Screening Assessment

Benzenesulfonamide, 2-methyl

Chemical Abstracts Service Registry Number 88-19-7

Environment and Climate Change Canada
Health Canada

December 2017

Synopsis

Pursuant to section 68 of the *Canadian Environmental Protection Act, 1999* (CEPA), the Minister of the Environment and the Minister of Health have conducted a screening assessment of benzenesulfonamide, 2-methyl, hereinafter referred to as 2-MBS. The Chemical Abstracts Service Registry Number (CAS RN[1]) for 2-MBS is 88-19-7. This substance is among those substances identified as priorities for assessment based on human health concerns.

2-MBS does not occur naturally in the environment. In 2011, there were no reports of manufacture above the reporting threshold of 100 kg for 2-MBS; between 1000 and 10 000 kg of 2-MBS were imported into Canada. It is used primarily as an intermediate for fluorescent pigments and plasticizer resins and as a plasticizer for hot-melt adhesives. 2-MBS is used in cosmetics as an ingredient in nail polish and may be formed in small amounts during the manufacture of the food additive saccharin (according to regulations specific to food-grade specifications for additives, saccharin can contain no more than 10 parts per million 2-MBS as an impurity).

The ecological risk of 2-MBS was characterized using the ecological risk classification of organic substances (ERC). The ERC is a risk-based approach that employs multiple metrics for both hazard and exposure based on weighted consideration of multiple lines of evidence for determining risk classification. Hazard profiles based principally on metrics regarding mode of toxic action, chemical reactivity, food web-derived internal toxicity thresholds, bioavailability, and chemical and biological activity are established. 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 based on their hazard and exposure profiles. The ERC identified 2-MBS as having low potential to cause ecological harm.

Considering all available lines of evidence presented in this screening assessment, there is low risk of harm to organisms and the broader integrity of the environment from 2-MBS. It is concluded that 2-MBS does not meet the criteria under paragraphs 64(*a*) or (*b*) of CEPA as it is 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.

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For the general population of Canada, potential exposures to 2-MBS were estimated as a total daily intake from environmental media (i.e., drinking water, dust) and food. As well, exposure from use of nail polish containing 2-MBS was characterized.

The critical health effects were developmental effects, as well as effects on the liver and kidney. Margins of exposure comparing effect levels for the critical health effects and the estimated exposures of the general population were considered adequate to address uncertainties in the health effects and exposure databases for 2-MBS.

On the basis of the information presented in this screening assessment, it is concluded that 2-MBS 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.

Therefore, it is concluded that 2-MBS does not meet any of the criteria set out in section 64 of CEPA.

Table of Contents

List of Tables

1. Introduction

Pursuant to section 68 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 benzenesulfonamide, 2-methyl (2-MBS) to determine whether this substance presents or may present a risk to the environment or to human health. This substance was considered a priority on the basis of other human health concerns (ECCC, HC [modified 2007]).

2-MBS was reviewed internationally through the Cooperative Chemicals Assessment Programme of the Organization for Economic Cooperation and Development (OECD), and a Screening Initial Data Set (SIDS) Initial Assessment Report (SIAR) is available (OECD 2002). These assessments undergo rigorous review and endorsement by international governmental authorities. Health Canada and Environment and Climate Change Canada are active participants in this process and consider these assessments reliable. The OECD SIAR for 2-MBS (OECD 2002), referred to as *o*-toluenesulfonamide in the SIAR, is used to inform the health effects characterization in this screening assessment.

The ecological risk of 2-MBS was characterized using the ecological risk classification of organic substances (ERC) (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 based on 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.

This screening assessment includes consideration of information on chemical properties, environmental fate, hazards, uses and exposures, including additional information submitted by stakeholders. Relevant data were identified up to October 2016. Empirical data from key studies as well as some results from models were used to reach the conclusions.

This screening assessment was prepared by staff in the CEPA Risk Assessment Program at Health Canada and Environment and Climate Change Canada and incorporates input from other programs within these departments. The ecological portion of this assessment is based on the ERC document (published July 30, 2016), which was peer-reviewed and subject to a 60-day public comment period. Additionally, the draft of this screening assessment (published February 11, 2017) was also subject to a 60-day public comment period.

