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DRAFT SCREENING ASSESSMENT
Heterocycles

Chemical Abstracts Service Registry Number
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4174-09-8

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Synopsis

Pursuant to section 74 of the Canadian Environmental Protection Act, 1999 (CEPA), the Minister of the Environment and the Minister of Health have conducted a screening assessment on four of seven substances referred to collectively under the Chemicals Management Plan as the Heterocycles Group. These four substances were identified as priorities for assessment as they met categorization criteria under subsection 73(1) of CEPA. Three of the seven substances were subsequently determined to be of low concern through other approaches, and decisions for these substances are provided in a separate report.[1] Accordingly, this screening assessment addresses the four substances listed in the table below.

Substances in the Heterocycles Group

CAS RN[2]	Domestic Substances List name	Common names
96-45-7	2-imidazolidinethione	ethylene thiourea (ETU)
100-97-0	1,3,5,7-tetraazatricyclo[3.3.1.13,7] decane	methenamine
110-91-8	tetrahydro-1,4-oxazine	morpholine
4174-09-8	3H-pyrazol-3-one, 2,4-dihydro-4-[(5-hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)methylene]-5-methyl-2-phenyl-	N/A

N/A Not applicable

In Canada, ETU is used as an intermediate, accelerator and vulcanizing agent in plastic and rubber formation. In 2008, less than 1 000 kg were manufactured in Canada and between 10 000 and 100 000 kg were imported into Canada.

In 2011, between 100 000 and 1 000 000 kg of methenamine were manufactured in Canada, and between 100,000 and 1 000 000 kg were imported into Canada during the same calendar year. The largest use of methenamine is as a cross-linking agent in phenolic and urea formaldehyde resins and in rubber. Methenamine is consumed during this process. Another use is as a chemical intermediate in nitration reactions for

[1] Conclusions for CAS RNs 132-65-0, 28984-69-2 and 68909-18-2 are provided in the Substances Identified as Being of Low Concern based on the Ecological Risk Classification of Organic Substances and the Threshold of Toxicological Concern (TTC)-based Approach for Certain Substances Draft Screening Assessment.

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explosives production and in the production of fuel tablets. Cosmetics may also contain methenamine at low levels as a preservative. Food packaging materials may also contain methenamine.

In 2011, between 1 000 and 10 000 kg of morpholine were manufactured in Canada, and between 100 000 and 1 000 000 kg were imported into Canada during the same calendar year. Primary uses of morpholine include use as an intermediate in the production of rubber accelerators, pharmaceuticals, pesticides, optical brighteners, antioxidants and as an industrial solvent. It is also used in closed water or steam systems to prevent corrosion, as an oil field production chemical and as a solvent and emulsifier in the preparation of wax coatings for fruits and vegetables. Morpholine has also been identified as a component in the manufacture of some food packaging materials (e.g. interior coatings).

In 2011, between 1 000 and 10 000 kg of CAS RN 4174-09-8 were imported into Canada. CAS RN 4174-09-8 is used as a colourant for plastic materials and articles, varnishes and coatings. It has been identified for use as colourants in polystyrene, polycarbonate and polyethylene terephthalate food packaging materials.

The ecological risks of the substances in the Heterocycles Group were characterized using the ecological risk classification of organic substances (ERC) approach. The ERC 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 established primarily on the basis of 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 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. The ERC identified the four substances in the Heterocycles Group as having low potential to cause ecological harm.

Considering all available lines of evidence presented in this draft screening assessment, there is low risk of harm to organisms and the broader integrity of the environment from ETU, methenamine, morpholine and CAS RN 4174-09-8. It is proposed to conclude that ETU, methenamine, morpholine and CAS RN 4174-09-8 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.

Laboratory studies show that ETU is carcinogenic. Exposure of the general population to ETU can occur from the diet, including drinking water, as a result of crop treatment with ethylene bis-dithiocarbamate fungicides that break down to ETU. These sources of exposure to ETU are being addressed under the Pest Control Products Act as part of

Health Canada's re-evaluation of ethylene bis-dithiocarbamate fungicides and will therefore not be addressed in this draft screening assessment.

The general population may be exposed by the dermal route to residual ETU through migration from rubber products. Risk to human health was therefore assessed by comparing estimates of exposure to ETU from rubber products with the levels associated with health effects in animal studies, including Health Canada's previously established point of departure for carcinogenicity. For both non-cancer and cancer effects, risk to human health was considered to be low.

General population exposure to methenamine can occur from use of cosmetics when it is used as a preservative, when it is used as products available to consumers and from its use in food packaging materials. For the general population, margins of exposure relative to critical effect levels for methenamine are considered adequate to address uncertainties in the health effects and exposure databases.

Exposure of the general population to morpholine is expected to be limited to the use of a small number of products available to consumers, primarily home and auto polishes/waxes and related auto care products. Morpholine may also be added to some wax coating compounds used on fresh produce, such as apples. As such, there is the potential for dietary exposure to trace levels of morpholine when coated produce is consumed. In the case of food packaging use, morpholine is not a significant source of dietary exposure. There is also the potential for exposure from disinfectant sprays. Health Canada (2002) previously conducted a safety assessment of the use of morpholine in wax coatings used on apples and determined that such use did not present a risk to humans. For the general population, a comparison of the levels of morpholine to which consumers may be exposed with the critical effect levels in laboratory studies is considered adequate to address uncertainties in the health effects and exposure databases.

CAS RN 4174-09-8 may be used as a colourant in food packaging materials though it is not expected to migrate from the packaging material. As exposure is considered to be negligible, risk to human health is considered to be low.

On the basis of the information presented in this draft screening assessment, it is proposed to conclude that ETU, methenamine, morpholine and CAS RN 4174-09-8 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 proposed to conclude that ETU, methenamine, morpholine and CAS RN 4174-09-8 do not meet the criteria set out in section 64 of CEPA 1999.

Table of contents

List of tables

1. Introduction

Pursuant to section 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 four of seven substances, referred to collectively under the Chemicals Management Plan as the Heterocycles Group, to determine whether they present or may present a risk to the environment or to human health. These four substances were identified as priorities for assessment as they met categorization criteria under subsection 73(1) of CEPA (ECCC, HC [modified 2007]).

The other three substances (listed in Table 1-1 below) were considered in the Ecological Risk Classification of Organic Substances 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 three substances are provided in the Substances Identified as Being of Low Concern based on the Ecological Risk Classification of Organic Substances and the Threshold of Toxicological Concern (TTC)-based Approach for Certain Substances Draft Screening Assessment (ECCC, HC 2017).

Table 1-1. Substances in the Heterocycles Group that were addressed under other approaches

CAS RN[3]	Domestic Substances List (DSL)ethylene name	Approach under which the substance was addressed	References
132-65-0	Dibenzothiophene	ERC/TTC	ECCC, HC 2017
28984-69-2	4,4(5H)-Oxazoledimethanol, 2-(heptadecenyl)-	ERC/TTC	ECCC, HC 2017
68909-18-2	Pyridinium, 1-(phenylmethyl)-, Et Me derivs., chlorides	ERC/TTC	ECCC, HC 2017

The other four substances will be addressed directly in this draft screening assessment.

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The ecological risks of substances in the Heterocycles Group were characterized using the Ecological Risk Classification of Organic Substances (ERC) Science Approach Document (ECCC 2016a). The ERC describes the hazard of a substance using key metrics including 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 factors including 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.

While the four substances considered in this draft screening assessment are collectively referred to as the Heterocycles Group, they lack sufficient similarities that would support a group approach to exposure, hazard and risk characterization; thus, their use and/or hazard profiles were independently assessed for risk to the environment and human health. The assessment of each substance forms its own chapter below.

This draft screening assessment includes consideration of information on chemical properties, environmental fate, hazards, uses and exposure. Relevant data were identified up to July 2016. Empirical data from key studies as well as some results from models were used to reach proposed conclusions. When available and relevant, information presented in assessments from other jurisdictions was considered. The approach includes the use of previously established points of departure for health effects for the substances ETU and morpholine from Health Canada's PMRA and Food Directorate, respectively. In addition, international assessment work and points of departure were adopted for methenamine from European assessment activities under the European Chemicals Agency (EChA).

This draft 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 ERC document was subject to an external peer-review and a 60-day public comment period. While external comments were taken into consideration, the final content and outcome of the draft screening assessment remain the responsibility of Environment and Climate Change Canada and Health Canada.

