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Perspective on the risk to infants in the Netherlands associated with *Cronobacter* spp. occurring in powdered infant formula

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ABSTRACT

Cronobacter spp. has been responsible for severe infections in infants. Relative risks associated with this organism in powdered infant formula (PIF) have been described in several studies. To set priorities and decide on risk management options, it is important for risk managers to have a quantitative perspective on the absolute level of risk of this pathogen within the totality of the burden of illnesses in the population. This study set-out to establish such a perspective for The Netherlands. It addresses the impact of heterogeneity in the distribution of the micro-organism in PIF on risk levels. Based on the assumptions in this study, 60% of formula-fed infants are estimated not to be exposed to *Cronobacter* spp. during their neonatal period. The mean exposure was calculated to be about 1 cfu per infant over the total neonatal period. Even after thorough mixing, artificially contaminated powder shows counts which are more variable than expected from a normal, homogeneous distribution. Therefore, mean exposure levels may not represent a good basis for calculating risks. The burden of disease of *Cronobacter* infections to the Dutch population was estimated to be 19–24 Disability Adjusted Life Years (DALYs) per year, of which 95% are due to meningitis. As compared to other illnesses *Cronobacter* infections represent 0.5–2.4% of the total estimated burden of foodborne infections and intoxications. The organism is estimated to be responsible for 0.5–0.7% of the meningitis burden to the entire population of The Netherlands.

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1. Introduction

Cronobacter spp. (previously referred to as *Enterobacter sakazakii*) has been reported to cause meningitis, bacteremia or septicemia, necrotizing enterocolitis and other infections in infants. Relatively large number (8) of *Cronobacter* infections have been reported for the Netherlands (Muytjens et al., 1983) as compared to other countries. A global quantitative risk assessment (MRA) study for *Enterobacter sakazakii* and other micro-organisms in powdered infant formula (PIF) was developed in 2004 during an FAO/WHO expert meeting (FAO/WHO, 2004). In this MRA, risk was estimated in terms of relative risk, comparing different "what-if" scenarios regarding contamination levels and risk mitigation measures. During a second expert consultation in 2006 a more elaborate risk assessment model was presented, that allows comparing scenarios to a baseline scenario to be chosen by the user (FAO/WHO, 2006). However, for specific countries, different baseline levels may exist and it remains important for risk managers to have a perspective on the absolute level of risk of a pathogen such as *Cronobacter* spp. in the population in their jurisdiction. So far, such information has not been assessed for most countries and this study tried to establish such an absolute level of risk for The Netherlands. Additionally, this study investigated the relevance of heterogeneity and clumping in the distribution of the pathogen in PIF when determining its risk in the infant sub-population.

Risk is a function of the probability of an adverse health effect and the severity of such event. In a quantitative risk assessment the risk of a food-hazard combination is estimated to provide guidance to management decisions. Microbial risk assessment consists of 4 activities. It starts with *hazard identification*, being the identification of the relevant microbial hazard for the food commodity or food category at hand. Then *hazard characterization* describes the probability of infection of the consumer as a function of hazard dose and the severity of adverse health events to the consumer. In *exposure assessment*, the probability and the level of exposure of consumers to the hazard are calculated. Finally, *risk characterization* combines the calculations and other details of all previous steps to describe the overall risk estimate, risk estimates for particular subpopulations and/or different risk scenarios and their attendant uncertainties.

The first publication to bring together the various components of risk due to *Enterobacter sakazakii* was compiled by Iversen and Forsythe and gave an overview of detection methods, heat resistance and survival in powder and it provided an indication of the temperatures that allow

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growth (Iversen and Forsythe, 2003). Based on the FAO/WHO risk assessments regarding PIF, two distinct groups of infants are considered to be most at risk: neonates of all birth weight classes regarding risk for meningitis during their neonatal period (28 days), and prematures and infants with low (<2500 g) and very low (<1500 g) birth weights with respect to risk of bacteremia during their first 2 months of life (FAO/WHO 2004, 2006). The severity of the impact of the disease largely depends on the type of disease. Of the infants suffering from meningitis a considerable percentage do not survive and many survivors suffer from severe sequellae. Infants suffering from one of the other types of infections have better prognoses (Bowen and Braden, 2008).

The FAO/WHO risk assessments on *Cronobacter* spp. related to PIF focused on providing relative risk estimates as meaningful absolute estimates of risk were not possible because reliable dose-response relationships for the pathogen are lacking. Unfortunately, thus, risk managers are not provided with a feel for the contribution of *Cronobacter* infection of infants to the overall burden of illness in the population that could help them in deciding on management priorities and actions. Control measures and other management actions are now derived from the impact on consumer exposure, i.e. hazard levels (prevalence) in PIF and ultimately in product consumed, derived from the MRA studies.

A starting point for any exposure assessment is the estimation of the numbers of the micro-organism under investigation in the implicated food commodity. A direct link between the concentration of *Cronobacter* spp. in PIF and illnesses due to consumption of PIF has so far not been established systematically. For *Cronobacter* spp., the average concentration in PIF considered in the FAO/WHO MRAs was based on prevalence data provided by organizations and companies worldwide combined with published data. The concentration was estimated to be in the range of $10^{-5.24}$ to $10^{-2.79}$ [cfu/g] under the hypothesis that contamination in a batch is homogeneous and if positive, there is only one cell and not a clump of cells (FAO/WHO, 2006). Micro-organisms, however, have been described to occur heterogeneously in powdered milk products such as PIF (Habraken et al., 1986). It is therefore not unlikely that in PIF with low concentrations of *Cronobacter* spp., most of the portions are free of the micro-organism, while some portions contain many more cells than the estimated $10^{-5.24}$ to $10^{-2.79}$ [cfu/g]. To calculate the risk to the infant sub-population in a country associated to *Cronobacter* spp., there is a definite need to determine whether or not this heterogeneity in distribution exists and to which extent it affects the risk to the consumers as compared to risk assessments assuming homogeneous distribution. This publication is, to our knowledge, the first study to address heterogeneity in PIF and its possible impact on risk for *Cronobacter* infection in infants. It is a preliminary study, as several aspects need more work and scrutiny before being conclusive.

