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Additional Risk Characterization Document – Update to the Human Health Assessment of Melamine

Health Canada

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Canada

Synopsis

An updated draft of the assessment for 1,3,5-triazine-2,4,6-triamine (Chemical Abstracts Service Registry Number [CAS RN] 108-78-1), commonly known as melamine, was published on October 17, 2020. It proposed that melamine was harmful to human health but not to the environment. Melamine is a substance included in the Certain Organic Flame Retardants (OFR) Substance Grouping under Canada's Chemicals Management Plan, which includes 10 organic substances having a similar function: application to materials to slow the ignition and spread of fire.

Since the publication of the updated draft assessment for melamine, new critical health effects were identified and exposure to melamine was re-examined. This current document contains an updated characterization of the human health risk associated with exposure to melamine to inform the melamine assessment. The public has the opportunity to comment on data and analysis included herein prior to it being considered in the finalization of the assessment of melamine, and, if appropriate, the corresponding risk management approach document. Data related to human health with respect to melamine, identified or generated since the publication of the updated draft assessment, are included herein.

Melamine does not occur naturally in the environment. It is not manufactured in Canada; however, imports of melamine, as a pure substance or blended into products, in the range of 10 million kg to 100 million kg were reported for the year 2011. In Canada, melamine has numerous industrial applications; its predominant use is in the manufacture of melamine-based resins for application in laminates and plastics, and as a flame retardant in polyurethane foams, paints, and coatings. Globally, melamine is used primarily in the synthesis of melamine–formaldehyde resins for similar applications, and in adhesives and moulding compounds (for example, for melaware). Due to its high nitrogen content, melamine has also been used globally as a fertilizer.

The main sources of exposure to melamine for people living in Canada are expected to be from the use of products available to consumers including melamine-containing tableware and kitchen utensils ("melaware" including bambooware), foam-containing products (for example, mattresses, upholstered furniture, infant and child restraint systems as well as booster seats), textiles, paints, sealants, and cooktop cleaner, as well as from food and environmental media (water, dust). Biomonitoring data were also available from the Unites States (U.S.) population.

Based principally on the weight of evidence from assessments from international agencies and other available information, critical effects associated with exposure to melamine are carcinogenicity, effects on the urinary system and reproductive toxicity. Available information indicates that melamine is not genotoxic. Comparisons between levels associated with critical effects in animal studies and estimates of exposure from environmental media, food and textiles are considered to be adequate to address uncertainties in the health effects and exposure data used to characterize risk. However, comparisons between levels associated with critical effects in animal studies and estimates of exposure from melaware including bambooware (through migration

into food/beverages), foam-containing products (including mattresses, upholstered furniture, infant and child restraint systems as well as booster seats), paints (brush/roller paint and in spray format), sealants, and cooktop cleaner are considered potentially inadequate to address uncertainties in the health effects and exposure datasets.

The human health assessment took into consideration those groups of individuals living in Canada who, due to greater susceptibility or greater exposure, may be more vulnerable to experiencing adverse health effects from exposure to substances. The potential for increased susceptibility during development and reproduction was assessed and age-specific exposure estimates were derived. Generally, infants and children were found to have higher exposure than adults. All of these populations were taken into consideration while assessing the potential harm to human health.

On the basis of information presented in this risk characterization document, exposure to melamine from melaware (including bambooware), foam-containing products (including mattresses, upholstered furniture, infant and child restraint systems as well as booster seats), paints, sealants, and cooktop cleaner may be harmful to human health.

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1. Introduction

Pursuant to section 68 of the *Canadian Environmental Protection Act, 1999* (*CEP*A) (Canada 1999), the Minister of the Environment and the Minister of Health conduct assessments of substances to determine whether they present or may present a risk to the environment or to human health.

The Updated Draft Screening Assessment of Certain Organic Flame Retardants Substance Grouping 1,3,5-Triazine-2,4,6-triamine (Melamine) was published in October 2020, hereinafter referred to as the updated draft assessment for melamine (ECCC, HC 2020). It proposed that melamine was harmful to human health but not for the environment. Since the publication of that assessment, new critical health effects were identified and exposure to melamine was re-examined. This current document contains an updated characterization of the human health risk associated with exposure to melamine to inform the melamine assessment.

The scope of this document is limited to assessing potential human health concerns for melamine. The data and analysis herein provide the opportunity for public comment on the new information prior to it being considered in the finalization of the assessment of melamine, and, if appropriate, the corresponding risk management approach document. No significant changes to the ecological assessment of melamine were identified from the publication of the updated draft assessment (ECCC, HC 2020) that warrant further public consultation.

This document includes data identified or generated since the publication of the last updated draft assessment report (October 2020). Targeted literature searches were conducted up to February 2023 for the human health component of this assessment. More recent studies or information provided via internal and external peer consultation for human health components may also be cited. Empirical data from key studies as well as some results from models were used to reach the proposed conclusions. When available and relevant, information presented in assessments from other jurisdictions was considered.

This additional document was prepared by staff in the Existing Substances Program at Health Canada and incorporates input from other programs within this department. This document has undergone external written peer review or consultation. Comments on the technical portions relevant to human health were received from Tetra Tech Inc. Additionally, the last updated draft of the assessment of melamine (published October 17, 2020) was subject to a 60-day public comment period. On the basis of these comments as well as new information received, an update of the draft human health risk characterization is presented here. While external comments were taken into consideration, the final content of the document remain the responsibility of Health Canada.

Assessments focus on information critical to determining whether substances meet the criteria as set out in section 64 of CEPA by considering scientific information, including information, if available, on subpopulations who may have greater susceptibility or

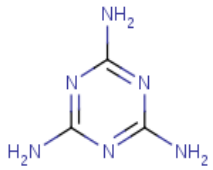
greater exposure, vulnerable environments, and cumulative effects[1], and by incorporating a weight of evidence approach and precaution[2]. This assessment presents the critical information and considerations on which the conclusions are based.

2. Substance identity

The substance 1,3,5-triazine-2,4,6-triamine (CAS RN 108-78-1), hereinafter referred to by its common name, melamine, is a discrete organic chemical characterized by a high nitrogen content. It belongs to the chemical subgroup of substances known as triazines. It is noted that the name melamine for the chemical is also commonly used for the plastic made from it (WHO 2009).

Information regarding substance identity of melamine is summarized in Table 2-1.

Table 2-1 Substance identity for melamine

CAS RN	Chemical structure	Molecular mass (g/mol)	Chemical formula
108-78-1		126.12	$C_3H_6N_6$

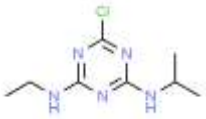
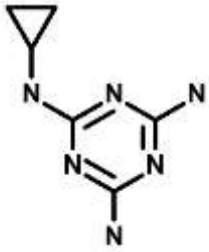
2.1 Selection of analogues

A read-across approach using data from analogues was used to inform the dermal absorption for the exposure assessment of melamine (section 5.1.3). Analogues were selected that were structurally similar to melamine (similar physical-chemical properties) and that had relevant empirical data on dermal absorption that could be used to read-across to melamine. Information on the identities and chemical structure of the analogues used to inform this assessment are presented in Table 2-2. For further information on the physical-chemical properties of the analogues, refer to Appendix A.

[1] The consideration of cumulative effects under CEPA may involve an analysis, characterization, and possible quantification of the combined risks to health or the environment from exposure to multiple chemicals.

[2] The determination of whether one or more of the criteria of section 64 of CEPA are met is based upon an assessment of potential risks to the environment and/or to human health associated with exposures in the general environment. For humans, this includes, but is not limited to, exposures from ambient and indoor air, drinking water, foodstuffs, and products available to consumers. A conclusion under CEPA is not relevant to, nor does it preclude an assessment against the hazard criteria specified in the *Hazardous Products Regulations*, which are part of the regulatory framework for the Workplace Hazardous Materials Information System for products intended for workplace use. Similarly, a conclusion that is based on the criteria contained in section 64 of CEPA does not preclude actions being taken under other sections of CEPA or other acts.

Table 2-2 Analogue identity

CAS RN	Domestic Substances List name (Common name)	Chemical structure and molecular formula	Molecular weight (g/mol)	Reference
1912-24-9	Atrazine	 $C_8H_{14}ClN_5$	215.68	PubChem 2004-
66215-27-8	Cyromazine	 $C_6H_{10}N_6$	166.18	PubChem 2004-

3. Physical and chemical properties

A summary of experimental and modelled physical and chemical properties of melamine that are relevant to its toxicity and environmental fate is presented in Table 3-1. Additional details were provided in the updated draft assessment (ECCC, HC 2020).

Table 3-1 A summary of physical and chemical properties for melamine

Property	Type	Value[a]	Temperature (°C)	Reference
Physical form	Experimental	solid, white powder, odourless	room temperature	ECHA c2007-2022
Melting point (ºC)	Experimental	345* to 361	NA	PubChem 2004–; Rumble 2018; ECHA

Property	Type	Value[a]	Temperature (°C)	Reference
				c2007-2022
Melting point (ºC)	Modelled	133	NA	MPBPVP 2010
Boiling point (ºC)	Experimental	Substance decomposes before boiling	NA	ECHA c2007-2022
Density (kg/m^3)	Experimental	1.57	20	ECHA c2007-2022
Vapour pressure (Pa)	Experimental	7.5×10^{-9}; 4.75×10^{-8}* (3.56×10^{-10} mmHg)	20	Hirt et al. 1960; ECHA c2007-2022
Vapour pressure (Pa)	Experimental	9.4×10^{-8}; 1.1×10^{-7}	25	Hirt et al. 1960; Crews et al. 2012
HLC (Pa·m^3/mol)	Modelled	1.86×10^{-9} (vapour pressure and water solubility estimate)	25	HENRY WIN 2011
Log K_{ow} (dimensionless)	Experimental	-1.14*	25	ECHA c2007-2022
Log K_{ow} (dimensionless)	Experimental	-1.22	22	SWISSI 2009; ECHA

Property	Type	Value[a]	Temperature (°C)	Reference
				c2007-2022
Log K_{ow} (dimensionless)	Experimental	-1.37	NA	Hansch et al. 1995
Log K_{ow} (dimensionless)	Modelled	-0.38	NA	KOWWIN 2010
Log K_{oc} (dimensionless)	Modelled	1.5* (MCI estimation method) 0 (K_{ow} estimation method)	NA	KOCWIN 2010
Log D	Modelled	-1.22 to -1.18 (at pH 6.5–8.0)	NA	ACD/ Percepta 2005
Log K_{oa} (dimensionless)	Modelled	10.8	NA	KOAWIN 2010
Water solubility (mg/L)	Experimental	3190, 3230*,3480	20	Crews et al. 2012; Yalkowsky and He 2003; ECHA c2007-2022; SWISSI 2009

Property	Type	Value[a]	Temperature (°C)	Reference
Water solubility (mg/L)	Experimental	4850	25	ECHA c2007-2022
pK_a (dimensionless)	Experimental	5	25	Weber 1970
pK_a (dimensionless)	Experimental	$pK_{a(base)}1$=7.3 $pK_{a(base)}2$=11.4	NA	SWISSI 2009
pK_a (dimensionless)	Modelled	$pK_{a(base)}$=5.3	NA	ACD/ Percepta 2005

Abbreviations: HLC, Henry's Law constant; log K_{ow}, octanol-water partition coefficient; log K_{oc}, organic carbon-water partition coefficient; log K_{aw}, air-water partition coefficient; log K_{oa}, octanol-air partition coefficient; Log D, distribution coefficient (usually for octanol-water); pK_a, acid dissociation constant; NA, not available; MCI, Molecular Connectivity Index

[a] Values in parentheses represent the original ones as reported by the authors or as estimated by the models.

* Indicates selected value for modelling.

4. Sources and uses

Melamine does not occur naturally in the environment. Melamine can be produced from urea, dicyandiamide, or hydrogen cyanide. Commercially produced melamine is manufactured using urea as a starting material (WHO 2009).

A survey issued pursuant to section 71 of CEPA (Canada 2013) and information obtained from voluntary stakeholder engagement indicated that between 10 million kg and 100 million kg of melamine were imported into Canada in 2011 (ECCC 2013-2014). Melamine was not manufactured in Canada in quantities above the reporting threshold of 100 kg (ECCC 2013-2014).[3]

[3] Values reflect quantities reported in response to the surveys issued pursuant to section 71 of CEPA (Canada 2013). See survey for specific inclusions and exclusions (Schedules 2 and 3).

Canadian import quantities of melamine, of approximately 9 million kg to 15 million kg between the years of 2011 and 2021, were reported by the Canadian International Merchandise Trade Database (Statistics Canada 2022). Canadian consumption of melamine was 9.7 million kg in 2019 and 8.8 million kg in 2020 (Malveda and Zhang 2020).

Uses of melamine are diverse and span numerous industrial sectors, globally and domestically in Canada. The known melamine uses and applications, including instances of adulteration of food products and feed, are summarized below.

In Canada, in response to a CEPA section 71 survey for the year 2011 and information obtained from voluntary stakeholder engagement (ECCC 2013-2014), melamine was used in consumer and commercial paints and coatings, in foam seating and bedding (which may comprise products such as pillows and mattresses), and in melamine-formaldehyde resin that is used for decorative laminates (ECCC 2013-2014). The substance was also used as a flame retardant in Canada (ECCC 2013-2014). In addition, melamine has applications as a plasticizer in concrete and in automobile brake tubes and hoses (ECCC 2013-2014). An internet search of Canadian products also showed use in thermally-fused melamine paper and shelves, whiteboards and flakeboards, paints, sealants for mechanical, electrical, and plumbing applications, and in inkjet ink from a variety of retailers. Globally, melamine is used primarily in the synthesis of melamine–formaldehyde resins for the manufacture of laminates (for example, for kitchen countertops, tabletops), cleaning sponges, plastics, coatings, commercial filters, products available to consumers such as glues or adhesives, cleaning products and moulding compounds for melamine-containing tableware and kitchen utensils (hereinafter referred to as melaware which also includes bambooware) (WHO 2009; BfR 2019; CPID c2001-2022).

According to responses to a CEPA section 71 survey, approximately 4% of all melamine imported into Canada in 2011 was used as a flame retardant (ECCC 2013-2014) which is consistent with what is observed worldwide. Melamine is used as a flame retardant mainly in polyurethane foams (EFRA 2007). Melamine is often used in combination with numerous other flame retardants such as 2-propanol, 1-chloro-, phosphate (3:1) (TCPP) (ECHA 2018), bicyclic phosphate, decabromodiphenyl ether (decaBDE), antimony oxide, Dechlorane Plus (DP), and others, and in polyolefin formulations for use in plastics and elastomers, to improve the overall flame retardant capability of the final product (Weil and Choudhary 1995). Melamine is also used in the production of other flame retardants, such as melamine cyanurate (CAS RN 37640-57-6), melamine phosphate (CAS RN 20208-95-1), melamine polyphosphate (CAS RN 218768-84-4), and melamine pyrophosphate (CAS RN 15541-60-3) (EFRA 2007).

Other global uses of melamine include its application as an impregnating or adhesive resin in wood-based panels for furniture and flooring, and in paper money, glossy magazines, and textiles (DSM 2010). While there is no confirmed textile use in Canada, melamine has been identified in infant clothing and textiles/fabrics in the U.S. (Zhu and Kannan 2020a; Zheng and Salamova 2020).

Melamine has applications in agriculture. Due to its high nitrogen content, melamine has been tested and used as a slow-release fertilizer (Wehner and Martin 1989; WHO 2009). Melamine is not used as an active ingredient or a formulant in registered pest control products in Canada (personal communication, email from the Pest Management Regulatory Agency, Health Canada to the Existing Substances Risk Assessment Bureau, Health Canada; June 2021; unreferenced). However, melamine is a metabolic by-product of the insecticide cyromazine, which is an insect growth inhibitor that can be applied as spray or in feed (Roberts and Hudson 1999; Zhu et al. 2009). In Canada, cyromazine is registered for use in products to control the Colorado beetle in potato crops, and insects in certain other crops and ornamentals not grown for cut flowers (PMRA 2021).

Melamine is not an approved food additive in the Lists of Permitted Food Additives incorporated by reference into Marketing Authorizations issued under the *Food and Drugs Act* (Health Canada [modified 2024]), nor would it be permitted for such use. Respondents to a CEPA section 71 survey did not report any uses of melamine in materials that come in contact with food (ECCC 2013-2014), but melamine may be used as a monomer in polymers like melamine-formaldehyde resins for the manufacture of food packaging products in Canada (for example, the interior coating of cans, excluding infant formula; coating of metallic closures of glass jars for baby foods and for glass and plastic bottles for liquid infant formulas; paper used to package bread or margarine; films for milk packaging) (personal communication, email from the Food Directorate, Health Canada to the Existing Substances Risk Assessment Bureau, Health Canada; July 2021; unreferenced).

In Europe, melamine is approved for use as a monomer in the manufacture of plastic materials and articles intended to come into contact with food, with a migration limit set at 2.5 mg/kg food (EU 2011). In the U.S., melamine and melamine-formaldehyde copolymer may be used in the formulation of adhesives used as components of articles for use in packaging, transporting, or holding food (indirect food additive) provided that the adhesive is separated from the food by a functional barrier (U.S. eCFR 2014a). Moreover, melamine-formaldehyde resin or polymer may be used as the food contact surface coating (indirect food additive) of articles intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food (U.S. eCFR 2014b).

Following identification of melamine-adulterated products (pet food, livestock- and fish-feed) in North America in 2007, and in certain foods worldwide (infant formula in China and other milk-based processed foods around the world) in 2008 due to the use of adulterated ingredients sourced from China, Maximum Levels (MLs) for melamine in foods were developed internationally to ensure the safety of consumers (Health Canada 2008, 2016a, 2022; CAC 2019; WHO 2009; Gossner et al. 2009; Dorne et al. 2013; IARC 2019). Further details may be found in Appendix B.

Based on notifications submitted to Health Canada under the *Cosmetic Regulations*, melamine is not used in cosmetics in Canada (personal communication, email from the Consumer and Hazardous Products Safety Directorate, Health Canada to the Existing Substances Risk Assessment Bureau, Health Canada; June 2021; unreferenced).

Melamine is not listed in the Drug Products Database nor the Pharmaceutical Drugs Directorate's internal Non-Medicinal Ingredient Database as a medicinal or non-medicinal ingredient present in final pharmaceutical products or veterinary drugs in Canada (DPD [modified 2022]; personal communication, email from the Pharmaceutical Drugs Directorate, Health Canada to the Existing Substances Risk Assessment Bureau, Health Canada; June 2021; unreferenced). Melamine is listed in the Natural Health Products Ingredients Database as a Non-Natural Health Product because it is not a naturally occurring substance included in Schedule 1 to the *Natural Health Products Regulations*; as such, it is not listed in the Licensed Natural Health Products Database as being present in currently licensed natural health products in Canada (NHPID [modified 2022]; LNHPD [modified 2021]; personal communication, email from the Natural and Non-prescription Health Products Directorate, Health Canada to the Existing Substances Risk Assessment Bureau, Health Canada; June 2021; unreferenced).