This draft screening assessment focuses on information critical to determining whether 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.[4] The draft

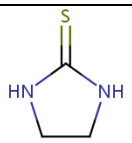
[4]A determination of whether one or more of the criteria of section 64 of CEPA are met is based upon an assessment of potential risks to the environment and/or to human health associated with exposures in the general environment. For humans, this includes, but is not limited to, exposures from ambient and indoor air, drinking water, foodstuffs, and products used by 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 hazardous products intended for workplace

screening assessment presents the critical information and considerations on which the proposed conclusion is based.

2. Identity of substances

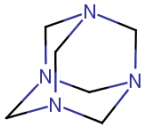
The substance 2-imidazolidinethione, commonly known as ethylene thiourea (ETU), herein referred to as ETU, is an organic chemical belonging to a substance group known as heterocycles (PubChem 2015). Information regarding the substance identity of ETU is summarized in Table 2-1.

Table 2-1. Substance identity for ETU

CAS RN	DSL name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)
96-45-7	2-imidazolidinethione (ETU)	 $C_3H_6N_2S$	102.2

The substance 1,3,5,7-tetraazatricyclo[3.3.1.13,7] decane, commonly known as methenamine, herein referred to as methenamine, is an organic chemical belonging to a substance group known as heterocycles (PubChem 2015). Information regarding the substance identity of methenamine is summarized in Table 2-2.

Table 2-2. Substance identity for methenamine

CAS RN	DSL name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)
100-97-0	1,3,5,7-tetraazatricyclo[3.3.1.13,7]decane (methenamine)	 $C_6H_{12}N_4$	140.2

The substance tetrahydro-1,4-oxazine**,** commonly known as morpholine, herein referred to as morpholine, is an organic chemical belonging to a substance group known as heterocycles (PubChem 2015). Information regarding the substance identity of morpholine is summarized in Table 2-3.

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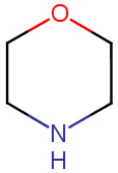
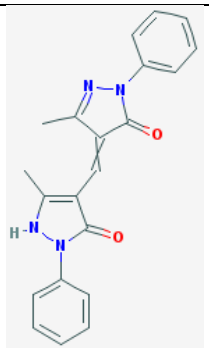
use, handling and storage. Similarly, a conclusion based on the criteria contained in section 64 of CEPA does not preclude actions being taken under other sections of CEPA or other Acts.

Table 2-3. Substance identity for morpholine

CAS RN[4]	DSL name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)
110-91-8	tetrahydro-1,4-oxazine (morpholine)	 C_4H_9NO	87.1

The substance 3H-pyrazol-3-one, 2,4-dihydro-4-[(5-hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)methylene]-5-methyl-2-phenyl- , herein referred to as CAS RN 4174-09-8, is an organic chemical belonging to a substance group known as heterocycles (PubChem 2015). Information regarding the substance identity of CAS RN 4174-09-8 is summarized in Table 2-4.

Table 2-4. Substance identity for CAS RN 4174-09-8

CAS RN[4]	DSL name	Chemical structure and molecular formula	Molecular weight (g/mol)
4174-09-8	3H-pyrazol-3-one, 2,4-dihydro-4-[(5-hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)methylene]-5-methyl-2-phenyl-	 $C_{21}H_{18}N_4O_2$	358.4

Physical and chemical properties of the four heterocycle substances are summarized in Appendix A. Additional physical and chemical properties are presented in ECCC (2016b).

3. Characterization of ecological risk

The ecological risks of substances in the Heterocycles Group were characterized using the ERC approach (ECCC 2016a). The ERC is a risk-based approach that considers multiple metrics for both hazard and exposure with weighted considerations 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, in contrast to an approach that relies on a single metric in a single medium (e.g., LC_{50}) 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, fish bioconcentration), acute fish ecotoxicity, and chemical import and manufacture volumes in Canada were either collected from scientific literature, from available empirical databases (e.g., OECD QSAR Toolbox), and from responses to surveys under section 71 of CEPA or they were generated using selected quantitative structure-activity relationship (QSAR) or mass-balance fate and bioaccumulation models. These data were used as inputs to other mass-balance models or to complete the substances hazard and exposure profiles.

Hazard profiles were established primarily on the basis of metrics regarding mode of toxic action, chemical reactivity, food web-derived internal toxicity thresholds, bioavailability, and chemical and biological activity. Exposure profiles were based on multiple metrics, including 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 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 modeled acute toxicity values could result in changes in classification of hazard, particularly metrics relying on tissue residue values (i.e., mode of toxic action), many of which are predicted values from QSAR models. However, the impact of this error is mitigated by the fact that overestimation of median lethality will result in a conservative (protective) tissue residue value used for critical body residue analysis. Error in 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 considering what is believed to be the current use quantity, and may not reflect future trends.

4. ETU

4.1 Sources and uses

ETU does not occur naturally in the environment. It is used primarily as an accelerator or vulcanizing agent for the curing of polychloroprene (neoprene) and polyacrylate rubbers (IARC 1974; IARC 2001; HSDB 1983-2017; Netherlands 1999). ETU is a degradation product, a metabolite and a residual in ethylene bis-dithiocarbamate fungicides, such as mancozeb and metiram. In its proposed re-evaluation decision, PMRA identified potential carcinogenic risk from dietary and water exposure to ETU derived from ethylene bis-dithiocarbamate fungicides (PMRA 2013, 2014). The re-evaluation is currently ongoing, and any required risk reduction measures will be addressed under the Pest Control Products Act to reduce exposure and risk to ETU.

According to information submitted pursuant to a survey under section 71 of CEPA (Canada 2009), less than 1000 kg of ETU were manufactured in Canada in 2008 and between 10 000 and 100 000 kg were imported into Canada that same year.[5] In the United States, the national production volume for ETU was between 0.45 and 4.5 million kg in 2012 (CDAT 2015).

Given its uses, ETU can be found in low amounts in some manufactured rubber consumer items. Additional information on uses in Canada is presented in Table 4-1.

Table 4-1. Additional uses in Canada for ETU

Use	ETU
Food additive[a]	No
Food packaging materials[a]	Yes
Drug Products Database[b]	No
Natural Health Products Ingredients Database[c]	No
Licensed Natural Health Products Database being present as a medicinal or non-medicinal ingredient in natural health products in Canada[c]	No

[5] Values reflect quantities reported in response to a survey conducted under section 71 of CEPA (Canada 2009). See survey for specific inclusions and exclusions (Schedules 2 and 3).

Use	ETU
List of Prohibited and Restricted Cosmetic Ingredients[d]	No
Notified to be present in cosmetics, based on notifications submitted under the Cosmetic Regulations to Health Canada[d]	No
Formulant in pest control products registered in Canada[e]	No (contaminant of concern monitored in active ingredients belonging to the ethylene bis-dithiocarbamates)

[a] (Email communication from Food Directorate to Existing Substances Risk Assessment Bureau; unreferenced)
[b] (Email communication from Therapeutic Products Directorate to Existing Substances Risk Assessment Bureau; unreferenced)
[c] (Email communication from Natural and Non-prescription Health Products Directorate to Existing Substances Risk Assessment Bureau; unreferenced)
[d] (Email communication from Consumer Product Safety Directorate to Existing Substances Risk Assessment Bureau; unreferenced)
[e] (Email communication from Pest Management Regulatory Agency to Existing Substances Risk Assessment Bureau; unreferenced)

4.2 Potential to cause ecological harm

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

On the basis of the low hazard and low exposure classifications determined for ETU using the ERC approach, this substance was classified as having a low potential for ecological risk. It is unlikely that ETU results in concerns for organisms or the broader integrity of the environment in Canada.

4.3 Potential to cause harm to human health

4.3.1 Exposure assessment

Environmental media and food

The primary source of exposure to ETU through diet and water intake is expected to be from the use of ethylene bis-dithiocarbamate fungicides is currently being evaluated, and risk to human health characterized, by Health Canada's PMRA (PMRA 2013, 2014).

Exposure from the use of ETU as an antimicrobial agent in food packaging materials, such as paper and paperboard-based materials, is expected to be negligible (personal communication, November 2015 email from the Food Directorate, Health Canada, to the existing Substances Risk Assessment Bureau, Health Canada; unreferenced).

No other data on levels of ETU in environmental media or food have been identified. ETU has not been measured in house dust, nor has it been detected in indoor air. There is the potential for soil and dust to contain ETU in the vicinity of farms or agricultural sites which have used ethylene bis-dithiocarbamate fungicides as noted and considered by PMRA (PMRA 2013, 2014).

Products available to consumers

Potential for exposure to ETU from use of products available to consumers were considered. As ETU is used in the curing of rubbers, the potential for dermal exposure to ETU from rubber-based products was considered. Although the curing of rubbers converts ETU to other compounds, residual amounts of ETU may be present (IARC 1974). Therefore, there is the potential for ETU to migrate from rubber surfaces.

