Draft Screening Assessment

Glycine, N,N-bis(carboxymethyl)-, trisodium salt

(Na_3NTA)

Chemical Abstracts Service Registry Number 5064-31-3

Environment Canada
Health Canada

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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 of glycine, N,N-bis(carboxymethyl)-, trisodium salt, hereinafter referred to as Na_3NTA, derived from its more commonly used name nitrilotriacetic acid trisodium salt. The Chemical Abstracts Service Registry Number (CAS RN[1]) for Na_3NTA is 5064-31-3. This substance was identified as a priority for assessment as it met categorization criteria under subsection 73(1) of CEPA.

According to the information submitted in response to a CEPA section 71 survey, 932 414 kg of Na_3NTA were imported into Canada in 2011 and there were no reports of manufacture of Na_3NTA in Canada above the reporting threshold of 100 kg. Reported uses in Canada include water treatment, cleaning and furnishing care, food packaging, paper products, fabric, textile and leather articles, personal care, photographic supplies, film and photochemicals, agricultural products, and metal chelation. Na_3NTA is used in products available to consumers, which mainly include cleaning products and cosmetics. Na_3NTA was also identified as an ingredient in disinfectant products. Additionally, Na_3NTA may be a component in cleaners and detergents used in food processing establishments, and has been identified as a formulant in pest control products registered in Canada.

The ecological risk of Na_3NTA was 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 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, Na_3NTA is considered unlikely to be causing ecological harm.

Considering all available lines of evidence presented in this draft screening assessment, there is low risk of harm to the environment from Na_3NTA. It is proposed to conclude that Na_3NTA does not meet the criteria under paragraphs 64(*a*) or (*b*) of CEPA as it is not entering the environment in a quantity of concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its

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biological diversity, or that constitute or may constitute a danger to the environment on which life depends.

The predominant sources of exposure to Na_3NTA from products available to consumers in Canada are cleaning products (wood floor cleaning liquid, wood floor polishing spray, boat cleaner) and cosmetics (hair dye, face moisturizer). There is also potential for exposure to Na_3NTA for the general population from drinking water.

The health effects dataset for Na_3NTA has been reviewed by the European Union , the European Commission's Scientific Committee on Consumer Safety and the Australian Government. The health effects data set for Na_3NTA has also been reviewed by Environment and Climate Change Canada and Health Canada as part of the assessment of NTA, as Na_3NTA and NTA both dissociate to release nitrilotriacetate, a common moiety of toxicological interest. In laboratory studies, Na_3NTA was found to be associated with marginal increases of hyperplasia and dysplasia of urinary tract epithelial cells which progress to formation of tumours such as adenomas and adenocarcinomas in laboratory rats and mice. Na_3NTA has been classified as a carcinogen by several organizations.

A comparison of the estimates of exposure and the critical effect levels resulted in margins of exposure that are considered adequate to address uncertainties in the health effects and exposure databases.

On the basis of the information presented in this draft screening assessment, it is proposed to conclude that Na_3NTA does not meet the criteria under paragraph 64(*c*) of CEPA as it is 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 proposed to conclude that Na_3NTA does not meet any of the criteria set out in section 64 of CEPA.

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List of Tables and Figures

1. Introduction

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 of glycine, N,N-bis(carboxymethyl)-, trisodium salt, hereinafter referred to as Na_3NTA. The Chemical Abstracts Service Registry Number (CAS RN[2]) for Na_3NTA is 5064-31-3. This substance was identified as a priority for assessment as it met categorization criteria under subsection 73(1) of CEPA.

The ecological risk of Na_3NTA was characterized using the ecological risk classification of organic substances (ERC) approach (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 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.

Na_3NTA was previously assessed internationally through the European Union and there is a European Union Risk Assessment Report (EU RAR) available. In addition, there is an existing Canadian Drinking Water Quality Guideline for nitrilotriacetic acid (NTA) published by Health Canada, which considers health effects information for Na_3NTA.

In addition, health effects data on this substance were previously included as supporting information in the screening assessment for NTA (glycine, N,N-bis(carboxymethyl)-) (CAS RN 139-13-9) conducted under the Challenge initiative of the Chemicals Management Plan (CMP). With respect to the exposure assessment, it was noted in the screening assessment for NTA that NTA and Na_3NTA cannot be distinguished analytically in environmental media and, accordingly, exposure estimates for environmental media encompassed NTA and its salts. This approach, along with updated use and monitoring data, is used in the current assessment.

The EU RAR and screening assessment for NTA will be used to inform the human health risk assessment for Na_3NTA, specifically the health effects assessment.

This draft screening assessment includes consideration of information on chemical properties, environmental fate, hazards, uses and exposures, including additional

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information submitted by stakeholders. Relevant data were identified up to May 2019. Empirical data from key studies as well as results from models were used to reach proposed conclusions. When available and relevant, information presented in assessments from other jurisdictions was considered.

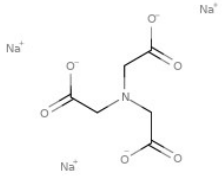
This draft screening assessment was prepared by staff in the CEPA Risk Assessment Program at Health Canada and Environment and Climate Change Canada and incorporates input from other programs within these departments. The ecological portion of this assessment is based on the ERC document (published July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

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[3]. This draft screening assessment presents the critical information and considerations on which the proposed conclusion is based.

2. Identity of substances

The CAS RN, *Domestic Substances List* (DSL) name, common names, chemical structure, molecular formula and molecular weight for the individual substance are presented in Table 2-1.