5. Potential to cause harm to human health

5.1 Exposure assessment

The potential for exposure to melamine via environmental media (drinking water, air, soil, dust), food, melamine-containing tableware and dishware, and products available to consumers is discussed in this section, as well as estimates of exposure based on biomonitoring data. Melamine is a metabolite and degradation product of cyromazine (WHO 2009; IARC 2019); therefore, its presence in the environment, food, and human biomonitoring data (that is, milk and urine) may be due to exposure to cyromazine.

5.1.1 Environmental media and food

5.1.1.1 Air

No data on concentrations of melamine in ambient or residential indoor air were identified.

5.1.1.2 Dust

No data on concentrations of melamine in dust in Canada were identified. Melamine and its derivatives were detected in all 341 indoor dust samples collected from 12 countries during the period of 2010 to 2014, including Kuwait (n = 24), South Korea (n = 30), Japan (n = 14), China (n = 50), Vietnam (n = 18), Saudi Arabia (n = 31), the United States (n = 15), Romania (n = 23), Greece (n = 30), India (n = 36), Pakistan (n = 25), and Colombia (n = 45). The highest concentrations of melamine were found in house dust collected from the U.S., ranging from 4800 ng/g to 58,000 ng/g (mean = 17,000 ng/g, median = 12,000 ng/g) (Zhu and Kannan 2018).

In 2016, floor and elevated surface dust samples were collected from 7 childcare centres in Seattle, Washington (n = 14) and 1 childcare centre in West Lafayette, Indiana (n = 6). Melamine was detected in the dust samples at concentrations ranging

from 159 ng/g to 66 600 ng/g (mean = 6920 ± 3470 ng/g, median = 1620 ng/g, detection frequency = 100%) (Zheng et al. 2020).

Due to the lack of Canadian data on melamine in dust, the Zheng et al. (2020) U.S. data were used to characterize human exposure to melamine from dust. Estimated intakes were 0.024 µg/kg bw/day and 0.23 µg/kg bw/day for infants 0 to 5 months old (highest exposed group) based on mean and maximum concentrations, respectively (see Appendix C).

5.1.1.3 Soil

No data on melamine concentrations in North American soils were identified and a soil predicted environmental concentration (PEC) was not determined in the ecological assessment of melamine (ECCC, HC 2020). As such, soil is not expected to be a significant source of human exposure to melamine.

5.1.1.4 Water

Canadian occurrence data for melamine in drinking or surface water were not available. Melamine concentrations in drinking water were provided in a European Food Safety Authority (EFSA 2010) Panel report. The EFSA report indicates that the data were provided by industry from various areas around the world (n = 20 tap water samples). Melamine concentrations ranging from 10 µg/kg to 200 µg/kg (mean = 50 µg/kg; values reported as mg/kg for all food groups including tap water in EFSA 2010) were reported. Individual results for each sample were not reported and there was no indication as to how many water samples had melamine concentrations below the limit of detection (LOD).

Melamine was measured in various sources of water (including surface water (n = 74), sea water (n = 10), tap water (n = 70), bottled water (n = 11), rain water (n = 24), wastewater (n = 14) and swimming pool water (n = 20)) collected from New York State, U.S. during 2015 and 2019. Melamine was found in tap water at concentrations ranging from less than the method quantification limit of 0.0050 µg/L to 0.188 µg/L, with a mean concentration of 0.033 µg/L and a detection frequency of 91% (Zhu and Kannan 2020b).

Melamine was monitored at drinking water intake points along the Rhine and Meuse rivers in the Netherlands in 2016. Mean annual concentrations in the Rhine area ranged from 0.97 µg/L to 1.36 µg/L at 3 collection points with maximum concentrations from 1.6 µg/L to 2.8 µg/L. Maximum concentrations for the Meuse area ranged from 0.98 µg/L to 5.8 µg/L at 4 collection points. Concentrations were found to be the highest between September and December 2016 (RIVM 2018a).

Due to the lack of Canadian data pertaining to this potential source, tap water data from the U.S. were used for exposure characterization of melamine from drinking water (Zhu and Kannan 2020b). Estimated intakes were 0.004 µg/kg bw/day and 0.025 µg/kg bw/day for formula-fed 0 to 5 months old infants (highest exposed group) based on mean and maximum concentrations, respectively (see Appendix C).

Dermal and oral exposure estimates while swimming in a pool were derived using algorithms from the U.S. Environmental Protection Agency (US EPA) Swimmer Exposure Assessment Model SWIMODEL (US EPA 2003, 2016) and concentrations of melamine measured in swimming pool water from Zhu and Kannan (2020b) (see Appendix C). Dermal exposures were negligible (less than 2.5 ng/kg bw/day) for all age groups and oral estimates were negligible for all age groups except children aged 4 to 8 years (approximately 0.0029 µg/kg bw/day). This oral intake is lower than the upper bounding drinking water intake estimate of 0.004 µg/kg bw/day for 4 to 8 years old children (see Appendix C).

5.1.1.5 Food

As indicated under “Sources and uses” (section 4), melamine may be used as a monomer in polymers like melamine-formaldehyde resins for the manufacture of food packaging products in Canada (for example, the interior coating of cans, excluding infant formula; coating of metallic closures of glass jars for baby foods and for glass and plastic bottles for liquid infant formulas; paper used to package bread or margarine; films for milk packaging) (personal communication, email from the Food Directorate, Health Canada to the Existing Substances Risk Assessment Bureau, Health Canada; July 2021; unreferenced). A probable daily intake of melamine was estimated by Health Canada to be 476 ng/kg bw for the general population (12 months of age and older) based on migration data submitted by companies for the use of melamine in coatings for canned food (personal communication, email from the Food Directorate, Health Canada to the Existing Substances Risk Assessment Bureau, Health Canada; July 2021; unreferenced). Note that this estimate does not include exposures resulting from melamine migration from melaware (a consumer product) into food, which will be discussed in section 5.1.2. In the U.S., melamine is permitted for use as an indirect food additive in the synthesis of melamine-formaldehyde resins intended for use in food processing and packaging.

Various international studies have investigated the migration of melamine from can coatings and jar closures into food and beverages. In the United Kingdom, Bradley et al. (2011) tested migration from resins based on melamine-formaldehyde and related analogues (methylolated melamine) used to cross-link coatings inside food cans and metal closures on glass jars. For 13 coatings tested, concentrations of melamine that migrated into food ranged from less than 1.5 µg/kg to 332 µg/kg depending on the conditions used (that is, fluid matrix, temperature variation). Using the same experimental conditions, 6 different laboratories in Europe observed similar concentrations ranging from 1.5 µg/kg to 327 µg/kg as a result of melamine migration from can coatings and closures (EFSA 2010). Bradley et al. (2011) also tested migration of melamine into 3 different food types (food types varied based on acidity, fat content, and presence of meat or fish) in various conditions and observed migration concentrations ranging from less than 23 µg/kg to 220 µg/kg. Magami et al. (2015) also tested 4 different cross-linking substances that contained residual amounts of melamine (less than 0.1% to 0.2%) used in epoxy-based coatings for food cans. The coatings were heated at a high temperature of 131°C in a food simulant (10% aqueous ethanol) for different periods (30 min to 180 min) followed by different storing periods (1 day to

30 days), and then reheated at 131°C for 1 hour. Migration of melamine from the coatings equated to 7% to 60% on a molar basis of the total melamine content of the cross linker used. The authors were able to show that the migration process was not by diffusion of melamine from the coating. Rather, the melamine formed by hydrolysis of the coating and was released as melamine itself, and it did not have a significant tendency to undergo hydrolysis to analogues such as ammeline, ammelide or cyanuric acid. The aforementioned data show that melamine may migrate from food packaging into food, and that the resulting concentrations in foods will increase if foods are subjected to heating, such as during the processing of food cans and bottles (EFSA 2010).

Melamine has been measured in a variety of foods in many countries, primarily as a follow-up to the identification of melamine-adulterated food and animal feed ingredients sourced from China (for example, raw milk, wheat and vegetable proteins) that were subsequently used in the manufacture of other foods or feeds (WHO 2009; Gossner et al. 2009; Hilts and Pelletier 2009; Dorne et al. 2013). Concurrently, there has been an increased demand for more rapid and/or more sensitive and accurate analytical techniques to determine melamine levels in such foods. Reviews of advances in analytical techniques to determine melamine in food and milk products reported lower ranges of LODs than those reported in the review of Rovina and Siddique (2015) published 2 years earlier (from 3.7×10^{-12} ng/g to 0.6 ng/g for milk products; as low as 1×10^{-5} mg/L for food samples as reported by Lu et al. 2017 and Nascimento et al. 2017).

Health Canada has conducted research to measure background levels of melamine in food sold in Canada, analyzing 94 samples of various infant formulas (analyzed in the "as purchased" form), 246 samples of dairy and soy-based dairy replacement products, and 378 samples of egg-containing products, soy-based meat substitutes, fish and shrimp products, and vegetable products (Health Canada [modified 2024]; Tittlemier et al. 2009, 2010a, 2010b). The Health Canada surveys focused on foods with the greatest probability of containing residual levels of melamine, such as dairy foods and other milk- and soy-containing products, vegetable products[4], and marine foods[5]. These surveys had a low detection limit (LOD = 4 µg/kg) and an overall detection rate of 27%.

In addition, the Canadian Food Inspection Agency (CFIA) conducted various surveys to measure melamine concentrations in similar and additional foods. These were either for investigative purposes to identify adulterated products (survey from 2007 to 2010) or were for monitoring programs (studies conducted from 2009 to 2020), to ensure continued compliance with Health Canada's Interim Maximum Levels for melamine in foods established in 2008 (Health Canada 2016a, 2020, 2024). These studies had higher detection limits than the Health Canada surveys (LODs ranging from 50 µg/kg to 100 µg/kg) and, as such, lower detection rates (0% to 5.6%).

[4] The pesticide cyromazine is approved for use on a variety of vegetables. Melamine is a degradation product of cyromazine.

[5] Melamine has reportedly been used as a binding agent in feed pellets for aquacultured seafoods.

The Health Canada surveys were generally considered the most relevant for estimating dietary exposure to melamine (personal communication from the Food Directorate, Health Canada to the Existing Substances Risk Assessment Bureau, Health Canada; August 2022; unreferenced). However, where higher maximum concentrations were found in the same food categories in the CFIA's surveys as those analyzed in the Health Canada surveys, or where additional food categories (to those analyzed in the Health Canada surveys) contained samples with detectable concentrations of melamine in the CFIA surveys, arithmetic means from those CFIA surveys were utilized (see Table D-1 of Appendix D).

Dietary exposure to melamine from all food sources shown in Table 5-1 was estimated using Statistical Analysis System (SAS) software where the full distribution of consumption values from the Canadian Community Health Surveys (CCHS) (Statistics Canada 2008, 2017) and arithmetic mean melamine concentration data for each food commodity type sampled were combined. Mean and 95th percentile exposure estimates for various age groups are provided in Table 5-1 (see Appendix D for melamine concentration levels and dietary exposure assessment methodology). Food consumption data for individuals over the age of one year old were obtained from the 2015 CCHS (Statistics Canada 2017), while food consumption data for infants under the age of one year old were obtained from the 2004 CCHS (Statistics Canada 2008). The 2015 CCHS does not contain consumption information for infants. Note that these estimates do not include exposures resulting from melamine migration from melaware, (a consumer product) which will be discussed in section 5.1.2.

Table 5-1 Estimated dietary melamine intake (µg/kg bw/day) from foods for different age groups in Canada

Age group (years)[a]	Mean	95th percentile
6 months to 11 months	0.72	1.7
1 to 3	0.35	0.89
4 to 8	0.24	0.72
9 to 13	0.17	0.56
14 to 18	0.12	0.41
19 +	0.11	0.37

[a] Males and females are both included in each age category.

Of note, melamine food packaging migration concentrations (less than 1.5 µg/kg to 332 µg/kg) reported in the European studies mentioned above are within the mean range of values reported in the Canadian food monitoring studies (see Appendix D, range: less than 4 µg/kg to 667 µg/kg).

5.1.1.6 Human milk

No data on concentrations of melamine in human milk in Canada were identified. Yurdakok et al. (2014, 2015) measured melamine in human milk of 77 healthy lactating mothers in Ankara, Turkey from June to September 2010 (babies were 3 days to 10 days old). Human milk samples (10 mL) from each mother were analyzed by high performance liquid chromatography (HPLC) with the LOD and limit of quantitation

(LOQ) determined at 10.6 µg/L and 41.6 µg/L, respectively. Melamine was detected in 16 of 77 samples (20.8%) with concentrations ranging from 10.1 µg/L to 76.4 µg/L (mean = 27.1 µg/L; or between LOD and LOQ), as reported by the authors. There was no influence of body mass index on the distribution of melamine concentrations (mothers grouped into normal, overweight, and obese weight groups). In another Turkish study, the presence of melamine in human milk was investigated in milk samples collected from mothers of infants born in Şanlıurfa between May 2017 and April 2018. Melamine was detected in 40% of mothers. The melamine concentrations present were not quantified in the study (Yalçin et al. 2020).

Melamine concentrations were measured, using HPLC, in human milk samples (n = 100, randomly selected) collected between 2009 to 2012 as part of the U.S. National Children's Study (Zhu and Kannan 2019a). Melamine was detected in 94% of the samples with concentrations ranging from not detected (LOD = 0.020 ng/mL, LOQ = 0.067 ng/mL) to 7.14 ng/mL (mean = 0.338 ng/mL, median = 0.204 ng/mL).

Since no Canadian data were identified regarding melamine presence in human milk, data from the study in the U.S. (Zhu and Kannan 2019a) were used for exposure characterization. Daily intake estimates in infants aged 0 to 5 months from melamine presence in human milk were 0.042 µg/kg bw/day and 0.89 µg/kg bw/day for mean and maximum concentrations, respectively.

5.1.1.7 Intake estimates from environmental media and food

Estimated exposures to melamine for the general population of Canada from environmental media and food resulted in total mean and high-end intake estimates ranging from 0.066 µg/kg bw/day to 0.75 µg/kg bw/day and 0.38 µg/kg bw/day to 2.0 µg/kg bw/day, respectively (details are provided in Appendix C). Formula-fed infants 0 to 5 months of age had the highest estimated exposures.

5.1.2 Migration from melaware

Melamine reacts with formaldehyde to produce a thermoset plastic called "melamine" or "melaware" which can be used as tableware and kitchen utensils. Some melaware articles are prepared using bamboo fibre as a filler during the manufacturing process and the resulting plastic is sometimes referred to as "bambooware" (BfR 2019).

Studies on migration of melamine from melaware and bambooware into foods, water and other beverages were identified and some of these studies are summarized in Table 5-2.

Table 5-2 Summary of studies on the migration of melamine from melaware into foods, water and other beverages

Products tested	Purchase location	Experimental conditions	Migration concentrations of melamine	Reference
Melaware plates (n=6), previously used melaware cups (n=11)	Denmark	3% acetic acid; temperature range of 20°C to 95°C	<1.500 mg/L to 2.940 mg/L	Lund and Petersen 2006
Melaware articles (plates, bowls, utensils, etc.) (n=27)	Germany	3% acetic acid or distilled water; temperature range of 40 °C to 100°C for 10 min to 24 hr	0.001 mg/kg (70°C for 10 min) to 1.2 mg/kg (40°C for 24 hr)	BfR 2010a as cited in EFSA 2010
Melaware cups (n=12)	Germany	3% acetic acid, apple juice, tomato juice, tea made of red fruit, coffee, or cola drink; 2 hrs at temperature range of room temperature to 70°C	0.0007 (room temperature) to 1.192 mg/kg[a] (70°C)	BfR 2010b as cited in EFSA 2010
Melaware articles (bowls, cups, etc.)	Germany, Netherlands, UK	Food and liquid matrices; temperature range of 40°C to 100°C; some were microwaved; some exposed to hot foods or liquids	Not detected to 4.194 mg/kg[b]	Bradley et al. 2010
Melaware bowls (n=5) and cups (n=5)	Germany, the Netherlands, and the UK	3% acetic acid; 2 hrs at 70°C; some were microwaved; some exposed to hot foods or juice	<0.14 mg/kg to 4.60 mg/kg	FERA 2010 as cited in EFSA 2010
Melaware cups (n=6) and dishes (n=3)	Italy	While milk, vegetable soup, tannin-free tea water; filled at temperature range of 60°C to 80°C, cooled for 2 hrs to room temperature	0.008 mg/kg (60°C) to 0.105 mg/kg[a] (80°C)	ISAN 2010 as cited in EFSA 2010
Melaware cups (n=152)	Netherlands	Variety of food simulants and beverages; 24 hr at temperature range of 40 to 70°C; some were microwaved	Not detected to 4.194 mg/kg (40°C)	TNO 2010 as cited in EFSA 2010
Melaware cups (n=25)	Taiwan	3% acetic acid or distilled water; temperature range of 20°C to 90°C[c]	0.030 mg/L (at 20°C) to 19.030 mg/L (at 90°C)	Chien et al. 2011
Melaware dishware items (n=246)	Malaysia	3% acetic acid or water; 25°C and 100°C	0.00131 mg/L to 0.140 mg/L (at 25°C)	Chik et al. 2011

Products tested	Purchase location	Experimental conditions	Migration concentrations of melamine	Reference
			0.00405 mg/L to 0.509 mg/L (at 100°C)	
Melaware children's bowls (n=50)	Ordered from and manufactured in China	Solutions of different pHs; heated at 95°C for 30 min over a series of 10 runs[d]	<0.0041 mg/L to 0.0767 mg/L	Lynch et al. 2015
Melaware tableware (n=72) and previously used melaware tableware (n=18)	Italy	3% acetic acid; 2 hrs at 70°C	<0.25 mg/kg to 6.5 mg/kg (new tableware) <0.25 mg/kg to 3.36 mg/kg (previously used tableware)[b]	Mannoni et al. 2017
Melaware tableware (n=5)	Iran	3% acetic acid or distilled water; 90°C for 30 min and 90 min	1.545 mg/kg to 5.956 mg/kg (30 min) 1.342 mg/kg to 8.737 mg/kg (90 min)[e]	Haghi et al. 2019
Melaware cooking spoons (n=3)	Germany	3% acetic acid, apple juice, sauerkraut juice, plum puree diluted with water, or strained tomatoes diluted with water; 2 hrs at 100°C	12 mg/L to 67 mg/L (3% acetic acid) 8 mg/L to 75 mg/L (juices / foods)[f]	Ebner et al. 2020
Melaware articles typically filled with hot liquids (for example, mugs, cups, bowls) (n=111)	Germany	3% acetic acid; 2 hrs at 70°C; repeated 3 times in succession and reported results are for the third migrate	<LOQ to 8.37 mg/L	BfR 2019
Bambooware articles typically filled with hot liquids (for example, mugs, cups, bowls) (n=180)	Germany	3% acetic acid; 2 hrs at 70°C; repeated 3 times in succession and reported results are for the third migrate	<LOQ to 20.7 mg/L	BfR 2019
Melamine bowls (n=10)	USA, Japan	Water; temperature range of 25°C to 100°C	0.00241 mg/L to 3.94 mg/L[g] (water at 25°C)	Takazawa et al. 2020

Products tested	Purchase location	Experimental conditions	Migration concentrations of melamine	Reference
		1% acetic acid or 10% methanol; temperature of 25°C	0.0466 mg/L to 5.64 mg/L[g] (water at 90 to 100°C) 0.526 mg/L[g] (1% acetic acid) 0.565 mg/L[g] (10% methanol)	

[a] Migration concentrations were reported as µg/L.
[b] In samples with a similar density to water, 1 kg is approximately equal to 1 L.
[c] Migration was significantly higher in 3% acetic acid than in distilled water.
[d] Highest migration rates were noted in solutions of pH 3 in this study. Migration rates at all pHs dropped by 85% between the first and tenth runs.
[e] Migration concentrations have been converted from ppm. Concentration ranges of migration measured in distilled water and 3% acetic acid overlapped, though the minimum and maximum concentrations in 3% acetic acid were higher than those for distilled water at both incubation temperatures.
[f] Migration concentrations were reported as mg/dm^2.
[g] Migration concentrations were reported as ng/cm^2. Converted to ng/mL by multiplying with the surface area of a bowl (80.4 cm^2/mL) provided in Takazawa et al. 2020 and conversion factor (0.001) to get mg/L.

