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Canada

Screening Assessment

Triazines and Triazole Group

Chemical Abstracts Service Registry Numbers
61-82-5
2893-78-9
3089-11-0

Environment and Climate Change Canada
Health Canada

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Synopsis

Pursuant to section 68 or 74 of the *Canadian Environmental Protection Act, 1999* (CEPA), the Minister of the Environment and the Minister of Health have conducted a screening assessment of three substances which fall within the Triazines and Triazole Group. The Chemical Abstracts Service Registry Numbers (CAS RN[1]), the *Domestic Substances List* (DSL) names and the common names of the substances in the Triazines and Triazole Group are listed in the table below.

Substances in the Triazines and Triazole Group

CAS RN	DSL name	Common name
61-82-5	1*H*-1,2,4-triazol-3-amine	Amitrole
2893-78-9	1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione, 1,3-dichloro-, sodium salt	Sodium dichloroisocyanurate (NaDCC)
3089-11-0[a]	1,3,5-triazine-2,4,6-triamine, *N*,*N*,*N'*,*N*',*N*'',*N*''-hexakis(methoxymethyl)-	Hexa(methoxymethyl)melamine

[a] This substance was not identified under Subsection 73(1) of CEPA but was included in this assessment because it was considered a priority on the basis of other human health concerns.

Amitrole, NaDCC, and hexa(methoxymethyl)melamine were not reported to be manufactured in Canada above the reporting threshold in the year 2008 or 2011. NaDCC and hexa(methoxymethyl)melamine were reported to be imported into Canada in total annual quantities in the range of 100 000 to 1 000 000 kg, and amitrole was not reported to be imported above the reporting threshold in the year 2008 or 2011.

In Canada, amitrole was not reported to be present in any products with commercial or consumer use above the reporting threshold. Although amitrole is currently registered as a herbicide, these products are all in the process of being discontinued. NaDCC can be used in a variety of products, including water treatment products, cleaning products, and disinfectants. NaDCC is also an active ingredient in pest control products. Hexa(methoxymethyl)melamine may be used as a component in the manufacture of some food packaging materials. It may be used in commercial applications, such as paints and coatings, automotive, aircraft and transportation applications, but with no reported consumer use in Canada.

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The ecological risks of the substances in the Triazines and Triazole Group were characterized using the ecological risk classification of organic substances (ERC), which is a risk-based approach that employs multiple metrics for both hazard and exposure, with weighted consideration of multiple lines of evidence for determining risk classification. Hazard profiles are based principally on metrics regarding mode of toxic action, chemical reactivity, food web-derived internal toxicity thresholds, bioavailability, and chemical and biological activity. Metrics considered in the exposure profiles include the potential emission rate, overall persistence, and long-range transport potential. A risk matrix is used to assign a low, moderate or high level of potential concern for substances on the basis of their hazard and exposure profiles. Based on the outcome of the ERC analysis, the three substances in the Triazines and Triazole Group are considered unlikely to be causing ecological harm.

Considering all available lines of evidence presented in this screening assessment, there is low risk of harm to the environment from amitrole, NaDCC, and hexa(methoxymethyl)melamine. It is concluded that amitrole, NaDCC, and hexa(methoxymethyl)melamine do not meet the criteria under paragraphs 64(*a*) or (*b*) of CEPA, as they are not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity, or that constitute or may constitute a danger to the environment on which life depends.

From a human health perspective, the health effects of concern for amitrole include reproductive toxicity and carcinogenicity. There were limited substance-specific health effects data available for NaDCC. Structurally similar chemical substances, sodium cyanurate and cyanuric acid, were used as analogues for read-across. NaDCC, sodium cyanurate, and cyanuric acid have been reviewed internationally through the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives (JECFA). The JECFA identified health effects of concern for sodium cyanurate, including effects on the urinary tract and heart in laboratory studies, which were considered the critical effects for NaDCC.

There were limited substance-specific health effects data for hexa(methoxymethyl)melamine. A structurally similar chemical substance, melamine, was used as an analogue for read-across. In laboratory studies with melamine, effects on the bladder and urinary system were considered the critical effects in this assessment, and it is also possibly carcinogenic.

Given there are no consumer uses of amitrole in Canada and exposure of the general population is not expected, the potential risk to human health is considered to be low. The margins of exposure between levels of exposure of the Canadian general population from non-pesticidal use of NaDCC in products available to consumers (i.e., water treatment tablets and cleaning products) and critical effect levels were considered adequate to address uncertainties in the health effects and exposure databases. Similarly, for hexa(methoxymethyl)melamine, margins between levels of exposure of the

general population from its potential presence in drinking water and critical effect levels were considered adequate to address uncertainties in the health effects and exposure databases.

Considering all the information presented in this screening assessment, it is concluded that amitrole, NaDCC, and hexa(methoxymethyl)melamine do not meet the criteria under paragraph 64(*c*) of CEPA, as they are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

It is therefore concluded that amitrole, NaDCC, and hexa(methoxymethyl)melamine do not meet any of the criteria set out in section 64 of CEPA.

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1. Introduction

Pursuant to section 68 or 74 of the *Canadian Environmental Protection Act, 1999* (CEPA) (Canada, 1999), the Minister of the Environment and the Minister of Health have conducted a screening assessment of three of six substances from groups which were originally referred to under the Chemicals Management Plan as the Triazoles Group and the Cyanurates Group, to determine whether these substances present or may present a risk to the environment or to human health. Three substances from the two groups have since been merged and are hereinafter referred to collectively as the Triazines and Triazole Group. The substances in this group were identified as priorities for assessment as they met categorization criteria under subsection 73(1) of CEPA or were considered a priority on the basis of other human health concerns (ECCC, HC [modified 2017]).

Two of the six substances (the CAS RNs[2] 101-37-1 and 288-88-0) were considered in the Ecological Risk Classification of Organic Substances (ERC) and the Threshold of Toxicological Concern (TTC)–based Approach for Certain Substances science approach documents (ECCC 2016a; Health Canada 2016), and were identified as being of low concern to both human health and the environment. As such, they are not further addressed in this report. Conclusions for these two substances are provided in the Screening Assessment for Substances Identified as Being of Low Concern using the Ecological Risk Classification of Organic Substances and the Threshold of Toxicological Concern (TTC)–based Approach for Certain Substances (ECCC, HC 2018). Another of the six substances, 1,3,5-triazine, hexahydro-1,3,5-trinitro- (CAS RN 121-82-4), will be part of a future screening assessment.

Amitrole and NaDCC have been evaluated in Canada through Health Canada's Pest Management Regulatory Agency (PMRA) (Health Canada 2006, 2014) and an analogue of hexa(methoxymethyl)melamine used in this assessment was evaluated by Environment and Climate Change Canada (ECCC) and Health Canada (HC) under the Chemicals Management Plan (CMP) (ECCC, HC 2020). In addition, there were several international reviews or classifications available for the substances in the Triazines and Triazole Group, i.e., from the European Food Safety Authority (EFSA 2014), the US Environmental Protection Agency (US EPA 1988, 1992, 1996, 2006), the European Commission (EC 2001), the European Chemicals Agency (EU 2008, 2016), the US National Toxicology Program (NTP 2016) and the International Agency for Research on Cancer (IARC 2001, 2019). Also NaDCC and two structurally similar substances have been reviewed through the Joint FAO/WHO Expert Committee on Food Additives

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(JECFA 2004). These assessments were used to inform the health effects characterization in this screening assessment.