Table 2-1. Substance identity

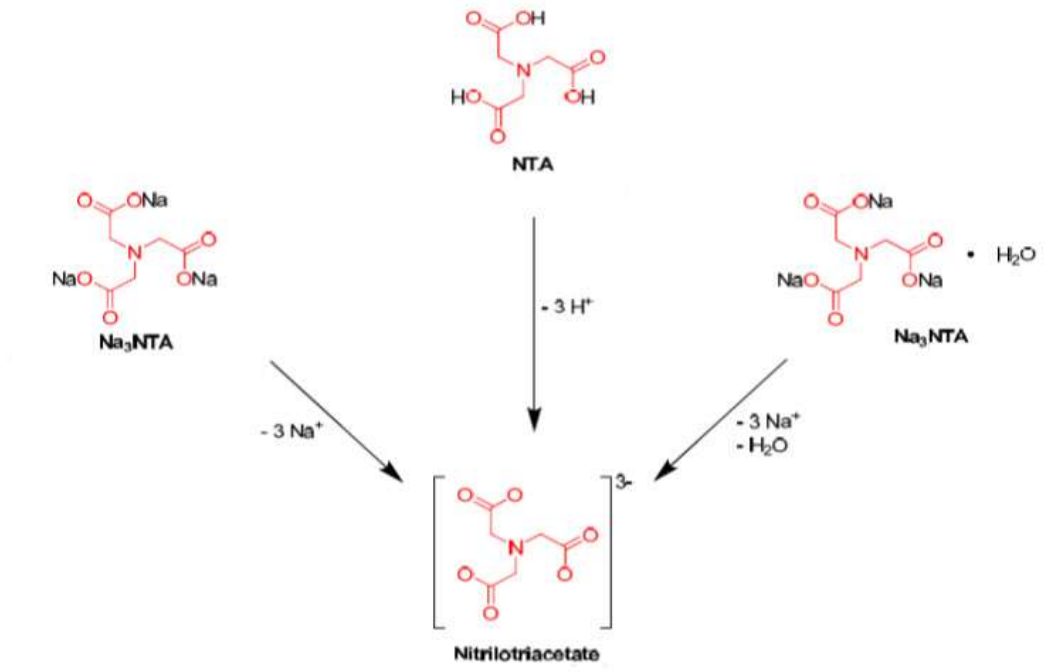
CAS RN	DSL name (common names)	Chemical structure and molecular formula[a]	Molecular weight (g/mol)[a]
5064-31-3	Glycine, N,N-bis(carboxymethyl)-, trisodium salt (Nitrilotriacetic acid trisodium salt; Trisodium NTA; Na_3NTA)	 $C_6H_9NO_6 \cdot Na_3$	257.08

[3]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 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.

[a] ChemID Plus 1993

NTA and its sodium salts, including Na_2NTA, $Na_3NTA•H_2O$, and Na_3NTA, can dissociate to nitrilotriacetate ions in water, which is the common moiety (Figure 2-1).

Figure 2-1. NTA Forms and dissociation components



[Long description: Dissociation of trisodium nitrilotriacetic acid trisodium salt, nitrilotriacetic acid, and trisodium nitrilotriacetate monhydrate into the common moiety nitrilotriacetate.]

3. Physical and chemical properties

A summary of physical and chemical properties of Na_3NTA are presented in **Error! Reference source not found.**, with the range in values indicated for each property. Additional physical and chemical properties are reported in ECCC (2016b).

Table 3-1. Range of experimental and predicted physical and chemical properties (at standard temperature) for Na_3NTA

Property	Value or range	Type of data	Key reference(s)
Physical state	Solid	Experimental	ECHA c2007-2019
Vapor pressure (Pa)	1.0×10^{-7}	Estimated	ECHA c2007-2019
Water solubility (mg/L)	6.4×10^5 to 4.6×10^7	Experimental	EC 2008; ECHA c2007-2019
Log K_{ow} (dimensionless)	-13.2 to -2.62	Estimated	ECHA c2007-2019; EC 2008
pK_a (dimensionless)	1.2	Estimated	ECHA c2007-2019

Abbreviations: K_{ow}, octanol-water partition coefficient; pK_a, acid dissociation constant

4. Sources and uses

Following the publication of the screening assessment for NTA, Na_3NTA was included in a survey issued pursuant to a CEPA section 71 notice (Canada 2012). For the calendar year of 2011, Na_3NTA was reported to be imported into Canada at a volume[4] of 932 414 kg. There were no reports of manufacture of Na_3NTA in Canada above the reporting threshold of 100 kg (Environment Canada 2013).

Uses of Na_3NTA in Canada were reported to include water treatment, cleaning and furnishing care, food packaging, paper products, fabric, textile and leather articles, personal care, photographic supplies, film and photochemicals, agricultural products, and in metal chelation (Environment Canada 2013).

Na_3NTA can be used in Canada in various products available to consumers, such as cleaning products, including a boat cleaner, wood spray polish, wood floor cleaner, and automotive cleaner (SDS 2014; SDS 2015a; SDS 2015b; SDS 2016). In addition, according to notifications submitted under the *Cosmetic Regulations* to Health Canada, Na_3NTA is found in various cosmetic products, such as facial moisturizers, hair conditioners, hair shampoos, hair styling products, face exfoliants, body washes, and permanent hair dyes (personal communication, email from the Consumer and Hazardous Products Safety Directorate (CHPSD), Health Canada (HC), to the Existing Substances Risk Assessment Bureau (ESRAB), HC, dated Feb. 4, 2019; unreferenced). Under the Natural Health Product Ingredients Database (NHPID),

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

Na_3NTA is listed as a non-medicinal ingredient (NMI) with a reported function as a chelating agent (NHPID [modified 2019]); however, there are no natural health products identified in Canada containing Na_3NTA (LNHPD [modified 2019]).

