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# A Hazard Does Not Always Equate to a Risk: *Cronobacter* is a rare opportunistic pathogen and the greatest risk is only for a small sub-population of infants and only associated with powdered infant formula or human breast milk

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## ABSTRACT

*Cronobacter* infections can result in a rare, but severe disease in infants and especially neonates. Powdered infant formula (PIF), formula for special medical purposes and human milk fortifiers are considered relevant for the exposure and risk of this organism. Recently, there have been a number of recalls due to the presence of *Cronobacter* spp. in infant cereals. These products are, however, generally not consumed by neonates or very young infants and there have been no reported *Cronobacter* infections in infants under the age of 12 months linked to the consumption of an infant cereal. Therefore, *Cronobacter* should not be considered a risk in these foods. The same reasoning can be followed for any other food product apart from PIF. The focus for *Cronobacter* control should be on PIF for infants less than 6 months of age, breast milk, and general hygiene in the environment and food preparation area for this age group, and even more so for newborns less than 2 months of age, premature infants and infants with weakened immune systems.

## 1. What is *Cronobacter*

*Cronobacter* spp. are opportunistic pathogens that belong to the family Enterobacteriaceae. It is now most widely accepted that *Cronobacter* spp. have a natural association with eukaryotic plants and their roots (Schmid et al., 2009). In 2007, the bacteria that were formally known as *Enterobacter sakazakii* were reclassified as *Cronobacter* spp. There are currently seven species in the genus *Cronobacter*, namely, *C. condimenti*, *C. dublinensis*, *C. malonaticus*, *C. muytjensii*, *C. sakazakii*, *C. turicensis* and *C. universalis* (Forsythe, 2018).

*Cronobacter* spp. are known to survive for many months or even years in manufacturing sites of dried infant foods, dairy powder and powdered infant formula (Chase et al., 2017; Craven et al., 2010; Kim et al., 2007; Reich et al., 2010; Yan et al., 2015). *Cronobacter* spp. are more frequently found in dry processing environments compared to other members of the Enterobacteriaceae (Mousavi et al., 2023). For example, *Cronobacter* spp. was found in 69% of the processing environment of 55

facilities manufacturing milk powder in the US while *Salmonella* was detected in 5.5% of these 55 facilities (Hayman et al., 2020).

*Cronobacter* infections can result in rare, but life-threatening meningitis (brain abscess hydrocephalus, cysts), necrotizing enterocolitis (intestinal necrosis and pneumatosis intestinalis) and septicemia. Infants and particularly pre-term infants are susceptible to infection due to their immature immune system. For unknown reasons, *Cronobacter* meningitis appears to be more common in full-term and late pre-term infants, whereas *Cronobacter* bacteremia appears to be more common in early pre-term infants (Bowen & Braden, 2006). Those at greatest risk of *Cronobacter* infection are neonates ( $\leq 28$  days), particularly pre-term, low birthweight ( $< 2500$  g), and immunocompromised infants (FAO/WHO, 2006).

Almost all species of *Cronobacter*, except for *C. condimenti*, have been shown capable of causing human illness (Lindsay et al., 2024). A number of different virulence factors have been described in the genus, but more research is needed in terms of understanding the virulence of all the

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species in the genus *Cronobacter* (Lindsay et al., 2024).

From a regulatory standpoint, all the different species of *Cronobacter* which were reclassified as various species of *Cronobacter* from the originally named *Enterobacter sakazakii*, should be considered as pathogens (FAO/WHO, 2008). An international *Cronobacter* spp. standard has been established, but only for Powdered Infant formula (PIF) and formula for special medical purposes and human milk fortifiers (Mousavi et al., 2023). This was based on the strength of evidence of a causal association between its presence in reconstituted PIF and illness in infants (CAC, 2008). Some jurisdictions describe *Cronobacter* spp. specifications in dried infant formulae and dried dietary foods for special medical purposes intended for infants below 6 months of age (EC, 2005). Therefore, manufacturers of such products should respond to its presence, no matter what species is identified.