The ecological risks of substances in the Triazines and Triazole Group were characterized using the ERC approach (ECCC 2016a). The ERC describes the hazard of a substance using key metrics, including the mode of toxic action, chemical reactivity, food web–derived internal toxicity thresholds, bioavailability, and chemical and biological activity, and considers the possible exposure of organisms in the aquatic and terrestrial environments on the basis of such factors as potential emission rates, overall persistence, and long-range transport potential in air. The various lines of evidence are combined to identify substances as warranting further evaluation of their potential to cause harm to the environment or as having a low likelihood of causing harm to the environment.

This screening assessment includes consideration of information on chemical properties, environmental fate, hazards, uses, and exposures, including additional information submitted by stakeholders. Relevant data for the health assessment were identified up to April 2018. Empirical data from key studies, as well as some results from models, were used to reach the conclusions. When available and relevant, information presented in assessments from other jurisdictions was considered.

This screening assessment was prepared by staff in the CEPA Risk Assessment Program at Health Canada and Environment and Climate Change Canada and incorporates input from other programs within these departments. The ecological portion of this assessment is based on the ERC document (published July 30, 2016), which was subject to an external review as well as a 60-day public comment period. Additionally, the draft of this screening assessment (published April 13, 2019) was subject to a 60-day public comment period. While external comments were taken into consideration, the final content and outcome of the screening assessment remain the responsibility of Health Canada and Environment and Climate Change Canada.

This screening assessment focuses on information critical to determining whether the substances meet the criteria as set out in section 64 of CEPA by examining scientific information and incorporating a weight of evidence approach and precaution.[3] This

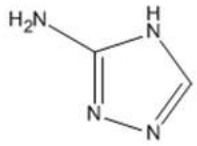
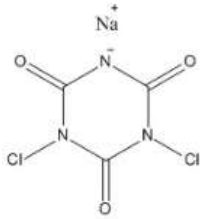
[3] A determination of whether one or more of the criteria of section 64 of CEPA are met is based on an assessment of potential risks to the environment and/or to human health associated with exposures in the general environment. For humans, this includes, but is not limited to, exposures from ambient 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 based on the criteria contained in section 64 of CEPA does not preclude actions being taken under other sections of CEPA or other acts.

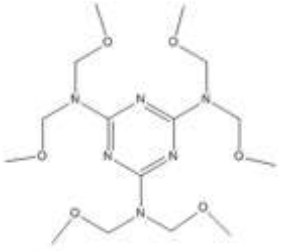
screening assessment presents the critical information and considerations on which the conclusions are based.

2. Identity of substances

The CAS RN, *Domestic Substances List* (DSL) names, and common names for the individual substances in the Triazines and Triazole Group are presented in Table 2-1.

Table 2-1. Substance identities

CAS RN	DSL name (common name or acronym)	Chemical structure and molecular formula	Molecular weight (g/mol)
61-82-5	1H-1,2,4-Triazol-3-amine (Amitrole)	 $C_2H_4N_4$	84.1
2893-78-9	1,3,5-Triazine-2,4,6(1H,3H,5H)-trione, 1,3-dichloro-, sodium salt (NaDCC)	 $C_3Cl_2N_3NaO_3$	219.9

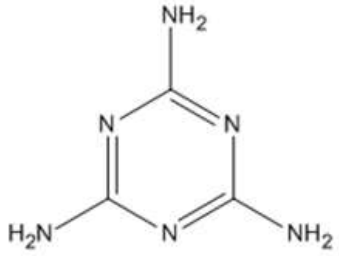
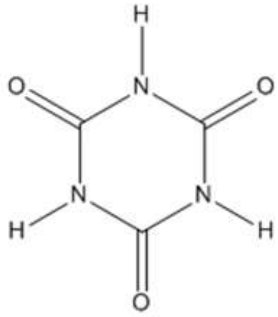
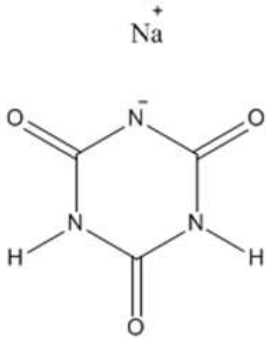
CAS RN	DSL name (common name or acronym)	Chemical structure and molecular formula	Molecular weight (g/mol)
3089-11-0	1,3,5-Triazine-2,4,6-triamine, N,N,N',N',N'',N''-hexakis(methoxymethyl)-(Hexa[methoxymethyl]melamine)	 $C_{15}H_{30}N_6O_6$	390.4

2.1 Selection of analogues and use of (Q)SAR models

A read-across approach using data from analogues and the results of (quantitative) structure–activity relationship ([Q]SAR) models, where appropriate, has been used to inform the human health assessment. Analogues were selected that were structurally similar to substances within this group and that had relevant empirical data that could be used to read-across to substances with limited empirical data. Similarity in physical-chemical properties was also considered. The applicability of (Q)SAR models was determined on a case-by-case basis. Details of the read-across data and (Q)SAR models chosen to inform the human health effects characterization of the Triazines and Triazole Group are further discussed in the relevant sections of this report and in Appendix B.

Information on the identities and chemical structures of the analogues used to inform this assessment is presented in Table 2-2.

Table 2-2. Analogue identities

CAS RN	DSL name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)
108-78-1	1,3,5-Triazine-2,4,6-triamine (Melamine)	 $C_3H_6N_6$	126.1
108-80-5	1,3,5-Triazine-2,4,6(1H,3H,5H)-trione (Cyanuric acid)	 $C_3H_3N_3O_3$	129.1
2624-17-1	1,3,5-Triazine-2,4,6(1H,3H,5H)-trione, monosodium salt (Sodium cyanurate)	 $C_3H_2N_3NaO_3$	151.1

Melamine (CAS RN 108-78-1) was used as an analogue to inform the human health effects characterization of hexa(methoxymethyl)melamine. It was considered appropriate based on similarities in chemical structure, as hexa(methoxymethyl)melamine contains a melamine core as well as physical-chemical properties, and a similar capacity to be metabolized.

Two of the selected analogues, cyanuric acid (CAS RN 108-80-5) and sodium cyanurate (CAS RN 2624-17-1), which were used as analogues for NaDCC, are the corresponding acid and salt of one another. The analogues are both structurally similar to NaDCC, but they are unchlorinated. The unchlorinated acid, cyanuric acid, is what reaches the gastrointestinal tract after metabolites of NaDCC contact saliva (JECFA 2004). This acid, as well as its corresponding salt, were used to inform the human health assessment conducted by the JECFA for NaDCC (JECFA 2004).

3. Physical and chemical properties

A summary of physical and chemical property data of the substances in the Triazines and Triazole Group is presented in Table 3-1. Additional substance-specific physical and chemical properties are presented in ECCC (2016b).

Table 3-1. Experimental and modelled physical and chemical properties (at standard temperature) for substances in the Triazines and Triazole Group

Property	Amitrol	NaDCC	Hexa(methoxymethyl)melamine	Key references
Vapour pressure (Pa)	5.87×10^{-5} (modelled)	< 0.006 (experimental); 1.94×10^{-12} (modelled)	1.41×10^{-6} (modelled)	ECHA 2017a; EPI Suite c2000–2012
Water solubility (mg/L)	2.80×10^{5} (modelled)	2.48×10^{5} (experimental)	149.3 (modelled)	ECHA 2017a; EPI Suite c2000–2012
Log K_{ow} (dimensionless)	-0.97 (modelled)	-0.06 (modelled)	1.61 (modelled)	ECHA 2017a; EPI Suite c2000–2012

Abbreviation: K_{ow}, octanol–water partition coefficient

4. Sources and uses

All of the substances in the Triazines and Triazole Group have been included in surveys issued pursuant to section 71 of CEPA (Environment Canada 2009, 2013). Table 4-1 presents a summary of information reported on the total annual manufacture and total annual import quantities for the substances in the Triazines and Triazole Group.

