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Screening Assessment

Other Polymers Group

Chemical Abstracts Service Registry Numbers

27083-27-8 and 32289-58-0

55818-57-0

67762-15-6

125826-44-0

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Synopsis

Pursuant to section 74 of the *Canadian Environmental Protection Act, 1999* (CEPA), the Minister of Environment and the Minister of Health have conducted a screening assessment of four substances referred to collectively under the Chemicals Management Plan as the Other Polymers Group. Substances in this group were identified as priorities for assessment as they met categorization criteria under subsection 73(1) of CEPA. Their Chemical Abstracts Service Registry Number (CAS RN[1]), *Domestic Substances List* (DSL) names and acronyms are listed in the table below.

Substances in the Other Polymers Group

CAS RN	DSL name	Acronym
55818-57-0	Phenol, 4,4'-(1-methylethylidene)bis-, polymer with (chloromethyl)oxirane, 2-propenoate	DGEBA-DA resin
32289-58-0 27083-27-8[a]	Poly(iminocarbonimidoyliminocarbonimidoylimino-1,6-hexanediyl), hydrochloride Guanidine, *N*,*N*'''-1,6-hexanediylbis[*N*'-cyano-, polymer with 1,6-hexanediamine, hydrochloride	PHMB
67762-15-6	Soybean oil, polymer with maleic anhydride, pentaerythritol and phthalic anhydride	Soya alkyd resin
125826-44-0	Hexanedioic acid, polymer with 2,2-dimethyl-1,3-propanediol, 1,6-hexanediol, hydrazine, 3-hydroxy-2-(hydroxymethyl)-2-methylpropanoic acid and 1,1'-methylenebis[4-isocyanatocyclohexane], compd. with *N*,*N*-diethylethanamine	Polyurethane-33

[a] This CAS RN was previously assessed under the second phase of polymer rapid screening, but it is being reassessed as it is equivalent to CAS RN 32289-58-0.

DGEBA-DA resin, PHMB (CAS RNs 32289-58-0 and 27083-27-8), soya alkyd resin, and polyurethane-33 were identified in the second phase of polymer rapid screening (ECCC, HC 2018) as having either low water solubility/extractability or low potential for exposure and were characterized as having low potential for ecological risk. However, they were identified on the basis of structural alerts, toxicological information and/or uses associated with significant consumer exposure as requiring further assessment due to potential human health risk. The present assessment further elaborates on the potential for DGEBA-DA resin, PHMB (CAS RNs 32289-58-0 and 27083-27-8), soya

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alkyd resin, and polyurethane-33 to cause harm to human health in order to reach an overall conclusion under section 64 of CEPA.

While conducting this assessment, it was determined that CAS RN 27083-27-8 is synonymous with CAS RN 32289-58-0; the former is described by the starting monomers, and the latter is described by the resulting polymer. As a result, the two CAS RNs can be used interchangeably. Although it had been determined that CAS RN 27083-27-8 did not meet the criteria under section 64 of CEPA during the second phase of polymer rapid screening, this CAS RN is being reassessed in this report. It is additionally noted that PHMB may also be identified by two other CAS RNs (28757-47-3 and 1802181-67-4) outside of Canada; these additional CAS RNs are not on the DSL and would be subject to notification and assessment under the *New Substances Notification Regulations (Chemicals and Polymers)* [NSNR (C&P)] prior to being imported or manufactured in Canada.

DGEBA-DA resin does not occur naturally in the environment. In Canada, it is reported to be used as a binder, sealant, and reactive oligomer in the coating, automotive and adhesive industries, as well as in printing inks and overprint varnishes, packaging (including food packaging materials), books, newsprint, cosmetics, toners, and colourants. According to the information submitted in response to a CEPA section 71 survey, between 100 000 and 1 000 000 kg of DGEBA-DA resin were either manufactured in or imported into Canada in 2014. Although DGEBA-DA resin contains acrylates (a reactive functional group [RFG] associated with adverse human health effects), almost all DGEBA-DA resin in commercial and consumer applications is present in its cured-form, lacking the free acrylates present in the monomers and any other RFGs or structural features associated with human health concerns. Acrylate groups present in the uncured substance are associated with dermal sensitization, subchronic toxicity with effects on the prostate, and genotoxicity. However, a negligible amount of unreacted material is expected to be present in the cured DGEBA-DA resin. Neither direct exposure (oral, inhalation, dermal) nor indirect exposure of the general population to DGEBA-DA resin through residues in drinking water is expected.

PHMB does not occur naturally in the environment. PHMB is used globally as a preservative or antimicrobial agent, mostly in cosmetics, natural health products, non-prescription drugs, pesticides, fabric softeners, contact lens solutions, and hand washes (including hand sanitizers). According to the information submitted in response to a CEPA section 71 survey, the substance is not manufactured in Canada, but between 100 and 1 000 kg of PHMB were imported into Canada in 2014. In Canada, direct exposure (oral, dermal, inhalation) of the general population to PHMB is expected. The greatest risk is associated with inhalation exposure. On April 7, 2017, the European Commission’s Scientific Committee on Consumer Safety adopted the opinion that the use of PHMB as a preservative in cosmetic products at concentrations up to 0.1% is safe but that its use in sprayable formulations is not advised. PHMB has high inhalation toxicity, and Commission Regulation (EU) 2019/831 states that PHMB should not be used in applications that may lead to exposure of the end user’s lungs by inhalation (EU