Consumer products that contain neoprene include shoes and certain soft rubber containers (lunch bags) and diving gear. To determine concentrations of ETU in neoprene and associated rubber products, Health Canada undertook a marketplace analysis of 33 different products (CPSD 2016a). Products were cut into 1 cm^3 pieces of approximately 1 gram and incubated overnight at 40ºC in an equal parts mixture of methanol and water. The released concentration of ETU for each product was then determined. These products (9 were neoprene-based) were shown to release from 0.0022 to 0.0838 mg of ETU per kilogram of material (CPSD 2016a). The highest concentration was taken to indicate the total potentially leachable amount of ETU in a rubber or neoprene-based product.

For determination of a systemic exposure to ETU through the dermal route from a solid rubberized material matrix, the migration of diethyl thiourea, a structurally and chemically similar substance to ETU in chloroprene rubber products, where its function is the same as ETU, was considered. The migration rate of the substance from the material is dependent on its concentration in the rubber product, and the ratio of concentration versus migration was considered across several samples (Danish EPA 2012). An analysis of data from five samples showed a range of ratios spanning from 339,000:1 to 609,000:1, relating concentration in the material to migration rate. The upper and lower 95% confidence intervals for the ratio between concentration and migration rate were 342,000:1 and 635,000:1 respectively. A lower ratio of 300,000:1 was selected to conservatively estimate the migration rate of ETU. The lower ratio presumes that a larger amount of ETU will migrate from the material (Danish EPA 2012). Using this ratio, an initial migration rate was determined for a 2.268 kg (5 pound) adult wetsuit, where the ETU concentration was adopted from the compositional analysis of marketplace products that showed the highest concentration of ETU (for a neoprene water sock) of 0.0838 mg/kg. This gave a total potential amount of 0.1901 mg of ETU in an adult wetsuit, with an initial migration rate of 2.78×10^{-7} mg/cm^2/hour.

Adult exposure to ETU from wearing a full body wetsuit covering 16925 cm^2 (body surface area minus surface area of the head) (Health Canada 1998) for up to 30 days

per year was considered. A stepwise daily loss of ETU was determined for each period of use on the basis of the migration rate. ETU migration was considered to occur from both the inside and outside surface of the wetsuit (i.e., into the skin and out into the surrounding environment). Following each daily exposure, the concentration of ETU in the product was recalculated to give a new daily migration rate based on the remaining concentration (See Tables 12-1 and 12-2, Appendix 12). Similarly, exposure of a child was also considered, where body surface area was considered to be 8450 cm^2 and body weight to be 27 kg, with a neoprene wetsuit weight of 1.34 kg containing 0.095 mg of ETU.

Exposure estimates for several durations were developed. Adult exposure to ETU from a wetsuit for a single day was determined to be 0.00024 mg/kg-bw, using the above migration rate for a single day and the dermal absorption value previously established by Health Canada of 45% (PMRA 2013, 2014). Averaged exposure estimates using the same methodology were derived for 10 and 30 day durations, resulting in a daily exposure of 0.00006 and 0.00002 mg/kg-bw/day, in adults, respectively. A single day exposure to ETU for a child was determined to be 0.000315 mg/kg-bw, and 10 and 30 day amortized doses were 0.00008 and 0.00003 mg/kg-bw/day, respectively (See Tables 12-3 and 12-4, Appendix 10). Lifetime average daily exposures from ETU were calculated for use in risk characterization for cancer, assuming 30 days of exposure per year for adults. After 30 days, the total mass migrated to the skin was determined to be 0.0951 mg. The application of a 45% dermal absorption factor results in an absorbed mass of 0.0427 mg. This exposure was amortized over the course of a year, to give a resulting lifetime average daily exposure of 1.65×10^{-6} mg/kg-bw/day for a 70.9 kg adult. For children, the resulting daily exposure over the course of a year was determined to be 2.16×10^{-6} mg/kg-bw/day.

4.3.2 Health effects assessment

PMRA (2013, 2014), the United States Environmental Protection Agency (US EPA 2000), the National Toxicology Program (NTP 1992), and the International Agency for Research on Cancer (IARC 1974) summarized the health effects literature and/or characterized the hazard of ETU. These reports were used to inform the health effects characterization in this draft screening assessment.

Briefly, it was determined that the critical endpoints identified by the PMRA were appropriate for the assessment for cancer and for acute (1 day) non-cancer exposures. However a literature search conducted from the year prior to the publication date of the PMRA assessment (June 2014) to July 2016 identified a new health effects study (Maranghi et al. 2013) with a lower point of departure for a different non-cancer endpoint. This was determined to be applicable for the determination of risk following short duration exposures (10 to 30 days). The following paragraphs provide critical endpoints and corresponding effect levels for ETU that are used for risk characterization, as cited from PMRA (2014) and other sources.

In carcinogenicity studies, mice and rats orally administered ETU exhibit thyroid tumours with a clear mode of action, i.e., neoplasia of thyroid follicular cells due to increased secretion of thyroid stimulating hormone (TSH) from the pituitary. TSH production occurs in response to chronic inhibition of thyroid peroxidase by ETU, resulting in decreased thyroid hormone production. In mice, chronic exposure to ETU has also resulted in pituitary gland neoplasia and liver adenomas and carcinomas. Using the most sensitive tumour (i.e., liver tumour induction in female mice), Health Canada previously derived an oral cancer slope factor of 0.06 mg/kg-bw per/day and indicated a lack of evidence to support a threshold mode of action for this effect (PMRA 2014). The US EPA has classified ETU as a probable human carcinogen (Group 2B) and calculated an oral cancer slope factor of 0.11 $(mg/kg\ per\ day)^{-1}$ (US EPA 2000). On the basis of thyroid gland tumours in CD rats, other groups have derived oral cancer slope factors for ETU ranging from 0.006 $(mg/kg\text{-}bw\ per\ day)^{-1}$ (Frakes 1988) to 0.045 $(mg/kg\text{-}bw\ per\ day)^{-1}$ (OEHHA 2009).

In a short-term feeding assay, F344/N rats were administered 0, 83 and 250 ppm ETU in food. A lowest-observed-adverse-effect level (LOAEL) of approximately 4.15 mg/kg-bw/day was calculated (on the basis of 83 ppm in food), where after 7 days of exposure to ETU, female rats exhibited a statistically significant increase in thyroid hyperplasia, male rats exhibited increased plasma TSH and a statistically significant increase in relative thyroid weight, and all rats exhibited statistically significant follicular cell labelling (indicating cell proliferation in the thyroid) and statistically significant decreased plasma T_4 (Elcombe et al. 2002). This LOAEL is lower than those identified for developmental effects in other studies (NTP 1992) and is considered to be appropriate for risk characterization following a single day exposure.

Maranghi et al. (2013) reported endocrine and reproductive effects from exposure of pregnant Sprague Dawley (SD) rats to ETU. SD rat dams were exposed to 0, 0.1, 0.3 and 1.0 mg/kg-bw per day of ETU via oral gavage from gestational days (GD) 7 to 20 and during post-natal days (PND) 1 to 22. Dams exhibited statistically significant effects at the lowest dose (0.1 mg/kg-bw/day) including all of the following: increased frequency of deliveries before GD 22, increased body weight gain between GD 7 and GD 21 (but with normal food consumption), increased food consumption and decreased body weight gain from PND 1 to PND 23, and increased relative thyroid weight at PND 23. Non-statistically significant effects at 0.1 mg/kg-bw/day included an increase in the number of dams having stillborns (3 of 14 dams vs. 0 of 11 control dams) and increased absolute thyroid weights. On PND 1, dams in the low dose group had statistically significant decreased serum levels of T3 and T4 and a trend to reduced TSH levels. By PND 23, serum levels of T3 and T4 were normal, but TSH was elevated and statistically significant. Thyroid histology at PND 23 showed effects that exhibited dose-dependency and were statistically significant at higher doses, including increased vacuolization of epithelial cells, reduction in the size of the follicular lumen, reduction and/or absence of colloid in these same follicles and increased pyknotic nuclei. These changes were supported by histomorphometric analysis that showed decreases in follicle and colloid area and increases in follicular epithelium height. Rat pups (F1 generation; potentially

exposed to ETU in utero and via breast milk) were orally gavaged from PND 23 to PND 60 (males) and from PND 23 to PND 70 (females) with the same dose levels that dams received. Pups were followed after birth and exhibited statistically significant early incisor eruption, ear pinna detachment and eye opening. At PND 23, male and female pups showed the same, but less severe, changes in thyroid histology as exposed dams. Subsequent direct dosing of male pups with ETU from PND 23 to PND 60 exacerbated these low dose cellular effects on the thyroid, and dosing of female pups exacerbated increases in pyknotic nuclei and reductions in follicular colloid at the lowest dose. As adults, the F1 females exhibited statistically significant effects from low dose (0.1 mg/kg-bw/ day) ETU exposure including dose-dependent reduction in number of estrous cycles measured over the period from PND 55 to PND 70 (1.4 vs. 3.1 in control), increased estrous cycle length (10 vs. 4.8 in control) and reduced days in proestrus (2.8 vs. 3.9 in control). The use of 0.1 mg/kg-bw per day as a point of departure is considered to be protective for the characterization of risks resulting from short duration exposures (10 to 30 days) to ETU.