Table 4-1. Summary of information on Canadian manufacturing and imports of substances in the Triazines and Triazole Group submitted pursuant to section 71 surveys of CEPA[a]

Common name or acronym	Total manufacture (kg)	Total imports (kg)	Survey reference

Amitrole	NR	NR	Environment Canada 2009[b]
NaDCC	NR	100 000–1 000 000	Environment Canada 2013
Hexa(methoxymethyl)melamine	NR	100 000–1 000 000	Environment Canada 2013

Abbreviation: NR, not reported
[a] Values reflect quantities reported in response to CEPA section 71 surveys (Environment Canada, 2009, 2013). See surveys for specific inclusions and exclusions (schedules 2 and 3).
[b] Volumes were updated based on targeted stakeholder follow-ups in 2018.

According to information submitted in response to a CEPA section 71 survey and via targeted stakeholder follow-up, amitrole was not reported to be present in any products with commercial or consumer use above the reporting threshold of 100 kg (Environment Canada 2009; personal communication, emails from stakeholders to the Existing Substances Risk Assessment Bureau, HC, 2018, unreferenced). In Canada, amitrole is present in a registered herbicide. Health Canada's Pest Management Regulatory Agency (PMRA) initiated a special review of amitrole under section 17(2) of the *Pest Control Products Act* on April 12, 2018. The registrant of technical grade amitrole has since chosen to discontinue registration of the active ingredient and its uses. All pesticide products containing amitrole are in the process of being discontinued and the special review of amitrole is now closed. Products containing amitrole will remain registered until the last date of permitted use (September 27, 2022) (personal communication, emails from the Pest Management Regulatory Agency, HC, and from a stakeholder, to the Existing Substances Risk Assessment Bureau, HC, 2018 and 2019, unreferenced). Amitrole was not found in the Drug Product Database (DPD [modified 2017]). Amitrole is not a permitted food additive and was not identified to be used in food packaging materials or in incidental additives used in food processing establishments in Canada (personal communication, emails from the Food Directorate to the Existing Substances Risk Assessment Bureau, Health Canada, 2015, 2017, unreferenced). Cosmetic uses were not identified for amitrole in Canada, and amitrole is not listed in the Natural Health Products Ingredients Database (NHPID) or the Licensed Natural Health Products Database (LNHPD) (personal communication, emails from the Consumer and Hazardous Products Safety Directorate, HC, to the Existing Substances Risk Assessment Bureau, Health Canada, 2015, 2017, unreferenced; NHPID [modified 2018]; LNHPD [modified 2018]). Amitrole has been identified in other non-pesticidal uses, including lubricants for engines, which are expected to be specialized uses not relevant to consumers (e.g., SDS 2015a, 2015b). No consumer uses of amitrole in Canada were identified.

According to information submitted in response to a CEPA section 71 survey and targeted follow-up with industry stakeholders, NaDCC is used for water treatment for swimming pools and/or spas, and for laundry and dishwashing with the potential for

consumer use (Environment Canada 2013). NaDCC is an active ingredient in pest control products, primarily in swimming pool algicides and bactericides (personal communication, emails from the Pest Management Regulatory Agency, HC, to the Existing Substances Risk Assessment Bureau, Health Canada, 2017, unreferenced). In Canada, NaDCC may be used in incidental additives in food processing establishments where it is a component in the formulations of closed recirculating water treatment products where the treated water will not come in contact with food. It may also be used as a component in dish detergents and food contact surface cleaners and sanitizers which are followed by a potable water rinse, and in sanitizers for food contact surfaces without a potable water rinse in Canada (personal communication, emails from the Food Directorate, HC, to the Existing Substances Risk Assessment Bureau, HC, 2018, unreferenced). In Canada, NaDCC is an active ingredient in various disinfectants in food premises, hospital/health care facilities, barns, and institutional/industrial settings based on the internal Drug Product Database (DPD [modified 2017]; personal communication, emails from the Therapeutic Products Directorate, HC, to the Existing Substances Risk Assessment Bureau, HC, 2018, unreferenced). NaDCC is not a permitted food additive in Canada (personal communication, emails from the Food Directorate to the Existing Substances Risk Assessment Bureau, Health Canada, 2015, 2017; unreferenced). Cosmetic uses were not identified for NaDCC in Canada, and NaDCC is not listed in the Natural Health Products Ingredients Database or the Licensed Natural Health Products Database (personal communication, emails from the Consumer and Hazardous Products Safety Directorate, HC, to the Existing Substances Risk Assessment Bureau, Health Canada, 2015, 2017, unreferenced; NHPID [modified 2018]; LNHPD [modified 2018]). NaDCC can be used in a variety of cleaning products, drinking water treatments, and disinfectants (e.g., SDS 2010, 2015c, 2017a, 2017b).

Hexa(methoxymethyl)melamine is used in paints and coatings, and in automotive, aircraft, and transportation applications, but with no reported consumer use (Environment Canada, 2013). Hexa(methoxymethyl)melamine is not on the PMRA List of Active Pesticide Ingredients or the PMRA Pesticide Formulants List (personal communication, emails from the Pest Management Regulatory Agency, HC, to the Existing Substances Risk Assessment Bureau, Health Canada, 2015, unreferenced). In Canada, hexa(methoxymethyl)melamine may be used in food packaging materials as a component in adhesives (non-food contact), as a crosslinking or curing agent in the manufacture of interior can coatings, and as a component in filters used in the manufacture of juices. Use of the substance as a component in incidental additives used in food processing establishments has not been identified. Additionally, hexa(methoxymethyl)melamine is not a permitted food additive in Canada (personal communication, emails from the Food Directorate, HC, to the Existing Substances Risk Assessment Bureau, Health Canada, 2015, 2017, unreferenced). Hexa(methoxymethyl)melamine was not found in the Drug Product Database (DPD [modified 2017]). Cosmetic uses were not identified for hexa(methoxymethyl)melamine in Canada, and hexa(methoxymethyl)melamine is not listed in the Natural Health Products Ingredients Database or the Licensed Natural Health Products Database (personal communication, emails from the Consumer and Hazardous Products Safety

Directorate, HC, to the Existing Substances Risk Assessment Bureau, Health Canada, 2015, 2017, unreferenced; NHPID [modified 2018]; LNHPD [modified 2018]). Hexa(methoxymethyl)melamine can be used as a crosslinking agent, may be found in polymer mixtures, and may be used to synthesize other substances. Hexa(methoxymethyl)melamine may be used to promote various desirable properties such as increasing the thermal stability and strength of final products (e.g., Dsikowitzky and Schwarzbauer 2015; Jeon 2013; Liu et al. 2017; Rahman et al. 2009). Internationally, hexa(methoxymethyl)melamine may be found in textiles, paints and coatings, automobiles, plastic and rubber products, foam products, adhesives, resins, and other uses that are specialized or industrial (e.g., Cakic et al. 2015; Danish EPA 2005; Dsikowitzky and Schwarzbauer 2015; Jeon 2013; Kailasam et al. 2010; Lee et al. 2014; Pathak et al. 2007; SDS 2012, 2014). Some uses reported in response to CEPA section 71 surveys are not identified above due to confidentiality.

