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Health Canada's Human Health Risk Assessment Supporting Standard Development for Melamine in Foods

**Bureau of Chemical Safety
Food Directorate
Health Products and Food Branch**

**A PAHO/WHO Collaborating Center for
Food Contamination Monitoring**



November, 2008



Canada 

Health Canada's Human Health Risk Assessment Supporting Standard Development for Melamine in Foods

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Background

On September 12, 2008, the Canadian Food Inspection Agency (CFIA) informed Food Directorate officials at Health Canada of reports from New Zealand that infant formula manufactured in China was being found contaminated with melamine (1,3,5-triazine-2,4,6-triamine). The government of China officially notified the Canadian Embassy, on September 11, 2008, that their General Administration of Quality Supervision, Inspection and Quarantine (AQSIQ) has launched a full investigation of the issue of contamination of infant formula manufactured in China.

Since this discovery, there have been numerous confirmed reports of melamine contamination of Chinese dairy products, including infant formulas. The presence of cyanuric acid, an analogue of melamine, has not been confirmed (WHO, 2008a). High levels of melamine in any food product are thought to be due to deliberate contamination in an attempt to artificially increase the apparent protein content. Melamine is high in nitrogen, which is often used as an indicator of protein content. Melamine was associated in 2007 with a North American investigation involving pet food, which prompted testing and the implementation of a compliance verification strategy for vegetable protein products (wheat, rice, soy and corn gluten and protein concentrates) entering Canada from all countries. The current issue of melamine presence in Chinese dairy products is considered to be a new and separate issue.

To date, no melamine-contaminated infant formulas have been discovered in Canada and no melamine related illnesses associated with any food have been reported in Canada. However, the investigation into melamine contamination was expanded to include other potentially affected products in addition to infant formula; namely, products made from milk or milk-derived ingredients. Milk-derived ingredients include whole milk powder, non-fat milk powder, whey powder, lactose powder, and casein. The CFIA has taken a number of actions including product sampling, testing, food recalls and advisories related to products that may be contaminated with melamine.

Melamine is a synthetic chemical used in a variety of commercial and industrial applications including the production of resins and foams, cleaning products, fertilizers and pesticides. It is not naturally occurring, has no accepted food uses and is not permitted to be added to food in Canada. Although Canada does not allow the addition of melamine to food, very low levels of melamine could be found in food due to its presence in the environment as a result of the use of this material in various industrial applications. In general, the low levels of melamine (in the range of parts per billion or ppb) in any food from these sources would not represent a health risk to humans.

Further information on melamine can be found on the web sites of the [CFIA](#) and [Health Canada](#).

Health Canada scientists in the Bureau of Chemical Safety have reviewed all of the available data concerning the possible health effects of melamine and cyanuric acid and have conducted a risk assessment to identify levels of melamine and cyanuric acid that would not be associated with an unacceptable health risk. This assessment also supported the development of interim standards (maximum levels) for melamine and cyanuric in infant formula and sole source nutrition products, including meal replacement products, as well as other food products containing milk and milk-derived ingredients.

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Hazard Characterization

Oral repeat dose studies, including cancer bioassays, have been conducted with melamine in mice, rats and dogs. The main target organs identified in subchronic and chronic assays appear to be the bladder and kidney. In National Toxicology Program (NTP) cancer bioassays, transitional cell papillomas and carcinomas of the urinary bladder were seen in high dose group F344/N male rats (263 mg/kg bw/day), along with indices of chronic inflammation of the kidney (NTP, 1983). A TD50 dose has been estimated at 735 mg/kg bw/day (Gold et al., 1989). Additional observations included the development of bladder stones (calculi) and hyperplastic epithelial changes of the urinary bladder. No significant neoplastic effects were observed in female rats or B6C3F1 mice of both sexes. There was a significant correlation seen between the development of bladder tumours in male rats and calculi formation. Subsequent mechanistic studies with artificially-induced polyuria (NaCl added to diets) indicated that suppression of calculi formation resulted in reduced proliferative lesions of the bladder and a lower incidence of tumours (Ogasawara et al., 1995). As additional studies have shown that melamine is not a tumour initiator and was not mutagenic / genotoxic in a wide variety of in vitro and in vivo assays, the mode of action for the bladder tumour formation is considered to be non-genotoxic or epigenetic (OECD SIDS Melamine, 1993).