2019). Cosmetic products containing PHMB can be purchased by Canadians. The International Nomenclature of Cosmetic Ingredients (INCI) database identifies CAS RN 32289-58-0 under the INCI name of “polyaminopropyl biguanide,” and according to notifications submitted under the *Cosmetic Regulations* to Health Canada, this substance has been present in 271 cosmetics since 2015. Around half of these products list this substance at less than 0.1%, but a small number of products show concentrations of up to 3%. Considering a concentration of 0.1% PHMB in a cosmetic spray product, margins of exposure (MOEs) of 22.7 and 7.4 for adults and children, respectively, were estimated. The calculated MOEs for cosmetic spray products are considered inadequate to address uncertainties in the health effects and exposure databases. PHMB is listed with a non-medicinal role for topical use only, up to 0.1%, as a preservative antimicrobial, and is not permitted in sprayable formulations, in the Natural Health Products Ingredients Database. Indirect exposure of the general population to PHMB through environmental residues in drinking water is not anticipated. PHMB is also a dermal sensitizer. Cross-sensitization from respiratory exposure is not known. Therefore, the MOEs for PHMB when used in applications where it can be inhaled are not sufficient to address uncertainties in the health effects and exposure datasets.

On the basis of further evaluation, soya alkyd resin and polyurethane-33 were identified as meeting the criteria used to identify polymers of low concern of the NSNR (C&P). Both of these substances are used in coatings, such as paints. Polymers of low concern are generally of low ecological and human health hazard. As such, these two polymers are not a concern to human health.

Considering all available lines of evidence presented in this screening assessment, there is low risk of harm to the environment from DGEBA-DA resin, PHMB (CAS RNs 32289-58-0 and 27083-27-8), soya alkyd resin, and polyurethane-33. It is concluded that these substances 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.

Considering all the information presented in this screening assessment, it is concluded that DGEBA-DA resin, soya alkyd resin, and polyurethane-33 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 to human life or health in Canada. However, it is concluded that PHMB (CAS RNs 32289-58-0 and 27083-27-8) meets the criteria under paragraph 64(*c*) of CEPA as it is entering or may enter 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 DGEBA-DA resin, soya alkyd resin, and polyurethane-33 do not meet any of the criteria set out in section 64 of CEPA, but that PHMB (CAS RNs 32289-58-0 and 27083-27-8) does meet the criteria in section 64 of CEPA.

It is also concluded that PHMB (CAS RNs 32289-58-0 and 27083-27-8) meets the persistence criteria but not the bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations* of CEPA.

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1. Introduction

Pursuant to section 74 of the *Canadian Environmental Protection Act, 1999* (CEPA) (Canada 1999), the Minister of Environment and the Minister of Health have conducted a screening assessment of four substances referred to collectively under the Chemicals Management Plan as the Other Polymers Group to determine whether these substances present or may present a risk to the environment or to human health. The substances in this group were identified as priorities for assessment as they met categorization criteria under subsection 73(1) of CEPA (ECCC, HC [modified 2017]).

The substances considered in this screening assessment have been previously evaluated using a rapid screening approach. The approach and results of its application are presented in the Second Phase of Polymer Rapid Screening: Results of the Screening Assessment (ECCC, HC 2018). Application of these approaches identified PHMB (CAS RNs[2] 32289-58-0 and 27083-27-8), DGEBA-DA resin, soya alkyd resin, and polyurethane-33 as having low potential to cause ecological harm. The ecological rapid screening approach is summarized in Appendix A of this screening assessment. These results, in conjunction with any other relevant information that became available after the publication of the report on the second phase of polymer rapid screening, are considered in support of the conclusions made under section 64 of CEPA in this screening assessment.

PHMB, identified under CAS RN 27083-27-8, was assessed during polymer rapid screening, and it was concluded that it did not meet the criteria of section 64 of CEPA on the basis of information received from a survey issued pursuant to section 71 of CEPA (Canada 2015) which indicated a low quantity in commerce. It was subsequently determined that CAS RN 27083-27-8 is synonymous with PHMB (CAS RN 32289-58-0); the former is described by the starting monomers, while the latter is described by the resulting polymer. Because these two CAS RNs represent the same substance, a re-assessment of PHMB, considering both CAS RNs 27083-27-8 and 32289-58-0, is conducted in this screening assessment. The combined import volume associated with the two CAS RNs did not change the previous conclusion of low potential for PHMB to cause ecological harm.

While the four substances considered in this screening assessment are collectively referred to as the Other Polymers Group, the substances in this group, with the exception of the two CAS RNs for PHMB, lack structural similarities that would support

[2] The Chemical Abstracts Service Registry Number (CAS RN) is the property of the American Chemical Society and any use or redistribution, except as required in supporting regulatory requirements and/or for reports to the Government of Canada when the information and the reports are required by law or administrative policy, is not permitted without the prior, written permission of the American Chemical Society.

a group approach to exposure, hazard and risk characterization. Therefore, their exposure and hazard profiles were independently assessed for risk.

This screening assessment includes consideration of additional information on chemical properties, environmental fate, hazards, uses and exposures, including additional information submitted by stakeholders. Relevant data were identified up to January 2022. Empirical data from key studies as well as results from models were used to reach the conclusions. When available and relevant, information presented in assessments from other jurisdictions was considered.

This screening assessment was prepared by staff in the CEPA Risk Assessment Program at Health Canada and Environment and Climate Change Canada, and incorporates input from other programs within these departments. The Second Phase of Polymer Rapid Screening: Results of the Screening Assessment (ECCC, HC 2018), on which some of the results of this screening assessment are based, has undergone external review and was subject to a 60-day public comment period. Additionally, the draft of this screening assessment was published October 3, 2020, and was subject to a 60-day public comment period. While external comments were taken into consideration, the final content and outcome of this screening assessment remain the responsibility of Health Canada and Environment and Climate Change Canada.