5. Potential to cause ecological harm

5.1 Characterization of ecological risk

The ecological risks of the substances in the Triazines and Triazole Group were characterized using the ecological risk classification of organic substances (ERC) approach (ECCC 2016a). The ERC is a risk-based approach that considers multiple metrics for both hazard and exposure, with weighted consideration of multiple lines of evidence for determining risk classification. The various lines of evidence are combined to discriminate between substances of lower or higher potency and lower or higher potential for exposure in various media. This approach reduces the overall uncertainty with risk characterization compared to an approach that relies on a single metric in a single medium (e.g., median lethal concentration) for characterization. The following summarizes the approach, which is described in detail in ECCC (2016a).

Data on physical-chemical properties, fate (chemical half-lives in various media and biota, partition coefficients, and fish bioconcentration), acute fish ecotoxicity, and chemical import or manufacture volume in Canada were collected from scientific literature, from available empirical databases (e.g., OECD QSAR Toolbox 2014), and from responses to surveys issued pursuant to section 71 of CEPA or they were generated using selected (quantitative) structure-activity relationship ([Q]SAR) models or mass-balance fate and bioaccumulation models. These data were used as inputs to other mass-balance models or to complete the substance hazard and exposure profiles.

Hazard profiles were based principally on metrics regarding the mode of toxic action, chemical reactivity, food web–derived internal toxicity thresholds, bioavailability, and chemical and biological activity. Exposure profiles were also based on multiple metrics, including the potential emission rate, overall persistence, and long-range transport potential. Hazard and exposure profiles were compared to decision criteria in order to classify the hazard and exposure potentials for each organic substance as low,

moderate, or high. Additional rules were applied (e.g., classification consistency, margin of exposure) to refine the preliminary classifications of hazard or exposure.

A risk matrix was used to assign a low, moderate or high classification of potential risk for each substance on the basis of its hazard and exposure classifications. ERC classifications of potential risk were verified using a two-step approach. The first step adjusted the risk classification outcomes from moderate or high to low for substances that had a low estimated rate of emission to water after wastewater treatment, representing a low potential for exposure. The second step reviewed low risk potential classification outcomes using relatively conservative, local-scale (i.e., in the area immediately surrounding a point source of discharge) risk scenarios, designed to be protective of the environment, to determine whether the classification of potential risk should be increased.

ERC uses a weighted approach to minimize the potential for both over-and under-classification of hazard and exposure, and of subsequent risk. The balanced approaches for dealing with uncertainties are described in greater detail in ECCC (2016a). The following describes two of the more substantial areas of uncertainty. Error in empirical or modelled acute toxicity values could result in changes in the classification of hazard, particularly metrics relying on tissue residue values (i.e., mode of toxic action), many of which are predicted values from (Q)SAR models (OECD QSAR Toolbox 2014). The impact of this error is mitigated; however, by the fact that an overestimation of median lethality will result in a conservative (protective) tissue residue value used for critical body residue analysis. Error in the underestimation of acute toxicity will be mitigated through the use of other hazard metrics, such as structural profiling of mode of action, reactivity, and/or estrogen binding affinity. Changes or errors in chemical quantity could result in differences in classification of exposure, as the exposure and risk classifications are highly sensitive to emission rate and use quantity. The ERC classifications thus reflect exposure and risk in Canada on the basis of what is estimated to be the current use quantity, and may not reflect future trends.

Critical data and considerations used to develop the substance-specific profiles for the substances in the Triazines and Triazole Group, and the hazard, exposure, and risk classification results, are presented in ECCC (2016b).

The hazard and exposure classifications for the three substances in the Triazines and Triazole Group are summarized in Table 5-1.

Table 5-1. Ecological risk classification results for the three substances in the Triazines and Triazole Group

Substance	ERC hazard classification	ERC exposure classification	ERC risk classification
Amitrole	low	low	low
NaDCC	high	low	low
Hexa(methoxymethyl)melamine	low	high	low

On the basis of low hazard and low exposure classifications according to information considered under ERC, amitrole was classified as having a low potential for ecological risk. According to information considered under ERC, amitrole was found to have a reactive mode of action; this is supported by the re-evaluation conducted by the PMRA (Health Canada 2014), which states that birds and small wild mammals may be at risk in and around the site of application of amitrole when used as a pesticide due to the consumption of contaminated food items. However, the potential effects and how they may manifest in the environment were not further investigated in the ecological portion of this screening assessment due to the low exposure of this substance from non-pesticidal uses. Considering current use patterns, this substance is unlikely to be resulting in concerns for the environment in Canada.

According to information considered under ERC, NaDCC was classified as having a low exposure potential. NaDCC was classified as having a high hazard potential on the basis of the agreement between the reactive mode of action and elevated toxic ratio, both of which suggest that this chemical is likely of high potency. NaDCC was classified as having a moderate potential for ecological risk; however, the risk classification was decreased to low potential for ecological risk following the adjustment of risk classification based on a low potential for local-scale exposures (see section 7.1.1. of the ERC approach document [ECCC 2016a]). The potential effects and how they may manifest in the environment were not further investigated due to the low exposure of NaDCC. On the basis of current use patterns, this substance is unlikely to be resulting in concerns for the environment in Canada.

According to information considered under ERC, hexa(methoxymethyl)melamine was classified as having a high exposure potential on the basis of overall persistence and large reported use volume according to information submitted in response to a CEPA section 71 survey (Environment Canada 2013). The ERC classified this substance as having a low hazard potential and subsequently having a low potential for ecological risk. This substance is unlikely to be resulting in concerns for the environment in Canada.

6. Potential to cause harm to human health

6.1 Exposure assessment

Potential exposures to substances in the Triazines and Triazole Group from environmental media, food, and products available to consumers are presented in this section. Additional details regarding the exposure scenarios are summarized in Appendix A.

6.1.1 Environmental media

There were no environmental monitoring data identified in Canada for the substances in the Triazines and Triazole Group.

Potential exposure to the general population through environmental media from amitrole is not expected, as the manufacturing and import volumes for this substance were below the reporting threshold of 100 kg (Environment Canada 2009; personal communication, emails from stakeholders to the Existing Substances Risk Assessment Bureau, HC, 2018, unreferenced).

For NaDCC, the Environmental Assessment Unit (EAU) Drinking Water Spreadsheet was used to estimate potential exposure to the general population through environmental media from non-pesticidal uses, which could result in down-the-drain releases by consumers (Health Canada 2015). The upper bound of the total annual volume reported in Canada (i.e., 1 000 000 kg) was used as input into a consumer (i.e., down-the-drain) release scenario. This volume accounts for all the uses reported pursuant to a CEPA section 71 survey; as the volume includes both pesticidal and non-pesticidal uses, it is expected to be a conservative input for assessing non-pesticidal uses only. Other inputs used include a total estimated removal percent of the substance by wastewater treatment plants of 61.5% (ECCC 2016b), an emission factor of 100% (as a conservative assumption), and a flow rate of 21.33 m^3/s (50^{th} percentile) for a default river. The theoretical intakes of drinking water by the general population for this scenario were estimated to range from 5.9×10^{-4} mg/kg bw per day for formula-fed infants to 1.2×10^{-4} mg/kg bw per day for adults based on an estimated water concentration of 5.5 µg/L. The theoretical intake values estimated as a result of releases from industrial activities (with consideration of volume used, removal percentage, number of release days per year, releases being solely to wastewater, and river flow rate) were lower than those estimated as a result of releases from consumer use.