4.3.3 Characterization of risk to human health

Products available to consumers

Dermal exposure to the general population was considered in order to characterize risk to human health from potential ETU exposure from rubber (neoprene-based) products.

Potential dermal exposures to ETU from wearing a neoprene-based wetsuit were considered relative to short-term health effects of ETU identified in laboratory animals. Pregnant women and children were assessed for single and multiple (10 and 30 days) exposures from wearing a neoprene-based wetsuit for 8 hours. Daily exposure was considered to be a function of the ETU concentration remaining in the wetsuit on a given day.

For a single day exposure from a wetsuit, a pregnant woman was considered to be exposed to 2.4×10^{-4} mg/kg-bw of ETU. Comparison with an effect level of 4.15 mg/kg-bw/day identified on the basis of thyroid effects in rats exposed to ETU over 7 days results in a margin of exposure (MOE) of 17300. This MOE is considered adequate to account for uncertainties in health effects and exposure databases.

For a single day exposure from a wetsuit, a child was considered to be exposed to 3.15×10^{4} mg/kg-bw/day of ETU. Comparison with an effect level of 4.15 mg/kg-bw/day identified on the basis of thyroid effects in rats exposed to ETU over 7 days results in an MOE of 13180. This MOE is considered adequate to account for uncertainties in health effects and exposure databases.

For children and pregnant women that may wear a neoprene-based wetsuit over the course of several days, exposure to ETU was considered for 10 and 30 days of wear. The resulting amortized daily systemic doses of ETU were determined to be 6.0×10^{-5}

and 2.0×10^{-5} mg/kg-bw/day, respectively, for adults and 8.0×10^{-5} and 3.0×10^{-5} mg/kg-bw/day, respectively, for children. Comparison with an oral LOAEL of 0.1 mg/kg-bw/day identified on the basis of thyroid effects in rats orally exposed during pregnancy and lactation results in margins of exposure of 1670 and 4970, respectively, for adults and 1250 and 3330, respectively, for children. These MOEs are considered adequate to account for uncertainties in health effects and exposure.

Regarding the potential risk of carcinogenicity, the highest derived amortized daily exposure to ETU associated with wearing a neoprene wetsuit for 30 days per ETU (2.16×10^{-6} mg/kg-bw per day for children) was multiplied by the oral slope factor of 0.06 $(\text{mg/kg-bw per day})^{-1}$ derived by PMRA on the basis of liver tumours in female mice, resulting in a risk level of 1.3×10^{-7} (approximately 1 in 7.7 million). It should be recognized that this value is an overestimate of true daily lifetime exposure and risk, as the majority of the lifetime exposures would occur as an adult, where calculated daily exposures are lower due to differences in skin surface area and body weight between children and adults.

Risk to human health is therefore considered to be low for dermal exposure to ETU from rubber and neoprene-based products.

While exposure of the general population to ETU is not of concern at current levels, this substance is considered to have a health effect of concern because of its potential carcinogenicity. Therefore, there may be a concern for human health if exposures were to increase.

5. Methenamine

5.1 Sources and uses

Methenamine does not occur naturally in the environment. It is produced by the reaction of formaldehyde and ammonia in water at low pressure. According to information submitted pursuant to a survey under section 71 of CEPA (Canada 2012), between 100 000 and 1,000 000 kg of methenamine were manufactured in Canada in 2011 and between 100 000 and 1 000 000 kg were imported into Canada that same year.[6] In the United States, the national production volume (production and import) for methenamine was approximately 42.2 million kg (approximately 93 million pounds) for the year 2012 (CDAT 2015).

[6] Values reflect quantities reported in response to a survey conducted under section 71 of CEPA (Canada 2012). See survey for specific inclusions and exclusions (Schedules 2 and 3).

The main reported use of methenamine is as a cross-linking agent resins and in rubber production. The substance is consumed in this use, which accounts for approximately 95% of the substance in commerce. These resins are used primarily for wood materials and wood adhesives (ECHA 2008; OECD 2007; AGDH 2016a). They are also used in coatings, binders/refractories, auto parts, and manufactured items with consumer products, including toys, sporting goods, seals and tubing adhesives (ECHA 2008; AGDH 2016a). About 3% is used as a chemical intermediate in nitration reactions for explosives production (ECHA 2008; AGDH 2016a). The production of fuel tablets accounts for 2% of methenamine volumes (ECHA 2008; AGDH 2016a). Additional information on uses in Canada is presented in Table 5-1.

Table 5-1. Additional uses in Canada for methenamine

Use	Methenamine
Food additive[a]	No
Food packaging materials[a]	Yes
Drug Products Database[b]	No
Natural Health Products Ingredients Database[c]	Yes
Licensed Natural Health Products Database being present as a medicinal or non-medicinal ingredient in natural health products in Canada[c]	Yes
List of Prohibited and Restricted Cosmetic Ingredients[d]	No
Notified to be present in cosmetics, based on notifications submitted under the Cosmetic Regulations to Health Canada[d]	Yes
Formulant in pest control products registered in Canada[e]	Yes

[a] Email communication from Food Directorate to Existing Substances Risk Assessment Bureau; unreferenced.
[b] Email communication from Therapeutic Products Directorate to Existing Substances Risk Assessment Bureau; unreferenced.
[c] Email communication from Natural and Non-prescription Health Products Directorate to Existing Substances Risk Assessment Bureau; unreferenced.
[d] Email communication from Consumer Product Safety Directorate to Existing Substances Risk Assessment Bureau; unreferenced.
[e] Email communication from Pest Management Regulatory Agency to Existing Substances Risk Assessment Bureau; unreferenced.

Notifications submitted under the Cosmetic Regulations to Health Canada indicate that methenamine is used in certain cosmetic products in Canada with an upper concentration of 0.3% (personal communication, November 2015 email from the Consumer Product Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada; unreferenced). Methenamine is listed in the Natural Health Products Ingredients Database (NHPID) with a medicinal role as it is

classified as a natural health product (NHP) substance falling under item 2 (an isolate) of Schedule 1 to the Natural Health Products Regulations (NHPR), as well as with a non-medicinal role for topical use only as preservative antimicrobial in NHPs, up to 0.16% according to CIR (1992) (NHPID 2017). Methenamine is listed in the Licensed Natural Health Products Database (LNHPD) as “a medicinal or non-medicinal ingredient in a limited number of currently licensed NHPs; not used in any other currently registered drugs” (DPD 2015; LNHPD 2017).

Methenamine has been identified as a component in the manufacture of a variety of food packaging materials, including paint, ink and adhesives that do not come in contact with food. It has also been identified for use as a component in preservatives and fungicides used in the manufacture of some food contact materials, including paper and paperboard and resins (personal communication, November 2015 email from the Food Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada; unreferenced).

Information from the American Cleaning Institute’s (ACI) website suggested use of methenamine in household cleaning products, including all purpose liquid cleaners, dish detergents, laundry detergents and laundry pre-treatment products, and in laundry fabric conditioners. Follow up with ACI on this confirmed that as of 2012, ACI found only three products (wrinkle and stain removers) in the United States that contained morpholine. For methenamine, ACI found that methenamine was not an ingredient in cleaning products but it may be found as a by-product of some preservatives that may be used in cleaning products at low levels. In those cases, methenamine is not expected to be present in cleaning products at greater than 0.05%. To determine the Canadian disposition for this product class, information was sought from the Canadian Consumer Specialty Products Association (CCSPA). CCSPA surveyed its members and reported back that methenamine and morpholine have very limited use in household cleaning products in Canada.

5.2 Potential to cause ecological harm

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

Methenamine has been classified as having high potential for exposure on the basis of potential emission rates. This substance has been classified as presenting a low ecological hazard and a low potential for ecological risk. It is unlikely that it results in concerns for organisms or the broader integrity of the environment in Canada.