As *Cronobacter* disease surveillance systems do not exist in most countries and it is classified as a notifiable disease in only a few countries, the true incidence of invasive infant *Cronobacter* infections is unknown. However, estimates from US lab-based surveillance suggest that around 18 infant cases of invasive *Cronobacter* infection (0.49 cases/100,000 infants) occur annually (Patrick et al., 2014). In the last decade there does not seem to be an increasing or decreasing trend in the number of reported cases (Fig. 1) although the number of cases is irregular. Since it is now a notifiable disease (since 2024) in the whole of the US (CDC, 2024b), future trending data might become more reliable. The majority of cases occur in infants (i.e., <1 year of age) and those individuals greater than 70 years of age as shown in Patrick et al. (2014).

## 2. Epidemiology

The 2008 WHO/FAO risk assessment, which reviewed 120 cases of *Cronobacter* infections (1961–2008) revealed that 95% of infants became ill within the first 2 months after birth, 8 cases occurred in infants older than 6 months and 2 cases in children older than 1 year, both of whom had underlying disease conditions (FAO/WHO, 2008). PIF was the foodstuff most associated with those cases. A more recent metadata study (Stryzko et al., 2020) reviewed all cases of *Cronobacter* bloodstream infection or meningitis among infants reported to the US Centers for Disease Control and Prevention (CDC) and in the literature (1961–2018; n = 183). The number of reported cases was sporadic from 1971 until 2001, after which the organism gained increased attention. From 2001 to 2018, there did not seem to be a trend upward or downward in the number of reported cases. Nearly all infants (95% [140/148]) became ill within the first 2 months after birth, 67% (100/150) in the neonatal period ( $\leq 28$  days); the median age at symptom onset was between 7 and 28 days. Stryzko et al. (2020) described the feeding histories for 102 infants. Among these infants, 81

(79%) reported recent consumption of PIF, with or without other supplemental feeding types, and 48 (47%) consumed PIF exclusively. In cases of *Cronobacter* infection from vehicles other than PIF, Stryzko et al. (2020) reported 4 cases which involved exclusive consumption of liquid infant formula, and 2 cases where contaminated bottled water appeared to be involved. Expressed/non-expressed breast milk (Stryzko et al., 2020) and powdered breast milk fortifier (Bowen & Braden, 2006) have also been implicated.

However, finding *Cronobacter* in opened PIF containers does not prove that the PIF was intrinsically contaminated, as opposed to being contaminated after the container was opened or during preparation. The cases in which no source/vehicle was identified, as well as the cases occurring among infants who did not consume PIF or expressed breast milk, suggested other cross-contamination modes of transmission are possible, including environmental cross-contamination from preparation surfaces, reconstituted water use, and infant feeding accessories, where the organism can be frequently found (Samadpour et al., 2024). The study of Stryzko et al. (2020) did not report an epidemiological link with any other supplementary or complementary food such as infant cereal. Infant cereals are consumed by infants as they commence their transition to solids foods (weaning period), usually not before 4 months of age, and infant cereals are usually marketed for infants aged 6 months and older. The association of PIF with *Cronobacter* infection has also been highlighted by Lindsay et al. (2024) who listed 6 potential outbreaks in infants and 14 recalls of *Cronobacter* spp., from 1988 to 2023, related to the presence, or possible presence, of *Cronobacter* spp. These data reiterate the findings of the 2004 and 2006 FAO/WHO meetings that amongst infants, neonates and infants less than 2 months of age are at the greatest risk of infection regardless of source.

