

Fédération
Internationale
des Industries
des Aliments
Diététiques

International
Special
Dietary
Foods
Industries



194, rue de Rivoli
F - 75001 PARIS
FRANCE

Tél. : 33/(0)1 53 45 87 87
Fax : 33/(0)1 53 45 87 80

andree.bronner@isdifederation.org

ISDI Background Information on *Enterobacter sakazakii* in Powdered Infant Formula

ISDI takes reports identifying powdered infant formula as a source and vehicle for *E. sakazakii*¹ infections very seriously. Reported cases of *E. sakazakii* infection in which powdered infant formula was identified as a source are uncommon and have occurred mainly in hospitalised, pre-term and very low-birth weight infants; nevertheless they were serious episodes.

Overview of the current situation

- Over the past 20 years evidence has developed to implicate *Enterobacter sakazakii* as the cause of some cases of fatality and disease in premature babies, immunocompromised newborn infants and more recently fragile newborn infants of up to a few weeks of age.
- The number of reported cases is very low but has been increasing recently, however it remains at a very low level. This is largely due to improved awareness and detection. According to WHO, one targeted review found a total of 48 cases reported between 1961 and 2003, mainly in hospital settings. A few cases have been reported since then in New Zealand and France.
- *E. sakazakii* is considered by the FAO/WHO as well as by the EFSA of relevance for infants (young children < 1year) but of particular concern for preterm, low birth weight and immunocompromised infants up to 28 days. A review of cases (English literature) between 1961-2003 found that 52 percent (approx 25 cases) were among low-birth weight infants most likely to get some kind of infant formulae.
- Given the serious effects of *E. sakazakii*, ISDI is working with the manufacturers of infant foods and global health agencies to minimize any possible risks associated with powdered infant formulas.
- Additionally ISDI is being working very closely with national and international health authorities to understand and take action to prevent infections by this pathogen. As such, one of ISDI's members was very pleased to participate in the February 2004 FAO/WHO workshop *Enterobacter sakazakii* in Powdered Infant Formula. In

¹ Biering *et al.*, 1989, Simmons *et al.* 1989 ; Van Acker *et al.*, 2001 ; CDC, 2002.

addition ISDI is member of the Codex Alimentarius Drafting Group in charge of the revision of the Code of Hygiene Practices for Infant Formulae including the revision of the existing microbiological specifications.

About *E. sakazakii*

- *E. sakazakii* is a vegetative microorganism belonging to the family of the Enterobacteriaceae. It is an opportunistic pathogen widely found in the environment.
- During many years the only published data on the isolation of *E. sakazakii* were cases of neonatal meningitis or necrotizing enterocolitis related to powdered infant formulae. This led to the establishment of a causal link. In some later cases the organism was isolated on utensils such as mixers used in bottle kitchens and even though in some cases *E. sakazakii* could not be isolated from the infant formulae, a causal relationship was assumed.
- The risk of illness due to very low levels of *E. sakazakii* in reconstituted infant formulae is considered very low by experts. This risk increases dramatically in case of the use of contaminated utensils to prepare the bottles and improper handling and storage before feeding allowing *E. sakazakii* to grow to high levels.
- It is however only very recently that information on the widespread occurrence of *E. sakazakii* has become available. Recent publications have demonstrated that this microorganism can be found in a wide variety of foods, water and environments including homes and hospitals. Contrary to common belief *E. sakazakii* is therefore to be considered a widespread microorganism. Further research in this field is continuing and is expected to provide additional information on the widespread distribution of this organism and contribute to the better understanding on exposure.
- *E. sakazakii* has also been isolated in hospitals from clinical samples taken from adults and a recent article has even reported the presence of *E. sakazakii* in mother's milk stored in a milk bank.
- This new information shows indeed that infants above 4 – 6 months which are no longer exclusively fed with infant formulae are frequently exposed to *E. sakazakii*, without consequences.
- As a widespread bacteria, *E. sakazakii* can potentially also be found in infant food manufacturing environments. This is usually the source of its possible presence in the infant formula powder. In general, the very low level of *E. sakazakii* in powdered infant formula, or contamination through preparation equipment does not result in adverse effects unless the growth of *E. sakazakii* bacteria is allowed through improper handling and storage.

How does *E. sakazakii* behave? Is it heat-resistant?

- *E. sakazakii* grows very rapidly in reconstituted infant formulae kept at room temperature. It is particularly well adapted to growth at temperatures around 37 – 44°C.
- Certain strains show an increased tolerance and resistance to temperatures around 50 – 60°C. In different publications this characteristic has been referred to as thermo-tolerance and has led to the misunderstanding that this microorganism is heat-resistant.
- As shown in different publications, *E. sakazakii* is not heat-resistant and is readily killed at temperatures above 60°C, as applied in industrial processes, e.g. pasteurisation. This fact is acknowledged by governmental agencies such as the US-FDA and is not a point of debate among experts.

The vast majority of *E. sakazakii* infections occur in hospital neonatal intensive care units. Risk of infection arises when reconstituted formula is kept at room temperature (or warmer) for prolonged periods of time. Improved training and hygiene in hospitals are critically important in avoiding *E. sakazakii* outbreaks.