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

2. DGEBA-DA resin

2.1 Substance identity

DGEBA diacrylate resin (diglycidyl ether of bisphenol-A acrylate; DGEBA-DA resin; CAS RN 55818-57-0) is an epoxy acrylate resin. A list of additional chemical names (for example, trade names) is available from SciFinder (SciFinder 2018). DGEBA-DA resin is produced by reaction between DGEBA epoxy resin (CAS RN 25068-38-6) and acrylic

[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.

acid (Nishikubo et al. 1974; Mohtadizadeh and Zohurian-Mehr 2013; Baig et al. 2012). This ring-opening/esterification reaction replaces epoxide rings with two terminal acrylate groups. The reaction and representative structure of DGEBA-DA resin are presented in Figure 2-1. No residual monomers (that is, DGEBA epoxy resin and acrylic acid) are expected to remain as the process involves several purification stages to remove all impurities (Mohtadizadeh and Zohurian-Mehr 2013). As in the case of DGEBA epoxy resin, the average degree of polymerization (*n*) for DGEBA-DA resin is expected to be ≤ 0.1, with an average molecular weight of 500 g/mol (Canada 2015; ECHA 2017; Cui et al. 2014). This low *n* means that the majority of DGEBA-DA resin (theoretically more than 90%) comprises bisphenol A diglycidyl ether diacrylate (DGEBA-DA; CAS RN 4687-94-9; a *Domestic Substances List* (DSL) substance), that is, when *n* = 0 (Canada 2015).

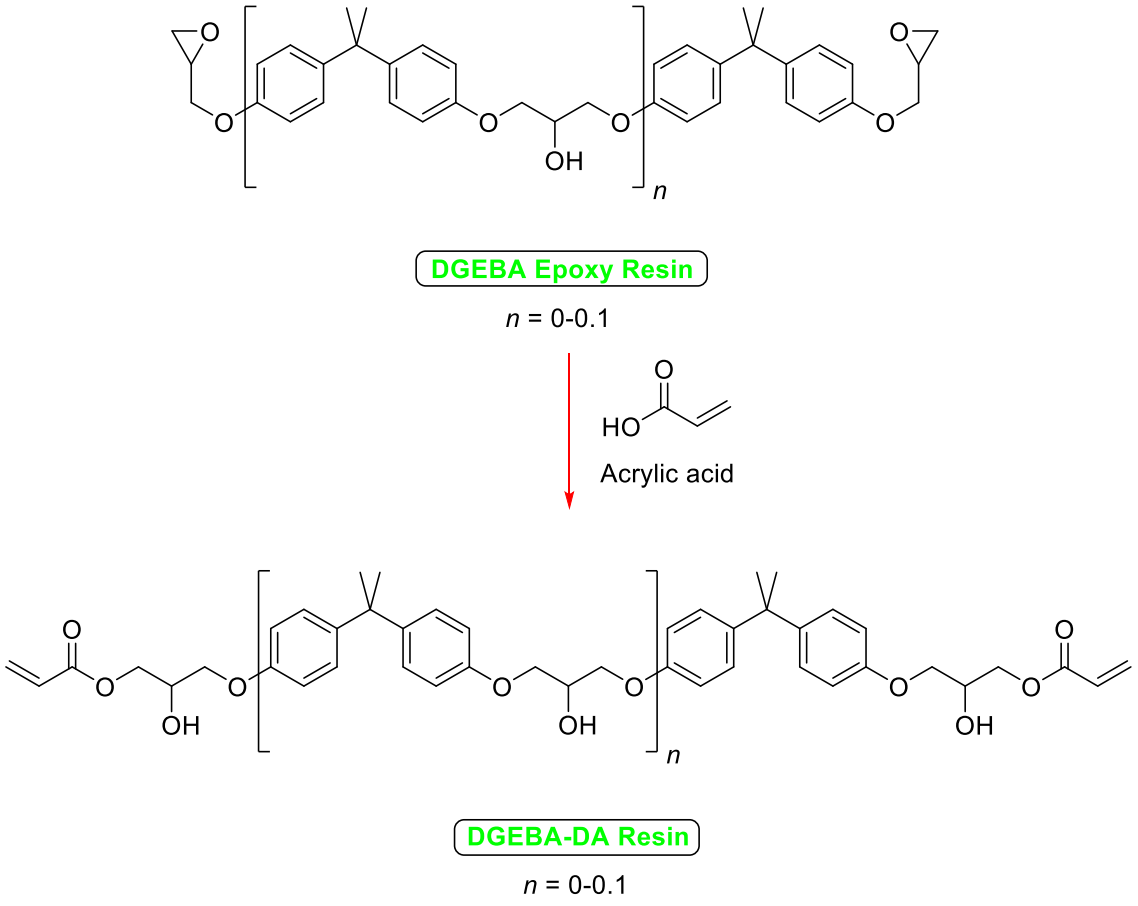


Figure 2-1. Synthesis and representative structure of DGEBA-DA resin

The performance characteristics of DGEBA-DA resin are due to the presence of the bisphenol A (BPA) moiety (rigidity, toughness, and elevated temperature performance), the ether linkages (chemical resistance), and the hydroxyl and acrylate groups (reactivity with a variety of curing agents) (Pascault and Williams 2010). Theoretically, two terminal acrylate groups are present in DGEBA-DA resin (Figure 2-1). Acrylates are a reactive functional group (RFG) associated with adverse human health effects (US EPA 2010).