The lowest identified dose for general toxic effects was < 63 mg/kg bw/day, based on the toxicological significance of minimal urolithiasis induction in Fischer 344 male rats following dietary melamine exposure for 13 weeks (63-1500 mg/kg bw/day; Melnick et al., 1984). Subsequent benchmark dose analysis (10% response rate) of the urolithiasis occurrence and incidence of hyperplasia of the bladder epithelium from subchronic oral feeding studies generated Benchmark Dose Levels (BMDLs; lower limit of a one-sided 95% confidence interval on the benchmark dose) of 35 mg/kg bw/day and 104 mg/kg bw/day, respectively (U.S. EPA version 1.4.1). As bladder stone formation is considered an appropriate precursor for any potential tumour development, the former value is recommended as an appropriate toxicological reference.

In reviewing the available scientific information about the health effects of melamine, Health Canada scientists established a toxicological reference dose (TRD) for melamine of 0.35 mg/kg body weight per day to ensure that all age groups are protected. This means that a person could ingest up to 0.35 mg of melamine each day for each kilogram of body weight with reasonable assurance that there would be no adverse health effects.

Toxicological Uncertainties

The main symptoms reported from China for infants consuming melamine contaminated infant formula involved primarily kidney effects of varying severity (stones, blockage, renal insufficiency, failure). However, in experimental feeding studies with melamine, the main effects have been bladder-related (stones, hyperplastic epithelial changes, tumours), although some indications of kidney toxicity were noted in female rats (chronic inflammation, fibrosis). This apparent discrepancy between species could be due to a number of factors, including functional and/or anatomical differences between the rat and human kidney, renal clearance capacity, developmental stage or the presence of additional contaminants. In the 2007 melamine pet food contamination issue involving wheat gluten, the presence of structurally related triazine contaminants, namely ammeline, ammelide and cyanuric acid, was confirmed. Subsequent short term experimental feeding studies conducted with cats have shown that while melamine and cyanuric acid separately did not produce kidney effects, combined dosing resulted in crystal formation in kidney tissue, clinical signs of renal damage and kidney lesions (Puschner et al.,

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2007). Similar indications of renal crystal formation and kidney damage have been observed in experimental feeding studies involving exposure of pigs and fish to combined doses of melamine and cyanuric acid (Reimschuessel et al., 2008). In addition, acute oral dosing studies with rats have shown only the combined mixture of melamine plus cyanuric acid or melamine and all three related triazines previously mentioned produced kidney crystals and damage (Dobson et al., 2008).

While the current hazard characterization is specific to toxic effects produced by melamine alone, consideration will be given to revising this position when combined results for specifically melamine and cyanuric acid are provided. This approach is consistent with the World Health Organization's recommendation (WHO 2008b) to use currently derived toxicological reference values that are based on melamine toxicity, since there are no available studies that have investigated the combined toxicity of melamine and cyanuric acid together that would allow for the derivation of a tolerable intake value for the presence of both compounds. As a result, the toxicological reference dose established by Health Canada scientists for melamine (0.35 mg/kg bw/day) was used to provide the basis for the development of interim standards for both melamine and cyanuric acid in foods.

Theoretical Exposure Assessment and Risk Management - Health Canada's Interim Standards for Melamine in Foods

Infant formula and sole source nutrition products, including meal replacements

Health Canada and the Canadian Food Inspection Agency (CFIA) have been analyzing infant formula sold in Canada although to date, no infant formulas contaminated with melamine have been found in Canada. In fact, no formulas produced in China are approved for sale in Canada. All infant formulas must undergo a rigorous pre-market evaluation and be approved by Health Canada before they are permitted to be sold in Canada. Nonetheless, Health Canada contacted all the major infant formula manufacturers whose products are sold on the Canadian retail market. These manufacturers have confirmed that they do not use milk ingredients from China. While infant formula from China is not approved for sale, there is the possibility that illegally imported product is being sold in some stores, for example, those that carry ethnic foods. As a precaution, Health Canada and the CFIA have been working with retailers to ensure that no unapproved infant formulas from China or elsewhere are available on the shelves of Canadian stores.

Although to date, no contaminated or illegally imported infant formulas have been found, Health Canada developed an interim standard (maximum level) specific to infant formula and sole source nutrition foods, as an interim risk management measure. Until additional details on background levels of melamine in foods are generated, any interim standards will be based on toxicological considerations only.

Using the infant formula intakes presented in Table 1, various theoretical melamine exposure scenarios were developed for formula-fed infants to determine an interim standard.