Na_3NTA may be used as a component of cleaners and sanitizers, and hand treatments used in Canadian food processing facilities. Na_3NTA may also be used as a boiler water additive, not to exceed 5 parts per million in boiler feedwater, and not to be used where steam will be in contact with milk and milk products (personal communication, email communication from Food Directorate (FD), Health Canada (HC), to the Existing Substances Risk Assessment Bureau (ESRAB), HC, dated Feb. 4, 2019; unreferenced). . In addition, Na_3NTA may be used in food packaging materials as a component in adhesives, also in products used in the manufacture of paper or paperboard, PVC based film products, and printing inks (personal communication, email communication from FD, HC, to the ESRAB, HC, dated Feb. 4, 2019; unreferenced).

In Canada, Na_3NTA is listed in 6 marketed drug products, which are disinfectant products for hospital and health care facilities, domestic use, and use in food premises (personal communication, email from the Therapeutic Drug Directorate (TPD), HC, to the ESRAB, HC, dated Jan. 18, 2019; unreferenced).

Na_3NTA was historically used as an active ingredient in registered pest control products. Currently, it is used as a formulant in various registered pest control products in Canada (personal communication, email from the Pest Management Regulatory Agency (PMRA), HC, to the ESRAB, HC, dated Jan. 10, 2019; unreferenced).

5. Potential to cause ecological harm

5.1 Characterization of ecological risk

The ecological risk of Na_3NTA was 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 [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, and fish bioconcentration), acute fish ecotoxicity, and chemical import or manufacture volume in Canada were collected from the 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) 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 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 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 with 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 (Q)SAR models (OECD QSAR Toolbox 2014). 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 (CBR) analysis. Error with 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 Na_3NTA, and the hazard, exposure and risk classification results, are presented in ECCC (2016b).

On the basis of low hazard and low exposure classifications according to information considered under ERC, Na_3NTA was classified as having a low potential for ecological

risk. It is unlikely that this substance is resulting in concerns for the environment in Canada.

6. Potential to cause harm to human health

6.1 Exposure assessment

Environmental media

To assess potential exposure to Na_3NTA from environmental media, the same approach as outlined in the screening assessment for NTA was taken, where measured concentrations of $[NTA]^{3-}$ in the environment were attributed solely to the release of Na_3NTA. Both NTA and Na_3NTA are converted into the common nitrilotriacetate form, and the measured concentrations of $[NTA]^{3}$- represent the contributions from all forms of NTA (neutral compounds or salts) in the environment.

The screening assessment for NTA considered historical release and disposal data for NTA and its salts obtained from the National Pollutant Release Inventory (NPRI), for 1994 to 2007 (Environment Canada, Health Canada 2010). In 2012, it was identified that NTA and its salts had reported releases to air of 1.8 tonnes by one facility in Canada based on the NPRI (NPRI 2019). The US EPA SCREEN3 modeling tool (SCREEN3 2011) was used to estimate ambient air concentrations of Na_3NTA in Canada based on NPRI reported releases of 1.8 tonnes and facility information (details on the SCREEN3 model and parameters are found in Appendix A). The modeled air concentration was used to estimate exposures to outdoor air, however, these air concentrations resulted in negligible human exposures (< 2.5 ng/kg bw/day). In addition, due to the very high water solubility of this substance, the predominant exposures from the environment are expected to be through drinking water.

There are a number of studies that have measured concentrations of NTA in Canadian municipally treated drinking water, surface water, groundwater and industrial water. The maximum concentration of NTA measured in treated drinking water in Canadian municipalities was 20.4 µg/L from a 1976-1977 national survey of NTA in drinking water (Malaiyandi et al. 1979). This value was used to determine exposure to drinking water in the screening assessment for NTA, and is also considered in this draft screening assessment as no new data in Canadian drinking water have been identified. The value of 20.4 µg/L results in a daily intake from drinking water of 2.67×10^{-3} mg/kg bw/day in formula fed 0 to 5 month olds, which are the most exposed age group. Details of parameters for estimating drinking water intakes can be found in Appendix B. Currently, the maximum acceptable concentration (MAC) of NTA in drinking water is 400 µg/L, as defined in the Guidelines for Canadian Drinking Water Quality (Health Canada 2008).

The Canadian market use of Na_3NTA as reported in 2011 (932 414 kg) (Environment Canada 2013) is approximately 29 times lower than that reported in 1977 (>27 million kg), which suggests that NTA levels in various water sources may have decreased since the 1970s (Environment Canada, Health Canada 2010). However, no additional

information on current Canadian reporting volumes or concentrations of NTA in drinking water were identified.

Food

In Canada, Na_3NTA may be used as a component in various food packaging materials. Na_3NTA may be a component in adhesive products used in food packaging applications, and in printing inks, however, no exposure is expected as there is no potential for direct food contact from these uses. Na_3NTA may also be used as a component of products used in the manufacture of paper or paperboard, and in polyvinyl chloride (PVC) based film products, for food packaging materials. These applications have potential for direct food contact; however, exposure is considered to be negligible as Na_3NTA is present at less than 0.01% in the finished paper products and finished products of PVC film packaging (personal communication, email from the FD, HC, to the ESRAB, HC, dated Feb. 4, 2019; unreferenced).

Na_3NTA may also be a component in cleaners that are used for surfaces in contact with food, in hand cleaners, and in sanitizers, including dish and laundry detergents, used in food processing facilities in Canada. The use of the aforementioned cleaning products is followed by a potable water rinse, which is expected to remove any residual Na_3NTA, therefore, exposure through food is not expected (personal communication, email from the FD, HC, to the ESRAB, HC, dated Feb. 4, 2019; unreferenced). Na_3NTA may also be used as a boiler water additive, where it is not to exceed 5 parts per million in boiler feedwater, and not to be used where steam will be in contact with milk and milk products. While there is potential for direct food contact, exposure from this source is expected to be negligible (personal communication, email from the FD, HC, to the ESRAB, HC, dated Feb. 4, 2019; unreferenced).

