

Recommendation for the Preparation of Powdered Infant Formula

PRACTICE ISSUE EVIDENCE SUMMARY

Best Practice Issue (state as a question, PICO):	
What are the recommendations for decreasing the risk of <i>Enterobacter sakazakii</i> (<i>Cronobacter</i> spp.) infection and illness from powdered infant formula among infants in the community?	
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Date of Final Approval:	To be Reviewed:
Purpose: (goals, scope, intended users, settings, and patient/client groups)	
<p>The goal from a population health perspective is to ensure that the nutritional needs of all infants are safely met by determining the safe preparation of powdered infant formula.</p> <p>According to Health Canada, infants are considered at greatest risk of <i>Enterobacter sakazakii</i> (<i>E. Sakazakii</i>) infection if they are pre-term or low birth weight infants less than 2 months of age, or immunocompromised infants.</p>	
Definitions:	
<p>PIF: powdered infant formula</p> <p>WHO: World Health Organization</p> <p>FAO: Food and Agriculture Organization of the United Nations</p> <p>Infants: ≤1 year of corrected gestational age (ADA, 2000)</p> <p>Infants at greatest risk: Infants who are</p> <ul style="list-style-type: none"> a) born pre-term* (<37 weeks gestation) for the first 60 days of life, or b) born at a low birth weight (<2500 grams) for the first 60 days of life, or c) immunocompromised** and less than one year of age. <p>*Health Canada's response regarding actual vs. corrected age for preterm infants: "When the risk assessment was done, they were looking at the actual age and not the corrected age. Therefore, it is defined as two months from the time the baby is born." (Couture, 2012)</p> <p>**Health Canada's response: "The FAO/WHO risk assessment acknowledges that there is no commonly understood definition of the term 'immunocompromised.' However, within the risk assessment, immunocompromised is defined as people who are more susceptible to infections. In other words, people who have undergone transplant surgery, chemotherapy, malnutrition, taking immunosuppressive treatment or people with chronic diseases, etc." (Couture, 2012) Due to the lack of a clear definition provided by Health Canada, caregivers are advised to consult the infant's health care provider as to whether their infant is considered immunocompromised.</p> <p>Note on nomenclature of <i>Enterobacter sakazakii</i> (<i>Cronobacter</i> spp.): <i>Enterobacter sakazakii</i> has recently been reclassified into a new genus, <i>Cronobacter sakazakii</i>. To be consistent with previous literature it will be referred to as <i>Enterobacter sakazakii</i> (<i>Cronobacter</i> spp.) in this document. (Dietitians of Canada, 2011)</p>	

Evidence Review: (Please list type and grade of evidence reviewed)

Unlike liquid and ready-to-feed infant formulas, PIF is not a commercially sterile product. PIF has been associated with serious illness and death in infants due to infections with *E. sakazakii*. During production, PIF can become contaminated with harmful bacteria, such as *E. sakazakii*. Using current manufacturing technology, it is not feasible to produce sterile PIF. Although there are heat treatment steps that occur in the process, PIF can be re-contaminated due to the addition of dry ingredients and from the manufacturing environment. *E. sakazakii* can form a strong biofilm to equipment which resists cleaning and disinfecting and can lead to recontamination of subsequent batches of PIF (FAO/WHO, 2004). There are many points in the manufacturing process and during preparation where contamination and recontamination can occur. For instance, *E. sakazakii* has been found on air filters, equipment, employee shoes and in the soil around PIF manufacturing plants. PIF has been found to be contaminated with *E. sakazakii* at a rate of 2.9 to 14.2% of samples tested (Dietitians of Canada, 2011).