Epoxy acrylates (such as DGEBA-DA resin) are curable via initiated free-radical polymerization of their terminal double bonds (C=C). Cured epoxy acrylates, therefore, no longer contain any acrylate groups but rather a cross-linked/polymerized structure with no RFG associated with adverse human health effects. Several curing methods for epoxy acrylates include light [ultraviolet (UV) radiation], heat, high/radio frequency and electron beam (EB) radiation. UV curing is used most frequently since it is environmentally benign and occurs rapidly at lower temperature (Kim et al. 2015; Hong et al. 2005). Cured epoxy acrylates are growing in importance in adhesives, inks, and photoresist applications (Sun and Chmielewski 2017; Kirk-Othmer 2004). They have much greater strength, stiffness, and toughness than conventional epoxy acrylates. Cured epoxy acrylates also have considerable chemical resistance and mechanical properties at both room and elevated temperatures (Petrie 2006; Chattopadhyay et al. 2005; Ahmad et al. 2005; Aalta-Korte 2012). One study showed that cured DGEBA-DA resin (Figure 2-2) has a cross-linked structure with a number average molecular weight (Mn) of 810 to 3070 g/mol, depending on the curing conditions (Matsubara and Ohtani 2006).

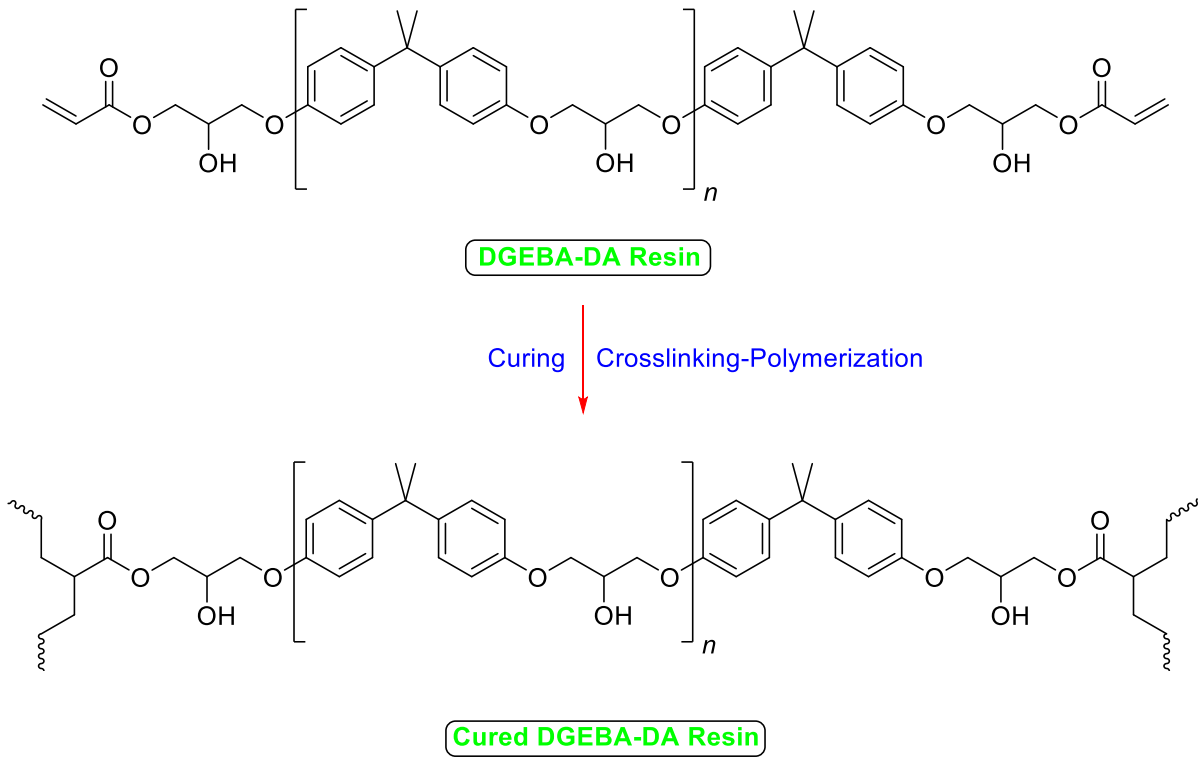


Figure 2-2. Crosslinking-polymerization of DGEBA-DA resin by curing

2.2 Physical and chemical properties

A summary of physical and chemical properties for DGEBA-DA resin is presented in Table 2-1.

Table 2-1. Physical and chemical property values for DGEBA-DA resin

Property	DGEBA-DA resin	Key reference(s)
Physical state	Liquid	ECHA 2017, Canada 2015
Molecular weight (g/mol)	472-822 (avg. 500)	ECHA 2017, Canada 2015
Melting point (°C)	< -110 °C	ECHA 2017
Boiling point (°C)	220 °C (decomposition)	ECHA 2017

Property	DGEBA-DA resin	Key reference(s)
Vapour pressure (Pa)	< 1 x 10^{-4} @ 20 & 50 °C 0 @ 40 °C < 2 x 10^{-3} @ 145 °C	ECHA 2017
Water solubility	Insoluble/negligible	Nishikubo et al. 1974, Canada 2015
Density (g/cm^3)	1.195 @ 20 °C 1.18 @ 25 °C	ECHA 2017, Canada 2015
Hydrolysis (half-life, 25 °C)	Stable @ pH 4 110 hours @ pH 7 38 hours @ pH 9	ECHA 2017
Photodegradation (half-life)	0.7 – 78.5 hours	ECHA 2017
Octanol-water partition co-efficient (log K_{ow})	3 to 3.8	ECHA 2017, Cannon et al. 2000
Absorption-desorption (log K_{oc})	3.55	ECHA 2017
Biodegradation	Inherently biodegradable: 42% after 28 days	ECHA 2017

2.3 Sources and uses

DGEBA-DA resin is prepared industrially. Uncured DGEBA-DA resin is predominantly encountered in industrial settings. It is marketed in different physical forms and requires an admixture with curing agents to form the nonreactive cross-linked polymer (Pascault and Williams 2010).