Products available to consumers

Cosmetics

Na_3NTA has a reported function in cosmetics as a chelating agent (EC 2019) and is found in body wash products, hair conditioners, hair shampoos, hair styling products, facial moisturizers, face exfoliants, and permanent hair dyes in Canada (personal communication, email from the CHPSD, HC, to the ESRAB, HC, dated Feb. 4, 2019; unreferenced). A facial makeup, fragrance, hair shampoo, skin cleanser (body and face), hair dye, foot lotion and nail polish containing Na_3NTA had been previously assessed in the screening assessment for NTA; however, additional sentinel exposure scenarios from use of cosmetics, specifically a facial moisturizer and permanent hair dye have since been identified, and will be considered for risk characterization in the current assessment.

Dermal exposures were estimated from the use of these products as the dermal route is expected to be the primary route of exposure due to the low vapour pressure of the substance.

Dermal absorption

To estimate systemic exposure from the dermal route of exposure, a 10% dermal absorption value from the screening assessment for NTA was used (Environment Canada, Health Canada 2010).

The sentinel scenarios for dermal exposure to cosmetics are presented in Table 6-1 below. Additional dermal scenarios for the other cosmetic product types listed, as well as other relevant age groups, were considered, but exposure estimates were lower than those presented in Table 6-1. Details on the method and parameters used to derive estimates of dermal exposure to Na_3NTA are available in Appendix C.

Table 6-1. Estimated exposures by the dermal route to Na_3NTA from the use of cosmetics

Product scenario	Maximum Concentration[a]	Exposure Estimate
Face moisturizer; daily (19+ years)	0.1%	4.1×10^{-3} mg/kg bw/day[b]
Face moisturizer; per event (9-13 year old)	0.1%	2.6×10^{-2} mg/kg per event[c]
Permanent hair dye; daily (14-18 years)	0.1%	7.0×10^{-4} mg/kg bw/day[b]
Permanent hair dye; per event (14-18 years)	0.1%	0.21 mg/kg bw per event[c]

[a] Personal communication, email from the CHPSD, HC, to the ESRAB, HC, dated Feb. 4, 2019; unreferenced
[b] Systemic exposure assuming 10% absorption through the dermal route
[c] Dermal deposition

Other products

Na_3NTA has been identified as an ingredient in various cleaning products at a maximum concentration of 1%; these products include a spray boat cleaner, a wood furniture polish spray, concentrated liquid wood floor cleaner, and a spray automotive cleaner (SDS 2014; SDS 2015a; SDS 2015b; SDS 2016). In addition, Na_3NTA is found in a liquid concentrate disinfectant at a concentration of 0.04%, and a spray disinfectant at 2.0×10^{-4}% with identified domestic uses (personal communication, email from the TPD, HC, to the ESRAB, HC, dated Jan. 18, 2019; unreferenced). Exposure estimates from use of a bathroom cleaner containing Na_3NTA were derived in the screening assessment for NTA; however, additional cleaning products (e.g., spray boat cleaner, a wood furniture polish spray, concentrated liquid wood floor cleaner, and a spray automotive cleaner) have since been identified, and will be considered for risk characterization.

Inhalation, oral and dermal exposures from the use of cleaning products were estimated using ConsExpo Web (ConsExpo Web 2019). Although the substance has a low vapour pressure, the inhalation route is considered due to exposures to aerosols resulting from the use of spray cleaning products. Exposure to cleaning products is expected to be

intermittent long-term in duration. For dermal exposures, the 10% dermal absorption is applied to these scenarios. The sentinel exposure estimates for Na_3NTA for these various cleaning products are presented in Table 6-2. Additional scenarios for other cleaning and disinfectant products (i.e., spray automotive cleaner, spray disinfectant product, and liquid concentrated disinfectant product) were evaluated, but exposure estimates were lower than those presented in Table 6-2, and are not presented. Details on the method and parameters used to derive exposure estimates to Na_3NTA are available in Appendix C.

Table 6-2. Estimated exposures to Na_3NTA from cleaning products

Product scenario	Maximum Concentration	Dermal Exposure	Inhalation Exposure[a]	Oral Exposure
Spraying and polishing wood furniture polish spray; per event (19+ years)	1%[b]	0.1 mg/kg bw per event[e]	5.3×10^{-2} mg/kg bw per event	N/A
Spraying and polishing wood furniture polish spray; intermittent long-term (19+ years)	1%[b]	9.9×10^{-3} mg/kg bw/day[f]	5.2×10^{-3} mg/kg bw/day	N/A
Spray boat cleaner; per event (19+ years)	1%[c]	0.13 mg/kg bw per event[e]	N/A[g]	N/A
Spray boat cleaner; intermittent long-term (19+ years)	1%[c]	3.59×10^{-5} mg/kg bw/day[f]	N/A[g]	N/A
Mixing and applying wood floor cleaning liquid; per event (19+ years)	0.1%[d]	5.04×10^{-3} mg/kg bw per event[e]	N/A	N/A
Mixing and applying wood floor cleaning liquid; intermittent long-term (19+ years)	0.1%[d]	2.22×10^{-4} mg/kg bw/day[f]	N/A	N/A
Crawling on floor treated with floor cleaner; per event (1 year)	0.1%[d]	1.8×10^{-3} mg/kg bw per event[e]	N/A	1.4×10^{-4} mg/kg bw per event