***Enterobacter sakazakii* (Cronobacter spp.)**

The WHO and FAO microbiological risk assessment on PIF collated all documented cases of *E. sakazakii* (*Cronobacter* spp.) in infants and young children (<3 years of age) between 1961 and 2008. There were 140 documented cases with 75% of them in infants less than 2 months of age. The majority of affected infants were low birth weight, very low birth weight or preterm. *E. sakazakii* infection has been reported all over the world with the majority of cases identified in developed, wealthier nations. The FAO/WHO report estimated that in 50-85% of documented cases, PIF was the direct or indirect (i.e. contaminated equipment used to prepare formula) source of contamination. The prevalence of infection may be underestimated due to a lack of surveillance equipment and unreported cases. There are at least 3 documented cases of *E. sakazakii* in Canada (1990, 1991 and 2007). The estimated incidence among infants is about one per 100,000 and among low birth weight neonates to be 8.7 per 100,000 (FAO/WHO, 2004). Although infection with *E. sakazakii* is rare, the potential consequences of infection are severe. *E. sakazakii* infection can cause meningitis, septicemia, bacteraemia, necrotizing enterocolitis, brain abscess, hydroencephalitis, neurological impairment and death (Dietitians of Canada, 2011). Mortality rates have been reported to be from 20 to >50% (FAO/WHO, 2004).

E. sakazakii can be killed in approximately 15 seconds when combined with water heated to 70°C or higher. The bacteria grow between the temperatures of 5.5°C and 49°C, with optimal growth between 37-43°C. When held at 37°C, the bacteria can double in approximately 20 minutes. The ability to grow at low temperatures increases the risk of infection if reconstituted formula is inappropriately prepared or held. At 6°C the bacteria can double in approximately 14 hours. Refrigerator temperature should be set to ≤4°C and should be confirmed with a fridge thermometer (FAO/WHO, 2006). Formula should be cooled rapidly (15 minutes or less), to reduce possible growth of other pathogenic organisms.

Current Recommendations:

WHO/FAO recommendations (excerpt from 2004 Risk Assessment);

- *In situations where infants are not breastfed, caregivers, particularly of infants at high risk*, should be regularly alerted that powdered infant formula is not a sterile product and can be contaminated with pathogens that can cause serious illness; they should be provided with information that can reduce the risk.*
- *In situations where infants are not breastfed, caregivers of high-risk infants, should be encouraged to use, whenever possible and feasible, commercially sterile liquid formula or formula which has undergone an effective point-of-use decontamination procedure (e.g. use of boiling water to reconstitute or by heating reconstituted formula).*

*According to the WHO/FAO, all infants less than 2 months are considered high risk.

Formula Can statements:

The statement on the Enfamil A+ can reads: "Powdered infant formula is not sterile and should NOT be fed to premature infants or infants who might have immune problems unless directed and supervised by your baby's doctor."

The statement on the Nestle Good Start can reads: "This powdered infant formula is not recommended for premature or immunocompromised infants unless directed by your baby's doctor."

Current Health Canada Recommendations and Recommendations for Implementation for the Community:

The WHO recommends using previously boiled safe water that has cooled to no less than 70°C (158°F) to reconstitute PIF for all infants (WHO, 2007). Health Canada recommends this method of preparation for infants who are preterm or low birth weight under 2 months of age, or infants who are immunocompromised. Health Canada also recommends this method for all infants when bottles are prepared for **later use** (Health Canada, 2010). For all healthy, full-term infants

and infants no longer in the greatest risk category, Health Canada states that cooled, previously boiled water can be used to reconstitute PIF for bottles to be **fed immediately**.

Recommendations:

It is recommended that Health Canada guidelines be adopted for implementation as this is currently the WRHA Population and Public Health standard for information.

Caregivers should be encouraged to discuss with their doctor or health care provider whether their infant fits in the 'greatest risk' category as defined by Health Canada. Caregivers of infants at greatest risk who are unable to use sterile liquid formula, or to reconstitute PIF with water at 70°C, should be advised to use harm reduction strategies as outlined below. All caregivers should be provided with information on safe, hygienic formula preparation.