For hexa(methoxymethyl)melamine, the EAU Drinking Water Spreadsheet was used to estimate potential exposure to the general population through drinking water from industrial releases to wastewater (Health Canada 2015). The upper bound of the total annual volume reported in Canada (i.e., 1 000 000 kg) was used as input into an industrial release scenario, which accounts for all industrial uses reported pursuant to the survey. Industrial releases are considered to be higher for this substance compared

to potential releases that may occur from consumer uses. Other inputs used include an emission factor of 0.6% (OECD 2002) which is based on the emission of melamine production and processing, assumed removal by wastewater treatment plants of 0%, and a flow rate of 21.33 m^3/s (50^{th} percentile) for a default river. Without adjusting for removal by drinking water treatment, intake values for drinking water are estimated to range from 1.4×10^{-3} mg/kg bw per day for formula-fed infants to 2.8×10^{-4} mg/kg bw per day for adults, based on an estimated water concentration of 13 µg/L.

Internationally, hexa(methoxymethyl)melamine has been detected in various waters. For example, the substance was detected in German rivers, ranging from <10 to 880 ng/L, likely as a result of release of industrial wastewaters (e.g., from coating and automotive sectors) and in the Rhine River up to 6.5 µg/L (Dsikowitzky and Schwarzbauer 2015). In another study, hexa(methoxymethyl)melamine was detected in river systems with concentrations up to 6.16 µg/L in Germany (Eberhard et al. 2015). Tousova et al. (2017) have also reported concentrations of hexa(methoxymethyl)melamine in European waters with a median concentration of 27.8 ng/L.

6.1.2 Food

The use of NaDCC in sanitizers for food contact surfaces without a potable water rinse results in a worst-case, probable daily intake estimate of 2.29 µg/kg bw per day (personal communication, emails from the Food Directorate, HC, to the Existing Substances Risk Assessment Bureau, HC, 2018, unreferenced).

Hexa(methoxymethyl)melamine may be used as a crosslinking or curing agent in the manufacture of can coatings. Because the substance reacts with the other polymeric components of the coating, it becomes bonded to the polymeric backbone, and only residual levels of unreacted substance are expected to migrate. As such, the estimated probable daily intake from this use is 0.0045 µg/kg bw per day. This estimate represents exposure for the general population and is considered to be negligible (personal communication, emails from the Food Directorate, HC, to the Existing Substances Risk Assessment Bureau, Health Canada, 2017, unreferenced).
Hexa(methoxymethyl)melamine is also used as a component in filters used in the manufacture of juices; however, exposure from this source is negligible. Exposure from the use of hexa(methoxymethyl)melamine in non-food contact adhesives is not expected (personal communication, emails from the Food Directorate, HC to the Existing Substances Risk Assessment Bureau, HC, 2018, unreferenced).

6.1.3 Products available to consumers

Products containing amitrole available to consumers in Canada have not been identified. Therefore, exposure to amitrole by the Canadian general population from consumer uses is not expected.

Potential exposures to NaDCC from non-pesticidal products available to consumers by the Canadian general population were considered, and the exposure scenarios that resulted in the highest exposures are presented here. NaDCC in water dissociates into hypochlorous acid (HClO, which is the source of free available chlorine) and the stabilizer isocyanuric acid (which reduces the degradation of chlorine from sunlight) (JECFA 2004; Pinto and Rohrig 2003).

Table 6-1 presents estimated exposures from NaDCC from water treatment tablets and cleaning abrasive powders. For the water treatment exposure scenario, long-term use would more likely consist of using only one tablet (or less) per litre. However, the use of two tablets per litre of water was assumed as a conservative approach for daily exposure. Although exposures may occur from floor cleaning liquids (SDS 2010), such exposures were estimated to be less than the scenarios in Table 6-1.

Table 6-1. Estimated exposures from NaDCC to the Canadian general population

Exposure scenario	Age group	Product concentration	Oral exposure	Dermal exposure[a]	Inhalation exposure	Total exposure
Water treatment tablets[b]	Infants to adults	17%	1.8 mg/kg bw per day for formula-fed infants to 0.36 mg/kg bw per day for adults	N/A	N/A	1.8 mg/kg bw per day for formula-fed infants to 0.36 mg/kg bw per day for adults
Cleaning abrasive powder: application exposure[c]	Adults	1.5%	N/A	0.83 mg/kg bw per event	Negligible	0.83 mg/kg bw per event

Abbreviation: bw, body weight; N/A, not applicable.
[a] Dermal absorption was considered to be equivalent to oral absorption.
[b] SDS, 2015c.
[c] SDS, 2017a.

Exposures to hexa(methoxymethyl)melamine are expected to be limited to specialized or industrial uses that would not result in exposure to the Canadian general population.

6.2 Health effects assessment

In Canada, the PMRA reviewed amitrole (Health Canada 2014). Internationally, the JECFA (JECFA 2004) summarized the health effects information and characterized hazard related to NaDCC and structurally similar substances, sodium cyanurate and cyanuric acid. The PMRA also evaluated NaDCC in their Re-evaluation Decision Document (Health Canada 2006), based in part on the US Environmental Protection Agency (EPA) Reregistration Eligibility Document (RED) for Chlorinated Isocyanurates (US EPA 1992). The US EPA indicated that the chlorinated isocyanurates do not appear to induce significant acute, sub-chronic, or chronic toxicity. The US EPA also indicated that the available toxicity data suggest that these compounds do not meet their toxicity criteria for requirement of post-application/re-entry and/or mixer/loader/applicator exposure monitoring data (US EPA 1992). Environment and Climate Change Canada and Health Canada (ECCC, HC 2020) summarized the health effects information and characterized hazard related to melamine, a structurally similar substance hexa(methoxymethyl)melamine. Therefore, these assessments inform the

health effects assessment for the three respective substances, including the selection of critical effects and points of departure.

Literature searches were conducted up to April 2018 for all three substances and for the three structurally similar substances, sodium cyanurate, cyanuric acid, and melamine. No health effect studies, which would impact the risk characterization (i.e., result in different critical endpoints or more conservative points of departure than those stated in Health Canada 2014; JECFA 2004; and ECCC, HC 2020), were identified.

6.2.1 Substance-specific hazard data for risk characterization

There were limited chemical-specific health effects data for some substances in the Triazines and Triazole group. Analogues were considered by Health Canada and the JECFA based on similarities in chemical structure and physical-chemical properties (see Appendix B). The chemical-specific data are presented first, followed by analogue data used to inform the health effects characterization of substances in the Triazines and Triazole group.

Amitrole

Internationally, amitrole has been classified for carcinogenicity by the International Agency for Research on Cancer (IARC) as Group 3 (not classifiable as to its carcinogenicity to humans) (IARC 2001) and by the US National Toxicology Program (NTP) as “Reasonably Anticipated to be a Human Carcinogen” (NTP 2016). The US EPA initially categorized amitrole as a probable human carcinogen (category B2) (US EPA 1988) and the substance was reclassified as “not likely to be carcinogenic to humans” after a subsequent review (US EPA 2006). Amitrole has been classified for reproductive toxicity as a Reproductive Category 2 (suspected) under the European Chemical Agency (ECHA) Globally Harmonised System (GHS) (EU 2008) and as reproduction category 1B (presumed) under the European Food Safety Authority (EFSA 2014) and EU (2016). Amitrole has also been reviewed in a Reregistration Eligibility Decision (RED) (US EPA 1996) and by the European Commission (EC 2001). In Canada, Health Canada’s PMRA re-evaluated the potential risks of amitrole (Health Canada 2014).