DGEBA-DA resin has been included in a voluntary survey (ECCC 2015) as well as a mandatory survey issued pursuant to section 71 of CEPA (Canada 2015). Table 2-2 below presents a summary of the total reported manufacture and import quantities for the substance in 2014. These sources indicate that the primary uses for DGEBA-DA resin in Canada are as a binder, sealant, and reactive oligomer in the coating, automotive, and adhesive industries. It is also used in printing inks and overprint varnishes, packaging, books, newsprint, toners, and colourants. In UV ink vehicles, DGEBA-DA resin polymerizes to a dried ink film when applied to paper or plastic.

Table 2-2. Summary of information on Canadian manufacturing and import quantities of DGEBA-DA resin in 2014 submitted pursuant to a voluntary survey and to a survey under section 71 of CEPA

Total manufacture[a] (kg)	Total imports[a] (kg)	Survey reference
100 000–1 000 000	100 000–1 000 000	Canada 2015 ECCC 2015

[a] Values reflect quantities reported in response to a voluntary survey (ECCC 2015) and a mandatory survey issued pursuant to section 71 of CEPA (Canada 2015). See mandatory survey for specific inclusions and exclusions (Schedules 2 and 3).

Globally, DGEBA-DA resin is used in screen ink vehicles, clear coatings for paper, wood and metal decorating, and laminating adhesives (Ash and Ash 2007; US FDA 2017). Epoxy acrylates (including DGEBA-DA resin) are used in UV and EB curing of coatings, UV and EB varnishes for paper and board, wood (furniture and flooring), plastics (including compact discs and optical fibers), and metal surfaces as well as lithographic and silk-screen inks for paper and board (Fouassier and Rabek 1993; Petrie 2006). Epoxy acrylates provide varnishes with high gloss, good adhesion, and excellent scuff resistance. It is also used in exterior can coatings (Pham and Marks 2004). DGEBA-DA resin has been used in cosmetics, such as gel nail and top gel products in manicuring (Choi et al. 2015).

A number of domestic government databases were searched to determine whether DGEBA-DA resin is registered and/or approved for uses in Canada. These uses for DGEBA-DA resin are listed in Table 2-3.

Table 2-3. Additional uses in Canada for DGEBA-DA resin

Use	DGEBA-DA resin
Food packaging materials[a]	Yes
Notified to be present in cosmetics, based on notifications submitted under the *Cosmetic Regulations* to Health Canada[b]	Yes
Known toy use[c]	Yes

[a] Personal communication, email from the Food Directorate, Health Canada, to the New Substances Assessment and Control Bureau, Health Canada, dated September 2017; unreferenced.
[b] Personal communication, email from the Consumer and Hazardous Products Safety Directorate, Health Canada, to the New Substances Assessment and Control Bureau, Health Canada, dated September 2017; unreferenced.
[c] Toy Industry Association (TIA 2017).

2.4 Potential to cause ecological harm

Critical data and considerations used during the second phase of polymer rapid screening to evaluate the substance-specific potential to cause ecological harm are presented in ECCC (2016).

DGEBA-DA resin was identified as having low water extractability/solubility in the second phase of polymer rapid screening (ECCC, HC 2018). Therefore, this substance was characterized as having a low potential for ecological risk. It is unlikely that this substance is resulting in concerns for the environment in Canada.

2.5 Potential to cause harm to human health

2.5.1 Exposure assessment

2.5.1.1 Direct exposure

As indicated in section 2.1, DGEBA-DA resin contains a substantial amount of DGEBA-DA (CAS RN 4687-94-9). Therefore, the studies performed on DGEBA-DA may apply to DGEBA-DA resin.

When used industrially, direct exposure of the general population to DGEBA-DA resin is not expected. The release of DGEBA-DA resin from end-use applications (commercial and consumer) is very limited as this resin is reacted with hardeners/curing agents into a cross-linked system that is stable against thermal and hydrolytic breakdown (Matsubara and Ohtani 2006; Canada 2015; PSS/Ashland 2016; GPS/BASF 2011). In general, it is expected that all epoxy acrylates (such as DGEBA-DA resin) would react completely to form part of a stable polymer matrix from which they are no longer able to be released.

DGEBA-DA resin may be employed as a component in printing ink used in food packaging. The printing inks are used on the outside of packaging materials and therefore have no direct food contact. Dietary exposure to DGEBA-DA resin through its use in food packaging materials is therefore not expected [personal communication, emails from the Food Directorate, Health Canada, to the New Substances Assessment and Control Bureau, Health Canada, dated September 2017; unreferenced].

According to notifications submitted under the *Cosmetic Regulations* to Health Canada, DGEBA-DA resin is used in certain cosmetics in Canada, such as adhesive in nail products. No information is available for additional products available to consumers (personal communication, email from the Consumer and Hazardous Products Safety Directorate, Health Canada, to the New Substances Assessment and Control Bureau, Health Canada, dated September 2017; unreferenced). Although DGEBA-DA resin has been used in cosmetics, dermal absorption is not expected to be significant because it is used in cured form (Draelos 2015).

According to the Canadian Toy Industry Association (TIA 2017), DGEBA-DA resin is used as a component of polyurethane foams and paints in toys. Because it is used in cured form, the intake of DGEBA-DA resin through exposure to toys is considered negligible.

