determine furan's potential risk to human health as well as studies on mechanism of formation and reduction methods.

Dr. Beru then reviewed the data needs from the Federal Register request for data and concluded with the charge and question for the Committee:
The Food Advisory Committee and Contaminants and Natural Toxicants Subcommittee are being asked to provide input on data that would be helpful in further evaluation of potential risks posed by the presence of furan in food.

Taking into consideration the data needs already identified in the Federal Register notice published May 10, 2004, and the presentations at this meeting, are there any additional data that are needed to fully assess the risk of furan in foods?

Scientific Overview of Furan in Foods

Analysis of Furan in Foods
Dr. Kim Morehouse,
Division of Chemistry Research and Environmental Review
Office of Food Additive Safety, CFSAN, FDA

Dr. Morehouse summarized why FDA investigated furan and briefly reviewed an initial semi quantitative survey of furan in foods. He then reviewed the method, including analytical techniques, participation in a round robin method analysis, and sample preparation. He then reviewed the FDA's more extensive preliminary survey of furan levels in food. He explained the findings concerning furan in infant formula, baby foods, and adult foods. He noted that no furan was detected in a variety of common foods, including milk, margarine, and potato chips. Finally, he reviewed an experiment on the effects of postproduction cooking on furan levels in food.

Dr. Morehouse said that FDA is moving ahead with an analysis of more foods based on the USDA food consumption data base, higher use foods, and foods reported in literature to contain furan. In addition, FDA is continuing to investigate the effects of heating on the concentration of furan.

For more information concerning the method and foods analyzed, Dr. Morehouse referred the audience to the following websites:
http://www.cfsan.fda.gov/~dms/furan.html and

http://www.cfsan.fda.gov/~dms/furandat.html.

During discussion, Dr. Morehouse was asked questions about zero furan results with potato chips, preparation of infant formula for analysis, an experiment on the effects of cooking, and the limit of quantitation versus the limit of detection.

An Exposure Assessment for Furan from the Consumption of Adult and Baby Foods
Mr. Jeremy Mihalov, M.S.
Division of Biotechnology and GRAS Notice Review

Office of Food Additive Safety, CFSAN/FDA

Mr. Mihalov reviewed an exposure assessment conducted by CFSAN on exposure to furan from consumption of adult and baby food. He reviewed the basic exposure model, assumptions used in developing the model, and sources of data used in the model. He also reviewed information from laboratory analyses on the types of foods in which furan was found and levels of furan in those foods. He then reviewed the results of the model, including overall furan exposure for adults and children, and exposures from individual foods and from formula consumption. He concluded that the variability of furan levels within a food type is small and noted that additional measurements will not affect exposure greatly. He also added that the number of food types tested is limited. Additional measurements in new food types will affect overall exposure and help define variability, while reducing uncertainty, he said.

During discussion, Dr. Mihalov was asked questions about the use of data for the mean versus the high-end consumer, about collection of fast foods or pet foods/animal feeds, the use of the Iowa State method for exposure modeling, and about the potential for the presence of furan in food packaging.

Furan: Mechanisms of Formation and Levels in Food
Dr. Don Forsyth, Research Scientist
Health Products & Food Branch
Health Canada

Dr. Forsyth reported on the investigative work and findings of Health Canada concerning furan. He noted that the FDA informed Health Canada of its investigation of furan in canned and bottled food commodities in late March 2004 and that Health Canada commenced work in April 2004.

Dr. Forsyth mentioned previous findings on furan and furan derivatives in food and reviewed three possible mechanisms of formation:

- Thermal degradation of carbohydrates
- Thermal oxidation of lipid
- Decomposition of ascorbic acid or its derivatives.

He reviewed the analytic methods used by Health Canada and Health Canada's research on mechanisms of formation.

Two pathways of furan formation were identified by Health Canada:

- Polyunsaturated fatty acids (linoleic, linolenic) via peroxidation and ring closure
- Decomposition of ascorbic acid derivatives, particularly dehydroascorbic acid and isoascorbic acid.

He reported on the results of their findings concerning levels of furan in a variety of foods, including baby foods.

For next steps, he noted the need for:

- ? Further studies on mechanism(s) of formation using model systems and precursor fortified food matrices
- ? Losses of furan during food processing and cooking
- ? Further surveys of canned and bottled products
- ? Participation in a round robin method validation study to be conducted with FDA and industry within the next few weeks,
- ? The update of health risk assessments as new data become available.

In discussion, following the presentation, committee members complimented Dr. Forsythe on the "impressive amount of work" completed since March 2004. Dr. Forsyth was asked about more details on potential formation mechanisms and the comparability of US FDA and Health Canada methods and data. Dr. Forsyth stressed that the results of the work are preliminary and that the round robin study is the next phase. All researchers will examine the same food and hope to get the same results, or adjust their methods for testing, he explained.

Furan-Induced Cytotoxicity, Cell Proliferation, and Tumorgenicity in Mouse Liver
Dr. Glenda Moser, Director of Toxicology
Integrated Laboratory Systems
Research Triangle Park, NC

Dr. Moser presented the results of research concerning furan-induced cytotoxicity, cell proliferation, and tumorigenicity. She summarized results from a 2-year NTP bioassay on rats and mice, including the incidence of hepatocellular adenomas and carcinomas and the appearance of cholangiosarcomas in rats at 2, 4, and 8 mg.furan/kg bw and hepatocellular neoplasms in mice at 8 mg/kg bw. Dr. Moser reviewed the multi-stage process of cancer development, including genotoxic and non-genotoxic or epigenetic mechanisms, and reviewed the results of published genotoxicity assays on furan.