For pesticide use, a quantitative risk assessment for tumorigenicity was conducted by the PMRA and a cancer unit risk (q1*) of 0.328 (mg/kg bw per day)$^{-1}$ was derived on the basis of thyroid follicular cell tumours in male rats (Health Canada 2012, 2014).

NaDCC

As there were limited chemical-specific hazard data available for NaDCC, a breakdown product and its corresponding sodium salt (cyanuric acid and sodium cyanurate, respectively) were selected as analogues by the JECFA (2004). Critical endpoints and

corresponding effect levels for sodium cyanurate and cyanuric acid to be used for risk characterization, as cited directly from JECFA (2004), can be found in section 6.2.2.

In contact with water, NaDCC is hydrolyzed to release free chlorine and creates equilibrium with chlorinated and non-chlorinated isocyanurates. Chlorinated isocyanurates react rapidly with saliva in the mouth to release free chlorine until there is no detectable chlorinated species remaining. The unchlorinated cyanuric acid is what reaches the gastrointestinal tract (Oxychem 1997, 2000 as cited in JECFA 2004).

Acute studies were conducted with rats and rabbits. Mortality was observed at 1671 mg/kg bw and above when administered orally or dermally. Short-term studies were conducted in rats from 59 days to 13 weeks. Developmental toxicity of NaDCC was assessed in dopamine-deficient (DD) mice with test animals gavaged on gestation days (GDs) 6 to 15 with 0, 25, 100, or 400 mg/kg bw per day. Reduced body weight and increased incidence of mortality was observed in animals receiving the high dose. Delayed ossification in the fetuses was also observed in the group receiving the high dose and was associated with maternal toxicity; there were no signs of fetotoxicity (Gargus, Phipps, and Gluck 1984; Gargus, Phipps, and Ralph 1985; Hammond et al. 1986; Tani et al. 1980, as cited in JECFA 2004).

Hexa(methoxymethyl)melamine

This section provides the critical effects and corresponding effect levels for hexa(methoxymethyl)melamine.

The US EPA (2007) characterized the toxicity of hexa(methoxymethyl)melamine in their hazard characterization using a mixture of hexa(methoxymethyl)melamine at 29% and a methylated melamine-formaldehyde polymer (CAS RN 68002-20-0) at 71% as the test material. The lowest no observed adverse effect level (NOAEL) for the mixture from the repeat-dose toxicity studies was 250 mg/kg bw/day. The NOAEL for the mixture for reproductive and developmental effects was 500 mg/kg bw/day. The NOAEL of 250 mg/kg bw/day, if adjusted to account for only 29% of the mixture being composed of hexa(methoxymethyl)melamine (conservatively assuming all the toxicity of the mixture could be the result of hexa[methoxymethyl]melamine), would be 72.5 mg/kg bw/day. Due to the potential for confounding from the presence of the polymer on the mixture toxicity, particularly given its presence at 71% of the mixture and given that it may be a formaldehyde releaser (ECHA 2017b), the use of analogue data from melamine was preferred.

6.2.2 Read-across/analogue hazard data for risk characterization

There was a lack of health effects data identified for NaDCC and hexa(methoxymethyl)melamine for repeat-dose toxicity. Sodium cyanurate and cyanuric acid were determined to be appropriate analogues for NaDCC, as they were identified as such by the JECFA (JECFA 2004). As there were limited chemical-specific hazard

data for hexa(methoxymethyl)melamine, a structurally similar substance, melamine, was selected as an analogue for read-across. Melamine was selected as the most suitable analogue with available hazard data for read-across to hexa(methoxymethyl)melamine based on similarities in chemical structure (OECD QSAR Toolbox 2013) and physical-chemical properties. Critical endpoints and corresponding effect levels for melamine to be used for risk characterization, as cited directly from ECCC, HC (2020), can be found in Section 6.2.2.

As such, these substances were used as surrogates where critical health effects data were required for risk characterization.

Sodium cyanurate/ cyanuric acid

Sodium cyanurate and cyanuric acid were included as part of the group evaluated by the JECFA (2004) and the committee also considered the toxicological data associated with sodium cyanurate and cyanuric acid to inform the hazard assessment of NaDCC because any residues of intact NaDCC in drinking water would be rapidly converted to cyanuric acid on contact with saliva. Sodium cyanurate is the corresponding salt of cyanuric acid.

This section provides the critical endpoints and corresponding effect levels for sodium cyanurate and cyanuric acid to be used for risk characterization, as cited directly from the JECFA (2004).

A chronic/carcinogenicity study was conducted in Charles River CD1 rats with sodium cyanurate. Test animals were exposed via drinking water for 2 years to 0, 400, 1500, 2400, or 5375 mg/L (equivalent to 0, 26, 77, 154, or 371 mg/kg bw per day). The critical effect level and corresponding hazard endpoint was an NOAEL of 2400 mg/L (154 mg/kg bw per day), based on lesions of the urinary tract and heart in males at the highest tested dose. There appeared to be no increase in tumour incidence (International Research and Development Corporation 1985, as cited in JECFA 2004). This chronic/carcinogenicity study was selected by JECFA as the key study for assessing risks from NaDCC as a drinking water disinfectant used for routine use and emergency management (JECFA 2004). In a two-year mouse study, there were no treatment-related changes in haematological, clinical chemistry, or urine analysis parameters, or incidence of tumour or histopathological lesions observed in B6C3F1 mice exposed to sodium cyanurate via drinking water up to the highest tested dose of 5375 mg/L (1523 mg/kg bw per day) (Serota et al. 1986 as cited in JECFA 2004).

For sodium cyanurate and cyanuric acid, oral acute studies were conducted in mice, rats, and rabbits with acute toxicity (lethality) values between 1500 mg/kg-bw and 10 000 mg/kg-bw. Short-term studies were conducted using sodium cyanurate in drinking water for 13 weeks in mice and rat at 1500 and 145 mg/kg bw per day, respectively. A reproductive study was done in rats for a minimum of 100 days of exposure before mating. Developmental studies were conducted via gavage in rats and rabbits. There

were no treatment-related effects observed in foetuses for any study (Aldridge et al. 1985; Consultox Laboratories Ltd. 1974; Laughlin et al. 1982; Rajasekaran et al. 1981; Rodwell 1990; Serota et al. 1982; Tice 1997, as cited in JECFA 2004). Sodium cyanurate was not found to have mutagenic activity (JECFA 2004). Although these short-term studies were considered by JECFA in its evaluation of risks from the use of NaDCC as a drinking water disinfectant, they were not selected as the key study (JECFA 2004).

Melamine

Melamine was determined to be an appropriate analogue to inform the health effects of hexa(methoxymethyl)melamine to be used for risk characterization.

This section provides critical effects and corresponding effect levels for melamine, as cited in ECCC, HC (2020).

A lowest observed adverse effect level (LOAEL) was identified in a 13-week feeding study in rats, in which a dose-dependent increase in the incidence of bladder calculi and increased calcareous deposits in the kidney (not dose-related) were observed in animals fed melamine at all doses tested, the lowest one being 63 mg/kg bw per day (US NTP 1983 and Melnick et al. 1984, as cited in ECCC, HC 2020). WHO (2009, as cited in ECCC, HC 2020) calculated a benchmark dose (BMD) and its lower confidence limit (BMDL10), based on this 13-week oral study, of 44.6 and 35 mg/kg bw per day, respectively, for a 10% increased incidence of the observed effects (urolithiasis occurrence and incidence of hyperplasia of the bladder epithelium).