Based on the studies conducted on food and beverages mentioned in Table 5-2, concentrations measured in food items heated in melaware appear to be higher than concentrations measured in items left at room temperature. EFSA (2010) examined the migration of melamine from melaware into food and water, citing some of the same data above as well as additional data provided by other European countries (that is, Finland, Cyprus, Netherlands). EFSA determined that migration of melamine from melaware is characterized by high variability, depending on various factors such as manufacturing process, alterations to the surface due to service life, time and temperature conditions of use, as well as characteristics of food (for example, acidic, aqueous, fatty or dry).

EFSA estimated migration levels for different food classes (Table 5-3). The “typical” values were based on migrations from melaware in contact with hot foodstuffs at temperatures and for the amount of time expected during typical use. The “high” migration values were based on severe migration test conditions, such as the use of acidic food simulants (for example, 3% acetic acid), the application of heat and longer exposures. These were considered to be equivalent to microwave oven heating and scratching of articles during their service life. The German Federal Institute for Risk Assessment (BfR) examined migration of melamine from melaware and bambooware articles (cups, mugs, bowls). BfR measured a mean melamine migration concentration of 1.27 mg/L (95th percentile: 4.29 mg/L) from melaware articles and a mean of 2.64 mg/L (95th percentile: 7.71 mg/L) melamine migration concentration from bamboo articles (BfR 2019).

Table 5-3 Estimated melamine concentrations (mg/kg) from migration from melaware for each food type (as determined by EFSA 2010)

Food Type	Typical	High
Acidic foods	1.0	5.0
Aqueous foods[a]	0.6	3.0
Fatty foods	0.2	1.0
Dry foods	0.05	0.05

[a] Assumed to have same density as water but not specifically stated in EFSA (2010).

Exposure to melamine from use of melaware was estimated assuming that all foods and beverages come into contact with melaware (Table 5-4). A range of migration values were used including the lowest and highest values measured at room temperature, the highest EFSA-derived "typical" migration levels (acidic foods) (see Table 5-3) as well as the 95th percentile values identified in BfR (2019). Although migration studies were not identified for melaware in Canada, it is assumed that conditions and results for migration of melamine from such articles would be similar to data generated elsewhere. Exposure estimates for different age groups were derived using Canadian overall daily food consumption quantities for all age groups except 6 to 11 months which used food consumption presented in EFSA (2010) (see Table 5-4 and Appendix C for more details).

Table 5-4 Intakes of melamine from use of melaware and bambooware using Canadian consumption rates (see Appendix C for details)

Age group	Mean of total food consumption (g/day)[a]	Exposure using range of room temperature migration data (µg/kg bw/day)[b]	"Typical" Exposure using EFSA 2010 migration data (µg/kg bw/day)[c]	Exposure using BfR 2019 migration data (µg/kg bw/day)[d]
6 to 11 months	1000	0.077 to 433	110	471 to 847
1 year	1540.81	0.098 to 552	140	601 to 1080
2 to 3 years	1540.81	0.072 to 405	103	441 to 792
4 to 8 years	1760.47	0.054 to 302	77	328 to 590

Age group	Mean of total food consumption (g/day)[a]	Exposure using range of room temperature migration data (µg/kg bw/day)[b]	"Typical" Exposure using EFSA 2010 migration data (µg/kg bw/day)[c]	Exposure using BfR 2019 migration data (µg/kg bw/day)[d]
9 to 13 years	2057.76	0.034 to 193	49	210 to 378
14 to 18 years	2550.51	0.029 to 162	41	176 to 317
19+ years	2771.01	0.026 to 148	37	161 to 289

[a] See Table C-4 for details
[b] The lowest (BFR 2010b as cited in EFSA 2010) and highest (Takazawa et al. 2020) migrations of melamine from melaware observed at room temperature among the identified studies (Lund and Petersen 2006, BfR 2010b as cited in EFSA 2010, Chien et al. 2011, Chik et al. 2011, Takazawa et al. 2020).
[c] Exposure from melaware at highest typical migration level observed for acidic foods (1 mg/kg) derived by EFSA (2010).
[d] Exposure to melamine using 95th percentile migration from melaware articles (4.29 mg/L) and bambooware (7.71 mg/L) (BFR 2019). Assumed the density of water to convert mg/L to mg/kg (1 L = 1 kg).

EFSA (2010) estimated intakes of exposure to melamine from melaware articles with high migration potential using the highest migration rate as described in Table 5-2 (5 mg/kg). Intakes ranged from 250 µg/kg bw/day (for adults) to 910 µg/kg bw/day for children aged 1.5 years. Additional exposure scenarios were run to refine exposure in children (highest exposed group) using 2 scenarios. The first scenario used typical migration levels and the assumption that all food and beverages consumed came into contact with melamine containing articles. Mean intakes for children aged 1 to 6 ranged from 30 µg/kg bw/day to 80 µg/kg bw/day (95th percentile: 50 µg/kg bw/day to 120 µg/kg bw/day). The second scenario used high migration levels and the assumption that only the highest consumed food item came into contact with melamine containing articles. Mean intakes for children aged 1 to 6 ranged from 40 µg/kg bw/day to 110 µg/kg bw/day (95th percentile: 70 µg/kg bw/day to 230 µg/kg bw/day).

BfR (2019) estimated intakes of exposure to melamine from fillable melaware and bambooware for infants (12 to 36 months) and adults (19 to 50 years old) using the migration rates described above. For adults, consumption data for coffee beverages was used, while consumption data for fillable articles (milk, milk products and other non-alcoholic drinks) was used for infants. Mean intakes ranged from 90 µg/kg bw/day to 190 µg/kg bw/day (95th percentile: 280 µg/kg bw/day to 560 µg/kg bw/day) for infants and 10 µg/kg bw/day to 21 µg/kg bw/day (95th percentile: 33 µg/kg bw/day to 69 µg/kg bw/day) for adults.

5.1.3 Other products available to consumers

As noted in section 4, in Canada, melamine has uses in various types of products, in addition to melaware. Examples include paints and coatings, sealants, foam seats/backing/mattresses, thermally-fused melamine paper and shelves, whiteboards and flakeboards, inkjet ink, and more.

Due to considerations such as limited dermal contact, commercial and industrial use, and low melamine concentrations, exposure to paper and shelves, whiteboards and flakeboards, and inkjet inks were not assessed as exposure is expected to be low especially compared to other scenarios presented below.

Safety Data Sheets (SDSs) from limited paint products sold in Canada containing melamine show that the maximum concentration in paints is 10% (SDS 2019; TDS 2020). An SDS was also available for a sealant sold in Canada that contains melamine up to a maximum concentration of 60% (SDS 2022). Although the Technical Data Sheet (TDS) (TDS 2013) suggests that the product is likely for industrial and professional users, this product is available to general consumers at retail outlets. Melamine was also identified in a cooktop cleaner at a maximum concentration of 1% (SDS 2015). An analysis of melamine in 2 samples of electronic boards showed concentrations less than 0.002% w/w (8.4 mg/kg to 19.7 mg/kg) (Health Canada 2016b).

Both inhalation and/or dermal exposures from “per event use” were considered for users of airless paint spray equipment, brush, and roller paint applications, sealing, and caulking within the home, as well as use of cooktop cleaner.

With respect to dermal exposure from use of consumer products, no dermal absorption data were identified for melamine. The low empirical and modelled log K_{ow} values for melamine (-1.37 to -0.38) are indicative of poor dermal absorption (OECD 2002). Other substances in the same chemical subgroup as melamine, known as triazines, have dermal absorption data available. Atrazine (CAS RN 1912-24-9) has a maximum dermal absorption of 16% in human skin (Ademola et al. 1993). Dermal absorption of cyromazine (CAS RN 66125-27-8), a structurally similar substance to melamine, ranged from approximately 25% in an *in vivo* rat study (US EPA 1985) to 38% in both an *in vitro* human study and an *in vivo* rat study (JMPR 2006). The Pest Management Regulatory Agency (PMRA 2020a) cited a dermal absorption value of 27% in their evaluation of cyromazine based on the US EPA (1985) *in vivo* rat study. Results from the *in vivo* rat study for cyromazine (JMPR 2006) suggested that skin bound residues are not becoming systemically absorbed in their entirety; thus, the dermal absorption value of 38% observed in both the *in vitro* human and the *in vivo* rat study (JMPR 2006) is expected to be overly conservative as approximately 95% of the estimated absorption is from skin-bound residues. Based on a weight of evidence approach, taking into consideration data from structurally related compounds and the physical-chemical properties of melamine, an upper-bound dermal absorption estimate of 30% was selected for all dermal scenarios.

Table 5-5 summarizes dermal and inhalation exposures to paints, sealants and cooktop cleaner using ConsExpo Web (ConsExpo 2021). Refer to Appendix E for details on parameters.

Table 5-5 Estimated systemic exposure to melamine from products available to consumers

Exposure Route	Source	Melamine concentration	Age Group	Systemic exposure to melamine (mg/kg bw/event)[a,b]
Dermal[c] (intermittent)	Brush/roller paint	10%[d]	19 + years	1.5
Dermal (intermittent)	Pneumatic spray paint	10%[d]	19 + years	3.4
Inhalation (intermittent)	Pneumatic spray paint	10%[d]	19 + years	0.25
Dermal + inhalation (intermittent)	Pneumatic spray paint	10%[d]	19 + years	3.7
Dermal[b] (intermittent)	Sealant	30% to 60%[e]	19 + years	1.8 to 3.6
Dermal[b] (intermittent)	Cooktop cleaner	1%[f]	19 + years	0.012

[a] Estimated using ConsExpo Web (ConsExpo 2021).
[b] No dermal absorption data were identified for melamine. A value of 30% was selected based on data available for structurally similar compounds (refer to section 5.1.3).
[c] Due to the negligible vapour pressure associated with melamine, inhalation exposure from brush and roller paint, as well as cooktop cleaner applications are considered negligible
[d] SDS 2019, TDS 2020
[e] SDS 2022, TDS 2013
[f] SDS 2015

Foam products (seating, bedding etc.)

Melamine is found in flexible foam products and fabrics used for seating and bedding (which may comprise products such as pillows and mattresses) as well as in various children's products in Canada (ECCC 2013-2014; Health Canada 2015, 2019, 2023) and internationally (U.S. CPSC 2005; Ecology Center 2015; Zheng et al. 2020). Table 5-6 summarizes available information on the concentration of melamine in various foam products as well as fabrics associated with the foam products.

Table 5-6 Summary of studies that measured melamine in manufactured items

Manufactured item(s)	Concentration of melamine	Reference
Foam used in seats and backs of metal frame furniture	Reported to range from 28% to 29% w/w	ECCC 2013 to 2014
Polyurethane foam samples from children's products (for example, crib mattress, change pad, crib wedge) (n=6) purchased in Canada	Not detected (LOD = 0.031% w/w) to 0.43% w/w	Health Canada 2015
Foam from child restraint systems (n=10), other children's products (n=10), upholstered furniture (n=10), foam mattresses (n=10), mattress toppers (n=10), and pillows (n=1) purchased in Canada	< LOQ (0.00012% w/w) to 7% w/w (that is, detected above LOQ in 9 child restraint systems, 10 other children's products, 7 articles of upholstered furniture, 4 foam mattresses, children's products, 3 mattress toppers, 1 pillow)	Health Canada 2019
Children's products including foam and fabric samples (for example, foam chairs, pajamas, nap mat, mattress topper, blanket, crib sheets, toys, foam tiles, crib mattresses) (n=111 samples from 41 products) purchased in Canada[b]	Not detected (method LOD = 0.00009% w/w) to 0.17% w/w (that is, detected above LOD in 4 products (6 samples): 3 foam samples from 1 foam chair, 1 foam sample from nap mat, 1 foam sample from foam bath toy, 1 fabric sample from fabric/foam teether toy)	Health Canada 2023
6 types of upholstery foam multiple samples from each foam type	Not detected (LOD = 0.005% w/w) to 34% w/w	U.S. CPSC 2005
Child restraint systems (n=14) purchased in U.S.	Melamine detected in 3 of the 14 seats (foam and fabric) but concentrations were not quantified	Ecology Center 2015
Nap mats (n=26 including foam and polyester cover), from childcare centres in U.S.	Not detected[a] to 0.0017% w/w Melamine detected in foam and cover samples	Zheng et al. 2020

[a] Specific method detection limit (MDL) for melamine not specified; however, range of MDLs for melamine and melamine derivatives was reported to range from $1.0x10^{-9}$% w/w to $2.4x10^{-7}$% (reported as 0.01 ng/g to 2.4 ng/g) (Zheng et al. 2020).
[b] The presence of melamine in these product testing results may be from various melamine-based flame retardants.

Since melamine is an additive flame retardant and can migrate out of a matrix, dermal exposure may occur from prolonged daily skin contact with melamine-treated foam-containing upholstered furniture, mattresses, and infant and child restraint systems (including booster seats). This migration may be mediated by sweat (since melamine is associated with high water solubility) or non-aqueous components of the skin such as hair, keratin, and sebum. Log K_{ow}, commonly used as a measure of hydrophobicity, was also considered.[6] Data on migration of melamine were not identified at the time of publication of the updated draft assessment (October 17, 2020) and migration rates for melamine were extrapolated from migration rates in relation to the water solubility and log K_{ow} of other flame retardants reported by the European Chemicals Agency (ECHA 2018) for 2-Propanol, 1,3-dichloro-, phosphate (3:1) (TDCPP, CAS RN 13674-87-8) and Ethanol, 2-chloro-, phosphate (3:1) (TCEP, CAS RN 115-96-8), as shown in Table 5-7.

Table 5-7 Extrapolation of the rate of migration of melamine from foam-containing articles

Parameter	TDCPP	TCEP	Melamine
Water solubility (mg/L)	18.1	7820	3230
Log K_{ow} (unitless)	3.69	1.78	-1.14
Rate of migration from uncovered foam ($mg/cm^2/hr$)[a]	0.00297	0.0207	0.00936[b] 0.0217[c]

[a] The migration rates for TDCPP and TCEP were determined in migration studies performed on treated furniture foam by the Danish EPA (2015) as reported by ECHA (2018). The migration rates of TCEP and TDCPP were determined using children's products (that is, child restraint systems, baby slings, baby mattresses) by submerging pieces of foam from these products (usually with some of the fabric covering included in the samples) in sweat simulant and incubating them at 37°C for 3 hours (Danish EPA 2015). The migration rate for TDCPP used here is the average of the rates found across all samples for this flame retardant while the migration rate for TCEP was from a single item (ECHA 2018).
[b] Calculated based on plotting a straight line between water solubilities and migration rates for TDCPP and TCEP with equation $y = (2 \times 10^{-06} \times \text{water solubility}) + 2.9 \times 10^{-03}$.
[c] Calculated using quadratic equations based on TDCPP and TCEP migration rates, water solubilities, and log K_{ow}: For TDCPP, 0.00297 $mg/cm^2/hr$ = x (log of water solubility) + y (log K_{ow}) and for TCEP, 0.0207 $mg/cm^2/hr$ = x (log of water solubility) + y (log K_{ow}). Thus, 0.00297 = x (1.26) + y (3.69) and 0.0207 = x (3.89) + y (1.78). Solving for x and y results in: x = 0.005863 and y = -0.0012. For melamine, migration rate = (0.005863)(log of water solubility) + (-0.0012) (log Kow) = (0.005863) (3.51) + (-0.0012) (-1.14) = 0.0217 $mg/cm^2/hr$.

Since then, data on migration of melamine from foam became available. A migration test study for melamine was submitted to the Government of Canada during the public comment period for the updated draft assessment (ECCC, HC 2020). In this study, foam samples that contained melamine at concentrations of 9.5% to 19.5% were

[6] It is recognized that water solubility and log K_{ow}, in addition to molecular weight of a substance influence dermal absorption across skin (ten Berge 2009). The same physical-chemical properties are considered in estimation of migration rates.

compressed to 70% of their depth with a stack of 15 Whatman 50 mm filter papers soaked in artificial sweat solution on their surfaces. After incubation for 2 hours at 40°C, the filter papers were immersed in methanol and an aliquot was analyzed using gas chromatography with flame ionization detection (GC-FID). Migration rates for uncovered foam were reported in the range of 0.01211 mg/cm^2/hr to 0.08307 mg/cm^2/hr. These reported migration rates are in the same order of magnitude as the migration rates reported in Table 5-7 (derived using water solubilities and log K_{ow} values). When a mattress cover (that did not contain melamine) was placed in between the foam and the filter papers, melamine was not detected above the LOD (0.00225 mg/cm^2/hr). This result supports the theory that covering foam with an untreated textile would reduce the amount of melamine available for dermal exposure at the surface of foam-containing manufactured items. However, the study was only performed with one type of mattress cover and might not be representative of all textiles used to cover foam, and the LOD was in the same order of magnitude as the derived migration rate using water solubilities (Table 5-7). An additional study on the migration of melamine from foam was performed using subsamples of foam found to contain melamine at concentrations of 0.0038% w/w to 7.0% w/w (Health Canada 2019 and 2021). Subsamples of the foam were placed in a beaker, covered with a stack of 3 filter papers, and then wetted with 3 mL of synthetic sweat. After 5 minutes, the sample and filter paper were covered with a Plexiglas disk and a 1.5 kg glass reservoir was placed on top for 4 hours. The filter papers were removed and extracted using a 50% (v/v) acetonitrile:water solution. The solution was filtered and aliquots were analyzed using liquid chromatography with tandem mass spectrometry (LC-MS/MS). Migration rates for uncovered foam were found over the range 0.00011 mg/cm^2/hr to 0.026 mg/cm^2/hr (Health Canada 2021). This migration rate range overlaps with the range of derived migration rates (Table 5-7). Given that both sets of experimentally determined migration rates for melamine out of foam overlap with the derived migration rates presented in Table 5-7 despite differing experimental methods and concentrations of melamine in the foam samples used, the derived migration rates are considered to be reasonable estimates for use in the calculation of exposure estimates.