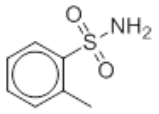
While external comments were taken into consideration, the final content and outcome of the screening assessment remain the responsibility of Environment and Climate Change Canada and Health Canada.

This screening assessment focuses on information critical to determining whether the substance meets the criteria as set out in section 64 of CEPA by examining scientific information and incorporating a weight-of-evidence approach and precaution.[2] The screening assessment presents the critical information and considerations that form the basis of the conclusion.

2. Identity of Substances

2-MBS is an organic chemical that is also known as *o*-toluenesulfonamide. Information regarding the substance identity of 2-MBS is summarized in Table 2-1.

Table 2-1. Substance identity

CAS RN[a]	DSL name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)
88-19-7	benzenesulfonamide, 2-methyl (2-MBS)	 $C_7H_9NO_2S$	171.22

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3. Physical and Chemical Properties

Key physical and chemical properties of 2-MBS are summarized in Table 3-1. Additional physical and chemical properties are presented in ECCC (2016b).

[2] 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 is 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.

Table 3-1. Physical and chemical property values for 2-MBS (at standard temperature and pressure)

Property	Value	Type of data	Reference
Water solubility (g/L)	1.6	experimental	OECD 2002
Vapour pressure (Pa)	6.6×10^{-5}	experimental	OECD 2002
Henry's law constant (Pa m^3/mol)	4.76×10^{-2}	modelled	ChemIDplus 1993-
log K_{ow} (dimensionless)	0.84	experimental	ECHA c2007-2015, Hansch et al. 1995
K_{oc} (dimensionless)	68	Estimated (from Log K_{ow})	HSDB 1983-
pKa	10.18	experimental	OECD 2002

Abbreviations: K_{ow} - octanol–water partition coefficient; pKa - acid dissociation constant.

4. Sources and Uses

2-MBS does not occur naturally in the environment.

On the basis of information submitted pursuant to section 71 of CEPA regarding commercial activity in Canada (Canada 2012), 2-MBS was not manufactured in Canada in 2011 above the reporting threshold of 100 kg. Between 1000 and 10 000 kg of 2-MBS were imported into Canada during the same calendar year[3] (Environment Canada 2013).

In the United States, there was no reported import or manufacturing of the substance in 2012 (CDAT [modified 2016]).

Globally, 2-MBS is used as a mixture with 4-MBS (*p*-toluenesulfonamide; CAS RN 70-55-3) as a plasticizer for hot-melt adhesives and as a chemical intermediate for fluorescent pigments and plasticizer resins (OECD 2002). In Canada, information regarding uses of 2-MBS was submitted in response to the recent section 71 survey under CEPA (Canada 2012), but is not presented herein due to confidentiality (Environment Canada 2013). These uses, however, are consistent with the global uses of this substance.

2-MBS is also used in cosmetics as an ingredient in a small number of nail polishes, where it is found in a mixture with 4-MBS (the mixture of the two isomers is referred to

[3] Values reflect quantities reported in response to surveys. See survey for specific inclusions and exclusions (schedules 2 and 3).

as tosylamide) (personal communications, emails from Consumer Product Safety Directorate, Health Canada, to Risk Management Bureau, Health Canada, 2015; unreferenced).

2-MBS has not been identified as having uses in food packaging materials in Canada. Although there are no approved food additive uses of 2-MBS, it may be formed in small amounts during the manufacture of saccharin, which is permitted for use as a sweetener in some foods sold in Canada. The use of saccharin (or its calcium, potassium or sodium salts) must comply with the *Food and Drug Regulations*, which require that food additives meet the specifications set out in the most recent edition of the *Food Chemicals Codex* (FCC), a publication of the United States Pharmacopeial Convention. The FCC specifications for the calcium and sodium salts of saccharin[4] set out acceptance criteria specifically for 2-MBS of not more than 10 ppm (USP 2016a, 2016b).

No uses were identified for 2-MBS in pesticides or drugs, including natural health products (PMRA 2010, 2015; DPD [modified 2015]; LNHPD [modified 2014]; NHPID [modified 2016], personal communications, emails from Therapeutic Products Directorate, Health Canada, to Risk Management Bureau, Health Canada, 2015; unreferenced).