In this preliminary study, also, a generic approach has been used to put the risk of *Cronobacter* spp. into perspective regarding the overall burden of illness in The Netherlands due to other foodborne diseases. A generic approach has been chosen because it is not possible to unequivocally describe the risk due to a number of different diseases and disease outcomes caused by different micro-organisms in a single unit of expression. In epidemiology the DALY concept (Disability Adjusted Life Years) has been designed to quantify and compare a large variety of adverse health effects and has been used as a tool to estimate the burden of disease and injury in a given population as well as to set priorities for resource allocation (Gold et al., 2002; Murray and Acharya, 1997). In essence, the DALY is a quantitative health indicator that reflects the total amount of healthy years lost due to morbidity (*YLD*) or premature death (*YLL*) as described by Homedes (1996). The DALY concept is the measure recommended by WHO for assessing the impact of foodborne illnesses (WHO, 2007) and in the Netherlands the DALY concept has been applied in a number of studies of foodborne and other risks (Havelaar et al., 2000, 2004; Melse et al., 2000; van Lier et al., 2007). Here we present a preliminary estimate of the Disability Adjusted Life Years (DALY) lost due to *Cronobacter* infections in infants in the Netherlands and compare them to other foodborne diseases.

2. Materials and methods

To generate data on the distribution of *Cronobacter* spp., powdered infant formula was artificially contaminated as described by Kandhai et al. (2006). In short, approximately 100 µl of an overnight culture of *Cronobacter sakazakii (Enterobacter sakazakii)* ATCC 29544 was added to 20 g of PIF using a perfume sprayer. After thorough drying in the presence of saturated LiCl, 5 g of the contaminated powder was added to 1 kg of powdered infant formula, simulating contamination of a larger batch of product. This powder was then thoroughly mixed, poured in a large container, whereupon 100 samples of 0.5 g were drawn. Samples were diluted (1:10) in sterile water, mixed, and 100 µl was plated on duplicate tryptone soy agar plates (Oxoid, Basingstoke, England) with a spiral plater (Eddy Jet; IUL Instruments, I.K.S., Leerdam, The Netherlands). Plates were incubated for 20 to 24 h at 37 °C before manual counting. The detection limit was 50 cfu/g.

Calculations were performed in Microsoft Excel 2003. Distributions were simulated using @Risk 5.0.1 (Palisade Corporation) performing 10,000 iterations by Latin Hypercube sampling with random seed generation.

3. Results and discussion

On a global level, the exposure to *Cronobacter* spp. due to intrinsic contamination of powdered infant formula can roughly be estimated by multiplying the levels in powdered infant formulae by the amount of formula consumed worldwide:

$$\begin{aligned} \textit{Yearly worldwide exposure} &= \textit{Estimated mean concentration}\,[\text{cfu}/\text{g PIF}] \\ &\quad \times \textit{Worldwide production}\,[\text{g PIF}/\text{year}] \\ &= 10^{-3.84}\,[\text{cfu}/\text{g PIF}]\cdot 4.81\cdot 10^{11}\,[\text{g PIF}/\text{year}] \\ &= 6.95\cdot 10^{7}\,[\text{cfu}/\text{year}] = 7.84\,[\log \text{cfu}/\text{year}] \end{aligned} \quad (1)$$

where the estimated mean concentration (geometric mean) was derived from the report of the FAO/WHO expert consultation (FAO/WHO, 2006) and the worldwide production was estimated as $4.81 \cdot 10^5$ tons based on Euromonitor estimates 1998–2005 (Cordier, 2008).

The yearly exposure of 7.84 [log cfu/year] is the minimal number of *Cronobacter* spp. that is ingested by all infants through PIF worldwide per year. This would roughly correspond to 1 ml of a full grown microbial culture. This exposure figure, however, does not take into account that the micro-organism may grow after reconstitution. Therefore, actual total exposure globally may be heavily underestimated, considering the growth opportunities for instance when prepared infant formula is stored for some time at temperatures allowing growth after being reconstituted at temperatures allowing survival of the contaminant (FAO/WHO, 2004, 2006).

A similar approach can be taken to estimate the annual exposure of a single infant consuming PIF. For a conservative estimate, an infant is assumed to be between 3 and 3.5 kg of body weight, being exclusively fed with infant formula, and consuming 6 bottles of 100 ml of prepared infant formula per day (on average containing 13.8 g PIF per bottle, resulting in a total consumption of 83 g of PIF per day) during its entire neonatal period (first 28 days of life). The average (geometric mean) number of *Cronobacter* spp. ingested by this infant is:

$$\begin{aligned} \textit{Exposure during neonatal period} &= 83\,[\text{g PIF}/\text{day}]\cdot 28\,[\text{days}] \\ &\quad \times 10^{-3.84}\,[\text{cfu}/\text{g PIF}] = 0.335\,[\text{cfu}] \end{aligned} \quad (2)$$

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