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Table 1. Maximum infant formula intakes and estimated melamine intakes based on various theoretical melamine concentrations (1.0, 2.5, and 20 ppm)

Age Group	Infant BW (kg) ¹	Maximum Infant Formula Intake (g/day) ²	Melamine Intakes (mg/kg bw/day) at various melamine concentrations (µg/g)		
			1.0 ppm	2.5 ppm	20.0 ppm
Premature infants	1.5	100	0.066	0.167	1.330
0-1 month	3.9	1080	0.277	0.693	5.540
2-3 month	5.5	1470	0.267	0.668	5.340
4-7 month	7.2	1440	0.200	0.500	4.000
8-12 month	9.0	960	0.107	0.267	2.140
12-18 month	10.6	900	0.085	0.213	1.700

Table 1 demonstrates that a melamine concentration of approximately 1 part per million (ppm) and lower in ready to consume infant formula will not lead to the toxicological reference dose of 0.35 mg/kg bw/day being exceeded by any age group. Therefore, on an interim basis, Health Canada has proposed that a 1.0 ppm interim standard be applied to all infant formula products or related sole source nutritional commodities in the form in which they are sold. This interim standard is being applied to the combined concentration of melamine and cyanuric acid, in consideration of the results of the hazard characterization, described above. Therefore concentrated and powdered infant formulas as sold would be covered by this interim standard. Note that upon dilution, values in these types of products would be far less than the interim standard, incorporating an added measure of protection. It remains Health Canada's policy that levels of potential contaminants in infant foods should be kept as low as reasonably achievable.

The Food Research Division of the Bureau of Chemical Safety, Health Canada has initiated an investigation to determine what, if any, background levels of melamine would be present in this commodity. Preliminary results indicate that background levels of melamine in infant formulas are well below the 1 ppm interim standard.

¹ The average weight of infants is based on the growths charts from the "Pediatricians Guide to your Children's Health and Safety" (<http://www.keepkidshealthy.com/growthcharts/girlsbirth.html>)

² The formula intake by infants for specific growth periods were utilized from "A Practical Guide to Baby Care" prepared by Institut National de Santé Publique du Québec (2001)

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Foods containing milk and milk-derived ingredients (other than infant formula and sole source nutrition products such as meal replacements)

Since the initial report of findings of melamine in infant formula products, it has been confirmed by international food regulatory authorities that other foods containing milk-derived ingredients from China and possibly other countries (whole milk powder, non-fat milk powder, whey powder, lactose powder, and casein) could be contaminated with melamine. The list of food products that have been implicated to date, and which have been posted to the CFIA's website, includes instant coffee, biscuits, chocolates, milk-based drinks, pretzels, cookies and cakes. In consideration of the possibility that certain foods containing a milk ingredient could be affected, Health Canada proposed to develop an interim melamine and cyanuric acid standard (maximum level) applicable to foods containing milk and milk-derived ingredients. This standard is in addition to the interim standard for infant formula and sole source nutrition products.

In order to establish interim standards, worst-case exposure scenarios were employed. It was assumed that all foods containing milk or milk-derived ingredients could be contaminated with melamine. Data available to Health Canada indicate that products containing milk and milk-derived ingredients make up approximately 50 percent (50%) of the diet of young children in North America, with the proportion of the milk-containing foods in the diet decreasing with age. Therefore, it was assumed that 50% of total food intake is contaminated. Total food intake values were derived from the Canadian Community Health Survey (CCHS), Cycle 2.2 on Nutrition, Statistics Canada, 2004, a survey that used a 24 hour dietary recall approach to record food consumption among participants. Estimates of food intakes, reported "as consumed", include the consumption of beverages other than drinking water.

Individuals under one year of age were not included in this assessment as it was assumed that they would have a limited diet, consisting of mostly mother's milk or infant formula, and thus their major source of food may be considered to fall under the 1 ppm interim standard for infant formula and sole source nutrition products, including meal replacements.

Various theoretical melamine concentrations were considered for foods containing milk and milk-derived ingredients (other than infant formula and sole source nutrition products), and a concentration of 2.5 ppm was demonstrated to be a level that would be protective. The results of the calculations are presented in Table 2.

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Table 2. Mean and 90th percentile total food consumption (CCHS, Cycle 2.2 - Nutrition, Statistics Canada, 2004) of foods containing milk and milk-derived ingredient¹, estimated melamine intakes, and percent contribution of the melamine intakes to the toxicological reference dose (TRD²) for various age-sex groups if melamine is assumed to be present in foods containing milk and milk-derived ingredients at a concentration of 2.5 mg/kg (ppm).