Five carcinogenicity studies have been conducted in rats and one in mice; in all cases, melamine was administered through the feed of the animals. In four of the rat studies, bladder tumours or papillomas were observed at doses ranging from 263 to 1200 mg/kg bw/day. In the one rat study where tumours were not observed, male and female Fischer 344 rats had been exposed to melamine in the diet for 24–30 months at doses of 5 to 100 mg/kg bw per day (Hazleton Laboratories 1983). No carcinogenic effects were observed in a two-year mouse feeding study at melamine doses of 327 to 1,065 mg/kg bw per day. However, 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 (ECCC, HC 2020).

The postulated mode of action for carcinogenicity starts with localized tissue irritation, to a threshold mechanism of reactive hyperplasia progressing to bladder neoplasia. There was *inadequate evidence* in humans for carcinogenicity but *sufficient evidence* in experimental animals—as such, the IARC has classified melamine as a Group 2B carcinogen (IARC 2019). As such, melamine is possibly carcinogenic to humans. Available information indicates that melamine is not genotoxic (WHO 2009, as cited in ECCC, HC 2020).

6.3 Characterization of risk to human health

Overall exposure of the general population to amitrole is not expected based on current use information, and the potential risk to human health is considered to be low.

Table 6-2 provides all relevant exposure estimates from non-pesticidal uses of products available to consumers and critical effect levels for NaDCC, as well as resulting margins of exposure.

Table 6-2. Relevant exposure estimates and critical effect levels for NaDCC, and margins of exposure, for determination of risk

Exposure scenario	Estimated systemic exposure	Critical effect level	Study type and duration	Critical effect	MOE
Water treatment tablets (daily, oral, infants to adults)[a]	1.8 mg/kg bw per day for infants to 0.36 mg/kg bw per day for adults	NOAEL (oral) = 220 mg/kg bw/day)[b]	2-year oral chronic rat study	Lesions of the urinary tract and heart in males	122 for infants to 611 for adults
Cleaning abrasive powder: application exposure (per event, dermal, adults)	0.83 mg/kg bw per event	NOAEL (oral)=220 mg/kg bw/day	2-year oral chronic rat study	Lesions of the urinary tract and heart in males	265 for adults

Abbreviations: bw, body weight; MOE, margin of exposure; NOAEL, no-observed-adverse-effect level.
[a] Drinking water exposures estimated from the consumer release scenario were less than those from the use of water treatment tablets.
[b] The NOAEL for sodium cyanurate was 154 mg/kg bw per day, equivalent to 220 mg/kg bw per day as anhydrous NaDCC.

The JECFA considered the safety of NaDCC in relation to its possible use as a disinfectant for drinking water in emergency situations, and for routine use in some water supplies. The Committee concluded that studies of the toxicity of sodium cyanurate were appropriate for assessing the safety of NaDCC because any residues of intact sodium dichloroisocyanurate in drinking water would be rapidly converted to cyanuric acid on contact with saliva. The JECFA identified the critical effect for risk characterization as lesions of the urinary tract and heart in male rats from a two-year study with sodium cyanurate. The NOAEL for sodium cyanurate was 154 mg/kg bw per day, equivalent to 220 mg/kg bw per day as anhydrous NaDCC.

No repeated-dose dermal toxicity studies were identified for NaDCC or sodium cyanurate. The oral two-year study in rats that was the basis for the oral NOAEL of 220 mg/kg bw per day was used for the characterization of risk from dermal exposure. The use of a chronic study for risk characterization was considered to be a conservative approach, as the dermal exposures to this substance are intermittent, short-term exposures. Furthermore, the US EPA Reregistration Eligibility Decision (RED) noted that sub-chronic dermal studies were not required to be submitted by industry for re-registration due to a lack of toxicity in sub-chronic oral studies at doses above use concentrations (US EPA 1992).

The calculated margins of exposure for NaDCC are considered adequate to address uncertainties in the health effects and exposure databases.

Table 6-3 provides all relevant exposure estimates and critical effect levels for hexa(methoxymethyl)melamine, as well as resultant margins of exposure, for determination of risk.

Table 6-3. Relevant exposure estimates and critical effect levels for Hexa(methoxymethyl)melamine, and margins of exposure, for determination of risk

Exposure scenario	Estimated exposure	Critical effect level	Study type and duration	Critical effect	MOE
Drinking water (daily, oral, infants to adults)	1.4×10^{-3} mg/kg bw per day for infants to 2.8×10^{-4} mg/kg bw per day for adults	BMDL10 (oral) = 35 mg/kg bw/day	13-week oral rat study	Increased urolithiasis and hyperplasia of the bladder epithelium	25 000 for infants to 125 000 for adults

Abbreviations: BMDL10, benchmark dose lower confidence limit; bw, body weight; MOE, margin of exposure.

WHO (2009) calculated a BMD and its lower confidence limit (BMDL10) for melamine, based on 13-week oral study with the lowest LOAEL, for a 10% increased incidence of the observed effects (urolithiasis occurrence and incidence of hyperplasia of the bladder epithelium). The BMDL10 of 35 mg/kg bw per day was supported by ECCC, HC 2020.

No repeated-dose dermal toxicity studies were identified for melamine, and the oral 13-week feeding study in rats for melamine (which is the basis for the BMDL10) was used for the characterization of risk from both oral and dermal exposure to hexa(methoxymethyl)melamine.

The US EPA (2007) characterized the toxicity of hexa(methoxymethyl)melamine in their hazard characterization using mixture data. Due to the potential for confounding from

the presence of the polymer (particularly being at 71% of the mixture), the use of analogue data from melamine is considered appropriate. Furthermore, the use of a BMDL10 of 35 mg/kg bw/day is more conservative than the endpoints in the mixture data. As such, the use of a point of departure based on melamine is considered a conservative approach.

The IARC has classified melamine as a Group 2B carcinogen (IARC 2019). Use of the BMDL10 is considered protective of the cancer endpoint based on the suspected mode of action leading to cancer; namely, irritation followed by hyperplasia followed by neoplasia.

The calculated margins of exposure for hexa(methoxymethyl)melamine are considered adequate to address uncertainties in the health effects and exposure databases.

Although exposure of the general population from amitrole is not expected, this substance is considered to have health effects of concern on the basis of its carcinogenicity and reproductive toxicity. Therefore, there may be a concern for human health if exposures were to increase.

Although exposure of the general population from hexa(methoxymethyl)melamine is not of concern at current levels, this substance is considered to have health effects of concern on the basis of the carcinogenicity of its analogue melamine. Therefore, there may be a concern for human health if such exposures were to increase.

6.4 Uncertainties in evaluation of risk to human health

There are some uncertainties with respect to the exposure and health effects database. Environmental modelling for NaDCC and hexa(methoxymethyl)melamine was used when Canadian monitoring data were unavailable. There is uncertainty from the extrapolation of health effects data from oral toxicity studies to the dermal route of exposure. The selection of sodium cyanurate/cyanuric acid and melamine as analogues for assessing the respective hazard potential of NaDCC and hexa(methoxymethyl)melamine is associated with uncertainty.