DGEBA-DA resin has low vapour pressure, and therefore inhalation exposure is not expected.

In summary, dietary exposure to DGEBA-DA resin through its use in food packaging materials is not expected, inhalation exposure to DGEBA-DA resin is not expected due to its low vapour pressure, and dermal exposure to DGEBA-DA resin is not expected to be significant because it is used in cured form.

2.5.1.2 Indirect exposure

In the event of an unforeseen environmental release of DGEBA-DA resin, it is not expected to become widely distributed in the aquatic environment given its very low water solubility. DGEBA-DA resin is inherently biodegradable and hydrolyzable. Consequently, the indirect exposure of the general population to DGEBA-DA resin through environmental media or drinking water is not expected.

2.5.2 Health effects assessment

During evaluation under the second phase of polymer rapid screening (ECCC, HC 2018), DGEBA-DA resin (CAS RN 55818-57-0) was identified as requiring further assessment as a result of the presence of acrylate RFGs which are associated with adverse human health effects, including subchronic toxicity, genotoxicity, and dermal sensitization.

A European Chemicals Agency document on the substance showed that DGEBA-DA resin has a low acute oral and dermal toxicity in rats, with an LD_{50} above 2 000 mg/kg bw. It is not a skin irritant in rabbits, but it is an eye irritant (ECHA 2011). It was positive in a local lymph node assay (LLNA) for dermal sensitization, with an EC_3 value of 13.8%, which is indicative of a weak sensitizer (>10%). In a 90-day subchronic study performed in Wistar rats (10 animals/sex/dose), the test substance was diluted in polyethylene glycol and administered by oral gavage at doses of 100, 300 or 1 000 mg/kg bw/day (ECHA 2011). A no-observed-adverse-effect level (NOAEL) of less than 100 mg/kg bw/day was established as a result of a decrease in prostate weight at the lowest dose tested, 100 mg/kg bw/day. Additional organ weight changes and clinical chemistry changes were also observed at higher doses. The substance was negative for genotoxicity *in vitro* in an Ames test (bacterial reverse mutation test). It was also negative in an *in vivo* mammalian micronucleus test for chromosomal aberrations using doses of 500, 1 000 and 2 000 µg/kg bw. Although there are no chronic or carcinogenicity studies in animals by any route, based on its toxicity profile (negative genotoxicity and no histopathological changes in repeated-dose oral studies), the substance is not expected to be carcinogenic (CPDB 2005). A combined repeated-dose and reproductive/developmental toxicity screening was conducted in rats at doses of 100, 300 and 1 000 mg/kg bw/day. There was no maternal toxicity and no embryotoxicity/teratogenicity at doses up to 1 000 mg/kg bw/day. As a result, the

NOAEL was considered to be greater than 1 000 mg/kg bw/day, indicative of low toxicity (ECHA 2011).

Toxicity data on DGEBA-DA (CAS RN 4687-94-9) (as opposed to DGEBA-DA resin) and other structurally-related compounds were limited to its potential for skin irritation and dermal sensitization (SDS 2018).

2.5.3 Characterization of risk to human health

In this assessment, the human health risks were established through consideration of both the hazard and the direct and indirect exposures of the substance for current uses identified from a voluntary survey (ECCC 2015) and a survey issued pursuant to section 71 of CEPA (Canada 2015).

BPA is a component of DGEBA-DA resin and was identified as being toxic under paragraphs 64(*a*) and 64(*c*) of CEPA with human health concerns for reproductive and developmental toxicity (Canada 2008). BPA is not expected to be released from this substance, and therefore does not pose a health concern as a result of direct or indirect exposure.

Free acrylate groups can react with skin proteins to cause an allergic response (dermal sensitization). However, given the negligible exposure of unreacted material in end-use products and the weak sensitization potential of the substance, a sensitization reaction is not expected and the risk to human health is low.

Free acrylate groups have also been associated with genotoxicity *in vitro* (Cameron et al. 1991). This effect is most often observed with simple aldehydes, such as methyl acrylate and ethyl acrylate (Moore et al. 1988). However, other small acrylates, such as butyl acrylate, were not found to be mutagenic *in vitro* (ECCC, HC 2017). Toxicological information on the substance did not show any evidence of genotoxicity *in vitro* or *in vivo*. In addition, free reactive aldehyde groups are not anticipated after polymerization, and no dermal absorption or oral exposure of unreacted material is anticipated. The risk for genotoxicity as a result of oral or dermal exposure is therefore low. Based on available information, the substance is not expected to be carcinogenic, and an estimation of the cancer risk to DGEBA-DA resin was therefore considered unnecessary.

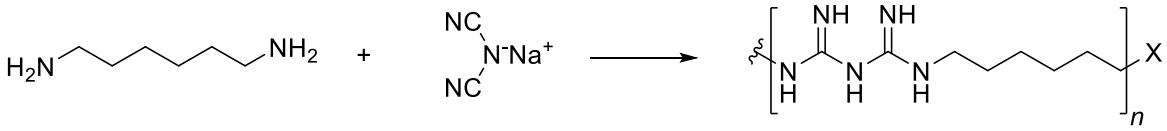
Lower mean absolute and relative prostate weights were observed at all doses tested. This effect was observed in a dose-related manner and was considered an effect of the test substance. As a result, the NOAEL is < 100 mg/kg bw/day and is considered a moderate hazard. The substance did not show any evidence of reproductive toxicity or developmental toxicity in rats. Despite the moderate hazard, calculation of a MOE was not required as exposure to the unreacted substance is not expected.