Using the migration rates derived for melamine as described above (Table 5-7) and a textile penetration factor (TPF) of 0.1 to account for the use of a textile covering (see Appendix E), dermal exposure intakes were estimated for children and adults in direct contact with fabric-covered foam-containing mattresses and related manufactured items (such as foam-containing upholstered furniture) as well as from the foam/fabric of infant and child restraint systems (including booster seats). This scenario is considered to also be representative of potential exposure from textile backings in furniture.[7] As shown in Table 5-8, the estimates of dermal exposure to melamine via prolonged daily dermal contact with foam mattresses or upholstered furniture were highest for children 0 to 5 months old at 0.29 mg/kg bw/day to 2.3 mg/kg bw/day. Dermal exposure intakes were also highest for children 0 to 5 months old in direct contact with foam-containing restraint systems at 0.07 mg/kg bw/day to 0.016 mg/kg bw/day (Appendix E). Finally,

[7] As shown in the Sources and uses section, melamine may be used in textiles internationally and has been detected in the textile of child car restraint systems.

due to melamine's negligible vapour pressure, inhalation exposure to melamine contained in foam furniture, foam-containing mattresses, and from the foam/fabric of infant and child restraint systems (including booster seats) is expected to be negligible.

Based on melamine's properties (additive flame retardant, high water solubility), it is expected that children may be exposed from mouthing a foam object (for example, crib wedge, foam chair for children). Although melamine concentration data in foam products were available, a melamine-specific migration rate from foam was not identified in the literature. In the absence of migration rates for mouthing, the same migration rates used for the dermal scenario were used to derive estimates of oral exposure to melamine via mouthing of a foam object for children aged 0 to 3 years (Table 5-8 and Appendix E).

Table 5-8 Estimated systemic exposure to melamine from mouthing and dermal contact with flexible polyurethane manufactured items

Exposure Route and Duration	Source	Age Group	Systemic exposure to melamine (mg/kg bw/day)[a]
Dermal (daily)	Foam in children's mattresses or upholstered furniture	0 to 5 months	0.29 to 2.30
Dermal (daily)	Foam in children's mattresses or upholstered furniture	6 to 11 months	0.26 to 2.04
Dermal (daily)	Foam in children's mattresses or upholstered furniture	1 year	0.25 to 2.04
Dermal (daily)	Foam in children's mattresses or upholstered furniture	2 to 3 years	0.16 to 1.66
Dermal (daily)	Foam in children's mattresses or upholstered furniture	4 to 8 years	0.13 to 1.42
Dermal (daily)	Foam in children's mattresses or upholstered furniture	9 to 13 years	0.09 to 1.08

Exposure Route and Duration	Source	Age Group	Systemic exposure to melamine (mg/kg bw/day)[a]
Dermal (daily)	Foam in mattresses or upholstered furniture	14 to 18 years	0.07 to 0.83
Dermal (daily)	Foam in mattresses or upholstered furniture	19+ years	0.06 to 0.66
Dermal (daily)	Foam/fabric in infant and child restraint systems (including booster seats)	0 to 5 months	0.07 to 0.16
Dermal (daily)	Foam/fabric in infant and child restraint systems (including booster seats)	6 to 11 months	0.062 to 0.14
Dermal (daily)	Foam/fabric in infant and child restraint systems (including booster seats)	1 year	0.058 to 0.13
Dermal (daily)	Foam/fabric in infant and child restraint systems (including booster seats)	2 to 3 years	0.040 to 0.092
Dermal (daily)	Foam/fabric in infant and child restraint systems (including booster seats)	4 to 8 years	0.034 to 0.078
Dermal (daily)	Foam/fabric in infant and child restraint systems (including booster seats)	9 to 13 years	5.3×10^{-2} to 6.2×10^{-2}

Exposure Route and Duration	Source	Age Group	Systemic exposure to melamine (mg/kg bw/day)[a]
Mouthing (Daily – Intermittent)	Foam in children's products	0 to 5 months	6.1×10^{-3} to 1.4×10^{-2}
Mouthing (Daily – Intermittent)	Foam in children's products	6 to 11 months	4.2×10^{-3} to 4.9×10^{-2}
Mouthing (Daily – Intermittent)	Foam in children's products	1 year	3.5×10^{-3} to 4.0×10^{-2}
Mouthing (Daily – Intermittent)	Foam in children's products	2 to 3 years	2.6×10^{-3} to 3.0×10^{-2}

[a] No dermal absorption data were identified for melamine. A value of 30% was selected based on data available for structurally similar compounds (refer to section 5.1.3).

Textiles

In a study by Zheng and Salamova (2020), melamine was measured in 86 items of new finished infant clothing purchased in the U.S. including shirts (n = 13), pants (n = 12), socks (n = 12), cloth diapers (n = 20), dresses (n = 2), onesies (n = 24), and outerwear (made of conventional and organic cotton, polyester, spandex, and nylon) (n = 3). Median melamine concentrations ranged from 9.7 ng/g for polyester items to 17,300 ng/g for nylon items, with an overall median of 35.7 ng/g for all samples. These values are below the values measured by Zhu and Kannan (2020a), described below. The study authors estimated dermal exposure to unwashed textiles ranging from 0.0121 ng/kg bw/day for children 6 to 12 months and 0.015 ng/kg bw/day for newborns (less than 1 month).

Melamine was measured in 77 textile samples purchased in the U.S. including infant clothing (n = 52), raw textiles (n = 19) and other (for example, cloth diapers, blankets) (n = 6) (Zhu and Kannan 2020a). A mean concentration of 4900 ng/g and a max concentration of 81,800 ng/g for the original (unwashed) textiles were reported. Zhu and Kannan (2020a) also reported concentrations of melamine in the textile samples after the textiles were washed with water and detergent. These concentrations were lower than the unwashed textiles (max = 12,400 ng/g after washing with water and 8340 ng/g after washing with detergent). The study authors estimated dermal exposure to unwashed textiles ranging from 1.89 ng/kg bw/day for 6 to 12 months old children and 2.34 ng/kg bw/day for newborns (less than 1 month old). Given that data for adult clothing was not available and using a slightly different approach than Zhu and Kannan (2020a), the concentrations from infant clothing were used to derive oral and dermal exposure estimates for all age groups. The estimated oral and dermal intakes for unwashed textiles were 53.9 ng/kg bw/day (6 to 11 months olds) and 1250 ng/kg bw/day (0 to 5 months olds) (highest exposed groups) (see Appendix E for details, including intakes for other age groups).

5.1.4 Biomonitoring

Studies in animals indicate that melamine is rapidly absorbed from the gastro-intestinal tract and rapidly eliminated from the body with a plasma-half-life of a few to several hours (EFSA 2010). The major route of elimination is via the urine and the limited information available suggests that the substance is hardly metabolised at environmentally relevant doses (EFSA 2010). The urinary half-life of melamine across various species is a few hours (3 hours to 6 hours) (Panuwet et al. 2012; Mast et al. 1983; Baynes et al. 2008; Wu et al. 2013; IARC 2019). More details on the toxicokinetics of melamine are provided in section 5.2.1. In biomonitoring studies, melamine is directly measured in urine and is considered a suitable biomarker of exposure (Panuwet et al. 2012; Zhu and Kannan 2019b; Sathyanarayana et al. 2019).

Panuwet et al. (2012) published the results for melamine measurements in 492 spot samples of human urine collected from the general U.S. population. These samples were collected in 2003-2004 as part of the U.S. National Health and Nutrition Examination Survey (NHANES) and included samples from both males and females aged 6 years and older (U.S. CDC 2010a). Melamine was detected in 76% of the samples (population: 6 + years old, GM: 2.37 ng/mL, 95th percentile: 12 ng/mL, maximum: 161 ng/mL, LOD = 0.66 ng/mL)[8]. Since the relative distribution of age groups (that is, 6 to 11 years, 12 to 19 years, etc.) was not available from Panuwet et al. (2012), this information was derived from demographic data collected by NHANES (U.S. CDC 2010b). Geometric mean and 95th percentile concentrations, based on the different age groups, are presented in Table 5-9. For the group aged 6 to 11 years old, due to the small sample size (n = 6) of this age group, 95th percentile intakes were not derived because they would be statistically unstable. In addition, one high concentration of 161 ng/mL melamine was recorded for this age group, whereas other concentrations among the 6 individuals ranged from 0.5 ng/mL to 6.7 ng/mL. Panuwet et al. (2012) did not discuss whether this high value was an artifact, therefore it was not used to estimate high-end intakes. The second-highest value of 6.7 ng/mL was used instead.

Melamine was measured in 213 urine spot samples collected from 19 healthy participants aged 11 to 56 years old (2 participants under 18) in Albany, New York. Melamine was detected in 99% of the samples at concentrations ranging from not detected to 58 ng/mL (mean = 3.3 ng/mL, LOQ = 0.08 mg/mL) (Zhu and Kannan 2019b).

Melamine was also measured in urine spot samples collected from 109 healthy children aged 4 months to 8 years in Seattle, Washington and New York City, New York. The samples were collected for 3 separate studies from 2013 to 2017 and included samples from both males and females. The mean age of the participants in the study was 2.7 years. Melamine was detected in 78% of the samples (mean = 27.8 ng/mL,

[8] Reported concentrations were not corrected for specific gravity. However, it is considered that this correction would not have much of an impact on the results, since the large sample of participants (492) would probably result in a normal distribution of urinary specific gravity. The range of urinary specific gravity reported in humans is 1.005 to 1.030 (Williamson and Snyder 2011).

median = 4.7 ng/mL, min = 0.4 ng/mL, max = 1085 ng/mL, LOD = 0.5 ng/mL, LOQ = 2.0 ng/mL) (Sathyanarayana et al. 2019). The study did not break down the data by age group; however, Sathyanarayana et al. (2019) stated that higher concentrations of melamine were measured in samples from older participants. As the data were not broken down per age group in the study, estimated intakes are based on a representative age category of 6 months to 4 years based on the average age of participants in the study of 2.7 years.

Melamine was also measured in spot urine samples collected from 123 children aged 4 to 6 years in the U.S. These data were collected as part of a follow-up for children whose mothers were involved in the Global Alliance to Prevent Prematurity and Stillbirth (GAPPS) study cohort which included pregnant women located in Seattle, Washington and Yakima, Washington. Urinary melamine was detected above the LOD in all samples (n = 123) (mean = 6.1 ng/mL ± 12.4, min = 0.41 ng/mL, max = 104.3 ng/mL, LOD = 0.08 ng/mL) (Melough et al. 2022).

Melamine was measured in the urine of 171 pregnant women from California, Georgia, Illinois, New Hampshire, New York, and Puerto Rico. The urine samples were collected between 2017 and 2020 during all 3 trimesters. Melamine was measured in 99% of the samples (n = 170). The urinary melamine concentrations ranged from below the LOD (LOD = 0.03 ng/mL) to 351 ng/mL (median = 1.6 ng/mL) (Choi et al. 2022). Wu et al. (2020) conducted a study in Taiwan in which melamine concentrations were measured in the serum and urine of pregnant women. The serum concentrations were below the LOD while urinary melamine concentrations measured were similar to the study by Choi et al. (2022), ranging from 0.20 ng/mL to 284.55 ng/mL (median = 3.33 ng/mL). Tsai et al. (2021) conducted a study in Taiwan in which melamine concentrations were measured in the urine of pregnant women in their third trimester. The urinary melamine concentrations were lower than the Choi et al. (2022) study, ranging from 0.20 ng/mL to 47.69 ng/mL (median = 2.31 ng/mL).

Reverse dosimetry was used to derive estimates of daily intakes using the urine concentrations identified in relevant studies and results are shown in Table 5-9 (details in Appendix F). No studies were identified showing the fraction of melamine excreted in human urine; however, several studies conducted in animals are available. Mast et al. (1983) showed that 90% of administered melamine was excreted in urine of male rats as melamine. In dogs, Lipschitz and Stokey (1945) showed that 60% to 86.5% of administered melamine was excreted as melamine 24 hours after a single oral dose of melamine. Cruywagen et al. (2011) showed that 54.1% of the administered melamine was excreted in the urine of sheep as melamine. Finally, although Liu et al. (2010) suggested that the amount excreted in monkey urine was much less than the oral dose, they could not document a mass balance for the excretion profile or cite the percentage of melamine dose excreted in the urine (more details available in section 5.2.1).

Given the lack of human data, and due to the variability in urinary excretion between species ranging from 54% to 90%, a value of 50% was conservatively used as the fractional urinary excretion (FUE) value in the calculation of intakes from the human biomonitoring data. Additionally, since information on urine volume excreted for each participant was not collected, ranges of typical 24-hour mean urine volumes identified

from various sources were used to calculate intakes (see Appendix F for urine volume ranges and references). Details regarding the reverse dosimetry are provided in Appendix F. There are various uncertainties with the estimated intakes from the available biomonitoring data which are outlined in section 5.4.

Table 5-9 Urinary melamine concentrations used to estimate intakes of melamine using reverse dosimetry (see Appendix F for details)

Study	Participants	Location	Geometric mean and [maximum] or [95th percentile] of urinary concentrations (ng/mL)	Intake estimates (µg/kg bw/day)[a]
Panuwet et al. 2012	6 to 11 years (n=6)[b]	United States	5.91 [6.7]	0.23 to 0.30 [0.27 to 0.34]
Panuwet et al. 2012	12 to 19 years (n=162)	United States	2.06 [10.47]	0.08 [0.42]
Panuwet et al. 2012	20 to 59 years (n=217)	United States	2.33 [12.44]	0.09 [0.50]
Panuwet et al. 2012	60+ years (n=107)	United States	2.93 [11.09]	0.12 [0.44]
Sathyanarayana et al. 2019	4 months to 8 years (n=109)	United States	27.8 [1085]	1.22 to 4.74 [47.74 to 184.88]
Melough et al. 2022	4 to 6 years (n=123)	United States	6.1 [104.3]	0.37 [6.26]
Choi et al. 2022	Pregnant women (n=171)	United States	1.6[c] [351]	0.06 [14.04]

[a] Intake estimates are based on the geometric mean or median concentration listed under previous column. Value in brackets refers to intake estimate derived from the maximum or P95 shown in previous column. Refer to Appendix F for more details on the reverse dosimetry calculations.

[b] For 6 to 11 year olds (n=6), 5 individuals showed urinary melamine concentrations between 0.5 and 6.7 ng/mL and 1 individual presented a urinary concentration of 161 ng/mL. Due to small sample size in this age group and the possibility that one of the concentrations was an outlier, a 95th percentile intake calculation would be statistically unstable. Therefore, the second highest concentration was used to determine the upper-bound intake.
[c] Median concentration

Other biomonitoring studies have been conducted in Taiwan (Wu et al. 2010a, 2018; Liu et al. 2011), Hong Kong (Kong et al. 2011) and Shanghai (Shi et al. 2020) but the results based on the U.S. population measured by Panuwet et al. (2012), Sathyanarayana et al. (2019), Melough et al. (2022) and Choi et al. (2022) were used as a surrogate for the Canadian population as they were considered most relevant.

5.1.5 Consideration of subpopulations who may have greater exposure

There are groups of individuals living in Canada who, due to greater exposure, may be more vulnerable to experiencing adverse health effects from exposure to substances. The potential for elevated exposure within the Canadian population was examined. Exposure estimates are routinely assessed by age to take into consideration physical and behavioural differences during different stages of life. In the assessment of background exposure from environmental media, food and drinking water, young children were associated with a higher estimated exposure than adults with formula-fed infants having the highest exposures. Infants and children also had a higher dietary exposure as a result of melamine migration from melaware. In the assessment of exposure to melamine in products available to consumers, products used by children that were assessed included mattresses, upholstered furniture, infant and child restraint systems (including booster seats), and textiles. Infants and children had higher exposure to melamine from textiles as well as manufactured items (for example, mouthing a foam object, dermal contact from sitting in an infant or child restraint seat, and lying on foam-containing mattresses) as compared to adults. In this exposure assessment, melamine biomonitoring data were available from persons at all life stages from infant to adult, including pregnant women (Panuwet et al. 2012; Sathyanarayan et al. 2019; Melough et al. 2022; Choi et al. 2022). Children have higher urinary melamine concentrations than adults. The mean urinary melamine concentrations for pregnant women (Choi et al. 2022) were similar to those of the average adult (Panuwet et al. 2012), while the maximum concentrations in pregnant women were higher than that of the average adult. Choi et al. (2022) examined the differences in urinary melamine concentrations in different ethnicities, and noted that higher concentrations of melamine were found in non-Hispanic Black women and non-Hispanic Asian women when compared to other groups (Hispanic, non-Hispanic White, and non-Hispanic other or multiple race).

5.2 Health effects assessment

Health effects information for melamine is summarized in this section. Further details including effects with cyanuric acid may be found in the Human Health Supplementary Data supporting documentation (Health Canada 2024). Health effects studies that could impact the risk characterization (that is, result in different critical endpoints or lower

points of departure than those stated in (ECCC, HC 2020)) were identified and are presented mainly in. In terms of classification, the International Agency for Research on Cancer (IARC) has classified melamine as Group 2B (possibly carcinogenic to humans) (IARC 2019).[9] The ECHA Committee for Risk Assessment (RAC) adopted an opinion proposing harmonized classification and labelling at the European Union level for melamine (ECHA 2020). The following classifications were adopted by consensus: Carc. 2, H351 and STOT RE 2, H373, (urinary tract). Additionally, according to notifications provided by companies to ECHA in Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) registrations for classification and labelling, melamine is suspected of damaging fertility (Repr. 2, H361f) with respect to the male reproductive system (testis, sperm) (ECHA 2022).

5.2.1 Oral toxicokinetics

Melamine was excreted in rat and monkey urine after single oral doses of 1.3 mg/kg bw and 1.4 mg/kg bw, respectively, but the following 2 metabolites were identified in addition to unchanged melamine after large single oral doses in the rat (250 mg/kg bw) and dog (125 mg/kg bw): dimelamine monophosphate and monomelamine-monooxalate (Lipschitz and Stokey 1945). The half-life for urinary elimination of melamine was 6 hours in dogs (Lipschitz and Stokey 1945). Also, based on extensive toxicokinetic studies in rats, melamine was not metabolized at lower doses compared to higher doses (1.3 mg/kg bw vs. 250 mg/kg bw), which suggests that oral exposure at environmental levels of melamine may not be metabolized in the body. In the rats dosed at 1.3 mg/kg bw/day, mass balance calculations showed that 98% of the dose was recovered as melamine 96 hours after dosing, confirming a lack of metabolism (Mast et al. 1983). In rats, the elimination half-life, urinary-excretion half-life, and renal clearance for melamine were 2.7 hours, 3.0 hours, and 2.5 mL/min, respectively (Mast et al. 1983). In the 3 monkeys orally gavaged at 1.4 mg/kg bw, the amount excreted in monkey urine was much less than the oral dose, but the authors could not document a mass balance for the excretion profile or cite the percentage of melamine dose excreted in the urine, because melamine was not radiolabelled in this study (Liu et al. 2010).