## 3. Routes of exposure and ubiquity of *Cronobacter* spp.

Previous investigations of cases and outbreaks have identified *Cronobacter* spp. in opened PIF. Often, however, the bacteria are not detected in lot-matched batches of unopened powdered formula (Stryzko et al., 2020). While PIF manufacturing facilities may be a source of *Cronobacter* (see above), going undetected in finished product through limitations in sampling plans, vulnerable infants may be exposed to environmental contamination of the PIF from the environment of the hospital or home (Kandhai et al., 2004). Samadpour et al. (2024) collected samples from 263 homes located in 36 continental US states from June 2022 to June 2023. *Cronobacter* spp. and *C. sakazakii* were isolated from 36.1 % and 24.7% of homes, respectively. More specifically, in the domestic kitchen environment, *Cronobacter* spp. were most frequently isolated from entryway floors (23%, 13 of 57 samples) and vacuum cleaner contents/floor sweepings (18%, 70 of 382 samples). Other sources of contamination included kitchen sponges (7%, 5 of 71 samples), kitchen sinks (5.3%, 14 of 265 samples), kitchen floors (3.5%, 10 of 282 samples), kitchen counters (3%, 8 of 283 samples), and refrigerator shelves (2%, 5 of 210 samples).

Besides PIF, infants can become exposed and infected through expressed breast milk and/or the breast milk pumping equipment (Bowen et al., 2017; Haston et al., 2023; McMullan et al., 2018). In all 3 of the latter cases described (one described in the first and two in the second publication), infants were less than 2 months of age.

*Cronobacter* spp. are ubiquitous and have been isolated from many different environments and foods, such as water, meat, cheese, milk, dried foods, cereals, herbs, spices and fruits/vegetables (Baumgartner et al., 2009; Friedemann, 2007; Schmid et al., 2009; Vasconcellos et al., 2018). The isolation of *Cronobacter* spp. from plant-based products, especially cereals, wheat flour, and starches is not uncommon (Brandão et al., 2017; Cechin et al., 2022; Jang et al., 2022; Lou et al., 2014). In a recent survey, the prevalence of *Cronobacter* spp. and *C. sakazakii* in US retail foods (n = 4009) was determined (Samadpour et al., 2024). *C. sakazakii* contamination frequencies of all food items showed a similar pattern to that of *Cronobacter* spp. The highest frequency of

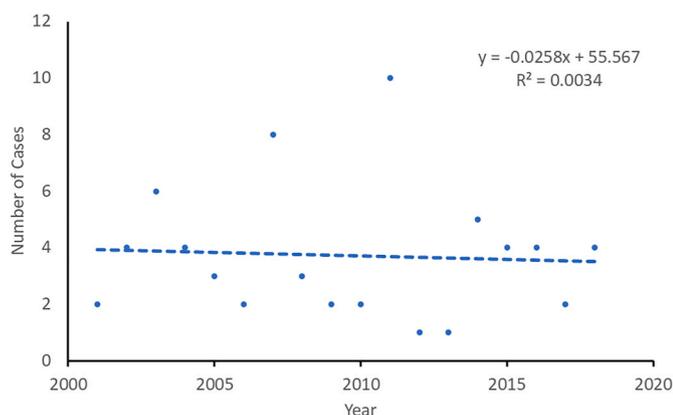


Fig. 1. Number of reported cases of invasive *Cronobacter* infections among infants in the United States from 2001 to 2018, retrieved from Stryzko et al. (2020).

contamination was observed for whole grain/baked goods/flours (25.8%). Of the 4009 food samples tested, 6.0% were positive for *Cronobacter* spp. and 5.1% were positive for *C. sakazakii*. An earlier study (Lou et al., 2014) recovered *Cronobacter* spp. from all wheat flours analysed.

#### 4. Assessment of the risk of *Cronobacter* spp. from infant cereals

Based on non-compliance to local and/or international *Cronobacter* spp. microbiological specifications, or food business operator findings in their plant, a number of recalls/withdrawals for PIF have been conducted over the past decade (see for example Table 1).