5.3 Potential to cause harm to human health

5.3.1 Exposure assessment

In considering environmental media, according to the Mackay model (level 1), water is the target compartment for methenamine (100%) in the environment (ECHA 2008). Under atmospheric conditions, methenamine has a half-life of 45 minutes because of reaction with the OH radical (ECHA 2008). It is highly water soluble and, upon reaching the aqueous environment, is degraded hydrolytically to ammonium and formaldehyde (ECHA 2008). Thus, exposure to methenamine from environmental media is expected to be low.

Dietary exposure to methenamine from its use as a component in the manufacture of food packaging results in an estimated probable daily intake of 0.00188 mg/kg-bw (personal communication, November 2015 email from the Food Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada; unreferenced).

General population exposure to methenamine may occur from the daily use of cosmetics, in which it is used as a preservative, with reported concentrations in six products of less than 0.3%. Product testing for methenamine in 24 household cleaning products, including laundry soaps/softeners, all-purpose cleaners, stain removers, soaps and shampoos, found low amounts in a shampoo and a laundry softener, with percentages of less than 0.08% (CPSD 2016b).

The highest repeated dermal exposure to methenamine is expected to occur from the daily use of cosmetics. This exposure was estimated on the basis of the use of body cream with a reported upper-limit of 0.3% methenamine. The mean use frequency considered was 1.1 times per day with 4.4 grams per application. Dermal exposure was determined to be 0.205 mg/kg-bw/day (1.1 events/day × 4.4 g body cream/event × 0.3% methenamine in body cream) (Lorentz 2005; Health Canada 1998).

5.3.2 Health effects assessment

Methenamine was reviewed internationally (ECHA 2008; OECD 2007), and these reviews were used to inform the health effects characterization in this draft screening assessment. On the basis of classifications by other national or international agencies for carcinogenicity, genotoxicity, developmental toxicity and reproductive toxicity, methenamine was not identified as posing a high hazard to human health nor is it identified on the ECHA's Candidate List of Substances of Very High Concern for Authorisation (ECHA [modified 2015]).

Critical effects for methenamine are potential for dermal sensitization at high doses (ECHA 2008; OECD 2007). In a local lymph node assay, methenamine had a positive effective concentration (EC3) of 30.6%, whereas the same study showed an EC3 of

0.96% for formaldehyde. It was suggested that formaldehyde is responsible for the potential sensitizing properties of methenamine (ECHA 2008). Developmental effects have been observed in beagle dogs (LOAEL = 31 mg/kg-bw/day in food; NOAEL = 15 mg/kg-bw/ day), including lower pup birth weights and increased mortality by the first month (Hurni and Ohder 1973; ECHA 2008). However, this study is of limited utility as one dog had to be sacrificed after a fight, and pups were treated differently (some were fed cows milk while others were not). Also, much higher doses (1000 mg/kg-bw/day) are required to produce similar developmental effects in rats, and doses of 1500 to 2500 mg/kg-bw/day are considered to have no effect on rat fertility (OECD 2007). Women administered methenamine as a therapeutic treatment for urinary infections at approximately 13 and 27 mg/kg-bw/day during pregnancy showed no apparent adverse effects on fetal development or birth outcomes (ECHA 2008). Noting the deficiencies in the beagle dog study, ECHA 2008 recommended the use of 27 mg/kg-bw/day as a human-derived NOAEL for risk assessment of developmental toxicity.

Methenamine is also used as an oral therapeutic for its urinary antibacterial effect. Maintenance doses up to 57 mg/kg-bw/day for weeks or months did not give rise to adverse effects in humans other than a low rate of gastrointestinal disturbances. Higher oral doses of methenamine of approximately 114 mg/kg-bw have been administered to humans for therapeutic purposes for 3 to 4 weeks; at this level of exposure, bladder irritation, painful and frequent micturition, albuminuria and haematuria have been noted. ECHA (2008) recommended the use of 57 mg/kg-bw/day as a human-derived NOAEL for use in repeated dose risk characterization. The systemic availability of methenamine after oral administration was assumed to be 100% by ECHA (2008).

5.3.3 Characterization of risk to human health

The risk from environmental media is expected to be low because of short atmospheric half-lives and hydrolytic degradation to ammonium and formaldehyde in aqueous media, which limit environmental concentrations.

The general population may be dermally exposed to methenamine from a variety of products including cosmetics and some cleaning products. Dermal exposure to methenamine from cosmetic products was estimated using body cream with an external applied dose determined to be 0.205 mg/kg-bw/day. This dermal exposure scenario is expected to cover any other consumer product exposures, as well as to the topical NHP listed in the LNHPD as containing methenamine as a non-medicinal ingredient. Oral and topical NHPs listed in the LNHPD as containing methenamine as a medicinal ingredient were subject to safety and efficacy assessment based on their recommended conditions of use prior to licensing in accordance with the NHPR. On the basis of the 50% dermal absorption rate reported in ECHA (2008), the systemic exposure from use of cosmetics was determined to be 0.102 mg/kg-bw/day. Comparison of this exposure to the human-derived developmental oral NOAEL of 27 mg/kg-bw/day results in a MOE of 265. This MOE is considered adequate to address uncertainties in health effects and exposure databases. It is noted that some individuals may be sensitive to methenamine (and/or

its breakdown products formaldehyde and ammonia), and sensitization reactions may occur from certain topical products. A safety assessment conducted on cosmetic uses found methenamine to be safe at concentrations up to 0.16%, as less than 0.2% formaldehyde would be released (CIR 1992). However, the maximum concentration noted in cosmetics of 0.3% is approximately 100-fold lower than the EC3 of 30.6%.

Potential daily dietary intake of methenamine from its use in the manufacture of food packaging materials was determined to be 0.00188 mg/kg-bw/day. Comparison with the human-derived developmental NOAEL of 27 mg/kg-bw/day results in a MOE of 14400. Oral exposures from food packaging are therefore not considered to be a risk to human health.

Exposure of the general population to methenamine is therefore considered to be of low risk to human health.

6. Morpholine

6.1 Sources and uses

Morpholine does not occur naturally in the environment. It is typically produced by the reaction of diethylene glycol with ammonia in the presence of hydrogen and catalysts (IPS 1995). According to information submitted pursuant to section 71 survey under CEPA (Canada 2012), between 1 000 and 10 000 kg of morpholine were manufactured in Canada in 2011 and between 100 000 and 1 000 000 kg were imported into Canadathat same year.[7] In the United States, the national production volume (production and import) for methenamine was between 4.5 and 45 million kg (10 and 100 93 million pounds) for the year 2012 (CDAT 2015).

A large amount of morpholine is used as an intermediate in the production of rubber accelerators, pharmaceuticals, pesticides, optical brighteners, and antioxidants and as an industrial solvent (Huntsman 2015; BASF 2016). Morpholine is also used in closed-water or steam systems to prevent corrosion and as a petroleum production chemical (IARC 1999). A variety of other industrial uses include adhesive and binding agents, tanning agents, surface treatments, emulsifiers, solvents for resins and waxes, reducing agents, process regulators, lubricants, hydraulic fluids, cutting fluids, colouring and anti-condensation agents (AGDH 2016b). Additional information on uses in Canada is presented in Table 6-1.

[7] [7] Values reflect quantities reported in response to a survey conducted under section 71 of CEPA (Canada 2012). See survey for specific inclusions and exclusions (schedules 2 and 3).

Table 6-1. Additional uses in Canada for morpholine

Use	Morpholine
Food (other)[a]	Yes
Food packaging materials[a]	Yes
Drug Products Database[b]	Yes
Natural Health Products Ingredients Database[c]	Yes
Licensed Natural Health Products Database being present as a medicinal or non-medicinal ingredient in natural health products in Canada[c]	No
List of Prohibited and Restricted Cosmetic Ingredients[d]	No
Notified to be present in cosmetics, based on notifications submitted under the Cosmetic Regulations to Health Canada[d]	No
Formulant in pest control products registered in Canada[e]	Yes

[a] Email communication from Food Directorate to Existing Substances Risk Assessment Bureau; unreferenced.
[b] Email communication from Therapeutic Products Directorate to Existing Substances Risk Assessment Bureau; unreferenced.
[c] Email communication from Natural and Non-prescription Health Products Directorate to Existing Substances Risk Assessment Bureau; unreferenced.
[d] Email communication from Consumer Product Safety Directorate to Existing Substances Risk Assessment Bureau; unreferenced.
[e] Email communication from Pest Management Regulatory Agency to Existing Substances Risk Assessment Bureau; unreferenced.