Product scenario	Maximum Concentration	Dermal Exposure	Inhalation Exposure[a]	Oral Exposure
Crawling on floor treated with floor cleaner; intermittent long-term (1 year)	0.1%[d]	8.1×10^{-5} mg/kg bw/day[f]	N/A	6.1×10^{-6} mg/kg bw/day

Abbreviations: N/A, Not Applicable
[a] Systemic exposures assuming 100% absorption through the inhalation route
[b] SDS 2015a
[c] SDS 2014
[d] SDS 2015b
[e] Dermal deposition
[f] Systemic exposure assuming 10% absorption through the dermal route
[g] This product is expected to be used outdoors.The predicted concentration in outdoor air was not estimated. Weather conditions, which can be highly variable and affect ventilation rate as well as temperature, and an undefined room volume (infinitely large) prevent the quantification of reasonable outdoor inhalation exposures (RIVM 2007)

6.2 Health effects assessment

The health effects assessment for Na_3NTA is based on the previous NTA screening assessment (Environment Canada, Health Canada 2010) since toxicological studies using both NTA and Na_3NTA were considered in the assessment. As previously stated, given that both Na_3NTA and NTA dissociate to a common moiety, all toxicological studies for the various forms of NTA were taken into consideration for this screening assessment. A literature search conducted from the year prior to the CEPA screening assessment to May 2019 identified 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 the screening assessment for NTA (Environment Canada, Health Canada 2010).The health effects dataset for Na_3NTA used the EU RAR 2008 as its basis of reference for human health hazard studies.

Na_3NTA has been classified as a carcinogen by several national and international agencies. It is considered a Group 2B carcinogen by the International Agency for Research on Cancer (IARC, 1999), a Category 3 carcinogen by the European Commission (ECHA c2007-2019, EU 2008), “reasonably anticipated to be a human carcinogen” by the US National Toxicology Program (NTP 2005); and a Group IIIB carcinogen (“possibly carcinogenic to humans”) by Health Canada (Health Canada 2008).

Details on the hazard studies for NTA and Na_3NTA are provided in the NTA screening assessment (Environment Canada and Health Canada 2010) and the EU RAR 2008.

6.3 Characterization of risk to human health

The main sources of exposure of the general population to Na_3NTA are through the consumption of drinking water and from the use of products available to consumers, including cosmetics.

Short term exposure durations

To characterize the effects of short-term dermal exposure, 50 mg/kg bw/day of Na_3NTA was used based on two short term dermal studies in rabbits (4 weeks and 3 months in duration) where no local irritation or systemic effects were observed (Nixon 1971).

For the oral and inhalation routes of exposure, a LOEL of 10 mg/kg bw/day was used to characterize the effects in risk characterization based on elevated blood glucose in all treated groups exposed to Na_3NTA in drinking water for 10 weeks (Mahaffey and Goyer 1972).

Intermittant long term and long term exposure durations

In conformity with the weight of evidence-based assessment of international and other national agencies, a critical effect for the characterization of risk to human health for Na_3NTA is carcinogenicity. Incidences of urinary stem tumours were increased in a dose-related manner in the standard carcinogenicity studies in both sexes of rats and mice. Based on the weight-of-evidence of the available genotoxicity data, Na_3NTA is not considered to be genotoxic. Although the mode of induction of tumours has not been fully elucidated, the tumours observed in experimental animals are unlikely to have resulted from direct interaction with genetic material (EU RAR 2008).

To characterize the effects for all routes of exposure, the LOAEL of 100 mg/kg bw/day was used based on hyperplasia of tubular and transitional cells in kidneys, ureters and urinary bladders of treated rats for 24 months (NCI, 1977). This was supported by other short term and chronic studies where hyperplasia of tubular and transitional cells in kidneys, ureters and urinary bladders of treated rats was observed at this concentration (Mahaffey and Goyer 1972; NCI 1977; Goyer et al. 1981). While no cytotoxicity was observed at this level, hyperplasia of the transitional cell epithelium represents the most sensitive effect underlying the tumour development. According to Environment Canada and Health Canada (Environment Canada, Health Canada 2010), a comparison of the effect level for non-cancer and preneoplastic/cancer endpoints indicates that urinary tract carcinogenicity was more sensitive than urinary tract toxicity.

Error! Reference source not found.3 and 6-4 provide all relevant per event exposure and hazard values for Na_3NTA, and intermittent-long term and daily exposures for potential cancer effects and hazard values for Na_3NTA, respectively. The resultant margins of exposure for determination of risk are also presented.

Table 6-3. Relevant per event exposure and hazard values for Na_3NTA, as well as resultant margins of exposure, for determination of risk

Exposure scenario	Exposure (mg/kg bw per event)	Critical effect level[ab]	Critical health effect endpoint	MOE
Permanent hair dye; dermal; 14-18 year old	0.21	50 mg/kg bw/ day	No observed gross or histological abnormalities on rabbit dermis (28 day study) at only dose tested	238
Face moisturizer; dermal; 9-13 years	2.6×10^{-2}	50 mg/kg bw/ day	No observed gross or histological abnormalities on rabbit dermis (28 day study) at any dose tested (up to 50 mg/kg bw/ day)	1 923
Wood furniture polishing spray; inhalation; 19+ years	5.3×10^{-2}	10 mg/kg bw/day	LOEL based on elevated blood glucose in rats(10 week study)	189
Wood furniture polishing spray; dermal; 19+ years	0.1	50 mg/kg bw/ day	No observed gross or histological abnormalities on rabbit dermis (28 day study) at any dose tested (up to 50 mg/kg bw/ day)	500
Wood floor cleaning liquid; dermal; 19+ years	5.0×10^{-3}	50 mg/kg bw/day	No observed gross or histological abnormalities on rabbit dermis (28 day study) at any dose tested (up to 50 mg/kg bw/ day)	10 000
Crawling on floor treated with wood floor cleaning liquid; dermal; 1 year old	1.8×10^{-3}	50 mg/kg bw/day	No observed gross or histological abnormalities on rabbit dermis (28 day study) at any dose tested (up to 50 mg/kg bw/ day)	27 250
Crawling on floor treated with wood floor cleaning liquid; oral; 1 year old	1.4×10^{-4}	10 mg/kg bw/day	LOEL based on elevated blood glucose in rats(10 week study)	72 632