5. Potential to Cause Ecological Harm

5.1 Characterization of Ecological Risk

The ecological risk of 2-MBS was characterized using the ecological risk classification of organic substances (ERC) (ECCC 2016a). The ERC is a risk-based approach that considers multiple metrics for both hazard and exposure based on 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., LC_{50}) for

[4] The FCC specifications for both calcium and sodium saccharin salts set out an acceptance criterion specifically for 2-MBS (*o*-toluenesulfonamide) of not more than 10 ppm (USP 2016a, 2016b). The FCC specification for saccharin includes an acceptance criterion for total "toluenesulfonamide" (both the *o*- and *p*-toluenesulfonamide) of not more than 0.0025% or 25 ppm. Specifications for potassium saccharin have not been established in the FCC but the Joint FAO/WHO Expert Committee on Food Additives (JECFA) has established specifications. These include an acceptance criterion for toluenesulfonamides of not more than 25 mg/kg (JECFA 2001). The acceptance criterion that was specific to 2-MBS was used for the purposes of the current assessment. However, even if the acceptance criterion for total toluenesulfonamide in saccharin and potassium saccharin was conservatively assumed, it would not impact on the conclusion of this assessment.

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 or manufacture volume in Canada were collected from scientific literature, from available empirical databases (e.g., OECD QSAR Toolbox), and from responses to surveys under section 71 of CEPA or 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 substance hazard and exposure profiles.

Hazard profiles based primarily on metrics regarding mode of toxic action, chemical reactivity, food web-derived internal toxicity thresholds, bioavailability, and chemical and biological activity were established. Exposure profiles were also composed of 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 based on 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 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 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 used for critical body residue (CBR) analysis. Error with underestimation of acute toxicity is 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 based on what is believed to be the current use quantity and may not reflect future trends.

Critical data and considerations used to develop the substance-specific profiles for 2-MBS and to determine the hazard, exposure and risk classification results are presented in ECCC (2016b).

Based on low hazard and low exposure classifications according to ERC for 2-MBS, this substance was classified as having a low potential for ecological risk and is therefore unlikely to result in concerns for organisms or the broader integrity of the environment in Canada.

6. Potential to Cause Harm to Human Health

6.1 Exposure Assessment

Environmental media

No results of measurement were identified for 2-MBS in ambient air or in soil. 2-MBS is not expected to be released to air given its low vapour pressure and high water solubility. It is also not expected to tightly bind to soil, but is expected to leach from soil and enter the water stream based on its high water solubility (1.6 g/L) and its estimated organic carbon-water distribution coefficient (Koc) of 68.

No results of measurement were identified for 2-MBS in Canadian drinking water; however, it was measured in urban water (<0.05 to 0.24 µg/L) in Germany (Richter et al. 2008). As a conservative but realistic approach, the concentration of 2-MBS measured in drinking water in the Berlin study was used to estimate 2-MBS daily intakes from drinking water for the general population in Canada. The maximum estimated daily intake of 2-MBS from drinking water ranged from 1.33×10^{-6} to 2.56×10^{-5} mg/kg bw per day for seniors (60 years+) and formula-fed infants (0-0.5 years), respectively.

In a National Research Council of Canada (NRC) Quebec City field study, a mass spectral library search of various substances was conducted on 50 dust samples collected in children's bedrooms during winter. 2-MBS was detected in 4 of the 50 dust samples at concentrations of 1.24-5.89 µg/g (Won and Lusztyk 2011). Maximal daily intake estimates from dust ranged from 2.05×10^{-7} to 2.98×10^{-5} mg/kg bw per day for seniors (60 years+) and infants (0-0.5 years), respectively. These exposure estimates may be considered conservative as they are based on limited data (detection frequency 8%) and use the highest concentration measured (i.e. 5.89 µg/g) to estimate exposures.

Food

Exposure to 2-MBS from food was modelled based on its possible presence as an impurity in the food additive saccharin (USP 2016a, 2016b). Estimated intakes were modelled assuming that saccharin could be present in a broader category of foods than it is actually permitted for use in food sold in Canada and that the saccharin that was added to those foods contained the maximum residue of 2-MBS that would be permitted under current regulatory standards of purity for the calcium and sodium salts of saccharin. Additional information on the parameters used to generate dietary estimates of exposure to 2-MBS is found in Appendix A and B.