Morpholine is listed as a formulant by PMRA in pest control products (personal communication, November 2015 email from the Risk Management Bureau, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada; unreferenced). Morpholine has been identified for use as an emulsifier in the preparation of wax coatings for fresh produce, such as apples (Health Canada 2002). Morpholine can be used as a component in the manufacture of certain food packaging materials, such as interior coatings. Incidental additives, such as boiler water additives, can also contain morpholine (personal communication, November 2015 email from the Food Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada; unreferenced). Morpholine is a non-medicinal ingredient in disinfectant drugs which are typically, but not exclusively, marketed to commercial facilities, such as hospitals or food premises (DPD 2015). It is listed without any role in the NHPID, and it is not listed in the LNHPD as being present in currently licensed NHPs (LNHPD 2017; NHPID 2017).

Morpholine is used in some consumer products, such as floor waxes and polishes. Additionally there are several auto care products to which the general population could

be exposed, such as car waxes, wax-based surface cleaners and tire products (CPID 2016).

6.2 Potential to cause ecological harm

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

On the basis of the low hazard and low exposure classifications determined for morpholine using the ERC approach, this substance was classified as having a low potential for ecological risk. It is therefore unlikely that this substance results in concerns for organisms or the broader integrity of the environment in Canada.

6.3 Potential to cause harm to human health

6.3.1 Exposure assessment

Environmental media exposures to morpholine could occur through fugitive air emissions and on-site land disposal (OECD 2013). Level III fugacity modelling, using loading rates of 1 000 kg/h each for air, soil and water, shows the following percent distribution when morpholine is released simultaneously to all three compartments: 0.4% to air; 41.7% to water; 57.9% to soil; and 0.09% to sediment (OECD 2013). After evaporation or exposure to the atmosphere, indirect photo-oxidation of morpholine is expected to occur by reaction with OH-radicals with a half-life of 0.9 hours (OECD 2013). Morpholine is considered resistant to hydrolysis because it does not contain labile functional groups. Therefore, hydrolysis is not expected under environmental conditions (OECD 2013). Multi-site environmental monitoring in lake water near an Ontario nuclear plant that uses morpholine in its cooling water system was considered (OPG 2014). Fifteen water samples were collected at various distances and depths in the vicinity of Darlington Nuclear Station, and all were below the detection limit of 1.0 ug/L and met the Ontario Ministry of the Environment interim provincial water quality objective of 4 ug/L (OPG 2014; MOEE 1994). Morpholine is considered readily biodegradable (92.6% in 22 days) after a lag phase of 15 days and will assist in limiting soil and water concentration (OECD 2013).

Exposure to morpholine by the general population is expected to be limited to a small number of consumer products, primarily home and auto polishes/waxes and related auto care products. Other products with incidental direct exposure include radiator leak stop, corrosion inhibitors as well as disinfectant drugs in which morpholine is used as a non-medicinal ingredient.

Several auto care products that could reasonably be expected to be used by the general public contain morpholine, including car waxes (<5%), surface cleaners (<3%), and tire care products (<1%). The primary route of exposure is expected to be dermal

as it is assumed that these products are used outdoors and/or in a garage. Inhalation is expected to contribute a very small fraction of the overall exposure because of the high rate of air flow, the viscous matrices of these products, and the moderate vapour pressure of morpholine. To assess the potential for harm to human health from dermal exposure to these products during use, a thin-film approach as outlined in the EPA-Versar document (US EPA 2011) was used. It was assumed that exposure from handling a cloth coated in the product can be described as a thin film. This approach characterizes the dermal deposition from a mineral oil substance following handling of a rag saturated with the oil material, i.e., the mineral oil thickness ("thin film") estimated to remain on the skin after wiping is 1.64×10^{-3} cm. This thickness was therefore assumed to apply to morpholine for characterizing dermal exposure for the application of the auto care products. Assuming equal density of morpholine and the whole product of 1010 mg/cm^3 and an exposed skin surface area of 455 cm^2 (half of both hands/palms), the dermal load was estimated to be 75.4 mg per 60-minute exposure event using car wax, the product with the highest reported morpholine concentration of 5%. Using the selected body weight of 70.9 kg (considered to be representative of an average Canadian adult) (Health Canada 1998), dermal exposure was estimated to be 0.53 mg/kg-bw/event.

Exposure to morpholine can occur from use of floor waxes formulated with morpholine at 1 to 2%, from over-the-counter disinfectant sprays with morpholine concentrations ranging from 0.15% to 0.64%, or from glass cleaners formulated with less than 0.5%. Dermal exposures from these products are expected to be covered by the previously described auto care scenario. Inhalation exposure to morpholine from floor wax and aerosol disinfectant sprays was estimated using algorithms and recommended defaults developed by RIVM (2006) and presented in the Cleaning Products Fact Sheet. The highest exposure scenario identified was for the use of floor wax. Using the default parameters for a water-based floor polish with evaporation occurring from an increasing area, the largest mean event concentration was determined to be 0.078 mg/m^3 for 90 minutes of exposure.

Health Canada assessed the safety of morpholine for its use in wax coating compounds for apples (Health Canada 2002). In that assessment, exposure of children and adults to morpholine was estimated to be approximately 8% and 5%, respectively, of Health Canada's acceptable daily intake (ADI) of 0.48 mg/kg bw/day. Compared to these uses, food packaging applications are not considered to be a significant source of dietary exposure to morpholine (personal communication, November 2015 and October 2016 emails from the Food Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada; unreferenced).

6.3.2 Health effects assessment

The Organization for Economic Cooperation and Development (OECD 2013), IARC (1999) and Health Canada's Food Directorate (Health Canada 2002; and supplemental report available upon request) summarized the health effects literature and characterized hazard for morpholine. These reports were used to inform the health effects characterization in this draft screening assessment, and the critical endpoints and corresponding effect levels for morpholine, are summarized below. A literature search was conducted from the year prior to the OECD Cooperative Chemicals Assessment Programme (CoCAM 5) assessment (OECD 2013) to July 2016. No health effects studies, which could impact the risk characterization (i.e., result in different critical endpoints or lower points of departure than those stated in OECD 2013), were identified.

A short-term, repeated inhalation exposure study was conducted in rats via whole body exposure. Animals were exposed to 80 mg/m^3 morpholine for 4 hours a day for 2, 4 or 8 days. This exposure level, based on 4 days of exposure, was established as the critical effect level on the basis of thyroid gland hypersecretion, as indicated by histological analysis and by increased ^{131}I (radioisotope of iodine) uptake (OECD 2013).

A chronic oral toxicity study was conducted in mice via drinking water. Animals had access to water containing 0, 2 500 or 10 000 mg/L of morpholine oleic acid salt for 96 weeks, and an absence of adverse effects were noted (Shibata et al. 1987). In setting an ADI for morpholine, Health Canada (2002) identified this as a key study, and a NOAEL of 96 mg/kg-bw/day was determined assuming complete dissociation of the morpholine salt in animals at the 2 500 mg/L exposure level. Using this NOAEL and several safety factors, an acceptable daily intake (ADI) of 0.48 mg/kg-bw per day was established. Absorption is assumed to be 100%, as indicated by animal studies showing that high levels (80-93%) of the orally administered radioactivity from ^{14}C-morpholine-HCl were excreted in the urine with minimal excretion in the feces (<2%) (Health Canada 2002).

In reproductive studies, morpholine did not cause developmental effects at the highest dose tested (225 mg/kg-bw/day). An unpublished prenatal developmental study was conducted in rat dams via the oral route of exposure. Animals were exposed to morpholine for 14 days (GD 6-19) at 75, 250 or 1000 mg/kg-bw/day. A maternal LOAEL of 250 mg/kg-bw/day was identified on the basis of mild regenerative anemia and increased liver weights. At 75 mg/kg-bw/day, there were fetal skeletal variations in the absence of maternal toxicity, including statistically significant increases in the mean number of fetuses with incomplete ossification of parietal bone and skull. The percentage of fetuses with the effect positively correlated with dose, and at the next dose level (250 mg/kg-bw/day), the prevalence of incomplete ossification was higher than the maximum observed in historical control data. This increase in skeletal variations (above the maximum observed in historical controls) therefore occurred in the

presence of maternal toxicity. As an outcome of the review, delayed ossification was not considered to be an adverse effect in this study (OECD 2013).