However, there have been limited recalls for infant cereals. The known recalls have resulted from agency surveillance findings, despite no established regulatory limit for *Cronobacter* spp. existing in all cases. The Belgian Food Safety Agency (FASFC) withdrew from sale a rice-based cereal flour following the detection of *Cronobacter* bacteria (AFSCA, 2021). The Swiss Federal Food Safety and Veterinary Office (FSVO) recalled an infant, cereal-based food after detecting contamination by *C. sakazakii* (BLV, 2020). Following on from both European recalls, clarification was sought from the EU Commission for the regulatory basis of the recalls. It was clarified that processed cereal baby foods and baby foods for infants can be given from 4 months of age (EC, 2006). However, as mentioned before, the *Cronobacter* spp. food safety criterion applies only to infant formulae as a category, and formula for special medical purposes and human milk fortifiers (CAC, 2008), and not to processed cereal based foods and baby foods (independently of the starting age of taking these foods, 4 or 6 months).

In 2024, the Canadian Food Inspection Agency (CFIA) recalled an oatmeal organic whole grain baby cereal due to the presence of *Cronobacter* spp. and subsequently initiated a second recall, linked to an oat banana and mango baby cereal (Government of Canada, 2024). The products were marketed for infants 6 months and 8 months of age and older, respectively.

#### 5. Infant cereals manufacturing

Infant cereals are low-moisture foods (LMF) generally manufactured using roller dryer technology (Cordier, 2008; Fellows, 2022). Ingredients include grains such as rice, wheat or oats which are mixed with water and/or other liquid ingredients (oil, water). The mixture is subjected to thermal processing validated to eliminate vegetative pathogens and to reduce spore-forming bacteria, before being spread onto a heated roller dryer to produce a thin sheet of cereal, which is milled. Additional ingredients such as fruit and vegetable flakes, vitamins, minerals and dairy powders are added. These ingredients are manufactured to comply with infant cereal finished product microbiological specifications.

Microbiological criteria for processed infant cereals include *Salmonella* as a food safety criterion. The recommended 2-class plan applied is  $n = 60$ , not detected in 25g, if in-process results indicate a potential for deviation, however, the 'n' may be reduced if in-process results indicate hygiene conditions are under control (ICMSF, 2011, pp. 339–347). The food safety criteria are accompanied by strict Enterobacteriaceae process hygiene criterion, usually as minimum, a 3-class plan of  $n = 5$ ;  $c = 2$ ;  $m = 0-10$ ;  $M = 10-100$  (ICMSF, 2011, pp. 339–347). Corresponding supplier management programs, good manufacturing practices (GMP), and environmental monitoring programs are expected to ensure hygienic conditions.

#### 6. Hazard versus risk

There is a significant difference between the presence of a hazard and a risk. Food legislation globally includes both hazard- and risk-based approaches for ensuring safety. In hazard-based approaches, simply the presence of a potentially harmful agent at a detectable level in food can be used as a basis for legislation and/or risk management action.