- Health professionals should receive information/guidance and effective training in the application of good hygiene practices for handling, storage and preparation of formula. Following the comprehensive instructions on manufacturers' labels best prevents the presence and growth of pathogenic bacteria in formula.
- ISDI strongly supports the use of freshly reconstituted infant formula as a means to eliminate these problems.
- ISDI questions the WHO-FAO report's recommendation to use boiling water in the preparation of infant formula and strongly discourages this practice. Water at 100°C can scald an infant and lead to nutritional damage.
- Breastfeeding should be recommended as the ideal to mothers. But those who cannot, or choose not to breastfeed, should receive accurate information and education about good hygiene practices concerning the preparation and use of formula. Mothers should be taught to correctly prepare and use formula before leaving hospital, when necessary.

Infant food manufacturers take extensive measures at the factory level to ensure the highest level of product quality and safety.

- ISDI member companies strictly comply with national legislation and international recommendations based on scientific expertise to provide safe and nutritionally adapted infant food.
- Along with their normal strict hygiene standards, manufacturers take additional actions to minimize possible contamination of powder products, including with Enterobacteriaceae.
- These include a series of rigorous processes that prevent contamination from production to the point of purchase by the consumer. For example, manufacturers:
 - Closely collaborate with suppliers to ensure the purchase of high quality ingredients. This includes monitoring of ingredients, especially those added after the final step of heat-processing which have to fulfil the same requirements as those of the final product;
 - Take extensive measures to minimize Enterobacteriaceae or coliforms in the manufacturing environment to prevent post-process contamination;
 - Train personnel to ensure that hygiene control measures are understood and closely followed; and
 - Test finished products to confirm the effectiveness of these procedures.
- In support to their efforts to control post-process contamination and to improve control measures, manufacturers have also been constantly improving the analytical methods allowing to efficiently detect Enterobacteriaceae and *E. sakazakii*.

Close cooperation between global and national health agencies; the infant foods industry; and health providers must continue. Collaboration on combined control measures will achieve the greatest degree of risk reduction.

- The FAO/WHO workshop noted that:
 - Reduction in the frequency of *E. sakazakii* contamination of infant formula powder might only reduce the risk of infection 4 to 5 fold, while minimising the time between preparation and consumption might reduce the risk 30 fold.
- Infant formula manufacturers will continue to refine manufacturing processes to further reduce the presence of Enterobacteriaceae in the processing environment, in particular after the drying step and up to the filling. Similarly, hospitals and consumers must act to minimize the risk of -contamination during preparation and handling.
- Further research about the ecology, taxonomy, virulence or other characteristics of this pathogen is needed and is supported by industry.

- ISDI will continue to work with FAO and WHO; governments, and other concerned parties to revise existing Codex Alimentarius standards and recommendations to ensure they contribute to reducing the risk of *E. sakazakii*

Public Health Authorities: in summary, what is the current situation?

In recent years Public Health Authorities in different countries have become more alert and have initiated surveillance activities as well as more structured risk assessment activities.

- In 2003 the German Federal Institute for Risk Assessment (BfR) organised an expert consultation, which concluded that there was a need for further investigations in different fields such as development of more suitable methods for *E. sakazakii* detection in order to gain more information on the incidence of this organism. It was also concluded that there was no urgent need to modify the regulations with respect to microbiological criteria.
- In the United States of America the FDA has performed limited surveys applying quite exhaustive sampling plans to investigate the occurrence of *E. sakazakii* in powdered infant formulae, which has led to several recalls that have been widely publicised. An additional survey is currently ongoing. In March 2003 an FDA/CFSAN meeting was organised to review and discuss the issue.
- The USA brought this issue to the attention of the Codex Committee on Food Hygiene (CCFH) during the 35th session and provided a risk profile of *E. sakazakii* in powdered infant formulae. As a consequence the CCFH set up a drafting group led by Canada to initiate the revision of the recommended International Code of Hygienic Practices for Foods for Infants and Children (CAC/RCP21-1979).
- The CCFH requested the FAO/WHO to convene an expert consultation on pathogens of concern in powdered infant formulae. This scientific and technical consultation has taken place in Geneva (2-5 February, 2004) attended by participants from different fields and countries (academia, public health authorities, epidemiologists, nutritionists, medical experts, international organisations and industry). The aim of this consultation was to provide the CCFH and in particular the drafting group as well as member states with input and recommendations (see comments above). The final report is available on the website of the FAO/WHO.
- The Drafting Group has been convened in November 2004 for the first time and a first draft has been submitted to CCFH in December. This document includes a proposal for new microbiological criteria as well as recommendations for the management by industry. This document will be tabled at the next CCFH in Argentina (March 2005).
- In the European Community, DG SANCO intends to review the legislation related to pathogens in infant formulae. The European Food Safety Agency (EFSA) has

therefore been mandated to establish a Working Group and to initiate the assessment. The initial meeting took place in January 2004 and an industry representative has been invited to attend one of the meetings. The final opinion was published in November 2004 and will serve as a basis for the EC to establish appropriate criteria. The opinion is available at the EFSA website.

- Discussions have taken place between the Food Standards Agency (UK) and industry representatives in different occasions.
- Surveys have also been performed in the Netherlands and are planned in other countries such as Denmark, Israel or Brazil. It is understood that other agencies may initiate similar activities in the near future.

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