In sheep that ingested 700 mg/day of melamine in pellets for 7 days, urine was the major route of melamine excretion (54.1% of that ingested), followed by feces (23.7% of ingested) (Cruywagen et al. 2011).

At 100 mg/kg bw/day oral dosing, there appears to be saturation of excretion. When Wu et al. (2010b) dosed Sprague-Dawley (SD) rats at 100 mg/kg bw, they wrote:

About 63.2% of the administered dose was recovered from the urine within 96 hours. The previous study indicated a value of 90% elimination [at a dose of 1.3 mg/kg bw] within the first 24 hours [Mast et al. 1983], and this discrepancy might result from a

[9] Grosse et al. (2017) initially reported the new classification for melamine as Group 2B in consideration of the same studies reviewed in IARC (1999) and more recent studies that were considered in this assessment. IARC (1999) had previously classified melamine as Group 3 (not classifiable as to its carcinogenicity to humans).

much higher dose (100 mg/kg, po[10]) in our study, possibly leading to the saturation of urinary elimination and delayed elimination time. This result suggests that most of the administered melamine was absorbed and eliminated via the urine in unchanged form.

Oral bioavailability of melamine ranged from 73 ± 13% to 98% in rats, confirming high and rapid oral absorption in the gastrointestinal tract (Yang et al. 2009; Wu et al. 2010b). Studies conducted by Yang et al. (2009), Wu et al. (2010b), and Pang et al. (2013) indicate that melamine does not extensively distribute to most tissues in rats after single or repeated oral dosing for 14 days at 100 mg/kg bw, being mostly restricted to the blood. Several authors reported plasma elimination half-lives ranging from 1.3 hours to 5 hours from various studies in rats and monkeys upon single oral doses of 1 mg/kg bw to 100 mg/kg bw (Wu et al. 2010b; Jacob et al. 2012; Dorne et al. 2013; Pang et al. 2013). Dorne et al. (2013) considered the rates comparable at these oral doses, and in all cases support the observation of rapid excretion of melamine in urine.

Wang et al. (2013) conducted a repeated dose toxicokinetic study in pigs. Pigs were fed melamine in the diet at doses of 0, 18, or 35 mg/kg bw/day for 42 days with a 5-day recovery period. There was a dose-related increase in residual melamine concentrations in all tissues measured (plasma, brain, duodenum, liver, heart, muscle, and kidney), and melamine concentration in the kidney was significantly higher than in other tissues ($p < 0.01$), with tissue residue concentrations decreasing after melamine withdrawal. After 42 days at 35 mg/kg bw/day, the half-life was 9.90 hr, with a steady state volume of distribution of 1.07 L/kg. Although slightly longer than the half-lives reported for other species, this study also confirmed that melamine was primarily eliminated via renal filtration. The authors noted that the clearance of melamine was consistent with the plasma clearance observed in pigs subjected to single intravenous doses (0.076 L/h/kg in this study versus 0.061 L/h/kg) conducted by Baynes et al. (2008).

Chu et al. (2013) conducted a toxicokinetic study in pregnant and developing rats. Pregnant females were given a single dose by gavage of 24 mg/kg bw melamine on gestation days (GD) 10, 15, or 20 and by gavage in pups on postnatal weeks 2, 4, 6 or 8 (P2W, P4W, P6W, or P8W, respectively). As reported by the authors, distribution of melamine in maternal serum was about 30% higher in late pregnancy than that in early pregnancy and it was 2-fold higher in postnatal serum in younger pups than in young adulthood (P2W vs. P4W to P8W). Melamine distribution in all postnatal organs was higher than that in prenatal organs. In younger pups, postnatal kidneys had the highest maximum concentration and the lowest clearance rate of melamine than the other postnatal organs (Cmax = 10.85 mg/kg vs. 1.06 mg/kg to 2.36 mg/kg and apparent clearance = 0.62 L/hr vs. 1.85 L/hr to 2.75 L/hr in liver, lung, heart, brain, and spleen, respectively at P2W). The increased distribution of melamine in serum and kidneys of 2-week old rats compared to other life stages suggests an increased risk of melamine toxicity to the kidney after birth, according to the authors. The developmental toxicity studies of Kim et al. (2011) and Stine et al. (2014) showed kidney toxicity in pregnant

[10] Refers to *per os* from Latin meaning "through the mouth" or "by mouth"

dams at oral doses of 800 mg/kg bw/day and 1000 mg/kg bw/day melamine; however, no kidney toxicity was observed in fetuses at these doses (although other effects were observed) and the dams were not allowed to litter.

EFSA (2010) also reported that there is indirect evidence that melamine is not metabolized in humans. In a study (Worzalla et al. 1974 as cited in EFSA 2010) in which [^{14}C]-ring-labelled hexamethylmelamine was administered to humans orally, 5% of the dose of hexamethylmelamine (as ^{14}C) was excreted as melamine in urine, but no metabolites of melamine were reported. The authors conducted the same study in rats dosed intraperitoneally with [^{14}C]-ring-labelled hexamethylmelamine. In this case, 2% of the dose of hexamethylmelamine (as ^{14}C) was excreted as melamine in urine, but no metabolites of melamine were reported. In both the rat and human studies, only 5% of the urinary radioactivity was unidentified.

Wu et al. (2013) conducted a study in humans in which the urinary melamine concentration was measured in 16 adults who had consumed hot noodle soup served in melamine or ceramic bowls at different periods. The total melamine excretion in urine was 8.35 ± 1.91 µg 12 hours after consuming noodle soup served in melamine bowls, and 1.31 ± 0.44 µg 12 hours after consuming noodle soup served in ceramic bowls. Peak urinary excretion occurred at the greater than 4 hour to 6 hour period. The estimated half-life for urinary elimination of melamine in humans is approximately 6 hours (Wu et al. 2013).

In summary, studies in animals indicate that melamine is rapidly absorbed from the gastro-intestinal tract and rapidly eliminated from the body with a plasma-half-life of a few to several hours (EFSA 2010). The major route of elimination is via the urine and the limited information available suggests that melamine is hardly metabolised at environmentally relevant doses. Urinary half-lives range from 3 hours to 6 hours depending on the species (Lipschitz and Stokey 1945; Mast et al. 1983; Wu et al. 2013; IARC 2019). In studies across species, rats were shown to have the highest elimination rate with 90% melamine excreted in urine after 24 hours, followed by dogs in which 61% melamine was excreted in urine after 6 hours. The excretion rate for monkeys could not be determined. Sheep were shown to have the slowest elimination rate with 54% of melamine excreted in urine (Mast et al. 1983; Yang et al. 2009; Liu et al. 2010; Wu et al. 2010b; Cruywagen et al. 2011; Pang et al. 2013; Wang et al. 2013).

5.2.2 Carcinogenicity/chronic toxicity

In a 2-year study, Fisher 344 (F344) rats were administered melamine in the diet for 2 years at doses of 0, 126/262, or 263/542 mg/kg bw/day in males/females, respectively. Transitional-cell carcinomas in the urinary bladder of male rats occurred at a significantly ($p \leq 0.016$) higher incidence in the high dose group (8/49) than in the controls (0/45). There was also a statistically significant association ($p < 0.001$) between bladder stones (observed in 10/49 males) and bladder tumours in male rats fed melamine at the high dose. Urinary bladder tumours were not observed in the low-dose (126 mg/kg bw/day) male rat group, while bladder stones were observed in only one of 50 rats in this low dose group (U.S. NTP 1983; Melnick et al. 1984). Due to the

statistically significant association between bladder stones and bladder tumours at the high dose (263 mg/kg bw/day), a re-evaluation of the histopathology from this study was conducted (Hard et al. 2009). The results showed a significant increase in the incidence of reflux nephropathy in male rats [7/50 vs. 1/49 in controls] but not of bladder stones [1/50 vs. 0/45 in controls] at 126 mg/kg bw/day (Hard et al. 2009), confirming the lack of tumours at this dose.

In another 2-year study conducted in an unnamed strain, rats were administered melamine in the diet at doses of 0, 67 or 667 mg/kg bw/day. An increase in the incidence of urinary bladder stones associated with an increased incidence of benign papillomas at the top dose was reported (American Cyanamid Co 1955). F344 rats were administered melamine in the diet for 24 months to 30 months at doses of 0, 5/5, 25/50, or 50/100 mg/kg bw/day in males/females, respectively. An increased incidence of bladder tumours was not observed. Although a dose-related trend for dilated glands in glandular gastric mucosa and inflammation in non-glandular gastric mucosa was observed at 5 mg/kg bw/day and higher, it was not specified whether this trend applied to one or both sexes. However, the secondary source stated that the no observed effect level (NOEL) was thought to be the high dose (Hazleton Laboratories 1983 cited in OECD 2002).

Two 36-week studies were conducted on male F344 rats only; in one, animals were administered melamine in the diet at doses of 0, 110, 367 or 1100 mg/kg bw/day (Okumura et al. 1992) and, in the other, animals were administered melamine in the diet at doses of 0, 430 or 1200 mg/kg bw/day (Ogasawara et al. 1995). In both studies, dose-related increases in the incidence of transitional cell/urinary carcinomas of the bladder and bladder papillomas were observed, which were associated with dose-related increases in the incidence of papillary/nodulary hyperplasia of the bladder epithelium. These increased incidences, along with a non-dose related increase in bladder stones, resulted in the determination of a lowest observed adverse affect level (LOAEL) of 110 mg/kg bw/day in the Okumura et al. (1992) study. Okumura et al. (1992) observed a significant statistical correlation between the incidence of bladder stones and tumours and concluded that melamine-induced calculi can induce carcinomas in the urinary bladder. Ogasawara et al. (1995) determined that the bladder stones were composed of equal molar ratios of melamine and uric acid, and concluded that proliferative lesions of the urinary tract of F344 male rats were directly due to the irritative stimulation of the calculi and not to molecular interactions between melamine itself or its metabolites with the bladder epithelium.

B6C3F1 mice were administered melamine in the diet for 103 weeks at doses of 0, 327/523 or 688/1065 mg/kg bw/day in males/females, respectively, which was followed by 2 weeks of no treatment with melamine. Acute and chronic inflammation and hyperplasia of the bladder, as well as bladder calculi, were observed in male mice at all doses and in females at the high dose. However, no carcinogenic effects were observed in this study (U.S. NTP 1983; Melnick et al. 1984).

In summary, 5 carcinogenicity studies have been conducted in rats and one in mice; in all cases, melamine was administered through the feed of the animals. In 4 of the rat studies, bladder tumours or papillomas were observed at doses ranging from

263 mg/kg bw/day to 1200 mg/kg bw/day, whereas the other one used lower doses (5 mg/kg bw/day to 100 mg/kg bw/day). No carcinogenic effects were observed in a 2-year mouse feeding study at melamine doses of 327 mg/kg bw/day to 1065 mg/kg bw/day.

5.2.3 Genotoxicity

Many *in vitro* genotoxicity studies have been conducted on melamine. All gene mutation studies in bacterial (*Salmonella typhimurium*, *Photobacterium phosphoreum*, Saccharomyces *cerevisiae*) and mammalian (mouse lymphoma and Chinese hamster ovary [CHO]) cells, chromosome aberration and sister chromatid exchange assays in CHO cells, a micronucleus study using CHO cells, and unscheduled DNA synthesis studies in rat hepatocytes and bacterial cells (*E. coli* and *S. typhimurium*) were negative (Seiler 1973; Litton Bionetics 1977a, 1977b, 1977c; American Cyanamid Co. 1981, 1982a, 1982b; Mast et al. 1982a; Haworth et al. 1983; Mirsalis et al. 1983; Galloway et al. 1987; Zeiger 1987; McGregor et al. 1988; Elmore and Fitzgerald 1990; Ishiwata et al. 1991; Selden et al. 1994; Yasunaga et al. 2004; Tu et al. 2015). A non-standard test, which measured lambda prophage induction in *E. coli* as an indicator of DNA damage, was positive both with and without metabolic activation (Rossman et al. 1991). A comet assay was conducted in the unicellular eukaryote, *Tetrahymena thermophila*. There was a dose-related increase in %DNA damage, percentage of tailed cells, and arbitrary units of DNA damage at all doses, but the increase was statistically significant at 2000 mg/L and 4000 mg/L.

In vivo studies in 2 micronucleus assays (mice administered melamine via oral gavage and intraperitoneal injection), plus one combining a *Pig-a* mutation assay (rats administered melamine via oral gavage), were negative for chromosomal aberration in the bone marrow and peripheral blood of mice and had no significant differences in micronucleus frequencies or in *Pig-a* mutation frequencies in red blood cells or in reticulocytes of rats (Pharmakon Research 1981; Mast et al. 1982b; Shelby et al. 1993; Tu et al. 2015). Overall, the genotoxicity data indicates that melamine is not genotoxic. Reviews of the data by IARC (2019) and ECHA (2020) also support this indication.

5.2.4 Carcinogenic mode of action

The mode of action for induction of the observed tumours has not been fully elucidated. It has been postulated, however, that the malignancies in the urinary bladder are based on a threshold mechanism due to reactive hyperplasia that develops in response to a localized tissue irritation effect, which then progresses to bladder neoplasia, and is supported by lack of any mutagenic or genotoxic activity in standard assays as reported by the World Health Organization (WHO 2009). WHO (2009) also noted that renal papillary mineralization was reported in some studies, but it is unknown if such mineralization may slough and provide a focal point for stones to form in the bladder.

5.2.5 Reproductive and Developmental Toxicity

In a 3-day study, male Kunming mice (12/group) were administered melamine as a suspension in 1% carboxymethylcellulose sodium (30, 140, or 700 mg/kg/day) or vehicle (control) via oral gavage (Chang et al. 2014). Testicular toxicity was evaluated on days 1 and 5 after the final exposure. There were no clinical changes or body weight changes observed between control mice and treated mice. There were no differences in blood levels of urea nitrogen, creatinine or testosterone between control mice and treated mice. After 1 day of exposure, the levels of epididymal sperm abnormalities in all the treated groups were much higher than in the control group with levels significantly higher in the 30 mg/kg/day and 700 mg/kg/day groups in particular. At 5 days after exposure, the abnormality levels were still higher than in the control group.

At 1 day after exposure, there were white precipitates in the bladders of one mouse in the 2 lower melamine dose groups (30 mg/kg/day and 140 mg/kg/day) and in half of the mice in the highest dose group (700 mg/kg/day).

At 5 days after exposure, the right bulbourethral gland of one mouse exposed to the highest dose (700 mg/kg/day) was notably swollen and hemorrhagic. There were no significant differences observed in the testicular or epididymal weights between the control and treated groups.

At 1 day after exposure, the apoptotic index of the seminiferous tubules significantly increased only in the lowest group (30 mg/kg/day). At 5 days after exposure, the apoptotic index of the seminiferous tubules significantly increased only in the highest group (700 mg/kg/day).

In all the treated groups, there were marked bladder lesions. In addition, there were morphological changes in the testis and epididymis in a dose-dependent manner. At 1 day after exposure, increased cauda epididymal histopathology scores and germ cell sloughing was observed in the testes of mice exposed to the highest dose. An almost total absence of spermatozoa or a mass of pyknotic and necrotic germ cells in the lumina of efferent ductules were observed in all treated mice.

At 5 days after exposure, the abnormal changes in the treated testes and epididymis became less severe.

There were no significant changes observed in the testicular histopathology score among control and treated groups 1 day or 5 days after the 3-day exposure. In all treated mice, there was dose-related damage to the structure of the blood–testis barrier including capillary endothelial cells, peritubular tissue, and inter-Sertoli cell junctional complex.

In a 5-day study, sperm abnormality of male mice was investigated by administrating healthy Kunming male mice (8/group) melamine at doses of 412 mg/kg bw/day, 824 mg/kg bw/day, and 1648 mg/kg bw/day via gastric gavage (Yin et al. 2013). The mice were sacrificed 35 days after the first administration. The abnormality rate of sperm was 2.31%, 2.83% and 5.63% in mice administered melamine at doses of 412 mg/kg bw/day, 824 mg/kg bw/day, and 1648 mg/kg bw/day, respectively. This was

a significant increase in sperm abnormality for all dose groups as compared to the negative control (Yin et al. 2013).

In the same study, histopathologic changes and apoptosis of spermatogenic cells of testis were investigated. Healthy Kunming male mice (8/group) were administered melamine at doses of 2 mg/kg bw/day, 10 mg/kg bw/day or 50 mg/kg bw/day via gastric gavage for 14 days (Yin et al. 2013).

At 2 mg/kg bw/day, no significant changes were noted in the mice. There were some irregular shaped nuclei in some spermatogenic cells. At 10 mg/kg bw/day, the basement membrane in seminiferous tubules was indistinct and spermatogenic cells at all stages exhibited a slightly loosened organization with decreased cell layers. In addition, irregular shaped nuclei were observed in some primary spermatocytes, secondary spermatocytes, and sperm cells. At 50 mg/kg bw/day, there was damage to the basement membrane of the seminiferous epithelium in seminiferous tubules, decreased layers of epithelial cell and structural damage in many spermatogenic cells at all stages. Swelling and lysis of nuclei was observed in primary spermatocytes, secondary spermatocytes, and the sperm cells in histopathological examination. It was noted that there was a reduction in the number of sperm and an absence of mature sperm in Sertoli cells. Compared with the control group, in mice treated with 50 mg/kg bw/day, there was a significant increase in apoptotic index of spermatogenic cells ($p < 0.05$).

In a 28-day study, ICR male mice (10/group) were administered melamine at doses of 2 mg/kg bw/day, 10 mg/kg bw/day or 50 mg/kg bw/day via oral gavage. Melamine was given as a suspension in edible oil and control mice were administered the edible oil by oral gavage (Sun et al. 2016a). The animals were sacrificed after the final day of treatment. In melamine-treated mice, the number of sperm were significantly lower and abnormal sperm rate significantly higher as compared to the control group. These changes were observed in a dose dependent manner.

In mice dosed at 10 mg/kg bw/day and 50 mg/kg bw/day melamine, downregulation of steroidogenic acute regulatory (StAR) protein and testosterone synthetic enzymes and significantly decreased testosterone levels were observed. There were slight lesions present in the testes as well as decreased Leydig cell number of mice dosed at 10 mg/kg bw/day. In histopathological examination of mice treated with 50 mg/kg bw/day melamine, disruption of the seminiferous tubule structure, decreased spermatogenic cell series, nuclei pyknosis and decreased sperm number and Leydig cell number were observed. There were no obvious gross lesions observed in the kidneys or testes of treated mice, and there was no significant difference in testis weight.