PIF Preparation Guidelines:

Infants at greatest risk (pre-term or low birth weight infants under 2 months of age or immunocompromised infants):

1. Caregivers should be informed that powdered infant formula (PIF) is not a sterile product and although minimal, there is a risk of bacterial contamination. Where possible, sterile liquid concentrate and liquid ready-to-feed formulas are recommended for those infants at greatest risk.

2. Two alternative methods are:

A) *Health Canada Approved Method*

When PIF is used for infants at greatest risk, it should be reconstituted with potable water that has been boiled for 2 minutes and allowed to cool to 70°C. This is the optimal method of formula preparation for this population as *E. sakazakii* bacteria is killed when heated to 70°C for 15 seconds. Caregivers should be informed that this is the method recommended by Health Canada.

- Boil potable water for 2 minutes and cool it in the same pot to no lower than 70°C. At room temperature, this will take approximately 30 minutes for 1 L of water.
- Add the appropriate amount of water to a washed and sterilized bottle. Then add the powdered formula as per the instructions on the formula can or from the healthcare provider and thoroughly mix. It may be necessary to stir the formula with a sterile spoon to reduce clumping.
- Rapidly cool the formula in 15 minutes or less to the desired feeding temperature (generally between room and body temperature) by holding the bottle under cold running water or by placing it into a container of cold/ice water. Care must be taken to prevent any water from getting above the lid of the bottle and into the formula, as this could contaminate the formula.
- Dry the outside of the bottle and test the temperature (via a sterile thermometer or by shaking a few drops onto the inside of the caregiver's wrist) before feeding. If it is too hot, cool it further.
- Reconstituted formula can be kept in the refrigerator for up to 24 hours or remain at room temperature for a maximum of 2 hours. Once feeding has started, use the bottle within 2 hours and discard leftovers.

B) *Harm Reduction Method*

The following method may minimize the growth of *E. sakazakii*, but does not kill the bacteria. If caregivers of infants at greatest risk are unable or choose not to prepare PIF with water at 70°C, they should be advised to prepare formula as follows:

- Reconstitute PIF immediately before feeding using previously boiled potable water. Using water chilled to ≤4°C (refrigerator temperature) may further reduce the risk (ADA, 2004). The use of chilled water will minimize the growth of *E. sakazakii* as the bacteria are unable to grow at this temperature. Formula should be warmed to the desired temperature and fed immediately. Parents should be advised that Health Canada recommends PIF be prepared with water at 70°C for infants at greatest risk.

3. When PIF is added to expressed breast milk or donor breast milk as a fortifier, feeds should be prepared as needed and given immediately to the infant to minimize bacterial growth. Breast milk should be either freshly expressed or chilled at ≤4°C (refrigerator temperature) (ADA, 2011).

Infants not identified at greatest risk:

1. When PIF is prepared for **immediate use** for infants not identified at greatest risk, it can be reconstituted with

previously boiled water. Sterile water should be stored in a sterile container (i.e. pot used for boiling water), and should be covered and stored at room temperature for no more than 24 hours or in the refrigerator for no more than 72 hours. It is preferable to prepare each feed fresh and feed immediately, because once reconstituted, formula is an excellent growth medium for microbes.

Health Canada recommends using previously boiled water to prepare PIF for all ages of infants as per manufacturers' instructions due to a lack of evidence regarding a safe age at which to stop boiling water for infant formula preparation (Health Canada, 2010). Age alone, is a poor predictor of infant vulnerability to foodborne illness and immune status varies among infants. Sterilizing water for healthy term infants has historically been recommended until infants are 4 months of age. By 4 months, infants are commonly putting many non-sterilized objects in their mouths.

Caregivers should be informed to follow manufacturers' instructions to prepare infant formula as per Health Canada's guidelines. If caregivers choose to stop boiling water at 4 months, they should be advised to use cold tap water and clean equipment washed in hot, soapy water when preparing infant formula for immediate use.

