

U. S. Department of Health and Human Services
U. S. Food and Drug Administration
Center for Food Safety and Applied Nutrition
Office of Nutritional Products, Labeling and Dietary Supplements
April 11, 2002; Revised October 10, 2002

Health Professionals Letter on *Enterobacter sakazakii* Infections Associated With Use of Powdered (Dry) Infant Formulas in Neonatal Intensive Care Units

Revisions: This letter revises the Dear Health Professional letter of 11 April 2002 with elimination of the recommendation to use boiling water for reconstitution of powdered infant formula. The reasons for this revision include potential for: 1) loss of heat sensitive nutrients, 2) changes in physical characteristics of some formulas, 3) inability to assure adequate destruction of *E. sakazakii*, 4) injury to hospital staff preparing formula. A statement has also been added in recognition of differences in infant formula preparation among hospital facilities. Detailed guidelines for preparation of infant formula are available on the web site of the American Dietetic Association at http://www.eatright.org/Public/NutritionInformation/02_formulaguide.cfm.

Dear Health Care Professional:

The U.S. Food and Drug Administration (FDA) is writing to inform you about a growing body of information pertaining to *Enterobacter sakazakii* infections in neonates fed milk-based powdered infant formulas. Clusters of *E. sakazakii* infections have been reported in a variety of locations over the past several years among infants fed milk-based powdered infant formula products from various manufacturers. One study tested milk-based powdered infant formula products obtained from a number of different countries and found that *E. sakazakii* could be recovered from 20 (14%) of 141 samples (1).

Enterobacter sakazakii is a gram-negative rod-shaped bacterium within the family *Enterobacteriaceae*. The organism was called "yellow-pigmented *Enterobacter cloacae*" until 1980 when it was renamed *Enterobacter sakazakii* (2). The majority of cases of *E. sakazakii* infection reported in the peer-reviewed literature have described neonates with sepsis, meningitis, or necrotizing enterocolitis (3-5) as a consequence of the infection, and the case-fatality rate among infected neonates has been reported to be as high as 33%. The pathogen is also a rare cause of bacteremia and osteomyelitis in adults (2).

The literature suggests that premature infants and those with underlying medical conditions may be at highest risk for developing *E. sakazakii* infection. Several outbreaks have occurred in neonatal intensive care units worldwide. (See, for example, van Acker et al.(3).) However, an apparently healthy full term newborn infant in Iceland also became ill prior to hospital discharge and suffered permanent neurological sequelae (4). Although the reservoir of the organism is unknown, a growing number of outbreaks of infection among neonates has provided compelling evidence that milk-based powdered infant formulas have served as the source of infection (3-5). Significantly, the results of one investigation (the "Belgium outbreak" investigation (3)) suggest that even low levels of *E. sakazakii* in milk-based powdered infant formula (i.e., levels that are within what a 1994 Codex Alimentarius document (6) provides as a currently accepted limit for the presence of coliforms in milk-based powdered infant formula) can lead to development of infection.

Exhibit 3

The Centers for Disease Control and Prevention (CDC) has communicated information to FDA about a fatal infection due to *E. sakazakii* meningitis in a neonatal intensive care unit in the United States. In CDC's subsequent investigation, a cluster of neonates with *E. sakazakii* infection or colonization were identified in association with a powdered infant formula containing these bacteria. CDC will discuss details of its investigation in an upcoming edition of the Morbidity and Mortality Weekly Report (MMWR).

As background information for health professionals, FDA wants to point out that powdered infant formulas are not commercially sterile products. Powdered milk-based infant formulas are heat-treated during processing, but unlike liquid formula products they are not subjected to high temperatures for sufficient time to make the final packaged product commercially sterile. FDA has noted that infant formulas nutritionally designed for consumption by premature or low birth weight infants are available only in commercially sterile liquid form. However, so-called "transition" infant formulas that are generally used for premature or low birth weight infants after hospital discharge are available in both non-commercially sterile powder form and commercially sterile liquid form. Some other specialty infant formulas are only available in powder form.

The FDA has become increasingly aware that a substantial percentage of premature neonates in neonatal intensive care units are being fed non-commercially sterile dry infant formula. In light of the epidemiological findings and the fact that powdered infant formulas are not commercially sterile products, FDA recommends that powdered infant formulas not be used in neonatal intensive care settings unless there is no alternative available. If the only option available to address the nutritional needs of a particular infant is a powdered formula, risks of infection can be reduced by:

- [*_section removed]
- Preparing only a small amount of reconstituted formula for each feeding to reduce the quantity and time that formula is held at room temperature for consumption; Recognizing differences in infant formula preparation among hospitals, individual facilities should identify and follow procedures appropriate for that institution to minimize microbial growth in infant formulas;
- Minimizing the holding time, whether at room temperature or while under refrigeration, before a reconstituted formula is fed; and
- Minimizing the "hang-time" (i.e., the amount of time a formula is at room temperature in the feeding bag and accompanying lines during enteral tube feeding), with no "hang-time" exceeding 4 hours. Longer times should be avoided because of the potential for significant microbial growth in reconstituted infant formula.

FDA urges health care providers to report adverse events associated with the use of infant formulas as soon as possible to FDA's MedWatch program by calling their toll-free number (1-800-332-1088) or through the Internet (<http://www.fda.gov/medwatch>). Healthcare providers should report invasive disease in infants due to *E. sakazakii*, particularly bloodstream infection or meningitis with onset in the healthcare setting, to CDC's Division of Healthcare Quality Promotion (1-800-893-0485).

At the current time, FDA is determining if additional specific measures may be needed to assure the safe use of dried infant formulas in neonatal intensive care settings or by other vulnerable infant populations, and will communicate additional recommendations if and when they become available.

Sincerely yours,

Christine J. Taylor, Ph.D.
Director
Office of Nutritional Products, Labeling and
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References:

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2. Lai KK. *Enterobacter sakazakii* infections among neonates, infants, children, and adults. *Medicine* 2001;80:113-23.
3. van Acker et al. Outbreak of necrotizing enterocolitis associated with *Enterobacter sakazakii* in powdered milk formula. *J Clin Microbiol* 2001;39:293-97.
4. Biering G et al. Three cases of neonatal meningitis caused by *Enterobacter sakazakii* in powdered milk. *J Clin Microbiol*. 1989 Sep;27(9):2054-6.
5. Simmons et al. *Enterobacter sakazakii* infections in neonates associated with intrinsic contamination of a powdered infant formula. *Infect Control Hosp Epidemiol* 1989;10:398-401.
6. Food and Agriculture Organization. 1994 Codex Alimentarius: code of hygienic practice for foods for infants and children. CAC/RCP 21-1979. Food and Agriculture Organization of the United Nations, Rome, Italy.

Section removed in October 2002 revision:

Reconstituting powdered formula using boiling water with subsequent refrigeration before feeding, recognizing that some loss of certain water soluble vitamins (e.g., thiamin, ascorbic acid) is likely to occur.

This document was issued on April 11, 2002
and revised on October 10, 2002.
For more recent information on Food Labeling
see <http://www.cfsan.fda.gov/label.html>

E. sakazakii Infections Associated with use of Powdered Infant Formulas - Tennessee, 2001 (Morbidity and Mortality Weekly Report, April 12, 2002) (available in [PDF](#))