Based on these assumptions, estimated dietary intakes of 2-MBS ranged from 1.22×10^{-4} to 2.35×10^{-4} mg/kg bw per day for teenagers (ages 12-19) and toddlers (ages 0.5 to 4), respectively. These estimates are considered to be very conservative for the following reasons: the food categories that were modelled were broad and included foods within that category that were not permitted to contain saccharin; it was assumed that individuals will always choose foods that contain saccharin and that those foods would contain saccharin at the maximum levels of use; and it was further assumed that saccharin always contains residues of 2-MBS at the maximum permitted impurity level.

Products Used by Consumers

Tosylamide (a mixture of 2-MBS and 4-MBS) is found in a small number of nail polishes at concentrations of 0.1 to 10%, but the concentration of each isomer within these products cannot be determined based on the cosmetic notifications submitted to Health Canada under the *Cosmetic Regulations* (personal communications, emails from Consumer Product Safety Directorate, Health Canada, to Risk Management Bureau, Health Canada, 2015; unreferenced).

Tosylamide is likely added to nail polish to form toluenesulfonamide-formaldehyde resin, which is indicated as a common component of nail polish. Following a database search of patents on the composition of nail polish, both 2-MBS and 4-MBS were found at a concentration of 5% each in nail polishes (Hausen et al. 1995). Exposure estimates were therefore generated for an adult (70.9 kg) applying nail polish containing 5% 2-MBS, and assuming a product amount of 0.05 g per application.

Dermal absorption of 2-MBS is expected to be low based on results from dermal absorption studies on the structurally similar tosylchloramide sodium (CAS RN 127-65-1). The Danish Environmental Protection Agency reported the use of tosylchloramide sodium data to refine dermal absorption of 2-MBS to 20% in an exposure scenario for a children's toy (Danish EPA 2015). Similarly, in an *in vitro* human dermal skin absorption study (OECD Test Guideline (TG) 428) on the tosylchloramide sodium (CAS RN 127-65-1), a mean absorption of 9.7 and 20% was obtained following an 8-hour exposure (and a post-exposure time of 16 hours) to 3 and 0.5% tosylchloramide sodium in water, respectively (ECHA c2007-2015). In this screening assessment, dermal absorption of 2-MBS was conservatively assumed to be 20%.

Systemic exposures (via the dermal route) of an adult applying nail polish containing 5% 2-MBS were estimated to be 7.1×10^{-3} mg/kg bw per application. Inhalation exposure is not expected based on the low vapour pressure of 2-MBS.

According to a Danish survey of chemical substances in toothbrushes, 2-MBS was detected in 3 out of 10 toothbrush samples selected among Aquafresh, Colgate, and a Danish brand (Jordan). Approximately 19.0 and 390 µg of 2-MBS per toothbrush was measured from 2 toothbrushes following a 10-hour incubation in simulated saliva at 37°C. According to the Danish EPA, these concentrations did not result in any health risk to the consumer by oral intake (Svendsen et al. 2004).

In a recent survey of chemical substances in toys, 2-MBS was detected in 3 out of 28 sampled toys on the Danish market, with concentrations ranging from 44 to 210 mg/kg. No health risk was identified for oral or dermal exposure at these concentrations (Danish EPA 2015).

The presence of 2-MBS in toothbrushes and toys is considered to be as a residual from its use as a chemical intermediate for plasticizer resins. Although 2-MBS has not been reported in products other than nail polish in the Canadian marketplace, there is a possibility that it may be found in toys and toothbrushes in Canada. However, exposure to 2-MBS is expected to be low from use of these products compared with that from nail polish, since the majority of the substance would be encapsulated in a plastic matrix; additionally, no health risk was identified by the Danish EPA from exposure to the sampled toothbrushes and toys (Danish EPA 2015).

6.2 Health Effects Assessment

The OECD (2002) SIAR summarizes the health effects related to 2-MBS (OECD 2002) and was used to inform the hazard evaluation of this screening assessment.

A literature search was conducted from the year prior to the OECD SIAR (March 2002) to 2015. No health effects studies, which could impact the risk characterization (i.e., result in different critical endpoints or lower points of departure/target margins of exposure than those stated in OECD 2002) were identified.