Taking into consideration the direct and indirect exposures to products available to consumers, the overall human health risk has been determined to be low.

3. PHMB

3.1 Substance identity

Poly(hexamethylenebiguanide) or PHMB (also known as polyhexanide, polihexanide, and polyaminoproyl biguanide) is a polymer of biguanide. While conducting this assessment, it was determined that CAS RN 27083-27-8 is synonymous with 32289-58-0; the former is described by the starting monomers, and the latter is described by the resulting polymer. As a result, the two CAS RNs can be used interchangeably. They are both listed on the DSL. It is additionally noted that PHMB may also be identified by two other CAS RNs: 28757-47-3 (PHMB without accompanying hydrochloride) and 1802181-67-4 (specific lower molecular weight PHMB hydrochloride from different starting monomers) (SCCS 2017; CIR 2017; ECHA 2017). The latter two CAS RNs are not listed on the DSL and would be subject to notification and assessment under the *New Substances Notification Regulations (Chemicals and Polymers)* [NSNR (C&P); Canada 2005] prior to being imported or manufactured in Canada. They are therefore not further considered in this report. It should be noted that cosmetic labels in Canada identify the ingredients with International Nomenclature of Cosmetic Ingredients (INCI) names, and the INCI name “polyaminopropyl biguanide” includes CAS RNs 27083-27-8 and 32289-58-0. Although the biguanide polymer, polyaminopropyl biguanide (CAS RN 133029-32-0), was indicated as an alternative name for PHMB (SCCS 2017), it should be clarified that the scope of this report does not include this CAS RN; the substances discussed here may be labelled using this INCI identifier. A list of additional chemical names (for example, trade names) for PHMB is available from SciFinder (2018). Several methods for manufacturing PHMB exist (Wei et al. 2009; East et al. 1997; O’Malley et al. 2006; de Paula et al. 2011). The synthesis of PHMB via the polycondensation of sodium dicyanamide with hexamethylenediamine and representative structure of PHMB are presented in Figure 3-1.



Hexamethylenediamine | Sodium dicyanamide | PHMB

n = 1-40 (average 10-13)

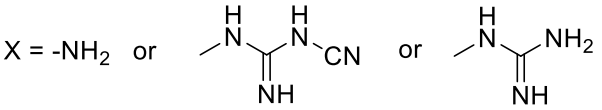


Figure 3-1. Synthesis and representative structure of PHMB

3.2 Physical and chemical properties

A summary of physical and chemical properties for PHMB is presented in Table 2-1.

Table 3-1. Physical and chemical property values for PHMB

Property	PHMB	Key reference(s)
Physical state	Solid	SCCS 2017
Molecular weight (g/mol)	1600-4220	SCCS 2017 EC 2015 Rowhani et al. 2007
Average *n*	10-13	SCCS 2017 CLH 2010 Rowhani et al. 2007
Melting point (°C)	78.9-136.3	SCCS 2017
Boiling point (°C)	205-210 (decomposed)	SCCS 2017
Vapour pressure (Pa)	0.6-1.3 x 10^{-7} (20 °C) 2.0-4.1 x 10^{-7} (25 °C)	SCCS 2017
Water solubility/extractability (%)	39.0 – 43.4 (soluble)	SCCS 2017 de Paula et al. 2011
Density (g/cm^3)	1.20	SCCS 2017
Hydrolysis	< 10% (50 °C, 5 d, *p*H 4, 7, 9)	ECHA 2011 CLH 2010
Octanol-water partition co-efficient (log K_{ow})	- 2.3	SCCS 2017 ECHA 2011 CLH 2010

Property	PHMB	Key reference(s)
Biodegradation	Not biodegradable*; 3.8% (99 d) 29% (35 d) 10.1% (56 d) No degradation (54 °C, 14 d)	SCCS 2017 ECHA 2011 CLH 2010

* Biodegradation methods: Organisation for Economic Co-operation and Development (OECD) 301B, 303A, and 306, respectively.

3.3 Sources and uses

PHMB is not a naturally occurring substance. It is prepared industrially and can be formulated for marketing in different physical forms (solid, liquid).

PHMB has been included in both a voluntary survey (ECCC 2015) and a mandatory survey issued pursuant to section 71 of CEPA (Canada 2015). Table 2-2 below presents a summary of the total reported manufacture and import quantities for the substance (both CAS RNs) in 2014. These sources indicate that the primary use of PHMB in Canada is as an antimicrobial preservative in cosmetics and pharmaceuticals (topical).

Table 3-2. Summary of information on Canadian manufacturing and import quantities of PHMB in 2014

Total manufacture[a] (kg)	Total imports[a] (kg)	Survey reference
NR	100 – 1 000	Canada 2015, ECCC 2015

Abbreviations: NR, not reported

[a] Values reflect quantities reported in response to a voluntary survey (ECCC 2015) and a mandatory survey conducted under section 71 of CEPA (Canada 2015). See mandatory survey for specific inclusions and exclusions (Schedules 2 and 3).

PHMB is used globally as a preservative and antimicrobial agent, mostly in cosmetics, natural health products (NHPs), non-prescription drugs (NPDs), pesticides, fabric softeners, contact lens solutions, and hand washes. It is effective against several strains of bacteria (Wessel 2013). As a sanitizer, PHMB is used to preserve wet wipes, to control odour in textiles, to prevent microbial contamination in wound irrigation and sterile dressings, to disinfect medical/dental utensils and trays, and farm equipment, and as an ingredient in veterinary products. It may be used as a component in sanitizers used to disinfect food contact surfaces in food processing establishments and hard surfaces in institutions and hospitals and to deodorize vacuums and toilets, and as an

antimicrobial agent to treat pet litter. As an alternative to ozone, PHMB is used in antimicrobial hand washes and rubs and air filter treatments. It is used as an active ingredient (a.i.) for recreational water treatment as a chlorine-free polymeric sanitizer. Further reported uses of PHMB include purification of swimming pool water, beer glass sanitisation, solid surface disinfection in breweries, and short-term preservation of hides and skins (SCCS 2017; TGA 2018).