2. When PIF is prepared for **later use** for all infants, it should be reconstituted with potable water that has been boiled for 2 minutes and allowed to cool in the same pot to no lower than 70°C.
 - Formula should be prepared in volumes no greater than 1 L so it can be cooled more rapidly in the refrigerator (WHO, 2007).
 - Reconstituted formula should be held in a covered, sterilized container, rapidly cooled and used within 2 hours when held at room temperature or rapidly cooled and refrigerated immediately at $\leq 4^{\circ}\text{C}$ for no more than 24 hours. Formula should be stored at the back of the body of the refrigerator as the temperature is cooler and fluctuates less than storage in the refrigerator door. All caregivers should be instructed to maintain their refrigerators at $\leq 4^{\circ}\text{C}$ confirmed with a refrigerator thermometer.
 - Reconstituted formula should be re-warmed in less than 15 minutes by immersing in warm water. The use of microwaves for reheating is not advised.
 - Once feeding has begun, formula should be used within 2 hours or discarded.

Potential Risks of Recommendations

The potential risks of preparing PIF with 70°C water must be weighed against the risks of possible infection with *E. sakazakii*. Caregivers should be informed of the risks and instructed on the precautions (Dietitians of Canada, 2011).

1. **Scalding:** Water at 70°C can scald an infant's skin in less than one second. Caregivers should be cautioned to cool and test formula temperature prior to feeding.
2. **Activating spore-forming bacteria:** Addition of very hot water (70°C) to PIF could activate bacterial spores (i.e. *Bacillus cereus*) that might be present in the formula. The risk is minimized if the formula is cooled rapidly, (less than 15 minutes) after reconstitution and fed immediately or refrigerated for a maximum of 24 hours.
3. **Potential nutrient loss:** There is limited evidence on the effects of heat on vitamin content in PIF. There may be some loss of vitamin C and thiamine, but this loss may be compensated for by extra nutrients added to products by manufacturers. It should be noted that any denaturation of protein in PIF when combined with 70°C water, would be similar to protein damage that might occur when liquid formulas are heated during sterilization.
4. **Inactivation of probiotics:** Manufacturers generally recommend water be cooled to 40°C when reconstituting probiotic containing formulas, as temperature hotter than this will destroy probiotics. Loss of the potential benefits of probiotics in the formula must be weighed against the potential risk of feeding PIF prepared with water at less than 70°C. Health professionals should be aware that probiotic products are available for purchase separate from infant formula.
5. **Clumping of formula:** Formula mixed with 70°C water may require extra mixing due to possible clumping. Ensure formula is well mixed prior to feeding.
6. **Special formulas may contain heat-sensitive ingredients, i.e. human milk fortifiers:** Caregivers should consult the infant's doctor or healthcare provider for advice. Reconstituting formula when needed to feed immediately will reduce the risk.
7. **Risk of bisphenol A (BPA) leaching into formula:** BPA is a chemical used in making hard clear plastic called polycarbonate. The chemical is a known endocrine disruptor which is potentially harmful when ingested by infants. Polycarbonate baby bottles should not be used to prepare formula mixed with water at high

temperatures. Very hot water causes BPA to migrate out of the bottle into the formula at a higher rate. Caregivers should be advised to use BPA-free alternatives, which are readily available. If alternative bottles are not available, the formula should be mixed in a BPA-free container with 70°C water as described in the guidelines above. The formula mixing container should be sterilized for infants at greatest risk and healthy, full-term infants <4 months of age. Once cooled to between room and body temperature (20-37°C), formula can be transferred to the polycarbonate bottle. This will reduce the amount of BPA leached from the bottle into the formula (Health Canada, 2010).

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Practice Implications:

These recommendations have been reviewed by:

Name and Credentials	Date Review Complete
Public Health Nutrition Practice Council	September 11, 2012; Updated and approved: June 1, 2015

Pediatric Nutrition Practice Council	September 12, 2012; Updated and approved: June 26, 2015
Nutrition Advisory Sub-committee	January 23, 2014; Updated and approved:
Chantelle Riddle-Yarycky, Infection Prevention & Control - Community	June 2014
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