2-MBS was rapidly eliminated mostly in urine in Wistar rats following oral administration, with approximately 85% in urine within 48 hours in males (300 mg/kg bw) and 43% to 92% in urine within 24 hours in females (20 mg/kg bw to 200 mg/kg bw; slower elimination was observed at larger doses) (Minegishi et al. 1972; Renwick et al. 1978). In human subjects orally given 0.2 mg/kg bw 2-MBS, it was eliminated more slowly than in rats, with about 56% recovery in urine in 24 hours and 86% in 48 hours (Renwick et al. 1978).

There are no repeated-dose dermal studies.

Overall, the genotoxic potential of 2-MBS is considered to be negative (OECD 2002).

Four studies relating to the carcinogenic potential of 2-MBS are discussed below.

In a lifetime feeding study conducted by Schmähl (1978) in Sprague-Dawley (SD) rats, there was a slight increase in papillomas of the bladder in a small number of animals in the mid-dose (20 mg/kg bw per day) and high-dose (200 mg/kg bw per day) groups. Carcinoma in the urinary bladder was observed in only one animal at the high dose. These results show low incidences, late onset, a fairly flat dose response, and a lack of reported urinary bladder hyperplasia. The reliability of the study results is considered to be low due to numerous study limitations.

A mechanistic study to investigate tumorigenicity conducted by Arnold et al. (1979) included two experiments that showed gestational exposure to 2-MBS elicited a dose-dependent increase in microscopic renal and bladder calculi and bladder lesions in SD rats. These effects could potentially lead to tumour development due to irritation of the bladder wall. In the first experiment, 2-MBS was administered via gavage to dams throughout gestation and lactation up to 250 mg/kg bw per day. After weaning, pups were fed equivalent diets and sacrificed at 8, 15, 21 and 105 days postpartum. Results showed a statistically significant dose-dependent increase in incidence of microscopic bladder calculi in urine of 21-day-old pups and 105-day-old rats. In the second experiment, SD rats were exposed to 0, 2.5, 25 or 250 mg/kg bw per day 2-MBS in the diet or 250 mg/kg bw per day 2-MBS with 1% NH_4Cl in drinking water to correct the urinary alkalinity to prevent the formation of calculi as suggested by Flaks et al. (1973). Rats were mated within the same group and, after weaning, their pups were administered the same dietary treatment as parental animals. Results from this experiment showed a significant dose-related increase in incidence of microscopic renal calculi and bladder lesions in 8-day-old randomly-selected pups, but not 21 or 105 day pups from dams given 2-MBS diet (no NH_4Cl); the addition of 1% NH_4Cl to the 250 mg/kg bw per day appeared to decrease the formation of calculi as no bladder lesions were observed.

The remaining animals from the second experiment (which included the parental animals and remaining pups) were used in a two-generation lifetime feeding study (Arnold et al. 1980). The administration of 2-MBS throughout lifetime (or termination of experiment at 127 weeks) did not yield a statistically significant or dose-related increase in the incidence of urinary bladder tumours in the parental animals or pups.

Although Schmähl's (1978) carcinogenicity study in SD rats reported a slight increase in urinary bladder tumours, these were deemed equivocal considering the numerous deficiencies noted. Overall, 2-MBS is not considered carcinogenic based on the lack of urinary bladder tumours in the two studies in SD rats by Arnold et al. (1979, 1980), as well as the negative results indicated by the genotoxicity database.

The two-generation study by Arnold et al. (1980) is also relevant to reproductive and developmental toxicity. Statistically significant decreased growth rates and feed intake in both generations and statistically significant decreased litter size were observed in the highest dose groups (250 mg/kg bw per day). Also in these groups, there was a significant decrease in average pup body weight (when adjusted for litter size at 4 days post-partum). Based on these results, the no-observed-adverse-effect level (NOAEL) and lowest-observed-adverse-effect level (LOAEL) for reproductive and developmental toxicity in the presence of maternal toxicity are 25 mg/kg bw per day and 250 mg/kg bw per day, respectively.

