

4. HAZARD CHARACTERIZATION

4.1 POPULATIONS AT RISK

While *E. sakazakii* has caused disease in all age groups, on the basis of the age distribution of reported cases, it was deduced that the group at particular risk is infants (i.e. children <1 year). Among infants, those who are immunocompromised and neonates (≤ 28 days) are considered to be at greatest risk, particularly neonates of low birth weight (<2 500 g according to WHO [1994]). Infants of HIV-positive mothers are also of concern, because they may specifically require infant formula¹ and they may be more susceptible to infection.

The United States FoodNet 2002 survey (C. Braden, personal communication, 2004) estimated that the rate of *E. sakazakii* infection among infants (based on isolation of the organism from sterile sites only) was 1 per 100 000, whereas the rate among low-birth-weight neonates was 8.7 per 100 000.

A review of cases in infants (including from outbreak investigations) reported in English-language literature from 1961 to 2003 found that 25 of 48 cases (i.e. 52%) of *E. sakazakii*-induced illness were amongst infants of low birth weight. While the increased risk cannot be firmly established from these data, it does strongly support the conclusion that low-birth-weight neonates are a high risk group for *E. sakazakii*-induced illness.

A common observation is that the age of patients with salmonellosis is distributed according to a bimodal distribution with peaks in children and the elderly. The reasons for a relative excess of cases in the very young include increased susceptibility upon first exposure or the increased likelihood of medical care being sought for the very young, and they may also be more likely to be tested than other age groups. Whatever their susceptibility to infection, once infected, infants (particularly medically immunocompromised infants) are more likely to suffer severe consequences or death from salmonellosis. Infants who are breastfed are less likely to become infected by *Salmonella*. In a case-control study to identify risk factors for sporadic salmonellosis, case patients were 44.5 times more likely to have a liquid diet containing no breastmilk and 13.2 times more likely to reside in a household where a member had diarrhoea (Rowe et al., 2004).

4.2 DOSE-RESPONSE

Due to the limited information available on *E. sakazakii*, particularly in terms of the number of organisms that ill patients were exposed to, it was not possible to develop a dose-response curve for this pathogen. For the purpose of undertaking a risk assessment, a fail-safe estimate of the infectivity per organism (r value of the exponential model) based on some estimate values can be

¹ The UN guidance for these infants is that where replacement feeding is acceptable, feasible, affordable, sustainable and safe, avoidance of all breastfeeding is recommended, and powdered infant formula may be an option.

made, assuming that all infected servings contain only one organism. Since growth will occur, this will always be a fail-safe value and the real value will be an even lower number.

In the Netherlands, ten cases of *E. sakazakii* infections in infants were reported over 40 years (1). A total of 12 500 babies are born per million people in the country per year. Of these babies, 2% are assumed to be born with a birth weight below 2 000 g. This means 250 babies of 2 000 g or less are born per million people per year. It should be noted that these assumptions were made based on the specific information available in one particular country and that the number of low-birth-weight babies will vary from one country to another. Also, low-birth-weight babies are generally considered to be of 2 500 g or less.

Because powdered infant formula is a source of nutrition for many infants at risk, a very large number of servings are consumed. Thus, there is a small possibility that even one or a few organisms in reconstituted powdered infant formula could cause illness. It was assumed that 300 feedings are provided to a baby in 1 month, and that within the baby's life the period of risk is 1 month. At the population level, where it is estimated that 250 babies per million people per year weigh 2 000 g or less, 75 000 feeds (250 babies \times 300 feeds) are consumed. In a 40-year period in the Netherlands, at the population level, 45 000 000 feeds were consumed by babies of 2 000 g, i.e. 75 000 (feeds per year per million people) \times 40 (no. of years) \times 15 (million population).

The probability (P) of infection is equal to the number of cases/number of exposures to one organism. For the approximation of the dose-response relation at low doses, $P = rD$, where r is the infectivity per organism and D is the dose or the amount of organism ingested. Since it is assumed that all infected servings just contain one organism, $D = 1$. Therefore $P = r \cdot 1$, which is equal to the number of cases/number of exposures to one organism. Thus $r =$ number of cases/number of exposures to one organism. If the probability of one organism being present in the feed is 0.025 (prevalence), the number of contaminated feedings per 40 years to babies of 2 000 g or less in this country, i.e. the number of exposures to one organism, is estimated as 45 000 000 \times 0.025 = 1 125 000 (2). As indicated earlier, the number of cases in this country in 40 years is 10 (1). Then r is calculated as follows:

$$(1)/(2) = 10/1\,125\,000 = 8.9 \times 10^{-6}$$

This value is based on a calculation using selected values such that the infectivity is overestimated. If the dose is less than 10 000, it can be assumed that " $1 - \exp(-rD) \approx (-rD)$ " and the effect of dose is in the linear range.

Pagotto et al. (2003) found only 2 out of 18 strains to be lethally infectious to suckling mice by the oral route, with only 1 of 4 mice dead at a dose of 10^7 cfu/mouse. This results (for the infective strains) in an r value of 2.5×10^{-8} (0.25×10^{-7}), meaning that all doses below 10^7 will probably give linear behaviour.

Based on these two estimates, it can be concluded that the best guess is that the dose-response relation at low doses is linear, but the basis of these two numbers is clearly not strong enough to conclude a value of the dose-response parameter relevant for human neonates.