IARC considers morpholine a Group 3 carcinogen ('not classifiable as to its carcinogenicity to humans') as there was inadequate evidence to support carcinogenicity in animals, and no human data was available for review (IARC 1999). Additionally, Health Canada's HPFB (Health Canada 2002; supplemental data) described the low likelihood of formation of relevant quantities of N-nitrosomorpholine (possible human carcinogen) from the ingestion of low levels of morpholine, including considerations of pH and physiological and metabolic differences between rats and humans.

Morpholine was weakly positive in in vitro genotoxicity assays (in yeast and mammalian cells) but not in bacterial assays (IARC 1999; OECD 2013). Considering the weight of evidence from in vitro and in vivo studies, it was concluded that morpholine is not mutagenic (OECD 2013).

6.3.3 Characterization of risk to human health

Exposure to morpholine from environmental media could occur through fugitive air emissions, releases to water and on-site land disposal. Indirect photo-oxidation of morpholine is expected to occur by reaction with OH-radicals with a half-life of 0.9 hours (OECD 2013). Limited water samples in Ontario near a large industrial were all below the detection limit of 1.0 ug/L and met the Ontario Ministry of the Environment interim provincial water quality objective of 4 ug/L (OPG 2014; MOEE 1994). Additionally, morpholine is considered to be readily biodegradable and this will assist in limiting soil and water concentration (OECD 2013). Given these considerations and that there were not measurements above the limit of detection for morpholine in raw lake water the risk from environmental media is considered to be low.

In order to characterize risk to human health from products available to consumers, inhalation and dermal exposure estimates were developed for the use of various products that contain morpholine. The highest per event inhalation exposure of the general population to morpholine from product use was estimated to be 0.078 mg/m^3 from floor wax application. In rats, short-term inhalation of 80 mg/m^3 morpholine resulted in thyroid hypersecretion. Comparing this critical effect level with the exposure estimates for the general population results in an MOE of 1025. This margin is considered adequate to address uncertainties in health effects and exposure databases.

The highest per event estimate of dermal exposure of the general population to morpholine from product use was estimated to be 0.53 mg/kg-bw/event from car wax application. A 50% dermal absorption factor was applied considering the short duration (less than 1 hour) as was previously described in the Threshold of Toxicological Concern (TTC)-based Approach for Certain Substances science approach document

(Health Canada 2016), resulting in an estimated systemic exposure of 0.26 mg/kg-bw/event. Comparison of this exposure to an oral NOAEL of 96 mg/kg-bw per day results in an MOE of 370. This is considered adequate to address uncertainties in health effects and exposure databases. Therefore, risk is considered to be low.

Health Canada's previous health hazard assessment of morpholine use in wax coating compounds on apples concluded that dietary exposure from those uses did not pose a risk to human health.

Risk to human health from exposure to morpholine is therefore considered to be low.

7. CAS RN 4174-09-8

7.1 Sources and uses

CAS RN 4174-09-8 does not occur naturally in the environment. According to information submitted pursuant to a survey under section 71 of CEPA (Canada 2012), between 1 000 and 10 000 kg of this substance were imported into Canada in 2011, with none manufactured in Canada.[8] No information was available on quantities used internationally.

There is limited information on the uses of CAS RN 4174-09-8. It has approved uses in Europe, and information from European Union legislation indicates it is used to colour plastic materials and articles, varnishes and coatings. This substance is also reported to be closely related to CI Class Solvent Yellow 93 (EC 2004). Similar uses as a colouring agent in some food packaging materials, such as polystyrene, polycarbonate and polyethylene terephthalate (PET) plastics, were identified by Health Canada's Food Directorate. Examples include polystyrene lids and polycarbonate bottles (personal communication, November 2015 email from the Food Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada; unreferenced). No other uses were identified.

7.2 Potential to cause ecological harm

Critical data and considerations used to develop the substance-specific profiles for CAS RN 4174-09-8 and the hazard, exposure and risk classification results are presented in ECCC (2016b).

CAS RN 4174-09-8 was classified, on the basis of mode of action, as having a high hazard potential. ERC classified this substance as having low potential for risk because

[8] Values reflect quantities reported in response to a survey conducted under section 71 of CEPA (Canada 2011). See survey for specific inclusions and exclusions (Schedules 2 and 3).

of its low exposure potential; however, given the high hazard of the substance identified in ERC, significant increases in use quantities could result in risk. Considering current use patterns, it is unlikely that this substance results in concerns for organisms or the broader integrity of the environment in Canada.

Although current use patterns and quantities in commerce are not of concern at current levels, there may be concerns if quantities were to increase in Canada, given the ecological effects associated with this substance.

7.3 Potential to cause harm to human health

7.3.1 Exposure assessment

Exposure from environmental media is expected to be very low for air and water given the vapour pressure (2.4×10^{-14} at 25 °C) and limited water solubility (0.1814 g/L). Level III fugacity modelling suggests the substance will be found in sediment and soil (EPI Suite 2012). No data was found on concentrations of this chemical substance in the environment.

The probable daily intake of CAS RN 4174-09-8 resulting from its use in food packaging applications is estimated to be 0.0077 µg/kg-bw. However, migration from food packaging material (e.g. hard plastic matrix) is expected to be limited. Therefore, dietary exposure from uses of CAS RN 4174-09- in food packaging materials is expected to be negligible. No other exposures are expected given its limited use profile (email dated October 2016 from the Food Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada; unreferenced).

7.3.2 Health effects assessment

No health effects data were identified for CAS RN 4174-09-8. This substance is related to CI Class Solvent Yellow 93 (CAS RN 4702-90-3) (EC 2004)—which also has no health effects data registered with ECHA (2016)—in both chemical structure and use pattern.

7.3.3 Characterization of risk to human health

The general population may be exposed to CAS RN 4174-09-8 through food packaging material, but dietary exposure, if any, is expected to be negligible (email from the Food Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada; unreferenced). Therefore, risk to human health is considered to be negligible.

8. Uncertainties in evaluation of risk to human health

Overall confidence in the exposure and hazard databases for the four substances is moderate.

There is uncertainty for the durations and frequencies of exposure for all substances. However, given the conservative nature of the exposure scenarios, the risk characterization is not expected to underestimate risk.

There is a relative lack of dermal toxicity studies for ETU. There is some uncertainty in using an oral LOAEL of 0.1 mg/kg-bw/day to characterize risk of dermal exposure to ETU for the general population because some evidence supports reduced toxicity of ETU via the dermal route compared with the oral route of exposure. This endpoint is therefore considered to be conservative and supports the proposed conclusion.

There is uncertainty associated with systemic exposures to methenamine and morpholine from the dermal route due to the lack of dermal absorption studies.

There is uncertainty associated with CAS RN 4174-09-8 due to the lack of health effects data for this substance.

9. Conclusion

Considering all available lines of evidence presented in this draft screening assessment, there is low risk of harm to organisms and the broader integrity of the environment from ETU, methenamine, morpholine and CAS RN 4174-09-8. It is proposed to conclude that ETU, methenamine, morpholine and CAS RN 4174-09-8 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 draft screening assessment, it is proposed to conclude that ETU, methenamine, morpholine and CAS RN 4174-09-8 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 proposed to conclude that ETU, methenamine, morpholine and CAS RN 4174-09-8 do not meet the criteria set out in section 64 of CEPA.

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Appendices

Appendix A. Physical and chemical properties

Table A-1. Physical and chemical properties of ETU

Property	Value	Type of data	Reference
Melting point (^{o}C)	203	experimental	EPI Suite 2012
Boiling point (^{o}C)	347	experimental	EPI Suite 2012
Water solubility (g/L)	20 at 30 °C	experimental	EPI Suite 2012
Density (g/mL)	1.417	experimental	EPI Suite 2012
Vapour pressure (Pa)	0.00027 @ 25 °C	experimental	EPI Suite 2012
Henry's law constant (Pa m^3/mol)	1.36	modelled (bond method)	EPI Suite 2012
Henry's law constant (Pa m^3/mol)	3.36×10^{-7}	experimental	EPI Suite 2012
log K_{ow} (dimensionless)	-0.66	modelled	EPI Suite 2012
log K_{oc} (dimensionless)	1.113	modelled (MCI method)	EPI Suite 2012
log K_{oc} (dimensionless)	0.817	modelled (Kow method)	EPI Suite 2012

Abbreviations: K_{ow}, octanol–water partition coefficient; K_{oc}, organic carbon–water partition coefficient