She reviewed background information on liver cytotoxicity and outlined a study conducted by her and her colleagues with male mice over a 13-week period. This work led to further carcinogenic study involving female mice over a 2-year period.

Their study, she reported, demonstrated a dose-dependent increase in furan-induced liver tumors in female B6C3F1 mice and a relationship between dose, cytotoxicity, and tumor induction for a model cytotoxic heptocarcinogen. Further points in her overview included the following: a threshold for liver tumors was seen; cytotoxicity and cell proliferation were reversible at 13 weeks; and mutations and other events may be secondary to hepatocyte cytolethality or increased cell proliferation.

She outlined areas of interest for further research, including:

- ? Do p450 inhibitors decrease liver tumorigenesis in mouse liver?
- ? Are liver tumors due to bolus dose?

- ? Are the positive genotoxic results due to direct damage to DNA, high doses tested and/or secondary to cell proliferation?
- ? What are the molecular or gene expression changes in liver tumors? Do they occur in cholangiosarcomas?
- ? Is there a threshold for cholangiosarcomas or mononuclear leukemia? Is the mode of action similar to that of liver tumors?
- ? Do biliary tract epithelial cells have pharmokinetic parameters similar to that of hepatocytes?
- ? What is the relevance of mouse liver findings to cholangiosarcomas and leukemia in humans?
- ? Are there populations of humans that are susceptible to furan-induced effects? Is age a factor?

In discussion following the presentation, Dr. Moser was asked about age-related data in mice, whether furan was similar to chloroform in effects being seen only with a bolus dose versus a chronic dose, whether studies indicate a threshold for furan toxicity, mechanism of furan detoxification, the involvement of Cyp2E1 in furan metabolism and toxicity, and potentially sensitive human populations.

Furan in Food
Summary and Charge to the FAC and SCNT
Terry C. Troxell, Ph.D., Director
Office of Plant and Dairy Foods, CFSAN, FDA

Dr. Troxell summarized the FDA actions to date concerning furan in foods, including the development of a quantitative method and the upcoming round robin study. He noted that the exploratory survey tested about 230 foods, when combined with the data from Canada. And, he said, more testing is underway.

He noted that some future actions on furan in foods include evaluation of received data, review of the NTP study by the Cancer Assessment Committee, and development of an action plan. He outlined data needs, including occurrence and exposure, mechanisms of formation, and toxicology of furan. And he reiterated the question before the committee:

> Taking into consideration the data needs already identified in the Federal Register notice requesting data on furan, and the presentations at this meeting, are there any additional data that are needed to fully assess the risk of furan in food?

We are in the early state in this process, Dr. Troxell explained. "We are trying to get our arms around this issue and need your thoughts to do the right set of work," he said. The committee asked Dr. Troxell whether FDA had a larger plan for heat-induced contaminants; whether TDS, home-prepared, and food-service foods would be included in surveys; and whether data were available on human exposures to furan and human serum levels.

Committee Discussion, Concluding Deliberations, Recommendations and Response to Question

Committee members discussed the presentation data and sought more information on how foods were selected for testing. They were informed that foods most likely to contain furan were selected first, as well as foods that are major contributors to the diet. Committee members encouraged FDA to continue to expand testing to additional foods.

When research is conducted in foods "as consumed," committee members noted the need to mimic foods as consumed when prepared by food service and restaurants.

Discussion also focused on particular subsets of the population that might be exposed to furans in the environment.

In a wide-ranging discussion, committee members offered numerous suggestions for further research. These research suggestions included the following:

- Whether the metabolism or effects of furan are different in such special populations as infants and children, the elderly, individuals consuming parenteral or intravenous diets, individuals with preexisting liver damage, and alcoholics;
- Whether furan's cycytotoxic and carcinogenic effects are related to administering furan in large bolus doses, and whether the same effects would be seen with equivalent low-dosage chronic exposures in water or food;
- Whether furan's carcinogenic effects are due to cytotoxicity, whether there is an effects threshold, and what that threshold may be;
- Determine if furan is present in human breast milk, the significance of levels found in breast milk, and the relation between breast milk levels and maternal food intake;
- Assess non-food environmental exposures to determine significance of food exposure to the total furan exposure;
- The presence of furan in food prepared in restaurants or at home, including baby foods prepared at home;
- Information on reproductive and developmental toxicology; and
- Need for a risk assessment that also considers the risks of changes in food processing that might be a consequence of risk management.

The committee meeting adjourned at 5 p.m.

I certify I attended the June 7-8, 2004 meeting of the Food Advisory Committee, and these summary minutes accurately reflect what transpired.

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Linda Reed Date
Acting Executive Secretary

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Sanford A. Miller, Ph.D. Date
Chair

[1] The entire meeting was open to the public. Copies of written information provided to the Committee for consideration are available from the Committee staff. The transcript of the meeting is available on the internet at http://www.fda.gov/ohrms/dockets/ac/cfsan04.html or through FDA Dockets Management Branch (HFA-305), 12420 Parklawn Drive, Rockville, Maryland 20857.