7. Conclusion

Considering all available lines of evidence presented in this screening assessment, there is low risk of harm to the environment from amitrole, NaDCC, and hexa(methoxymethyl)melamine. It is concluded that amitrole, NaDCC, and hexa(methoxymethyl)melamine do not meet the criteria under paragraphs 64(*a*) or (*b*) of CEPA, as they are not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity, or that constitute or may constitute a danger to the environment on which life depends.

On the basis of the information presented in this screening assessment, it is concluded that amitrole, NaDCC, and hexa(methoxymethyl)melamine do not meet the criteria under paragraph 64(*c*) of CEPA, as they are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

It is therefore concluded that amitrole, NaDCC, and hexa(methoxymethyl)melamine do not meet any of the criteria set out in section 64 of CEPA.

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Appendix A. Estimated human exposure to the Triazines and Triazole Group

Exposures were estimated on the basis of Canadian default body weights (bw), in other words, 7.5 kg of an infant, 15.5 kg of a toddler, 31.0 kg of a child, and 70.9 kg of an adult (Health Canada 1998), and anticipated use patterns (see Table A-1). When concentrations were used to determine exposure estimates, the highest values were used as a conservative approach. Dermal and inhalation absorption were assumed to be 100% (relative to oral absorption).

Table A-1. Product-Specific Exposure Parameters

Exposure scenario	Assumptions
Water treatment tablets (NaDCC)	Amount of substance in one tablet (as): 8.5 mg, where the concentration in the tablet is 17% (one tablet treats 1 L of clear, room-temperature water without organic debris, and two tablets treat 1 L of dirty, cloudy, stained, and/or cold water according to product instructions) (SDS 2015c). Drinking water intake (wi): 0–0.8 L/day for infant, 0.7 L/day for toddler, 1.1 L/day for child, 1.2 L/day for teenager, 1.5 L/day for adult, and 1.6 L/day for senior (Health Canada 1998). Although the use of water treatment tablets may be on an emergency or otherwise intermittent basis, daily exposure was conservatively assumed. Estimated daily oral exposure = (2 × as × wi)/(bw × 1 L)
Application exposures from cleaning products (NaDCC)	Cleaning abrasive powder: Concentration (co): 1.5% (SDS 2017a) Product amount (pa): 3.9 g (RIVM 2018). (This is based on consideration of rubbing action resulting in the product amount that is subject to dermal exposure. Please note that scattering action, with a contact rate of 2.8 mg/min. and a release duration of 1 minute, was also considered, but its addition did not significantly change the dermal exposure estimate for this product.) Estimated dermal exposure = (co/100 × pa × unit conversion)/bw

	Exposure from the inhalation route was estimated based on the Pesticide Handlers Exposure Database (PHED) for cleaning products in powder form. Estimated inhalation exposure = (co/100 × pa × 56.20 µg exposure/kg ai handled × unit conversion)/bw, where 56.20 µg exposure/kg active ingredient (ai) handled is the PHED unit exposure value for mixing and loading wettable powder (Pellerin and Macey 2001). Exposures from the inhalation route from other types of products are expected to not be a concern, given the negligible vapour pressure and non-powder/spray anticipated uses.

Abbreviation: bw, body weight.

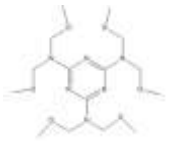
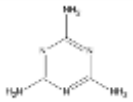
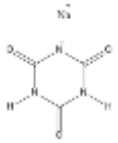
Appendix B. Read-across approach

Table B-1. Considerations for analogues of the Triazines and Triazole Group

Consideration	Rationale
1) Chemical structure. Emphasis was placed on analogues that contained a melamine or triazine core.	Analogues that have a similar chemical structure are more likely to have similar toxicity profiles.
2) Similar metabolites (predicted or observed). There were no empirical metabolism data for hexa(methoxymethyl)melamine. Metabolites were not predicted in the OECD QSAR Toolbox using the rat liver S9 metabolism and skin metabolism simulators. Metabolites were predicted using the skin metabolism simulators in OASIS Times, but not the *in vivo* rat liver metabolism simulator.	Analogues that are metabolized through similar pathways to similar degradation products are more likely to have similar toxicity profiles. Analogues found that have known toxic metabolites (i.e., formaldehyde) that are not expected to result from the metabolism of the target were not considered.
3) Common structural alerts.	Analogues with similar structural alerts are expected to share greater similarity in terms of toxicity.
4) Similar physical-chemical properties. Emphasis was placed on chemical structures with a similar molecular weight, water solubility, vapour pressure, and log $K_{o/w}$.	Analogues with similar physical chemical properties may potentially share similar toxicological profiles and bioavailability.
5) Availability of health effects data.	Only analogues with hazard data of sufficient quality and coverage of routes and durations of exposure relevant to exposure scenarios were considered applicable for read-across purposes.
6) Selection and use of an analogue by reliable international review.	JECFA selected sodium cyanurate to be the representative analogue for NaDCC in their 2004 review (JECFA 2004).

Abbreviations: JECFA, Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives; $K_{o/w}$, octanol/water partition coefficient; OECD, Organisation for Economic Co-operation and Development; QSAR, Quantitative Structure Activity Relationship.

Table B-2. Summary data[a] on physical-chemical properties and toxicity for the Triazines and Triazole Group and their analogues

Substance	Hexa (methoxymethyl) melamine	Melamine	NaDCC	Sodium cyanurate
CAS RN	**3089-11-0**	**108-78-1**	**2893-78-9**	**2624-17-1**
Structure				
MW (g/mol)	390.44	126.12 [b]	219.9	151.1
Vapour pressure (Pa)	1.4×10^{-6}	9.4×10^{-8}; 1.1×10^{-7} [b]	1.9×10^{-12}	1.88×10^{-14}
Henry's law constant ($atm \cdot m^3/mol$)	2.80×10^{-12}	1.86×10^{-9} [b]	3.10×10^{-12}	8.41×10^{-15}
Water solubility (mg/L)	1.49×10^{2}	4.85×10^{3} [b]	2.48×10^{5}	2.23×10^{4}
LogK_{ow}	1.6	–1.14[b]	–0.06	0.62
Oral LD_{50} (g/kg)	>5000 mg/kg[c,d]	3161 mg/kg bw (male rats) and above[e]	1671 mg/kg bw (female rats) and above[f]	>5000 mg/kg bw (for corresponding acid)[f]
Dermal LD_{50} (g/kg)	—	>1000 mg/kg bw (rabbit)[e]	>5000 mg/kg bw[f]	—
Genotoxicity	—	Negative	—	Negative[f]
Carcinogenicity	—	Positive	—	Negative[f]
Repeat dose toxicity (mg/kg bw/day)	—	BMDL10 (oral) = 35 mg/kg bw/day 13-week oral rat study Increased urolithiasis and hyperplasia of the bladder epithelium	—	NOAEL (oral) = 220 mg/kg bw/day 2-year oral chronic/ carcinogenicity rat study Lesions of the urinary tract and heart in males

Abbreviations: BMDL, lower confidence limit benchmark dose; bw, body weight; K_{ow}, octanol-water partition coefficient; LD_{50}, median lethal dose; MW, molecular weight; NOAEL, no-observed-adverse-effect level.

[a] Unless otherwise specified, data were retrieved from ECHA (2017a), EPI Suite (c2000–2012), or the Health Effects section of this report.

[b] ECCC, HC (2020).

[c] Haskell Laboratory (1991).

[d] Eastman Kodak (1991).

[e] Health Canada (2018).

[f] JECFA (2004).