In a 28-day study, female SD rats (10/group) received 10 mg/kg bw/day, 20 mg/kg bw/day, or 40 mg/kg bw/day melamine in corn oil that was given once daily by oral gavage (Sun et al. 2016b). The body weights steadily increased in all 3 treated groups and there were no statistically significant differences between the 3 groups. There were no obvious gross changes in the kidneys of any of the other treatment groups. There were no differences in duration of the estrous cycle. There was a dose dependent (but not significant) decrease in serum estrogen and progesterone levels. In

rats treated with 40 mg/kg bw/day melamine, necrosis of oocyte nucleus and granulosa cells, thin layers of granulosa cells, detachment of granulosa cells from the basement membrane, a significantly higher percentage of apoptotic granulosa cells and a significantly higher number of atretic follicles were observed.

In an 8-week study, female mice (120/group) were administered melamine (0, 10 and 50 mg/kg/day) in drinking water (Duan et al. 2015). While it was reported that there were 120/group, the sample size for each investigation was different. In melamine-treated mice, ovary weights were significantly smaller in the 10 mg/kg/day and 50 mg/kg/day groups as compared to control mice. There was a large proportion of oocytes that had a dark cytoplasm or were smaller in melamine-treated mice. The abnormal oocyte rate was higher in melamine-treated mice than in control mice. The numbers of ovulated oocytes were not significantly different between control and treated mice. The rate of polar body extrusion in oocytes was lower in treated mice as compared to the control group. In melamine-treated mice, abnormal oocyte cytoskeletons were noted as shown by increased rates of aberrant spindles and reduced actin microfilament expression. The litter sizes of melamine-treated mice (n = 4) in the highest dose group were significantly reduced when compared with those of controls (n = 4) (no other details on mating/litter).

In a 65-day study, male Swiss mice (10/group) were orally administered melamine dissolved in distilled water (50 mg/kg/day), formaldehyde dissolved in distilled water (25 mg/kg/day), a mixture of melamine and formaldehyde dissolved in distilled water, or a vehicle control via gavage (Khalil et al. 2017). The formaldehyde and mixture treated groups are not further discussed here. There were no statistical differences observed between the treatment and control groups with respect to the testes weight and mean gonadosomatic index value for testes. A significant reduction in the sperm concentration and sperm motility percentage, decreased plasma testosterone and LH hormones levels, decreased relative changes in the mRNA transcript levels for key steroidogenic enzymes and a significant inhibition of testicular enzyme activities were observed in the melamine-treated group. In addition, altered spermatogenesis process, cystic dilatation of the seminiferous tubules with marked vacuolation of the Leydig cells, extensive disorganization of the spermatogonial cells, as well as the apoptotic Sertoli cells were observed.

In a 91-day study, 8 male Kunming mice/group were administered melamine at doses 0 mg/L, 12.5 mg/L, 25 mg/L, and 50 mg/L melamine (equivalent to 2, 4, and 8 mg/kg bw/day) via drinking water (Chen et al. 2021). The animals were sacrificed after the final day of treatment. In melamine-treated mice, mRNA expression levels of p38 and downstream transcription factors MAX and Sap1a in testes were reduced. In addition, melamine treatment down-regulated the relative expression of phosphorylated p38 in testes (Chen et al. 2021).

In mice dosed at 8 mg/kg bw/day melamine, body weight decreased significantly at 2, 8, and 13 weeks after exposure compared with the control group. While the absolute testis weight was similar amongst the experimental group, the relative testis weight (g) was significantly increased in the low- and mid-dose groups as compared to the control group (Chen et al. 2021).

In all melamine-treated mice, sperm motility was significantly decreased as compared to control mice. In mice dosed at 4 mg/kg bw/day and 8 mg/kg bw/day melamine, sperm count was significantly reduced as compared to control mice (Chen et al. 2021).

In histopathological examination, the structures of seminiferous tubules in mice dosed at 4 mg/kg bw/day and 8 mg/kg bw/day melamine were loosened, disordered, and unclear as compared to the control. In all melamine-treated mice, the number of the seminiferous epithelium cell layers and their thickness were significantly reduced. In the low- and mid-dose groups, the diameter of seminiferous tubules was decreased as compared to the control group while it was significantly increased in mice dosed at 8 mg/kg bw/day melamine (Chen et al. 2021). It should be noted that the study did not indicate how the dose levels were calculated, how many animals were housed in a cage together, how and if water spillage was accounted for and how water consumption was tracked. As such, the reported dose conversions should be interpreted with caution.

In an extended one-generation reproductive toxicity (EOGRT) study conducted according to OECD TG 443 and submitted to ECHA, 10 to 28 Wistar Han rats/sex/dose were administered 0, 1000, 4000, 12,500 ppm of melamine in diet (ECHA c2007-2022). Specifically, there were 28 Wistar Han rats/sex/dose in the F0 generation, 20 Wistar Han rats/sex/dose in F1 cohort 1A, 25 Wistar Han rats/sex/dose in F1 cohort 1B and 10 Wistar Han rats/sex/dose in F1 cohort 2A, F1 cohort 2B and F1 cohort 3. The EOGRT study also included a developmental neurotoxicity and immunotoxicity component.

In the parental generation, the submitter reported a dose-related increased incidence and severity of retrograde nephropathy in the kidney in both males and females at 4000 ppm (on average corresponding to 268 mg/kg bw/day and 355 mg/kg bw/day, respectively) and 12,500 ppm (on average corresponding to 833 mg/kg bw/day and 1124 mg/kg bw/day, respectively). No effect on reproductive performance was observed up to the highest dose level tested (12,500 ppm). Sperm analysis revealed a marked increase in the number of sperm cells with detached head at 12,500 ppm (on average corresponding to 833 mg/kg bw/day).

In F1 Cohort 1B males, similar to the parental generation, sperm analysis revealed a marked increase in the number of sperm cells with detached head at 12,500 ppm (on average corresponding to 1200 mg/kg/day). Histopathological examination of the testis revealed an increased incidence and severity in tubular degeneration/atrophy starting at 4000 ppm (on average corresponding to 370 mg/kg/day), with related cellular debris in the epididymis. There were no other treatment-related changes in any of the other reproductive and developmental parameters investigated in this study (ECHA c2007-2022).

The submitters reported a reproductive toxicity no observed adverse effect level (NOAEL) of 4000 ppm (on average corresponding to 268 mg/kg/day in F0 males) in the parental generation based on tubular degeneration/atrophy in the testis with related minimal cellular debris in the epididymis in F0 males at 12,500 ppm (833 mg/kg bw/day). The submitters reported a reproductive toxicity NOAEL of 1000 ppm (on average corresponding to 89 mg/kg/day in F1 males) in F1 males based

on tubular degeneration/atrophy in the testis with related minimal cellular debris in the epididymis at and above 4000 ppm (370 mg/kg bw/day).

The developmental general toxicity NOAEL, the developmental neurotoxicity NOAEL and the developmental immunotoxicity NOAEL were reported to be at least 12,500 ppm (on average corresponding to 1200 mg/kg/day in males and 1227 mg/kg/day in females of the F1 generation), in the absence of adverse effects at this dose.

Mammary glands, ovaries, prostate, seminal vesicles, testes, and uterus were examined macroscopically and microscopically in the 13-week and 103-week chronic toxicity studies with rats and mice and were found to be unaffected by melamine at each of the doses used (Melnick et al. 1984).

Based on all of the studies outlined above, the LOAEL for reproductive toxicity is considered to be 10 mg/kg bw/day based on decreased sperm number, increased sperm abnormalities, disruption of the seminiferous tubule and testosterone synthesis observed a 28-day gavage mouse study (Sun et al. 2016a). Some reproductive effects (decreased sperm count, decreased sperm motility and structural changes in seminiferous tubules) were noted below 10 mg/kg bw/day (Chen et al. 2021); however, there is uncertainty with the reported doses. As such, those findings are being used to support the LOAEL of 10 mg/kg bw/day.

5.2.6 Repeat-dose oral toxicity

Studies of 28 days in rats resulted in observations of dose-dependent increases in urinary bladder calculi (containing melamine) and hyperplasia (tissue not specified in source), crystalluria and excretion of acid urine at doses of 266 mg/kg bw/day to 12,678 mg/kg bw/day of melamine (RTI 1982; American Cyanamid Co. 1984 as cited in US EPA 1984), as well as learning and memory deficits in a study in which rats were gavaged with melamine at 300 mg/kg bw/day (An et al. 2011; Yang et al. 2011). In another 28-day gavage study in rats, kidney microstructure was damaged and clinical chemistry parameters were significantly changed in serum (blood urea nitrogen, creatinine), kidney (glutamate, lactate, choline, glucose, amino acid, 3-hydroxybutyrate, pyruvate), liver (N-acetylglycoprotein, choline, creatine, lactate, trimethylamine-N-oxide, glutamate, glucose), and urine (succinate, citrate) at doses of 250 mg/kg bw/day to 1000 mg/kg bw/day. This metabonomic study showed that melamine caused renal dysfunction and disturbed the liver's glucose, protein, and nitrogen metabolism (Sun et al. 2012). In the oral feeding studies, a NOAEL of 133 mg/kg bw/day was determined by Research Triangle Institute (RTI) (1982), whereas no adverse effects were observed at doses of 40 mg/kg bw/day to 357 mg/kg bw/day in the other study (American Cyanamid Co. 1984 as cited in US EPA 1984). Melamine was administered by gavage to female rats for 28 days and there were no toxic lesions in kidneys at 40 mg/kg bw/day, but an increased number of atretic follicles, morphological changes and necrosis in the oocyte and granulosa cells as well as an increased number of apoptotic granolusa cells were observed in the ovaries at this dose. General health of the animals was not affected (Sun et al. 2016b).

Three different 13-week feeding studies in rats all showed dose-related increases in urinary bladder stones at doses ranging from 63 mg/kg bw/day to 1500 mg/kg bw/day in both sexes, and also increased calcareous deposits in the kidney proximal tubules. The lowest LOAEL was 63 mg/kg bw/day (lowest dose tested) based on the above effects. Relative incidences of bladder stones in both sexes were not changed when rats were administered melamine via the diet at 1500 mg/kg bw/day, depending on whether 1% ammonium chloride was added to the drinking water or not (U.S. NTP 1983; Melnick et al. 1984). Two 36-week feeding studies in male rats at doses ranging from 110 mg/kg bw/day to 1200 mg/kg bw/day resulted in a dose-related increase in hyperplasia of the bladder epithelium and non-dose related increase in bladder stones, as well as decreased body-weight gain at 430 mg/kg bw/day and higher (Okumura et al. 1992; Ogasawara et al. 1995).

5.2.7 Consideration of subpopulations who may have greater susceptibility

There are groups of individuals living in Canada who, due to greater susceptibility, may be more vulnerable to experiencing adverse health effects from exposure to substances. The potential for susceptibility during different life stages or by sex are considered from available studies. Available data for melamine consists of kinetic, short-term, chronic, reproductive, and developmental, genotoxicity and carcinogenicity data in experimental animals. Epidemiology studies were also considered. In this health effects assessment, several studies were conducted in both male and female experimental animals for melamine. Consideration was also given to developmental and neurological effects in the young, reproductive effects in males and females, and in pregnant female animals through developmental and reproductive toxicity studies in animals. While the reproductive critical health effect is specific to male mice, effects in female mice have been seen at a similar dose in another mouse study. These considerations were taken into account in the selection of the critical health effects for risk characterization.

5.3 Characterization of risk to human health

Based on assessments from international agencies (WHO 2009; EFSA 2010; IARC 2019) and available information from ECHA (2022), critical effects associated with exposure to melamine are carcinogenicity, effects on the urinary systems and reproductive toxicity.

Studies in rodents, particularly mice, have shown effects on the reproductive system. A LOAEL of 10 mg/kg bw/day for reproductive toxicity observed in a 28-day gavage mouse study based on significantly lower number of sperm, significantly higher abnormal sperm rate, downregulation of StAR protein and testosterone synthetic enzymes, significantly decreased serum testosterone levels, slight lesions present in the testes and decreased Leydig cell number (Sun et al. 2016a) is being used to characterize risk.

There is evidence to show that the effects on the urinary system are due to melamine’s propensity to form calculi or crystals in the kidney and/or bladder and it is the irritative

effects of these calculi that lead to other effects, including reactive hyperplasia and bladder tumours in rats.

On the basis of the available information, melamine is not genotoxic and a threshold mechanism for kidney specific carcinogenicity is supported.

The lower limit on the benchmark dose for a 10% response rate ($BMDL_{10}$) of 35 mg/kg bw/day derived by the WHO (2009) is based on the study with the lowest LOAEL for nephrotoxicity of 63 mg/kg bw/day, and it is protective of calculi or crystals formation since long-term rat feeding studies showed evidence for bladder tumours at 263 mg/kg bw/day of melamine. As the bladder tumours appear to be the result of a progression of events (bladder hyperplasia to irritation to neoplasia) from oral exposure to melamine, this BMDL is also protective of precursor events. The LOAEL of 10 mg/kg bw/day for reproductive toxicity is considered to be protective of these effects.

The main sources of exposure to melamine for the general population in Canada are expected to be from the use of foam products such as mattresses, upholstered furniture, infant and child restraint systems (including booster seats), and children's products (such as crib wedges and foam chairs), textiles, exposure from melaware migration, the use of products available to consumers including paints, sealants and cooktop cleaner and from food and environmental media (drinking water and dust).

No repeated dose dermal toxicity studies were identified; therefore, a LOAEL of 10 mg/kg bw/day from an oral study was used for characterization of risk from both oral and dermal exposure to melamine.

Table 5-10 provides all the relevant exposure values and the critical health effect level for melamine as well as the resultant margins of exposure (MOEs) for the characterization of risk.

Table 5-10 Relevant exposure values and the critical health effect level for melamine as well as the resultant MOEs for the characterization of risk

Scenario	Exposure estimate (mg/kg bw/day or mg/kg bw/event)[a]	MOEs based on the LOAEL[b] of 10 mg/kg bw/day
Environmental media and dietary exposure for a 0 to 5 months old (highest exposures)	0.0020[c]	5000
Dietary exposure from melaware as source (using range of migration levels measured at room temperature)	2.6×10^{-5} to (19 + years) to 0.552 [d] (1 year)	18 to 384,615

Scenario	Exposure estimate (mg/kg bw/day or mg/kg bw/event)[a]	MOEs based on the LOAEL[b] of 10 mg/kg bw/day
Dietary exposure from melaware as source (using highest “typical" migration level from EFSA 2010 data)	0.037 (19 + years) to 0.14[d] (1 year)	71 to 270
Dietary exposure from melaware and bambooware as source (using 95th percentile migration levels from BfR 2019)	0.161 (19 + years) to 1.08[d] (1 year)	9 to 62
Dermal contact from lying on foam-containing upholstered furniture or mattresses (daily) (all age groups)	0.06 to 2.3	4 to 164
Dermal contact from sitting in an infant or child restraint seat (including booster seats) (daily) (0 to 13 years)	0.034 to 0.16	63 to 1037
Mouthing of foam products (0 to 3 years)	2.55×10^{-3} to 4.87×10^{-2}	205 to 3925
Dermal contact from exposure to textiles (0 to 5 months)	1.25×10^{-3}	8000
Mouthing of textiles	7.79×10^{-5}	128,370

Scenario	Exposure estimate (mg/kg bw/day or mg/kg bw/event)[a]	MOEs based on the LOAEL[b] of 10 mg/kg bw/day
(0 to 5 months)		
Dermal contact from use of brush/roller paint (19+ years)	1.5	7
Dermal + inhalation exposure from use of pneumatic spray paint (19+ years)	3.7	2.7
Dermal contact from use of a sealant (19+ years)	1.8 to 3.6	3 to 6
Dermal contact from use of a cooktop cleaner (19+ years)	0.012	833

[a] Exposure estimates are presented as ranges for some scenarios based on ranges in the exposure parameters.
[b] LOAEL, lowest observed adverse effect level based on decreased sperm number, increased sperm abnormalities, disruption of the seminiferous tubule and testosterone synthesis observed in a 28-day mouse study (Sun et al. 2016a). Target MOE = 1000 (x10 for interspecies extrapolation; x10 for intraspecies variation; x10 for use of a LOAEL, considering severity of effect).
[c] This is the upper-end value based on upper-end intakes shown in Table C-1 Appendix C.
[d] Range of estimates from Table 5-4

Comparison of critical effect levels and estimates of exposure to melamine from environmental media, food, and textiles results in MOEs that are considered adequate (that is, greater than 1000) to account for the uncertainties in the exposure and health effects datasets used to characterize risk (Table 5-10).

The calculated MOEs from use of melaware and bambooware for prolonged exposure with foam products (such as mattresses, upholstered furniture, infant and child restraint systems including booster seats) for all age groups, as well as use of products available to consumers (such as paints, sealants, and cooktop cleaner) (Table 5-10), are considered inadequate (that is, less than 1000) to address uncertainties in the exposure and health effects datasets used to characterize risk.

Estimates of daily systemic exposure were also calculated using a reverse dosimetry approach from several biomonitoring studies (Panuwet et al. 2012; Sathyanarayana et al. 2019; Melough et al. 2022; Choi et al. 2022) in which concentrations of melamine were measured in spot urine samples (Table 5-9). Biomonitoring intakes provide an approximation of the exposure estimates from all potential routes and sources of exposure (NRC 2006). The estimates of daily systemic exposure based on geometric means of melamine concentrations ranged from 6×10^{-5} mg/kg bw/day for pregnant women to 4.74×10^{-3} mg/kg bw/day for 4 month to 8 year olds. The high-end estimates of daily system exposure based on maximum or 95th percentile melamine concentrations ranged from 3×10^{-4} mg/kg bw/day for 6 to 11 year olds to 0.185 mg/kg bw/day for 4 month to 8 year olds. These intakes are within the range of estimates of exposure derived with the use of modelling and support the determination that MOEs may be inadequate, in particular for young children.

The human health assessment took into consideration those groups of individuals living in Canada who, due to greater susceptibility or greater exposure, may be more vulnerable to experiencing adverse health effects from exposure to substances. The potential for increased susceptibility during development and reproduction was assessed and age specific exposure estimates were derived. Generally, infants and children were found to have higher exposure than adults. All of these populations were taken into consideration while assessing the potential harm to human health.

5.4 Uncertainties in evaluation of risk to human health

The key sources of uncertainty are presented in the table below.