Table A-2. Physical and chemical properties of methenamine

Property	Value	Type of data	Reference
Melting point (^{o}C)	65	experimental	EPI Suite 2012
Boiling point (^{o}C)	209	experimental	EPI Suite 2012
Water solubility (g/L)	449 at 12 °C	experimental	EPI Suite 2012
Density (g/mL)	1.27	experimental	EPI Suite 2012
Vapour pressure (Pa)	12.1 @ 25 °C	experimental	EPI Suite 2012
Henry's law constant (Pa m^3/mol)	1.65×10^{4}	modelled (bond method)	EPI Suite 2012
Henry's law constant (Pa m^3/mol)	1.66×10^{-4}	experimental	EPI Suite 2012
log K_{ow} (dimensionless)	-4.15	modelled	EPI Suite 2012
log K_{oc} (dimensionless)	1.000	modelled (MCI method)	EPI Suite 2012
log K_{oc} (dimensionless)	-1.632	modelled (Kow method)	EPI Suite 2012

Abbreviations: K_{ow}, octanol–water partition coefficient; K_{oc}, organic carbon–water partition coefficient

Table A-3. Physical and chemical properties of morpholine

Property	Value	Type of data	Reference
Melting point (°C)	-4.9	experimental	EPI Suite 2012
Boiling point (°C)	128	experimental	EPI Suite 2012
Water solubility (g/L)	1000	experimental	EPI Suite 2012
Density (g/mL)	1.007 @ 20 °C	experimental	EPI Suite 2012
Vapour pressure (Pa)	1060 @ 20 °C	experimental	EPI Suite 2012
Henry's law constant (Pa m^3/mol)	0.118	experimental	EPI Suite 2012

log K_{ow} (dimensionless)	0.86	modelled	EPI Suite 2012
log K_{oc} (dimensionless)	7.36	modelled (MCI method)	EPI Suite 2012

Abbreviations: K_{ow}, octanol–water partition coefficient; K_{oc}, organic carbon–water partition coefficient

Table A-4. Physical and chemical properties of CAS RN 4174-09-8

Property	Value	Type of data	Reference
Melting point (^{o}C)	282.3	modelled	EPI Suite 2012
Boiling point (^{o}C)	562.6	modelled	EPI Suite 2012
Water solubility (mg/L)	0.1814	modelled	EPI Suite 2012
Density (g/cm^3)	1.27	unknown	LookChem 2016
Vapour pressure (Pa)	2.4×10^{-14}@ 25 °C	modelled	EPI Suite 2012
Henry's law constant (Pa m^3/mol)	7.19×10^{-19}	experimental	EPI Suite 2012
log K_{ow} (dimensionless)	5.25	modelled	EPI Suite 2012
log K_{oc} (dimensionless)	5.16	modelled (MCI)	EPI Suite 2012

Abbreviations: K_{ow}, octanol–water partition coefficient; K_{oc}, organic carbon–water partition coefficient

Appendix B. Exposure to ETU from consumer products

Table B-1. Mass transfer from neoprene to estimate dermal exposure for adults

Day	Migration Rate ($mg/cm^2/hr$)	Mass Transferred In (mg)	Mass Transferred Out (mg)	Final Mass (mg)	New Concentration (mg/kg)
1	2.79E-07	0.03782	0.03782	0.11446	0.05047
2	1.68E-07	0.02278	0.02278	0.06890	0.03038
3	1.01E-07	0.01371	0.01371	0.04148	0.01829
4	6.10E-08	0.00825	0.00825	0.02497	0.01101
5	3.67E-08	0.00497	0.00497	0.01503	0.00663
6	2.21E-08	0.00299	0.00299	0.00905	0.00399
7	1.33E-08	0.00180	0.00180	0.00545	0.00240
8	8.01E-09	0.00108	0.00108	0.00328	0.00145
9	4.82E-09	0.00065	0.00065	0.00197	0.00087
10	2.90E-09	0.00039	0.00039	0.00119	0.00052
11	1.75E-09	0.00024	0.00024	0.00072	0.00032
12	1.05E-09	0.00014	0.00014	0.00043	0.00019
13	6.33E-10	0.00009	0.00009	0.00026	0.00011
14	3.81E-10	0.00005	0.00005	0.00016	0.00007
15	2.29E-10	0.00003	0.00003	0.00009	0.00004
16	1.38E-10	0.00002	0.00002	0.00006	0.00002
17	8.31E-11	0.00001	0.00001	0.00003	0.00002
18	5.01E-11	0.00001	0.00001	0.00002	0.00001
19	3.01E-11	0.00000	0.00000	0.00001	0.00001
20	1.81E-11	0.00000	0.00000	0.00001	0.00000
21	1.09E-11	0.00000	0.00000	0.00000	0.00000
22	6.57E-12	0.00000	0.00000	0.00000	0.00000
23	3.96E-12	0.00000	0.00000	0.00000	0.00000
24	2.38E-12	0.00000	0.00000	0.00000	0.00000
25	1.43E-12	0.00000	0.00000	0.00000	0.00000
26	8.63E-13	0.00000	0.00000	0.00000	0.00000
27	5.20E-13	0.00000	0.00000	0.00000	0.00000
28	3.13E-13	0.00000	0.00000	0.00000	0.00000
29	1.88E-13	0.00000	0.00000	0.00000	0.00000
30	1.13E-13	0.00000	0.00000	0.00000	0.00000

Table B-2. Parameters for derivation of exposure and risk for ETU from neoprene for adults

Parameter	Adult
Skin surface area minus head (cm^2)	16925
Body weight (kg)	70.9
Initial ETU concentration (mg/kg)	0.0838
Initial mass of suit (kg)	2.268
Initial ratio	300,000-1
Initial migration rate ($mg/cm^2/hr$)	2.793E-07
Initial mass of ETU in suit (mg)	0.1901
Total mass extracted (mg)	0.095050
45% dermally absorbed (mg)	0.042772
Amortized over a year (mg/day)	0.000117
Dose for adult (mg/kg-bw-day	1.65E-06
Unit risk (unitless)	9.92E-08

Table B-3. Mass transfer from neoprene to estimate dermal exposure for children

Day	Migration Rate ($mg/cm^2/hr$)	Mass Transferred In (mg)	Mass Transferred Out (mg)	Final Mass (mg)	New Concentration (mg/kg)
1	2.79E-07	0.01888	0.01888	0.05723	0.05047
2	1.68E-07	0.01137	0.01137	0.03449	0.03041
3	1.01E-07	0.00685	0.00685	0.02078	0.01833
4	6.11E-08	0.00413	0.00413	0.01252	0.01104
5	3.68E-08	0.00249	0.00249	0.00755	0.00665
6	2.22E-08	0.00150	0.00150	0.00455	0.00401
7	1.34E-08	0.00090	0.00090	0.00274	0.00242
8	8.05E-09	0.00054	0.00054	0.00165	0.00146
9	4.85E-09	0.00033	0.00033	0.00099	0.00088
10	2.92E-09	0.00020	0.00020	0.00060	0.00053
11	1.76E-09	0.00012	0.00012	0.00036	0.00032
12	1.06E-09	0.00007	0.00007	0.00022	0.00019
13	6.40E-10	0.00004	0.00004	0.00013	0.00012
14	3.86E-10	0.00003	0.00003	0.00008	0.00007
15	2.32E-10	0.00002	0.00002	0.00005	0.00004
16	1.40E-10	0.00001	0.00001	0.00003	0.00003
17	8.44E-11	0.00001	0.00001	0.00002	0.00002
18	5.08E-11	0.00000	0.00000	0.00001	0.00001
19	3.06E-11	0.00000	0.00000	0.00001	0.00001
20	1.85E-11	0.00000	0.00000	0.00000	0.00000
21	1.11E-11	0.00000	0.00000	0.00000	0.00000

22	6.70E-12	0.00000	0.00000	0.00000	0.00000
23	4.04E-12	0.00000	0.00000	0.00000	0.00000
24	2.43E-12	0.00000	0.00000	0.00000	0.00000
25	1.47E-12	0.00000	0.00000	0.00000	0.00000
26	8.84E-13	0.00000	0.00000	0.00000	0.00000
27	5.33E-13	0.00000	0.00000	0.00000	0.00000
28	3.21E-13	0.00000	0.00000	0.00000	0.00000
29	1.93E-13	0.00000	0.00000	0.00000	0.00000
30	1.17E-13	0.00000	0.00000	0.00000	0.00000

Table B-4. Parameters for derivation of exposure and risk for ETU from neoprene for children

Parameter	Children (Age 5 to 12)
Skin surface area minus head (cm^2)	8450
Body weight (kg)	27
Initial ETU concentration (mg/kg)	0.0838
Initial mass of suit (kg)	1.134
Initial ratio	300,000-1
Initial migration rate ($mg/cm^2/hr$)	2.793E-07
Initial mass of ETU in suit (mg)	0.0950