Spray boat cleaner; dermal; 19+ years	0.13	50 mg/kg bw/day	No observed gross or histological abnormalities on rabbit dermis (28 day study) at any dose tested (up to 50 mg/kg bw/ day)	385

[a] For all per event dermal scenarios identified, the critical effect level of 50 mg/kg bw/day was used. This was the only tested dose.
[b] Given that insufficient data was identified for short term inhalation, the most protective oral endpoint (10 mg/kg bw/day) reflective of increased glucose levels in rats was used, and assumed 100% absorption for route to route extrapolation.

With respect to the per event use of cosmetic products and various cleaning products, comparison of the critical effect levels to the estimated exposures resulted in MOEs ranging from 189 to 72 632. These MOEs are considered adequate to address uncertainties in the health effects and exposure databases.

Table 6-4. Relevant intermittent long-term and daily exposure and hazard values for Na_3NTA, as well as resultant margins of exposure, for determination of risk

Exposure scenario	Systemic exposure (mg/kg bw/day)[a]	Critical effect level	Critical health effect endpoint	MOE
Drinking water; oral; 0-5 month old	2.67×10^{-3} mg/kg bw/day	100 mg/kg bw/day	Oral LOAEL based on hyperplasia of tubular and transitional cells in kidneys, ureters and urinary bladders of treated rats - 24 month study	37 453
Permanent hair dye; dermal; 14-18 year old	7.0×10^{-4}	100 mg/kg bw/day	Hyperplasia of tubular and transitional cells in kidneys, ureters and urinary bladders of treated rats	142 857
Face moisturizer; dermal; adult	4.1×10^{-3}	100 mg/kg bw/day	Hyperplasia of tubular and transitional cells in kidneys, ureters and urinary bladders of treated rats	24 390
Wood furniture polishing spray; inhalation and dermal combined; 19+ years	1.5×10^{-2}	100 mg/kg bw/day[b]	Hyperplasia of tubular and transitional cells in kidneys, ureters and urinary bladders of treated rats	6 667

Wood floor cleaning liquid; dermal; 19+ years	2.2 x 10^{-4}	100 mg/kg bw/day	Hyperplasia of tubular and transitional cells in kidneys, ureters and urinary bladders of treated rats	454 545
Crawling on floor treated with wood floor cleaning liquid; dermal; 1 year old	8.1 x 10^{-5}	100 mg/kg bw/day	Hyperplasia of tubular and transitional cells in kidneys, ureters and urinary bladders of treated rats	> 1 000 000
Spray boat cleaner; dermal; 19+ years	3.59 x 10^{-5}	100 mg/kg bw/day	Hyperplasia of tubular and transitional cells in kidneys, ureters and urinary bladders of treated rats	> 1 000 000

[a] Assume 10% absorption for the dermal route
[b] For chronic inhalation, the lowest oral endpoint (100 mg/kg bw/day) was used and assumed 100% absorption for route to route extrapolation.

With respect to the intermittent long-term and daily use of cosmetic products and various cleaning products, as well as daily exposure to drinking water, comparison of the critical effect levels to the estimated exposures resulted in MOEs ranging from 6 667 to > 1 000 000. These MOEs are considered adequate to address uncertainties in the health effects and exposure databases. Even if the very conservative LOEL of 10 mg/kgbw/day as Na_3NTA based on the marginal increase of hyperplasia and dysplasia of urinary tract epithelial cells in experimental animals, is used for this purpose, the potential margins of exposure for all exposure scenarios would be adequate (667 - 278 551).

While exposure to the general population to Na_3NTA is not of concern at current levels, the common moiety, nitrilotriacetate, is considered to have a health effect of concern on the basis of its potential for carcinogenicity of the urinary tract. Therefore, there may be a concern for human health if exposures were to increase.

6.4 Uncertainties in evaluation of risk to human health

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

Table 6-5. Sources of uncertainty in the risk characterization

Key source of Uncertainty	Impact
Limited information is available concerning the potential toxicity of Na_3NTA following inhalation and dermal exposures.	+/-
Exposure estimates from drinking water were derived from Canadian monitoring data in municipally treated drinking water from the 1970s. This is expected to be a conservative estimate since the Canadian market use of Na_3NTA in 2011 is approximately 29 times lower than that reported in 1977 (Environment Canada, Health Canada 2010).	+

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

7. Conclusion

Considering all available lines of evidence presented in this draft screening assessment, there is low risk of harm to the environment from Na_3NTA. It is proposed to conclude that Na_3NTA does not meet the criteria under paragraphs 64(*a*) or (*b*) of CEPA as it is not entering the environment in a quantity of 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 Na_3NTA does not meet the criteria under paragraph 64(*c*) of CEPA as it is 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 proposed to conclude that Na_3NTA does not meet any of the criteria set out in section 64 of CEPA.