In an OECD TG 422 reproductive and developmental oral gavage toxicity study, 2-MBS was administered to SD rats (13/sex/group) at doses of 0, 20, 100 or 500 mg/kg bw per day; males were exposed for 42 days and females were exposed from 4 days pre-mating through day 3 of lactation (MHW 1999). Hematology and clinical chemistry were only conducted in males. At the mid-dose of 100 mg/kg bw per day and above, significant decreased body weight, increased cholesterol and liver effect (liver hypertrophy with ground glass appearance in both sexes, increased relative liver weight in females) and increased relative kidney weight in males were observed. Significant reduction in body weights of pups was observed at birth and day 4 in both sexes at 500 mg/kg bw per day; lower litter size was also observed but not statistically significant. The NOAEL and LOAEL from this study are considered to be 20 mg/kg bw per day and 100 mg/kg bw per day, respectively.

6.3 Characterization of Risk to Human Health

Overall, 2-MBS is not considered genotoxic or carcinogenic. Therefore, characterization of risk in this screening assessment is based on non-cancer effects.

The OECD TG 422 reproductive and developmental toxicity study was identified as an appropriate study for risk characterization. In this study, the NOAEL of 20 mg/kg bw per day and the LOAEL of 100 mg/kg bw per day were identified on the basis of statistically significant decreased body weight, increased cholesterol and liver (increased liver hypertrophy with ground glass appearance in both sexes, increased relative liver weight in females) and kidney toxicity (increased relative kidney weight in males).

The two-generation lifetime feeding rat study (Arnold et al. 1980) was also identified as an appropriate study for risk characterization since the study investigated both parental animals and offspring for a chronic duration. A NOAEL of 25 mg/kg bw per day was based on significant decreased growth rates and feed intake in parental animals and pups and significant decreased litter size and pup body weights at the next dose level (LOAEL of 250 mg/kg bw per day).

Estimated exposures were compared to the NOAELs of 20 to 25 mg/kg bw per day to derive margins of exposure (MOEs) for determination of risk (see Table 6-1 below). These are conservative critical effect levels for characterizing risk for acute exposures.

Table 6-1. Summary of MOEs (based on comparison of exposure to NOAEL range of 20 - 25 mg/kg bw per day).

Exposure Scenario	Estimated Exposure	MOE
Total daily intake from drinking water, dust and food[a]	2.98×10^{-5} to 2.53×10^{-4} mg/kg bw per day	79 000 to 830 000
Nail polish (acute, dermal)	7.1×10^{-3} mg/kg bw	2800

[a] See Appendix B for total daily intake of 2-MBS from water consumption, dust and food for various age groups.

Margins of exposure range from 2800 to 830 000 are considered adequate to address uncertainties in the exposure and hazard databases.

6.4 Uncertainties in Evaluation of Risk to Human Health

There is uncertainty from the lack of information regarding 2-MBS in products available to consumers other than nail polish in the Canadian marketplace. However, even if 2-MBS was found in toys and toothbrushes at similar concentrations as reported in the Danish assessment (Danish EPA 2015), risk to human health would not be expected.

There is also uncertainty in the use of a 5% concentration of 2-MBS in nail polish formulations that may not be the maximum concentration currently in the Canadian marketplace because reported concentrations, based on notifications submitted to Health Canada (personal communications, emails from Consumer Product Safety Directorate, Health Canada, to Risk Management Bureau, Health Canada, 2015; unreferenced) ranged from 0.1 to 10% for tosylamide, which is a mixture of 2-MBS and 4-MBS.

There is uncertainty with route-to-route extrapolation given the absence of dermal repeat-dose toxicology studies and, accordingly, oral NOAELs and a dermal absorption value were used to derive a MOE for the application of nail polish.

7. Conclusion

Considering all available lines of evidence presented in this screening assessment, there is low risk of harm to organisms and the broader integrity of the environment from 2-MBS. It is concluded that 2-MBS does not meet the criteria under paragraphs 64(*a*) or (*b*) of CEPA as it is not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

On the basis of the information presented in this screening assessment, it is concluded that 2-MBS 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.

Therefore, it is concluded that 2-MBS does not meet any of the criteria set out in section 64 of CEPA.

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Appendix A. Exposure factors used to derive estimates from environmental media

Exposures from environmental media (i.e., drinking water, dust and food) were estimated for different age groups based on Health Canada's exposure factors for the general population of Canada (Health Canada 1998). The relevant exposure factors are summarized in Table A-1.