Table 5-11 Sources of uncertainty in the risk characterization

Key source of uncertainty	Impact
No Canadian data on concentrations in drinking water, human milk, dust, or soil were available. Data from the U.S. were used to estimate daily intake from drinking water, human milk, and dust. Data from China were used to estimate daily intake from soil. Mean and/or maximum concentrations were used.	+/-
Canadian data on concentrations in food were used to estimate dietary exposure. Some food surveys had high detection limits or focused on foods with the greatest probability of containing melamine. Where data for certain items in food categories were lacking, surrogate products were used as a conservative estimate.	+/-
Assumption that all foods and beverages come into contact with melaware or bambooware.	+
Determination of melamine intake for 4 month olds to 60+ year olds based on urine samples from a non-Canadian population (U.S.) as a surrogate for the Canadian population.	+/-

Key source of uncertainty	Impact
Uncertainty associated with the source of melamine measured in urine. The presence of melamine may be from direct exposure to melamine, or from other sources such as the metabolism or degradation of the pesticide cyromazine, or other melamine-based flame retardants.	+
Assumption that melamine levels in human urine represent an excretion of 50% of daily intake (due to lack of human toxicokinetic data).	+/-
Limited hazard studies via the dermal and inhalation routes of exposures.	+/-
Lack of dermal absorption data for melamine.	+/-
Lack of empirical data on the relationship between the migration rate of melamine from foam and its concentration in foam.	+/-
Assumption that migration rate remains constant over time.	+/-
The extent of the effect of various textile coverings on melamine migration from polyurethane foam (PUF) are unknown.	+/-
Assumption that PUF would be covered in the estimate for dermal exposure from contact with foam.	-
No melamine-specific skin contact factor (SCF) has been identified; a factor of 1 was assumed.	+
Limited occurrence and toxicological data on co-exposure to melamine and cyanuric acid as well as potential synergistic toxicological effects.	+/-

+ = uncertainty with potential to cause over-estimation of exposure/risk; - = uncertainty with potential to cause under-estimation of exposure/risk; +/- = unknown potential to cause over- or under-estimation of risk.

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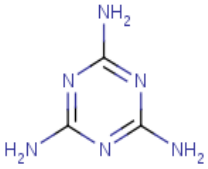
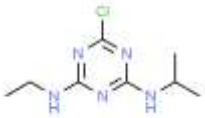
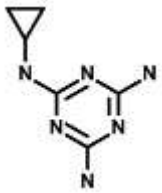
Appendix A. Summary of physical-chemical properties for melamine and analogues

Table A-1 Physical-chemical properties melamine, atrazine and cyromazine

Chemical name	Melamine	Atrazine	Cyromazine
Role	Target substance	Analogue	Analogue
CAS RN	108-78-1	1912-24-9	66215-27-8
Chemical structure			
Molecular weight (g/mol)	126.12 (PubChem 2004-)	215.68 (PubChem 2004-)	166.18 (PubChem 2004-)
Melting point (ºC)	345*-361 (PubChem 2004–; Rumble 2018; ECHA c2007-2022)	173-175°C (PubChem 2004-)	140.86 (EPI Suite 2012)
Boiling point (ºC)	Substance decomposes before boiling (ECHA c2007-2022)	Substance decomposes before boiling (PubChem 2004-)	346.43 (EPI Suite 2012)
Vapour pressure (Pa)	$7.5x10^{-9}$; $4.75x10^{-8}$* (3.56×10^{-10} mmHg) (Hirt et al. 1960; ECHA c2007-2022)	(2.80×10^{-7} mmHg) (EPI Suite 2012)	(3.36×10^{-9} mmHg) (EPI Suite 2012)
Water solubility (mg/L)	3190, 3230*,3480 (Crews et al. 2012; Yalkowsky and He 2003; ECHA c2007-2022)	214.1 at 25°C (EPI Suite 2012)	13,000 at 25°C (PMRA 2020a)

Chemical name	**Melamine**	**Atrazine**	**Cyromazine**
Role	Target substance	Analogue	Analogue
CAS RN	108-78-1	1912-24-9	66215-27-8
log K_{ow} (dimensionless)	-1.14* at 25°C (ECHA c2007-2022)	2.61 at 25°C (EPI Suite 2012)	-0.061 at 25°C (PMRA 2020a)

* Denotes values used in exposure modelling

Appendix B. Maximum Levels for melamine in foods and concentrations of melamine in Canadian food

Maximum Levels in Foods

Following identification of melamine-adulterated products (pet food, livestock- and fish-feed) in North America in 2007, and in certain foods worldwide (infant formula in China and other milk-based processed foods around the world) in 2008 due to the use of adulterated ingredients sourced from China, MLs for melamine in foods were developed internationally to ensure the safety of consumers (Health Canada 2008, 2016a; CAC 2019; WHO 2009; Gossner et al. 2009; Dorne et al. 2013; IARC 2019). These MLs help differentiate between the presence of background levels of melamine in food from legitimate or permitted uses of melamine or pre-cursors that breakdown to form melamine (for example, cyromazine) and intentional adulteration. In Canada, interim MLs for melamine were set in 2008 at 0.5 mg/kg for infant formula and sole source nutrition products, including meal replacement products, and at 2.5 mg/kg in food products containing milk and milk-derived ingredients, in order to ensure that foods available for sale in Canada have not been deliberately adulterated (Health Canada 2016a, 2020).

The Codex Alimentarius Commission (CAC) is the international food standards setting body established by the United Nation's Food and Agriculture Organization and the WHO, which has set MLs for melamine (CAC 2019). At its 33rd Session (CAC 2010a, 2010b), the CAC adopted a ML of 1 mg/kg melamine in powdered infant formula and 2.5 mg/kg melamine in all other foods and feed. At its 35th meeting (CAC 2012), an ML of 0.15 mg/kg for melamine in liquid infant formula, as consumed, was established.

Health Canada and CFIA monitoring of melamine in retail foods in Canada

Health Canada's Food Directorate conducted some surveys to monitor for the presence of melamine in various types of foods. The Food Directorate analyzed 94 samples of various infant formulas sold in Canada (Tittlemier et al. 2009). The samples were analyzed in the "as purchased" form (not prepared as consumed) and the analytical method used had an LOD of 4 µg/kg. Melamine concentrations were detected above the LOD in 71 samples (76%) and positive values ranged from 4.3 µg/kg to 346 µg/kg. The Food Directorate also analyzed 246 samples of dairy and soy-based dairy replacement products from Canadian retail outlets (Tittlemier et al. 2010a) such as milk, yogurt, milk or soy based beverages, milk powder products, desserts, candies, and cookies. Melamine was detected in 33 samples (13.4%). With the exception of one sample of recalled chocolate candy (not included in the estimate of dietary exposure), melamine concentrations in positive samples ranged from 4.4 to 282 µg/kg. Health Canada's Food Directorate also analyzed 378 samples of egg-containing products, soy-based meat substitutes, fish and shrimp products, and vegetable products to determine baseline levels of melamine (Tittlemier et al. 2010b). Melamine was detected in 98

samples (26%) which ranged from 4 µg/kg to 1100 µg/kg. The background concentrations of melamine in infant formulas, dairy and soy based dairy replacements, egg-containing products, soy-based meat substitutes, fish and shrimp products, and vegetable products are shown in Appendix D.

In addition, the CFIA conducted various surveys to measure melamine concentrations in food. The first survey, a directed compliance sampling, was conducted from 2007 to 2010 (n=818), primarily as an investigative survey to identify adulterated products (unpublished data, some products subject to recalls published during that time by CFIA). As such, sample selection was biased and the methodology resulted in a relatively high LOD of 1 mg/kg. The CFIA also conducted targeted melamine surveys from 2009/10 until 2011/12 (n=1785), analyzing similar products to those included in the Health Canada surveys at a LOD of 50 µg/kg, only 1.3% of samples were found positive (CFIA 2010, 2011, 2012a). Melamine was also included under the CFIA's National Chemical Residue Monitoring Program (NCRMP) from 2010/11 until 2015/16 (n=1 024), where eggs, fluid milk, milk powder, milk- and plant- based protein powders, and sodium caseinate were analyzed at a LOD of 50 µg/kg; no samples were found positive (CFIA 2012b, 2013, 2014; unpublished 2014/15 and 2015/16 melamine data). Since the publishing of the updated draft assessment for melamine in October 2020, two additional CFIA surveys on melamine were completed, a targeted survey in 2019/20 (n=519) (unpublished 2019 CFIA data) and a Children's Food Project survey in 2019/20 (n=47) (CFIA 2019), both at a LOD of 100 µg/kg. The former included samples of meal replacements and nutritional supplements, milk powder, both milk- and plant- based protein powders, chocolate- and milk- candies, chocolate syrups and spreads, and chocolate (for example, milk, dark, baking) where 5.6% of samples were found positive; while the latter included infant formulas (powdered, concentrated liquid and ready-to-feed) where only one sample was found positive. The purpose of all CFIA surveys other than the first one described above was to ensure continued compliance with Health Canada's Interim Maximum Levels for melamine in foods (Health Canada 2016a, 2020).

Appendix C. Estimates of daily intake of melamine (µg/kg bw/day) by the general population of Canada

Table C-1 General human exposure factors for different age groups in scenarios[a]

Age groups	Body weight (kg)	Inhalation rate (m^3/day)	Drinking water (L/day)	Soil ingestion rate (µg/day)	Dust ingestion rate (µg/day)
0 to 5 months	6.3	3.7	0.83	N/A	21.6
6 to 11 months	9.1	5.4	0.76	7.3	27.0
1 year	11	8.0	0.36	8.8	35.0
2 to 3 years	15	9.2	0.43	6.2	21.4
4 to 8 years	23	11.1	0.53	8.7	24.4
9 to 13 years	42	13.9	0.74	6.9	23.8
14 to 18 years	62	15.9	1.09	1.4	2.1
Adults (19+)	74	15.1	1.53	1.6	2.6

[a] Health Canada [modified 2022].

Table C-2 Mean and high-end (in bracket) estimates of daily intake of melamine (µg/kg bw/day) by the general population of Canada

Route of exposure	0 to 5 months (Human milk-fed[a])	0 to 5 months (formula fed[b])	6 to 11 months	1 year	2 to 3 years	4 to 8 years	9 to 13 years	14 to 18 years	Greater than or equal to 19 years
Drinking water[c]	N/A	0.004 (0.025)	0.003 (0.016)	0.0011 (0.006)	0.001 (0.005)	0.0008 (0.004)	0.0006 (0.003)	0.0006 (0.003)	0.0007 (0.004)
Food and beverages[d]	0.042 (0.89)	0.72[e] (1.7)	0.72 (1.7)	0.35 (0.89)	0.35 (0.89)	0.24 (0.72)	0.17 (0.56)	0.12 (0.41)	0.11 (0.37)
Soil[f]	N/A	N/A	<0.001	<0.001	<0.001	<0.001	<0.001	< 0.001	< 0.001
Dust[g]	0.024 (0.23)	0.024 (0.23)	0.021 (0.20)	0.022 (0.21)	0.0099 (0.095)	0.0073 (0.071)	0.0039 (0.038)	0.0002 (0.0023)	0.0002 (0.0023)
Total intake	0.066 (1.1)	0.75 (2.0)	0.74 (1.9)	0.37 (1.1)	0.36 (0.99)	0.25 (0.80)	0.17 (0.60)	0.12 (0.42)	0.11 (0.38)

Abbreviations: N/A, not applicable
[a] Human milk-fed infants are assumed to consume solely human milk for 6 months(Health Canada 2018). No data were identified on concentrations of melamine in Canadian human milk. The median human milk consumption is 127.95 g/kg bw/day (Arcus-Arth et al. 2005). Mean and maximum concentrations of melamine in human milk of 0.338 µg/L and 7.14 µg/L, respectively, reported by Zhu and Kannan (2019a) were used to derive estimates of daily intake from this source (the estimate based on the maximum concentration of melamine in human milk included in brackets).
[b] Exclusively formula-fed infants 0 to 5 months old are assumed to consume solely formula for 6 months (Health Canada 2018).
[c] No data were identified on concentrations of melamine in Canadian drinking water. The mean and maximum concentrations of 0.033 µg/L and 0.188 µg/L of melamine in tap water collected in the U.S. were used for estimating exposure (Zhu and Kannan 2020b). The values in brackets are estimates based on the maximum values.
[d] Unless specified otherwise (for example, human milk), the daily intake from food is estimated based on a full distribution of consumption data multiplied by point estimates (arithmetic mean) of occurrence (Appendix D). The mean and 95th percentile values (in brackets) are discussed in the text in section 5.1.1 and presented in Table 5-1
[e] Based on values in Table 5-1 for the 6 to 11 months old age group.
[f] No data on melamine concentrations in North American soils were identified. However, in China, soils were tested at 100 m and approximately 150 km away from melamine manufacturing factories. At 100 m away, melamine concentrations in soil ranged from non-detect to 41.1 mg/kg. At approximately 150 km away from the factories, concentrations in farmland soil ranged from non-detect to 0.176 mg/kg (Qin et al. 2010). Since concentrations measured further away than close to a melamine manufacturing facility would be more representative of melamine soil concentrations in Canada, the maximum concentration in farmland soil measured at 150 km away from the manufacturing facility was used in a deterministic estimate of daily intake and resulted in negligible estimated intakes.
[g] No data on concentrations of melamine in dust in Canada were identified. However, in the U.S., a study measuring dust in childcare centres detected melamine at concentrations ranging from 159 ng/g to 66,600 ng/g, with a mean value of 6920 ng/g (Zheng et al. 2020). The mean and maximum were used for estimating exposures. The values in brackets are estimates based on the maximum values.

Exposure to melamine from swimming pool water

Dermal and oral exposure estimates to melamine from swimming pool water were derived using the US EPA SWIMODEL (2003, 2016).

Table C-3 Parameters for oral and dermal intake estimates for exposure to melamine while swimming

Exposure scenario	Assumptions	Exposure
Swimming in pool	Population: 4 to 8 years, adult US EPA SWIMODEL (US EPA 2003, 2016) Kp : 0.001 cm/hr (US EPA 2003) Melamine concentration: 6.47 x 10^{-4} mg/L (Zhu and Kannan 2020b) Skin surface area: 8900, 18,700 cm^2, whole body	Dermal exposure: < 2.5 ng/kg bw/day (that is, negligible) for all age groups Oral exposure: 4 to 8 years: 2.9 ng/kg bw/day < 2.5 ng/kg bw/day (that is, negligible) for all other age groups

Exposure scenario	Assumptions	Exposure
	Exposure time: 2.7 hr/day (Health Canada 2022) Ingestion rate: 0.038 L/hr (Health Canada 2022)	

Melamine intake estimates from use of melaware and bambooware

Intake (µg/kg bw/day) = (Migration from melaware articles into food matrix (mg/g) x Consumption of food type per day (g/day) x 1000 µg/mg) / body weight

Table C-4 Parameters for melamine intake estimates from use of melaware and bambooware

Parameter	Value
Mean total food consumption (g/day)[a]	1000 (6 to 11 months)[b] 1540.81 (1 year) 1540.81 (2 to 3 years) 1760.47 (4 to 8 years) 2057.76 (9 to 13 years) 2550.51 (14 to 18 years) 2771.01 (19+ years)
Room temperature migration from melaware articles (mg/g)[c]	7×10^{-7} to 3.94×10^{-3}
"Typical" migration from melaware articles (mg/g)[d]	1×10^{-3}
95th percentile migration from melaware articles (mg/g) (BfR 2019)[e]	4.29×10^{-3}
95th percentile migration from bambooware articles (mg/g) (BfR 2019)[f]	7.71×10^{-3}
Body weight (kg)	See Table C-1

[a] Total food consumption amounts (all person, mean) for various age groups from CCHS 2015 from the Food Directorate (personal communication, email from Food Directorate, Health Canada to Existing Substances Risk Assessment Bureau, Health Canada; November 2023; unreferenced; Statistics Canada 2017).
[b] CCHS 2004 (personal communication, email from Food Directorate, Health Canada to Existing Substances Risk Assessment Bureau, Health Canada; April 2024; unreferenced; Statistics Canada 2008). Note: There is considerable coefficients of variation (CV) ranging from 16.6% to 33.3% associated with a number of the main food categories summed to give this value; therefore, data should be interpreted with caution.
[c] The lowest (BFR 2010b as cited in EFSA 2010) and highest (Takazawa et al. 2020) migrations of melaware observed at room temperature among the identified studies (Lund and Petersen 2006; BfR 2010b as cited in EFSA 2010; Chien et al. 2011; Chik et al. 2011; Takazawa et al. 2020).
[d] Highest typical migration level observed for acidic foods (1 mg/kg) derived by EFSA (2010).

[e] 95th percentile migration from melaware articles (4.29 mg/L) and bambooware (7.71 mg/L) (BFR 2019). Assumed the density of water to convert mg/L to mg/kg (1 L = 1 kg).

Appendix D. Summary of melamine occurrence data used to estimate dietary exposure and dietary assessment methodology

Table D-1 Summary of melamine occurrence data used to estimate dietary exposure and dietary assessment methodology‡

Food[a]	**# Samples**	**Arithmetic mean melamine concentration in µg/kg[b]**	**Source of survey with highest mean concentration[c]**
Baby food (pasta & beef or meat sauce)	3	<LOD	HC
Baby cereal	2	<LOD	HC
Infant formula – powder (milk, soy)	64	43.68	HC
Infant formula – concentrate (milk, soy)	24	17.94	HC
Infant formula – ready-to-consume (milk, soy)	6	28.98	HC
Milk - whole, 2%,1%, skim (incl. chocolate, goat, butter milk)	68	4.05	HC
Milk – evaporated, condensed	17	8.75	HC
Milk powder	65	63.26	CFIA
Malt drink powder	9	31.55	CFIA
Baking chocolate	118	2.00	CFIA
Yogurt & yogurt and probiotic drinks	42	4.3	HC
Chocolate/milk candy	10	4.90	HC
Milk coffee/coffee drink	12 (liquid) 44 (powder)	42.11 (liquid) 24.02 (powder)	HC (liquid) CFIA (powder)
Milk tea	26 (liquid) 3 (powder)	57.38 (liquid) 4.00 (powder)	CFIA (liquid) HC (powder)

Food[a]	**# Samples**	**Arithmetic mean melamine concentration in µg/kg**[b]	**Source of survey with highest mean concentration**[c]
Meal replacements	5 (ready-to-consume; RTC) 9 (powder) 1 (instant breakfast, liquid) 1 (instant breakfast, powder)	13.97 (RTC) 202.56 (powder) 4.44 (instant breakfast, liquid) 12.33 (instant breakfast, powder)	HC (RTC; instant breakfast, both liquid and powder) CFIA (powdered meal replacements)
Protein powders (milk- and plant- based)	154	13.25	CFIA
Gluten	8	22.75	CFIA
Cheese, breaded (to be baked or fried)	3	84.97	HC
Soy-based beverage (liquid & powder)	39 (liquid) 6 (powder)	4.07 (liquid) 4.00 (powder)	HC
Soybean paste & Miso	61	6.84	CFIA
Soy flour	1	4.08	HC
Pudding	3	8.01	HC
Egg (preserved, liquid, frozen)	6	10.35	HC
Egg rolls	1	118	CFIA
Meat substitute	29	5.28	HC
Mayonnaise and creamy salad dressings	23	4.05	HC
Pasta/noodle (dry and fresh)	15	4.15 (dry) 4.00 (fresh)	HC
Energy bar	14	5.38	HC

Food[a]	**# Samples**	**Arithmetic mean melamine concentration in µg/kg**[b]	**Source of survey with highest mean concentration**[c]
Cookies	172	14.36	CFIA
Cake (frozen and ready-to-consume)	8	4.54	HC
Chicken nugget, strip	3	11.85	HC
Shrimp	66	41.04	HC
Fish (tilapia, sole)	8	4.1	HC
Eel	3	65.68	HC
Spinach (frozen)	4	8.77	HC
Potatoes (canned, packaged, dried/instant)	19 (dried/instant) 5 (canned/packaged)	5.07 (dried/instant) 4.40 (canned/packaged)	HC
Mushrooms (canned, dried, pickled)	15 (pickled and/or canned) 5 (dried)	110.17 (pickled and/or canned) 88.70 (dried)	HC
Onions (fresh, frozen, dried, pickled, powdered)	6 (fresh, frozen, pickled) 4 (powdered/dried)	4.68 (fresh, frozen, pickled) 4.00 (powdered/dried)	HC
Tomatoes (canned, dried, jarred, juice, soup, fresh)	32	51.44	HC
Dried sauce, gravies, seasoning and soup mixes	8	23.42	HC

‡ Data sourced from Tittlemier et al. 2009, 2010a, 2010b; and where higher maximum concentrations or new food categories were analyzed, data from the CFIA (CFIA 2010, 2011, 2012a, unpublished 2019 CFIA targeted survey data).