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Appendices

Appendix A. SCREEN3: model and inputs

SCREEN3 is a screening-level Gaussian air dispersion model based on the Industrial Source Complex (ISC) model (for assessing pollutant concentrations from various sources in an industry complex) (SCREEN3 2011). The driver for air dispersion in the SCREEN3 model is wind. The maximum calculated exposure concentration is selected based on a built-in meteorological data matrix of different combinations of meteorological conditions, including wind speed, turbulence and humidity. This model directly predicts concentrations resulting from point, area and volume source releases. SCREEN3 gives the maximum concentrations of a substance at chosen receptor heights and at various distances from a release source in the direction downwind from the prevalent wind within one hour of a given release event. During a 24-hour period, for point emission sources, the maximum 1-hour exposure (as assessed by the ISC Version 3) is multiplied by a factor of 0.4 to account for variable wind direction. This gives an estimate of the air concentration over a 24-hour exposure (US EPA 1992; SCREEN3 2011). Similarly, for exposure events happening over the span of a year, it can be expected that the direction of the prevalent winds will be more variable and uncorrelated to the wind direction for a single event; thus, the maximum amortized exposure concentration for one year is determined by multiplying the maximum 1-hour exposure by a factor of 0.08 (US EPA 1992; SCREEN3 2011). Parameters used to estimate ambient air concentrations using the SCREEN3 model are presented in Table A-1 below.

Table A-1. Parameters used in SCREEN3 for air releases from industrial facilities

Source Type	Area
Effective emission Area[a]	100 m x 250 m
Receptor Height[b]	1.74 m
Source release height[a]	30 m
Adjustment Factor[c]	0.4
Urban-rural option[d]	Urban
Meterology[d]	1 (full meteorology)
Minimum and maximum distance[a]	0-3000 m

[a] Site specific; based on aerial photograph analysis and professional judgement
[b] Average adult height (Curry et al. 1993)
[c] Factor to account for variable wind direction over a 24-hour period (U.S. EPA 1992)
[d] Default in SCREEN3

Appendix B. Estimates of daily intakes of drinking water

The concentration of 20.4 µg/L identified from a 1976-1977 national survey of NTA in drinking water (Malaiyandi et al. 1979) was used to derive intake estimates from drinking water. Estimates were calculated based on default body weights of 74 kg for 19+ year olds, 62 kg for 14-18 year olds, 42 kg for 9-13 year olds, 23 kg for 4-8 year olds, 15 kg for 2-3 year olds, 11 kg for 1 year olds, 9.1 kg for 6-11 month olds, 6.3 kg for 0-5 month olds (Health Canada 2015). Drinking water intakes used to determine intake estimates are presented in Table B-1 below. The maximal extimates of daily intake from drinking water are presented in Table B-2 below.

Table B-1. Drinking water intake values used in the calculation to determine intake estimates for drinking water

Age group	Drinking water intake (L/day)[a]	Infant formula intake (L/day)[a]
0-5 months	N/A[b]	0.826[b]
6-11 months	N/A[b]	0.764[b]
1 year old	0.36	N/A
2-3 year old	0.43	N/A
4-8 year old	0.53	N/A
9-13 year old	0.74	N/A
14-18 year old	1.09	N/A
19+ year old	1.53	N/A

Abbreviations: N/A, Not Applicable

[a] Health Canada 2019

[b] It is assumed that infants younger than 1 year old consume drinking water through formula intake

Table B-2. Maximal estimates of daily intake of drinking water

Age Group	Estimated intake (mg/kg bw/day)
0-5 months	2.67×10^{-3}
6-11 months	1.71×10^{-3}
1 year old	6.7×10^{-4}
2-3 year old	5.8×10^{-4}
4-8 year old	4.7×10^{-4}
9-13 year old	3.6×10^{-4}
14-18 year old	3.6×10^{-4}
19+ year old	4.2×10^{-4}

Appendix C. Parameters to estimate human exposures from use of products available to consumers in Canada

Exposure estimates were calculated based on default body weights of 74 kg for 19+ year olds, 62 kg for 14-18 year olds, 42 kg for 9-13 year olds, 23 kg for 4-8 year olds, 15 kg for 2-3 year olds, 11 kg for 1 year olds, 9.1 kg for 6-11 month olds, 6.3 kg for 0-5 month olds (Health Canada 2015). The estimated inhalation, oral, and dermal exposure parameters for cosmetics and other products available to consumers are described in Tables C-1 and C-2, respectively. Exposures for products available to consumers were estimating using ConsExpo Web (ConsExpo Web 2019), unless stated otherwise. Defaults parameters from ConsExpo Web were used unless otherwise specified in Tables C-1 and C-2.

Table C-1. Exposure parameter assumptions for dermal cosmetic scenarios

Product (substance)	Assumptions
Face moisturizer	Acute dermal exposure (per event): Concentration in product: 0.1%[a] Dermal – Direct contact, instant application Product amount: 1.5 g (14-18 year old and 19+ year old), and 1.1 g (9-13 year old) (Ficheux et al. 2016) Retention factor: 1 Daily dermal exposure (dose averaged daily exposure in mg/kg bw/day): Frequency of use: 2.0 per day (19+ year old) (Loretz et al. 2005), 1.0 times per day (9-13 year old, and 14-18 year old) (Ficheux et al. 2015) (E*F) ÷ 365 days per year E (per event exposure) F (frequency of use per year): 730 per year (19+ year old), 365 per year (9-13 year old, and 14-18 year old)
Permanent hair dye	Acute dermal exposure (per event): Concentration in product: 0.1%[a] Dermal – Direct contact, instant application Product amount: 132.6 g (14-18 year old and 19+ year old) (Ramirez-Martinez et al. 2015) Retention factor: 0.1 Daily dermal exposure (dose averaged daily exposure in mg/kg bw/day):

	Frequency of use: 0.022 per day (19+ year old) and 0.011 per day (14-18 year old) (Bernard et al. 2016) (E* F) ÷ 365 days per year E (per event exposure) F (frequency of use per year): 8 per year (19+ year old), 4 per year (14-18 year old)

