

**Contaminant and Natural Toxicants Subcommittee¹
of the Food Advisory Committee
Center for Food Safety and Applied Nutrition (CFSAN)
Food and Drug Administration (FDA)**

**SUMMARY MINUTES
March 18-19, 2003
U.S. Department of Agriculture, APHIS
Riverdale, Maryland**

Members Present

Francis (Frank) F. Busta, Ph.D., Co-chair
James E. Heubi, M.D., Co-chair²
Alex D.W. Acholonu, Ph.D.
Robert D. Baker, MD, Ph.D.²
Larry R. Beuchat, Ph.D.²
Henry M. Blumberg, M.D.²
Margaret E. Briley, Ph.D., R.D., L.D.²
Lawrence J. Fischer, Ph.D.
Marion H. Fuller, D.V.M.
Lawrence N. Kuzminski, Ph.D.
Ken Lee, Ph.D.
Laurie J. Moyer-Mileur, Ph.D., R.D., C.D.²
Marguerite A. Neill, M.D.²
Virginia A. Stallings, M.D.²
Phillip I. Tarr, M.D.²
Patti J. Thureen, M.D.²

Member Absent

James R. Anderson, Ph.D.²

Acting Industry Representative

R. Bruce Tompkin, Ph.D.

Guest Speakers

John J. Alexander, M.D.
Matthew J. Kuehnert, M.D.
Maria Nazarowec-White, Ph.D.

FDA Participants

Sue Ann Anderson, Ph.D.
Robert L. Buchanan, Ph.D.
Donald H. Burr, Ph.D.

¹ The entire meeting was open to the public. For the verbatim transcript of the meeting, contact FDA Dockets Management Branch (HFA-305), 12420 Parklawn Drive, Rockville, Maryland 20857.

² Temporary voting member

Karl C. Klontz, Ph.D.
L. Robert Lake, Esq.
Christine J. Taylor, Ph.D.
Susan Walker, M.D.
Donald Zink, Ph.D.

FDA Staff Present

Jeanne E. Latham, M.S., R.D., Executive Secretary
Marion V. Allen
Anna Belousovitch ³
Vincent Keyes
Linda Marmen
Gillian Robert-Baldo
Kathleen Smith
Shawn Suggs-Anderson
Linda Webb

The Contaminants and Natural Toxicants Subcommittee (“Subcommittee”) of the Food Advisory Committee convened a meeting on March 18-19, 2003, at the U.S. Department of Agriculture, APHIS, Riverdale, Maryland. Co-chair Frank Busta, Ph.D., called the meeting to order at 8 a.m., Tuesday, March 18, 2003. Dr. Christine J. Taylor, Director of the Office of Nutritional Products, Labeling, and Dietary Supplements, CFSAN, welcomed everyone and made introductory remarks. Dr. Taylor gave a brief overview of FDA’s activities relative to *Enterobacter sakzakii* and powdered infant formula, and presented the charges and questions to the Subcommittee. The executive secretary read the conflict of interest statement into the record and announced the appointment of the temporary voting members. She briefly reviewed the function of Food Advisory Committees and subcommittees and the roles of the members of the Subcommittee and FDA. Co-chair James Heubi, Ph.D., welcomed the Subcommittee and temporary voting members, thanked them for participating, and asked each member to state their name and their area of expertise, which they did. Dr. Heubi also announced that Dr. James Anderson, one of the temporary voting members, would not be able to attend.

Presentations by Guest Speakers

Dr. Sue Ann Anderson started the presentations by discussing the current marketing and use of powdered infant formula in the United States.

Dr. Matthew Kuehnert by conference telephone discussed the CDC investigation of the case in Tennessee of *Enterobacter sakzakii* meningitis and death associated with powdered infant formula.

Dr. Karl Klontz discussed *Enterobacter sakzakii* case reports and outbreaks involving infants as reported in the peer-reviewed English medical literature.

³ CFSAN Contractor

Dr. John Alexander discussed clinical consequences of *Enterobacter sakazakii* infections.

Dr. Maria Nazrowec-White discussed the general microbiology of *Enterobacter sakazakii*, including the ecology, pathogenicity, and subtyping.

Dr. Donald Burr discussed microbial detection of *Enterobacter sakazakii* in the clinical setting and in food.

Dr. Robert Buchanan discussed thermal and other resistance characteristics of *Enterobacter sakazakii*.

Dr. Donald Zink discussed the FDA field survey of powdered infant formula finished products and selected ingredients for possible *Enterobacter sakazakii* contamination.

Public Comment

The Co-chairs commenced the open public hearing at 4 p.m. The following members of the public made oral presentations: Les Smoot, Ph.D., Nestle USA; Jon A. Vanderhoof, M.D., Mead Johnson Nutritionals; Russell J. Merritt, M.D., Ross Products Division of Abbott Laboratories, on behalf of the International Formula Council; and Jatinder Bhatia, MBBS, Medical College of Georgia.

Co-chair Busta opened the floor for preliminary discussion on clinical presentations.

The Co-chairs adjourned the session at 5:50 p.m.