[a] For the Health Canada surveys, food categories (other than baby foods and baby cereals) for which melamine was not detected in any of the samples were not presented in this table. The mean used in the exposure assessment for these food categories was set to the LOD of 4 µg/kg. Those relevant food categories include Bread (naan); Bread (crumbs); Croissant; Breakfast cereals; Calamari; Hot chocolate & choc. beverage powders; Cereal and milk hot drink powders; Cookie & Bread doughs; Cream; Milkshakes; Cream-based sauce (Bernaise and Tartar); Dessert dry mixes; Frankfurter corn dogs & sausage rolls; Ice cream & frozen soy desserts; Muffins; Pancake, waffle, muffin, and cake mixes; Pancakes and Waffles (frozen); Pastry; Toaster Strudel; Pies; Sauce (teriyaki, soy, hoisin); Soy-based cheese substitutes; and Tofu.

[b] For Health Canada's surveys, samples in which melamine was not detected were assigned a value equivalent to the LOD of 4 µg/kg, while for the CFIA surveys, samples in which melamine was not detected were assigned a value of zero in calculating arithmetic means due to the higher LODs of 50 and 100 µg/kg utilized in those surveys.
[c] The highest arithmetic mean melamine concentration when comparing corresponding food categories between Health Canada surveys and the various CFIA surveys was utilized in the exposure assessment. The Health Canada and CFIA surveys were not combined in order to calculate arithmetic means due to the significantly higher LODs in the CFIA surveys; rather, the higher mean concentration between the 2 was utilized. The treatment of samples below the LOD significantly affects the calculated arithmetic means when detection rates are low. For this reason, the lower bound arithmetic mean was used for the CFIA surveys, while the upper bound arithmetic mean was used for Health Canada surveys.

Dietary exposure assessment methodology and assumptions

Food consumption data for individuals over the age of one year old were obtained from the 2015 CCHS (Statistics Canada 2017). Food consumption data for infants under the age of one year old were obtained from the 2004 CCHS (Statistics Canada 2008). Measured and self-reported body weights collected through the CCHS were also used. The dietary intake assessment of melamine (refer to section 5.1.1.5) was conducted by Health Canada's Food Directorate. If consumption figures for certain foods were not available in the CCHS (milk coffee or tea), closely related foods were used (instant coffee or tea), and certain food types which were analyzed for melamine due to possible presence of milk-, soy- or egg-protein were used to represent concentrations in all these food types (that is, all chicken, frankfurter, egg, and cookie products). In both these cases, exposure may be overestimated due to the higher frequency of consumption of the surrogate foods. Similarly, the melamine concentrations detected in a limited number of processed spinach, potato, mushroom, onion, and tomato products were conservatively used to represent the melamine concentrations in all food products containing those vegetables, including the fresh vegetables. This is also expected to have overestimated the dietary exposure to melamine.

Appendix E. Exposure estimates of melamine from products

Based on the available information, dermal exposure intakes were estimated for direct contact with foam-containing mattresses and related manufactured items for all age groups and with foam-containing infant or child restraint systems for 0 to 13 year olds (includes booster seats). Oral exposure estimates were also derived for 0 to 3 year olds from mouthing (sucking) on foam-containing manufactured items intended for children as well as textiles. Dermal and inhalation (when relevant) exposure to paints, sealants and cooktop cleaner were estimated using ConsExpo Web (2021). Body weights used in the exposure estimates are presented in Table C-1. Other exposure parameters and values used to estimate exposures are presented in Table E-1 to Table E-5, and are based on conservative assumptions.

Table E-1 Parameters for melamine dermal intake estimates from exposure to products available to consumers

Exposure scenario	Assumptions
Brush/roller paint	Concentration: 10% (SDS 2019) Scenario: Brush or roller paint with high-solid paint in Paint Fact Sheet (RIVM 2007). Age group: 19 years and older Body weight: 74 kg Dermal exposure: Loading: Constant rate Weight fraction substance: 10% Contact rate: 30 mg/min Release duration: 120 minutes Absorption model: Fixed fraction Absorption fraction: 30%
Pneumatic spray paint	Concentration: 10% (SDS 2019) Age group: 19 years and older Body weight: 74 kg Scenario: Airless paint sprayer (PMRA 2020b)

Exposure scenario	Assumptions
	Inhalation exposure: Inhalation exposure (mg/kg bw/d) = unit exposure value (mg/kg ai) * volume of paint (L/day) * density (kg/L) * concentration (%) / body weight (kg) Volume of paint per day: 56.7 L (19 000 mL/can, 3 cans/day) Density: 1.5 kg/L (1.5 g/cm^3) (RIVM 2007) Concentration: 10% Unit exposure: 2.169 mg/kg ai (2169 µg/kg ai) (PMRA 2020b) Dermal exposure: Dermal exposure (mg/kg bw/d) = unit exposure (mg/kg ai) * volume of paint (L/day) * density (kg/L) * concentration (%) * dermal absorption (%) / body weight (kg) Volume of paint per day: 57 L (19 000 mL/can, 3 cans/day) Density: 1.5 kg/L (1.5 g/cm^3) (RIVM 2007) Concentration: 10% Dermal absorption: 30% Unit exposure: 99.297 mg/kg ai (99297 µg/kg ai) (PMRA 2020b)
Sealant	Concentration: 30% to 60% (SDS 2022) Scenario: Joint sealant in Do-It-Yourself Products Fact Sheet (RIVM 2022).

Exposure scenario	Assumptions
	Age group: 19 years and older Body weight: 74 kg Dermal exposure: Exposed area: 30 cm^2 Loading: Constant rate Weight fraction substance: 30% to 60% Contact rate: 50 mg/min Release duration: 30 minutes Absorption model: Fixed fraction Absorption fraction: 30%
Cooktop cleaner (dermal)[a]	Maximum reported concentration: 1% (SDS 2015) Scenario: All-purpose cleaning liquid in Cleaning Products Fact Sheet (RIVM 2018b). Age group: 19 years and older Body weight: 74 kg Dermal exposure: Exposed area: 910 cm^2 (surface area of hands) Loading: Instant application Weight fraction substance: 1% Product amount: 0.286 g Absorption model: Fixed fraction Absorption fraction: 30%

[a] Exposure estimated using ConsExpo Web (2021)

Dermal exposure intake estimates for exposure to melamine from polyurethane foam in manufactured items

Intake (mg/kg bw/day) =

[SA (cm^2) × SCF × TPF x M (mg/cm^2/hr) × ED (hr/day) × DA] / BW (kg)

Table E-2 Parameters for melamine dermal intake estimates from exposures to polyurethane foam in manufactured items

Symbol	Description	Exposure parameters for dermal exposure from lying on foam-containing mattresses or upholstered furniture	Exposure parameters for dermal exposure from sitting in an infant or child restraint seat (including booster seats)
SA[a]	Surface area of skin contact	520 cm^2 to 1750 cm^2 (0 to 5 months) 668 cm^2 to 2250 cm^2 (6 to 11 months) 753 cm^2 to 2650 cm^2 (1 year) 705 cm^2 to 3250 cm^2 (2 to 3 years) 922 cm^2 to 4450 cm^2 (4 to 8 years) 1332 cm^2 to 6700 cm^2 (9 to 13 years) 1642 cm^2 to 8600 cm^2 (14 to 18 years) 2005 cm^2 to 9350 cm^2 (19+ years)	520 cm^2 (0 to 5 months) 668 cm^2 (6 to 11 months) 753 cm^2 (1 year) 705 cm^2 (2 to 3 years) 922 cm^2 (4 to 8 years) 1332 cm^2 (9 to 13 years)[b]
SCF[c]	Skin contact factor	1	1
TPF[d]	Textile penetration factor	0.1	0.1
M[e]	Migration rate	0.00936 mg/cm^2/hr to 0.0217 mg/cm^2/hr	0.00936 mg/cm^2/hr to 0.0217 mg/cm^2/hr
ED[f]	Exposure duration	12.7 hr/d (0 to 5 months) 12.7 hr/d (6 to 11 months) 13 hr/d (1 year) 11.8 hr/d (2 to 3 years) 11.25 hr/d (4 to 8 years)	3 hr/d (0 to 13 years)

Symbol	Description	Exposure parameters for dermal exposure from lying on foam-containing mattresses or upholstered furniture	Exposure parameters for dermal exposure from sitting in an infant or child restraint seat (including booster seats)
		10.4 hr/d (9 to 13 years) 9.2 hr/d (14 to 18 years) 8 hr/d (19+ years)	
DA	Dermal absorption	0.3[g]	0.3[g]
BW	Body weight	Refer to Table C-1	Refer to Table C-1

[a] A range in surface areas (SA) was used to represent dermal contact with mattresses while only the lower SAs were used to represent dermal contact with infant or child restraint systems. For the lower SAs used, it was assumed that an individual is wearing shorts and a t-shirt that cover half of the limbs. The surface area of exposure is based on exposure to a fraction of the lower half of the limbs (arms and legs) and the back of the head. The surface areas of the limbs (Health Canada [modified 2022]) were multiplied by one half to account for clothing coverage and then were multiplied by one third to account for the triangular shape of limbs, where only one side is directly in contact with the mattress or child restraint seat (U.S. CPSC 2006). The surface area of the head (Health Canada [modified 2022]) was multiplied by a factor of 0.5 to represent exposure to the back of the head only. For the higher SA used, it was assumed that half of the body was in dermal contact with the mattress (U.S. EPA 2012).
[b] Infant and child restraint system regulations in Canada vary by province and territory (CPSAC 2019). On the basis of relevant age and weight considerations, dermal exposure estimates were derived for various age groups up to and including 9 to 13 year olds.
[c] No melamine-specific skin contact factor (SCF), that is, the fraction of substance on a surface adhering to skin, was identified in the literature. As such, a value of 1 was selected to assume that all of the chemical in contact with the skin is available for absorption.
[d] A textile penetration factor (TPF) was applied for melamine to account for the migration rates used for extrapolation (that is, TDCPP and TCEP) being determined using uncovered foam (ECHA 2018). No melamine-specific textile penetration data were identified in the literature. As such, a value of 0.1 (Driver et al. 2007 as cited in ECHA 2018) was used for the TPF.
[e] Migration rates from foam to surface of upholstery (extrapolated from TCEP and TDCPP migration rates as shown in Table 5-7).
[f] Exposure durations for sleeping adjusted from the median sleep times reported in US EPA (2011), Table 16-25 (0 to 6 months) and Table 16-26 (all other age groups). An exposure duration of 3 hours/day was selected for sitting in an infant or child restraint system (including booster seats) based on the leisure sitting duration reported in the U.S. CPSC (2006) and the highest 95th percentile daily time spent in vehicles for children aged less than 1 year to 19 years in the Canadian Human Activity Pattern Survey 2 (CHAPS 2) (2 hr 50 min for 5 to 11 year olds) (Matz et al. 2014).
[g] No dermal absorption data were identified for melamine. A value of 30% was selected based on data available for structurally similar compounds (refer to section 5.1.3).

Oral exposure intake estimates for exposure to polyurethane foam in manufactured items

Intake (mg/kg bw/day) = (SA (cm^2) × M ($mg/cm^2/hr$)× ED (hr/day)) / BW (kg)

Table E-3 Parameters for melamine oral intake (mouthing) estimates for exposure to polyurethane foam in manufactured items

Symbol	Description	Value
SA[a]	Surface area of direct mouthing	10 cm^2 (0 to 5 months) 10 cm^2 to 50 cm^2 (6 months to 3 years)
M[b]	Migration rate	0.00936 mg/cm^2/hr to 0.0217 mg/cm^2/hr
ED[c]	Exposure duration	24.5 min/d (0.408 hr/d)
BW	Body weight	Refer to Table C-1

[a] Surface area of object that is mouthed estimated to range from 10 cm^2 to 50 cm^2 based on information from U.S. CPSC 2006 and US EPA 2012.
[b] The migration rate range of 0.00936 mg/cm^2/hr to 0.0217 mg/cm^2/hr as presented in the dermal scenario was also used to estimate oral exposure. It is assumed that melamine is completely absorbed through the oral route and that a textile covering on a foam object would not affect migration (that is, no textile penetration factor, TPF, applied).
[c] The mouthing duration of 24.5 min/d for children's foam products such as nap mats, infant and child restraint systems, small furniture was based on the highest mean duration for "other objects" (for 6 to 9 month olds) in Norris and Smith (2002) [cited in US EPA (2011)].

Dermal exposure intake estimates for exposure to textiles

Intake = [SA (cm^2) × AW (mg/cm^2) × DA × MF × SCF× C (ng/mg)] / BW (kg)

Table E-4 Parameters for melamine dermal intake estimates from exposure to clothing (textiles)

Symbol	Description	Exposure parameters for dermal exposure to textiles
SA[a]	Surface area of skin contact	2670 cm^2 (0 to 5 months) 3440 cm^2 (6 to 11 months) 4130 cm^2 (1 year) 5640 cm^2 (2 to 3 years) 7860 cm^2 (4 to 8 years) 12,090 cm^2 (9 to 13 years) 15,690 cm^2 (14 to 18 years) 16,620 cm^2 (19+ years)
AW[b]	Area weight of textile	24 mg/cm^2

Symbol	Description	Exposure parameters for dermal exposure to textiles
DA[c]	Dermal absorption	0.3
MF[d]	Migration fraction	0.005
SCF[e]	Skin contact factor	1
C[f]	Melamine concentration	Mean concentration (unwashed textile): 4.9 ng/mg Max concentration (unwashed textile): 81.8 ng/mg
BW	Body weight	Refer to Table C-1
Intake	Melamine intake (mg/kg bw/day)	7.48×10^{-5} to 1.25×10^{-3} (0 to 5 months) 6.67×10^{-5} to 1.11×10^{-3} (6 to 11 months) 6.62×10^{-5} to 1.11×10^{-3} (1 year) 6.63×10^{-5} to 1.11×10^{-3} (2 to 3 years) 6.3×10^{-5} to 1.01×10^{-3} (4 to 8 years) 5.08×10^{-5} to 8.48×10^{-4} (9 to 13 years) 4.46×10^{-5} to 7.45×10^{-4} (14 to 18 years) 3.96×10^{-5} to 6.61×10^{-4} (19+ years)

[a] Total body surface area (minus head and hands) (Health Canada [modified 2022]
[b] The area weight of textile corresponds to “heavy cotton/synthetic mix” (US EPA 2012)
[c] No dermal absorption data were identified for melamine. A value of 30% was selected based on data available for structurally similar compounds (refer to section 5.1.3).
[d] BfR 2007. This value was also referenced in the calculation of exposure to textiles in Zhu and Kannan (2020a)
[e] No melamine-specific skin contact factor (SCF), that is, the fraction of substance on a surface adhering to skin, was identified in the literature. As such, a value of 1 was selected to assume that all of the chemical in contact with the skin is available for absorption.
[f] Zhu and Kannan (2020a)

Oral exposure intake estimates for exposure to textiles

Intake = (SA (cm^2)× AW (mg/cm^2) x MF × C (ng/mg)) / BW (kg)

Table E-5 Parameters for oral intake (mouthing) estimates for exposure to melamine in textiles

Symbol	Description	Value
SA[a]	Surface area of direct mouthing	10 cm^2 (0 to 5 months)

Symbol	Description	Value
		10 cm^2 to 50 cm^2 (6 months to 3 years)
AW[b]	Area weight of textile	24 mg/cm^2
MF[c]	Migration fraction	0.005
C[d]	Melamine concentration	Mean concentration (unwashed textile): 4.9 ng/mg Max concentration (unwashed textile): 81.8 ng/mg
BW	Body weight	Refer to Table C-1
Intake	Intake calculated in mg/kg bw/day	9×10^{-7} to 1.56×10^{-5} (0 to 5 months) 6×10^{-7} to 5.39×10^{-5} (6 to 11 months) 5×10^{-7} to 4.46×10^{-5} (1 year) 4×10^{-7} to 3.27×10^{-5} (2 to 3 years)

[a] Surface area of object that is mouthed estimated to range from 10 cm^2 to 50 cm^2 based on information from U.S. CPSC 2006 and US EPA 2012. For 0 to 5 month olds, a single value of 10 cm^2 was assumed given their smaller size and ability to move around.
[b] The area weight of textile corresponds to "heavy cotton/synthetic mix" (US EPA 2012).
[c] BfR (2012). This value was also referenced in the calculation of exposure to textiles in Zhu and Kannan (2020a)
[d] Zhu and Kannan (2020a)

Appendix F. Melamine intake estimates from biomonitoring data (using reverse dosimetry)

Reverse dosimetry was used to derive estimates of daily intakes from urine concentrations for individuals aged 0 to 5 months, 6 to 11 months, 1 year, 2 to 3 years, 4 to 8 years, 9 to 13 years, 14 to 18 years, and 19 years and older, as well as for pregnant women. The urine concentrations from the literature that were used to calculate intakes are presented in section 5.1.4. All other parameters are also presented below. Daily intakes are presented in section 5.1.4 and are calculated for reverse dosimetry as shown in the equation below.

Daily Intake (µg/kg bw/day) =

$$[[\text{Urine (ng/mL)}(\mu g/1000\ ng)] \times E_{urine}\ (mL/kg\ d)] / FUE$$

Table F-1 Reverse dosimetry parameters for melamine

Symbol	Description	Value
[Urine]	Urinary melamine concentration (ng/mL)	See Table 5-9 in section 5.1.4
E_{urine}	Daily urinary flow rate (mL/kg day)	22 to 85.2 (4 months to 8 years)[a] 30 (4 to 6 years)[b] 20 to 25 (6 to 11 years)[b] 20 (12 to 19 years)[b] 20 (20 to 59 years)[b, c] 20 (60+ years)[b]
FUE[d]	Fractional urine excretion	0.5 (common to all age groups)

[a] Average daily urinary flow rates were obtained from Table 4 in Aylward et al. 2015.
[b] Average daily urinary flow rates were obtained from Table 6 in Aylward et al. 2015.
[c] Value used to estimate intakes for pregnant women
[d] Due to the variability in urinary excretion between species, ranging from 54% to 90%, a value of 50% was conservatively used to calculate biomonitoring intakes.