Table A-1. Health Canada's exposure factors for the general population of Canada

Age groups[a]	Body weights[a] (kg)	Water intake[a] (L per day)	Dust ingestion rate[b] (mg per day)
Infants (0–6 mo)	7.5	0.8[c] or 0.3[d]	38
Toddlers (0.5–4 yr)	15.5	0.2	41
Children (5–11 yr)	21.0	0.4	31
Teenagers (12–19 yr)	59.4	0.4	2.2
Adults (20–59 yr)	70.9	0.4	2.5
Seniors (≥60+ yr)	72.0	0.4	2.5

Abbreviations: mo, months; yr, years.
[a] Based on Health Canada's exposure factors for the general population of Canada (Health Canada 1998).
[b] Based on Wilson et al. 2013.
[c] Assumed to be formula-fed, intake of water is for powder formula.
[d] Assumed to consume table foods.

Appendix B. Estimates of daily intake from food and estimates for total daily intake from water, dust and food

Estimates of dietary intake of 2-MBS were generated based on potential exposure to 2-MBS as an impurity in foods that are permitted to contain saccharin (USP 2016a, 2016b).

Although saccharin is only permitted for use as a food additive in certain foods (Health Canada [modified 2016]), the conditions of its use were applied to a much broader category of food for the purposes of the assessment. The exposure assessment is considered to be a very conservative approach due to the following assumptions:

- All food-grade saccharin contains 2-MBS as an impurity and the 2-MBS is at the maximum permitted level of 10 ppm;
- All fruits and fruit products contain 2 µg of 2-MBS per kg of food (assuming that all foods in this category would contain the maximum level of saccharin that is permitted in unstandardized fruit spreads, or 0.02%);

- All foods, primarily sugar[5] contain 9 µg of 2-MBS per kg of food (assuming that all sugar-based foods would contain the maximum level of saccharin that is permitted in toppings and topping mixes, or 0.09%);
- All soft drinks and alcohol contain 12 µg of 2-MBS per kg of food (assuming that all foods in this category would contain the maximum level of saccharin that is permitted in unstandardized alcoholic liqueurs 0.12%); and
- Individuals always choose foods that are sweetened with saccharin.

The amounts of foods consumed for each food category on a daily basis by each age group are described by Health Canada (1998). Daily food intakes were obtained from the 1970–1972 Nutrition Canada Survey.

Total intake resulting from the daily intake of water, dust and food are shown in Table B-1.

Table B-1. Estimates (mg/kg bw per day) of total daily intake of 2-MBS from water consumption, dust and food for various age groups in humans

Route of Exposure	0–6 mo breast-fed	0–6 mo formula-fed[a]	0.5–4 yr[a]	5–11 yr	12–19 yr	20–59 yr	≥60 yr
Drinking Water[b]	0	2.56×10^{-5}	3.10×10^{-6}	3.10×10^{-6}	1.62×10^{-6}	1.35×10^{-6}	1.33×10^{-6}
Dust[c]	2.98×10^{-5}	2.98×10^{-5}	1.56×10^{-5}	5.89×10^{-6}	2.18×10^{-7}	2.08×10^{-7}	2.05×10^{-7}
Food[d]	0	0	2.35×10^{-4}	1.61×10^{-4}	1.22×10^{-4}	1.82×10^{-4}	1.49×10^{-4}
Total Intake[e]	2.98×10^{-5}	5.54×10^{-5}	2.53×10^{-4}	1.70×10^{-4}	1.24×10^{-4}	1.84×10^{-4}	1.50×10^{-4}

Abbreviations: mo, months; yr, years.
[a] The *Food and Drug Regulations* do not permit the addition of saccharin or its salts to any infant foods, including infant formula. In addition to consumption of infant foods by those in the formula-fed 0-6 mo age group, some younger children in the 0.5-4yr age group may also consume some infant foods.
[b] Estimated concentration of 2-MBS in water = 0.24 µg/L (Richter et al. 2008).
[c] Estimated concentration of 2-MBS in dust = 5.89 µg/g (Won and Lusztyk 2011).
[d] Estimated concentration of 2-MBS in fruits and fruit products = 2 µg/kg, in foods, primarily sugar = 9 µg/kg, and in soft drinks and alcohol = 12 µg/kg.
[e] Maximal daily intake from drinking water, dust and food.

[5] Individual food items included in this food group i.e., white sugar, pancake syrup, jams, honey, puddings, chocolate candy, other candy, gelatin, desserts, and baby food-desserts (Health Canada 1998).