Age group	mean consumption of foods containing milk ingredients (g/kg bw) ¹	mean melamine intake (mg/kg bw/day) assuming a concentration of 2.5 ppm melamine	% of TRD ²	90 th percentile consumption of foods containing milk ingredients (g/ kg bw)	90 th percentile melamine intake (mg/kg bw/day) assuming a concentration of 2.5 ppm melamine	% of TRD
1 yr	53.16	0.13	38.0	84.82	0.21	60.6
2-3 yr	48.56	0.12	34.7	72.42	0.18	51.7
4 yr	41.38	0.10	29.6	62.74	0.16	44.8
5-6 yr	36.93	0.09	26.4	55.44	0.14	39.6
7-11 yr	26.37	0.07	18.8	41.51	0.10	29.6
12-18 yr M	18.95	0.05	13.5	30.81	0.08	22.0
12-18 yr F	16.50	0.04	11.8	27.13	0.07	19.4
19-35 yr M	17.29	0.04	12.3	27.56	0.07	19.7
19-35 yr F	15.52	0.04	11.1	25.09	0.06	17.9
36-50 yr M	16.08	0.04	11.5	24.66	0.06	17.6
36-50 yr F	15.75	0.04	11.3	24.91	0.06	17.8
51+ yr M	14.75	0.04	10.5	22.43	0.06	16.0
51+ yr F	14.70	0.04	10.5	23.24	0.06	16.6

As illustrated in Table 2, average and high (90th percentile) consumers of all age categories would not exceed the TRD of 0.35 mg/kg bw/day if 50% of all foods consumed contained milk or milk-derived ingredients and were contaminated at a concentration of 2.5 ppm melamine. One year olds in particular, the highest consuming group per kilogram of body weight, are well below the TRD. The calculations above are considered to be very conservative overestimates, due to the assumption that 50% of the total amount of foods consumed on a daily basis contains milk or milk-derived ingredients and to the assumption that all such products would be contaminated at this level. Indeed, fluid milk is produced from Canadian sources and milk powder for products produced within Canada must be registered by the CFIA and hence subject to stringent requirements, including controls aiming to ensure absence of sources of adulteration. Therefore, a 2.5 ppm interim standard is considered to be protective for the Canadian population; that is, the consumption of any finished food produced with milk and milk-derived ingredients containing up to 2.5 ppm melamine and cyanuric acid would not constitute a health risk for consumers. This interim standard is being applied to all food products containing milk or milk-derived ingredients.

1 The total consumption of foods containing milk and milk-derived ingredients was estimated based on data suggesting that 50% of the total diet could contain these ingredients.

2 The toxicological Reference Dose (TRD) employed by the Bureau of Chemical Safety (BCS) of Health Canada is 0.35 mg/kg bw/day.

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Risk Mitigation in Other Jurisdictions

Health Canada's interim standards for melamine in products containing milk and milk-derived ingredients are set to ensure that all age groups and segments of the population are protected. Similar standards have been established by other food regulatory agencies. The United States Food and Drug Administration has set a maximum level of 2.5 ppm melamine and its analogues for foods other than infant formula, but has indicated that while it could not establish a tolerance for melamine in infant formula, that analytical methods can reliably detect to a level of 1 ppm of melamine (US FDA 2008). Food Standards Australia New Zealand has set a maximum level of 1 mg/kg (ppm) melamine in infant formula, and 2.5 mg/kg for melamine in dairy-based foods and foods containing dairy based ingredients (FSANZ 2008). The New Zealand Food Safety Authority has set the same standards as FSANZ, as well as a 5 ppm standard for ingredients within finished products (NZFSA 2008). The European Commission, based on the European Food Safety Authority scientific advice (EFSA 2008), has set a 2.5 mg/kg (ppm) limit for all composite foods containing milk ingredients (EC 2008/798/EC). The Hong Kong Centre for Food Safety has amended its Harmful Substances in Food Regulations (Cap 134 AF), where milk, foods consumed primarily by children under 36 months and foods principally consumed by pregnant and lactating women shall not exceed melamine concentrations of 1 mg/kg. For all other foods, a 2.5 mg/kg maximum limit has been established (HKCFS 2008).

Further Actions

The purpose of this assessment was to identify the levels of melamine and melamine related compounds (such as cyanuric acid) in food which would not raise public health concerns. Should new scientific evidence become available concerning the combined toxicity of melamine and its analogues, Health Canada's risk assessment and interim standard will be reviewed. As part of Health Canada's commitment to this issue, the WHO Collaborating Centre for Food Contamination Monitoring within Health Canada, namely the Bureau of Chemical Safety in the Food Directorate, will support a WHO Expert Meeting in December 2008 to review toxicological aspects of melamine and cyanuric acid. The purpose of this meeting is to determine knowledge gaps requiring further investigation that will update the toxicological database and allow a better characterization of the toxicity of melamine and its analogues (WHO Melamine-Contamination Event).

Health Canada scientists will also continue to work closely with other international jurisdictions, including the US Food and Drug Administration (US FDA), the European Food Safety Authority, the European Commission, Food Standards Australia New Zealand, the New Zealand Food Safety Authority, the UK Food Standards Agency, the Agence Française de Sécurité Sanitaire des Aliments (AFSSA) and the Japanese Food Safety Commission.

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