[a] Personal communication, email from the CHPSD, HC, to the ESRAB, HC, dated Feb. 4, 2019; unreferenced

Table C-2. Inhalation, oral, and dermal exposure parameter assumptions for other products available to consumers

Exposure scenario	Assumptions
Wood furniture polish spray, spraying and polishing	Concentration in product: 1% (SDS 2015a) Scenario: spraying and polishing with wood furniture polish spray in Cleaning Products Fact Sheet (RIVM 2018) Frequency of use: 36 per year (cleaning outside of cabinet 3 times per year (mean)) (US EPA 2011) <u>Spraying (non-volatile substance)</u> Inhalation – exposure to spray: spraying Spray duration: 2 minutes Exposure duration: 240 minutes Product in pure form: no Product is used in dilution: no Room volume: 20 m^3 Room height: 2.5 m Ventilation rate: 0.6 change per hour Inhalation rate: 15.1 m^3/day (US EPA 2011 [modified]) Spraying towards person: no Mass generation rate: 1.8 g/s Airborne fraction: 0.3 Density non-volatile: 1.8 g/cm^3 Inhalation cut off diameter: 15 µm Aerosol diameter distribution: LogNormal Median diameter: 10.8 µm Arithmic coefficient of variation: 0.81 Maximum diameter: 50 µm Include oral non-respirable material exposure: no Dermal – direct contact: constant rate

Exposure scenario	Assumptions
	Exposed area: 2200 cm^2 Contact rate: 46 mg/min Release duration: 4 min <u>Polishing</u> Dermal – direct contact: instant application Exposed area: 225 cm^2 Product amount: 0.56 g <u>Intermittent long-term exposure (dose averaged intermittent long-term exposure in mg/kg bw/day):</u> (E* F) ÷ 365 days per year E (per event exposure) F (frequency of use per year): 36 per year (US EPA 2011)
Wood floor cleaning liquid, mixing and applying (adults)	Concentration in product: 0.1% (SDS 2015b) Scenario: mixing and applying wood floor cleaning liquid in Cleaning Products Fact Sheet (RIVM 2018) Frequency of use: 161 per year <u>Mixing and loading</u> Dermal – direct contact: instant application Exposed area: 225 cm^2 Product amount: 0.01 g <u>Application – cleaning</u> Dermal – direct contact: instant application Exposed area: 2200 cm^2 Product amount: 0.36 g <u>Intermittent long-term exposure (dose averaged intermittent long-term exposure in mg/kg bw/day):</u> (E* F) ÷ 365 days per year E (per event exposure) F (frequency of use per year): 161 per year
Crawling on floor treated with wood floor cleaner (1 year old)	Concentration in product: 0.1% (SDS 2015b) Scenario: post-application (rubbing-off) of wood floor cleaning liquid

Exposure scenario	Assumptions
	Calculations based on the US EPA Residential SOPs (2012), Section 7 (US EPA 2012). <u>Dermal (post-application – rubbing off)</u> Calculated using the following algorithm (US EPA 2012): Exposure = [deposited residue (mg/cm^2) * fraction available for transfer (%) * transfer coefficient (cm^2/hr) * exposure time (hrs) * dermal absorption (%)]/body weight Deposited residue (mg/cm^2): Calculated assuming 14.4 g of product per 22 m^2 of floor (ConsExpo Cleaning Fact Sheet (RIVM 2018)) * 1000 mg/g * 1 m^2/10000 cm^2 Transfer coefficient: 1927 cm^2/hr (adult transfer coefficient (6800 cm^2/hr) adjusted for the body surface area of a 1-2 year old (0.28 (5300 cm^2/18700 cm^2) (Health Canada 2019). Fraction available for transfer: 8% Exposure time: 2 hr; exposure time for hard surfaces represents time spent in kitchens and bathrooms Dermal absorption: 100% <u>Incidental oral (hand to mouth contact)</u> Calculated using the following algorithm (US EPA 2012): Exposure = [HR (mg/cm^2) * (F_M * SA_H (cm^2)) * (ET * N_Replen) * (1 – (1 – SE)$^{Freq\_HtM/N\_Replen}$)] HR: hand residue loading (mg/cm^2); calculated using the following algorithm: HR = [Fai_{hands} * Dermal exposure (mg) (calculated above)] / (SA_H * 2) Fai_{hands}: 0.15 (unitless); fraction of active ingredient on hands compared to total surface residue from jazzercise study SA_H: 150 cm^2; typical surface area of one hand F_M: 0.13 (unitless); fraction of hand mouthed per event

Exposure scenario	Assumptions
	SA_H: 150 cm^2; typical surface area of one hand ET: 2 hours; exposure time per day N_Replen: 4; number of replenishment intervals per hour SE: 0.48; saliva extraction factor Freq_HtM: 20; number of hand-to-mouth events per hour <u>Intermittent long-term exposure (dose averaged intermittent long-term exposure in mg/kg bw/day):</u> (E*F) ÷ 365 days per year E (per event exposure) F (frequency of use per year): 161 per year (RIVM 2018)
Spray boat cleaner, spraying	Product scenario: boat hull cleaner <u>Dermal</u> Estimated daily exposure via dermal route: (F *D* A* C) / BW C (concentration in product):1% (SDS 2014) F (film thickness): 0.00213 cm (Versar Inc. 1985) A (contact area of hand): 455 cm^2 D (density of product): 1.0 g/cm^3 <u>Intermittent long-term exposure (dose averaged intermittent long-term exposure in mg/kg bw/day):</u> (E* F) ÷ 365 days per year E (per event exposure) F (frequency of use per year): 1 per year