**Table 1**  
Recalls of Powdered Infant Formula 2022–2024.

Date	Description	Outbreak/ Recall/ Withdrawal	Concerned Countries	Food description
December 31, 2023	Reckitt/Mead Johnson Nutrition has voluntarily recalled certain Nutramigen Hypoallergenic Infant Formula Powder	Recall	USA	hypoallergenic infant formula Reckitt/Mead Johnson Nutrition Voluntarily Recalls Select Batches of Nutramigen Hypoallergenic Infant Formula Powder Because of Possible Health Risk   FDA
March 17, 2023	Perrigo/Nestlé: Gerber® Good Start® SootheProTM	Recall	USA/ Canada	Powdered Infant Formula Gerber infant formula recalled over potential <i>Cronobacter</i> contamination Plant-based infant formula Perrigo Issues Voluntary Recall of One Batch of Premium Infant Formula with Iron Milk-Based Powder Due to Elevated Levels of Vitamin D   FDA
February 20, 2023	Reckitt Voluntarily Recalls Two Batches of Enfamil Prosobee Brand Simply Plant Based Infant Formula 12.9oz Cans	Recall	USA; Guam; Puerto Rico	Infant formula ByHeart Issues Voluntary Recall of Five Batches of Its Infant Formula Because of Possible Health Risk   FDA
December 11, 2022	ByHeart Voluntarily Recalls Five Batches of ByHeart Whole Nutrition Infant Formula, Milk Based Powder with Iron for 0-12Mos 24oz Cans	Recall	USA	Infant formula Cronobacter prompts infant formula recall in Slovakia   Food Safety News
November 10, 2022	Infant formula from Czech Republic	Withdrawal	Slovakia	Infant formula FDA Advises Parents and Caregivers Not To Buy Or Give Mother's Touch Formula To Infants   FDA
September 21, 2022 to May	Mother's Touch Infant Formula	Recall	USA	Powdered infant formula Abbott Voluntarily Expands Recall of Powder Formulas Manufactured at One Plant   FDA (see also FDA, 2022 and Newman and Kang, 2022)
February 17, 2022 to May 30, 2022	Abbott Powdered Infant Formula –Voluntarily Recalls Similac Alimentum (400g) and Similac Human Milk Fortifier (0.9g x50 sachets)	Outbreak (4 cases, 2 deaths)	>15 countries worldwide	

In contrast, risk-based approaches also allow for the consideration of exposure information in assessing whether there may be unacceptable risks to health. Simply put, a hazard can be a biological, chemical or physical agent in a food with the potential to cause an adverse health effect, while “risk” takes into account the probability of an adverse health effect and the severity of that effect, after exposure to a contaminated food (CAC, 2024).

There are several situations relevant to food safety, where the presence of a hazard alone is not sufficient to result in a risk to human health and would not need to result in a recall. Some examples include:

- i) Most recently, we have seen with SARS-CoV-2, in an opinion paper (ICMSF, 2020), the ICMSF state that it is vital that one differentiates a hazard from a risk, i.e., the mere presence of an infectious agent, e.g., SARS-CoV-2, on food, thereby differentiating a hazard from a risk.
- ii) Foods containing low levels (e.g., 100 cfu/g) of *L. monocytogenes* and that prevent its growth pose very little risk (Chen et al., 2003). However, regulatory agencies may adopt a more precautionary approach to risk management, maintaining a “zero tolerance” policy for this organism.
- iii) The presence of low levels of *Clostridium botulinum* spores in foods and the environment occur routinely (Barker et al., 2016) and, with the exception of infants younger than 12 months (being the consumers particularly at risk for infant botulism) and specific highly susceptible adults (potential for adult intestinal toxemia), these spores are generally ingested with no harm (ICMSF, 2014).

There are no reported *Cronobacter* infections in infants under the age of 12 months linked to the consumption of an infant cereal. Besides the lack of epidemiological evidence, other factors should be considered when assessing whether the mere presence of *Cronobacter* spp. in an infant cereal could cause human illness, i.e., representing an unacceptable risk. These include:

- i) There appears to be a very strong correlation between the age of an infant and underlying illness conditions (see above).
- ii) Although the dose response of *Cronobacter* for humans is unknown, it is widely recognized that growth of the organism would increase the risk of infection for reconstituted powdered infant formula (PIF) fed to infants. The same thinking would likely apply for reconstituted infant cereal.
- iii) Infant cereals are generally marketed towards weaning infants 6 months of age and older. This age group gradually becomes exposed to many different foods, any of which could contain *Cronobacter* spp. However, it is recognized that there may be infrequent off-label use of infant cereal, e.g., some physicians may recommend feeding cereal to infants less than 6 months of age. However, this should only be for infants at the weaning stage, that is 4 months old and above, which is still low risk. The Dietary Guidelines for Americans and the American Academy of Pediatrics recommend that children only be introduced to foods other than breast milk or infant formula when they are about 6 months old, and they do not recommend introducing solid foods before 4 months of age (American Academy of Pediatrics, 2022; CDC, 2024a; U.S. Department of Agriculture and U.S. Department of Health and Human Services, 2020). A Codex-CCFH FAO/WHO review published in 2008 (FAO/WHO, 2008) of documented *E. sakazakii* (*Cronobacter* spp.) infections worldwide, identified roughly 120 individually documented cases among infants and young children up to 3 years of age. Six of these cases occurred among infants 6–11 months and two cases among children in the 12–36 months age group. Among the 5 invasive (urine, blood, cerebrospinal fluid (CSF), brain tissue) cases in the 6–11 months age group, 3 had other active medical problems. The majority of cases (ca. 80%) occurred in infants less than or equal to 60 days of