The Co-chairs called the meeting to order at 8:40 a.m. on Wednesday, March 19, 2003. Co-chair Busta asked for clarification of some points before the Subcommittee began its deliberations, and various industry representatives, as well as FDA speakers, provided responses to the Subcommittee's questions.

Review of Charge and Questions, Discussion, and Responses to Questions

The Co-chair Busta began a discussion of the FDA charges and questions.

Charge 1: Characterize the infants at risk.

Question 1: Given available information on *E. sakazakii* and powdered infant formula, is there a risk? If so, identify the populations of infants at risk: identify infants at risk including consideration of factors, such as the extent to which immune status, age and/or general health status, etc., may impact on the susceptibility of infants to *E. sakazakii* infections.

For Charge 1, Question 1, the Subcommittee was asked to come to consensus. The committee voted unanimously to the following answer to question 1:

Yes, there is a risk. Populations at risk are preterm infants born at less than 36 weeks gestational age up to a post-term age of 4 to 6 weeks, immunocompromised infants at any age, and term infants hospitalized in level 2 and level 3 neonatal intensive care units (NICUs). Every effort should be made to avoid feeding powdered infant formula to these at-risk infants. Use of powdered products for these at-risk infants should be considered only when no appropriate liquid product is available.

There is probably a low, but as yet unquantified, risk in healthy, term infants, which cannot be described with data available at this time.

Charge 2: If there is a meaningful risk, how can this risk be addressed?

Question 1: What intervention strategies can be used in infant formula manufacturing processes and plants?

The Subcommittee developed a four-part recommendation in response to this question.

- ?? Intervention strategies which reduce bacterial presence in powdered infant formula should be used in manufacturing processes and plants. These include, but are not limited to, prerequisite programs to assure the microbial quality of raw materials, hygienic design and maintenance of equipment, hygienic zoning in plant design, and continuous use and improvement of HACCP programs and their verification.
- ?? The Subcommittee encourages the development of a microbiological sampling and testing program through joint efforts by industry and the FDA, the purpose of which is to assure greater clinical safety of this product. It would be highly desirable to formally assess the contribution of such a microbiologic testing program when added to the intervention measures described above.
- ?? The Subcommittee recognizes that with the currently available processing technologies for powdered infant formula, the risk for illness due to *E. sakazakii* cannot be completely eliminated for the at-risk populations specified above. Whether the additional interventional strategies described above can achieve this result is not clear.
- ?? Recognizing the important clinical purposes for which powdered infant formula is used among the populations most at-risk for *E. sakazakii* infection, the Subcommittee strongly encourages and enjoins the powdered infant formula manufacturers to develop product formulations which combine the attributes of maximal infant growth promotion and microbiologic safety for use in the at-risk populations described above.

Question 2: Are there other intervention strategies? Include consideration of product labeling options for powdered infant formula (e.g., directions for preparation and use), and consider handling practices for the settings (hospitalized and non-hospitalized) in which powdered infant formula is prepared and consumed?

The Subcommittee answered Question 2 as follows:

FDA, with input from industry, should prepare educational documents to be attached to appropriate infant formula materials targeted to at-risk infants. These educational materials should alert all health-care users that powdered infant formulas are not sterile and the need for special handling, if used. The educational materials should be updated to reflect any new information that becomes available. They would be distributed through FDA outreach efforts.

Question 3: Is it possible, based on available information, to specify allowable lower levels of microbial detection of *E. sakazakii* in powdered infant formula, and do allowable levels vary by risk characteristics of the infant?

The Subcommittee answered Question 3 as follows:

Available information is insufficient to permit specification of an allowable lower level of microbial detection of *E. sakazakii* in powdered infant formula. Without knowledge for such specifications, it is not possible to answer the second part of the question.

Question 4: What are the critical knowledge gaps and research priorities relative to the need to address issues about the presence of *E. sakazakii* in powdered infant formula?

The Subcommittee compiled a list of gaps in knowledge and research needs, including the following:

- ?? Consider methods for post-drying inactivation of *E. sakazakii* in powdered infant formula and continued development of methods to detect *E. sak*
- ?? Continue to document occurrence of *E. sakazakii* in powdered infant formulas
- ?? Develop over time means, if possible, for sterilizing powdered infant formulas
- ?? Consider developing sterile liquid products for use with at-risk populations
- ?? Identify pathogenic factors, host-susceptibility factors and spectrum of disease
- ?? Population-based surveillance, perhaps through FoodNet, to provide denominators for incidence of *E. sakazakii* infections in infant populations
- ?? Assure that clinical laboratory procedures are able to isolate and identify *E. sakazakii*
- ?? Optimal therapy for infected infants

The Co-chairs adjourned the meeting at 2:15 p.m.

I certify I attended the March 18-19, 2003 meeting of the Contaminants and Natural Toxicants Subcommittee of the Food Advisory Committee, and these summary minutes accurately reflect what transpired.

Jeanne E. Latham 05/29/03
Jeanne E. Latham, M.S., R.D. Date
Executive Secretary

Francis F. Busta 30 MAY 2003
Francis F. Busta, Ph.D. Date
Co-Chair

James E. Heubi 6/02/03
James E. Heubi, M.D. Date
Co-Chair