age. And as mentioned earlier Stryzko et al. (2020) also reported that nearly all infants (95% [140/148]) became ill within the first 2 months after birth.

- iv) As stated above, a recent study of 263 US homes (2810 environmental samples) found the presence of *Cronobacter* spp. in approximately 25% of them. Thus, the possibility of environmental/cross-contamination of infant cereal (as well as PIF) cannot be excluded and has actually been hypothesized as being a significant cause of cross-contamination of infant foods.

Furthermore, in 2012, UNICEF and the World Food Programme detected *Cronobacter* species in certain lots of lipid-based ready-to-use foods (RUF) which are administered to children from 6 to 59 months of age and who suffer from mild or severe malnutrition (FAO/WHO, 2016). A WHO/FAO technical meeting was held to provide guidance on microbiological specifications. The meeting concluded that *Salmonella*, and not *Cronobacter*, was the pathogen of greatest concern for RUF impacting the age group 6–59 months of age, even for this more susceptible group (FAO/WHO, 2016). Therefore, there already exists expert guidance on products similar to infant cereals.

The above-mentioned recalls have set a precedent for recalling infant cereals that contain *Cronobacter* spp. without findings of inadequate GMP's in the corresponding production facilities (insanitary conditions) or any epidemiological associations to illness. The ICMSF considers these actions not to be risk-based decisions, and not based on currently available scientific evidence/information. Furthermore, such recalls result in unnecessary waste and costs, despite an objective lack of public health risk. Subjecting nutritional products, intended for consumption by children over 6 months to a recall due to the detection of *Cronobacter* would indicate manufacturing entities must establish industry-wide modifications to their manufacturing processes as well as finished product food safety criteria and specifications for raw materials that do not currently exist. The disruption to the infant nutrition and broader food industry could be significant, leading to a severe shortage of infant cereals (and possibly other types of powdered dairy products for infants greater than 6 months of age) globally, with a low likelihood of significant benefit to public health.

## 7. Conclusions

The ICMSF considers that there is no risk basis to support the regulatory testing of infant cereals for the presence of *Cronobacter* spp. and no food safety basis for the recall of such products should *Cronobacter* spp. be detected. In this pathogen/food scenario, the potential hazard is widespread and can be found in many different environments and foods, including powdered milk. Furthermore, although there have been some cases of *Cronobacter* spp. causing illness in infants greater than 6 months of age potentially linked to the consumption of PIF (FAO/WHO, 2008; see Annex 1) reported worldwide, to our knowledge there have no cases been linked to infant cereal. Thus, in this situation/case, the presence of a hazard in a food, i.e., *Cronobacter* spp. in infant cereals, which are manufactured and marketed to infants greater than 6 months of age, does not equate to a risk for infants greater than 6 months of age.

The same reasoning can be followed for any other food product. The focus of *Cronobacter* risk management should be on PIF for infants less than 6 months of age, expressed breast milk, and general hygiene in the environment and food preparation area for this age group, and even more so for newborns (less than 2 months) and premature infants and others in neonatal intensive care units.

## Data availability

No data was used for the research described in the article.

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