A number of domestic government databases were searched to determine whether PHMB is registered and/or approved for use in Canada. The identified uses for PHMB in Canada are listed in Table 3-3.

Table 3-3. Uses in Canada for PHMB

Use	PHMB
Incidental additive[a]	Yes
Internal Drug Product Database as medicinal or non-medicinal ingredients in disinfectant, human or veterinary drug products in Canada[b]	Yes
Natural Health Products Ingredients Database[c]	Yes
Licensed Natural Health Products Database as non-medicinal ingredient in NHPs in Canada[d]	Yes
Notified to be present in cosmetics, based on notifications submitted under the *Cosmetic Regulations* to Health Canada[e]	Yes

[a] Personal communication, email from the Food Directorate, Health Canada, to the New Substances Assessment and Control Bureau, Health Canada, dated September 2017; unreferenced. While not defined under the *Food and Drugs Act*, incidental additives may be regarded, for administrative purposes, as those substances which are used in food processing plants and which may potentially become adventitious residues in foods (for example, cleaners, sanitizers).

[b] DPD [modified 2017]; personal communication, email from the Therapeutic Products Directorate, Health Canada, to the New Substances Assessment and Control Bureau, Health Canada, dated December 2017; unreferenced.

[c] NHPID [modified 2021]; personal communication, email from the Natural and Non-prescription Health Products Directorate, Health Canada, to the New Substances Assessment and Control Bureau, Health Canada, dated December 2017; unreferenced.

[d] LNHPD [modified 2021]; personal communication, email from the Natural and Non-prescription Health Products Directorate, Health Canada, to the New Substances Assessment and Control Bureau, Health Canada, dated December 2017; unreferenced.

[e] Personal communication, email from the Consumer and Hazardous Products Safety Directorate, Health Canada, to the New Substances Assessment and Control Bureau, Health Canada, dated September 2017; unreferenced.

On April 7, 2017, the European Commission's Scientific Committee on Consumer Safety (SCCS) adopted the opinion that the use of PHMB as a preservative in cosmetic products up to a concentration of 0.1% is safe, but that its use in sprayable formulations is not advised. Commission Regulation (EU) 2019/831 states that PHMB should not be used in applications that may lead to exposure of the end user's lungs by inhalation (EU 2019).

In 2018, Australia's Therapeutic Goods Administration decided to amend the Poisons Standard to allow the use of PHMB in cosmetic preparations containing 0.3% or less, when packed and labelled for therapeutic use, and in other preparations containing 5% or less (TGA 2018).

3.4 Environmental fate and behaviour

3.4.1 Environmental persistence

According to the available hydrolysis and biodegradation data, PHMB (CAS RNs 32289-58-0 and 27083-27-8) is not expected to degrade and is expected to persist in water, sediment, and soil.

3.4.2 Bioaccumulation

Given its low log K_{ow} and high Mn, PHMB (CAS RNs 32289-58-0 and 27083-27-8) is not expected to bioaccumulate in organisms.

3.5 Potential to cause ecological harm

Critical data and considerations used during the second phase of polymer rapid screening to evaluate the substance-specific potential to cause ecological harm are presented in ECCC (2016).

PHMB (CAS RNs 32289-58-0 and 27083-27-8) was classified as having high hazard potential according to information considered in the second phase of polymer rapid screening (ECCC, HC 2018). On the basis of low exposure potential, this substance was characterized as having a low potential for ecological risk. It is unlikely that this substance (both CAS RNs) is resulting in concerns for the environment in Canada. Furthermore, the combined import volume associated with the two CAS RNs did not change the previous conclusion of low potential for PHMB to be causing ecological harm.

3.6 Potential to cause harm to human health

3.6.1 Exposure assessment

3.6.1.1 Direct exposure

As previously indicated, domestic product databases (Table 3-3) indicate that PHMB is present in a number of products including cosmetics, NHPs, NPDs, and other products available to consumers, as well as in food as an incidental additive.

Oral

The high molecular weight (> 1600 g/mol) and very low K_{ow} (- 2.3) of PHMB indicate that it likely has limited oral absorption and bioavailability. Toxicokinetic studies have shown the oral absorption for PHMB in rats is within the range of 2.6% to 8.5% (US EPA 2004; APVMA 2018; EU 2015; SCCS 2017). The studies were conducted in male/female rats with single/repeated low vs. high doses of low/high molecular weight radioactive PHMB. Bioavailability was determined as the sum of urinary excretion and radioactivity in tissues and residual carcass at study termination.

The United States Environmental Protection Agency evaluated a toxicological data package on PHMB (US EPA 2004). A screening level acute dietary risk assessment (indirect dietary exposure due to surface residues, including indirect food contact) was undertaken for males and females (aged 13 to 50) and determined that exposures were 21 and 23 µg/kg bw/day, respectively. Additionally, chronic dietary exposure was reported to be < 20 µg/kg bw/day for all adult populations and 74 µg/kg bw/day for children 7 to 14 years old.

If PHMB is used as a component of sanitizers intended for food contact surfaces, it could potentially become an adventitious residue in foods, if a sanitizer containing PHMB is used to clean surfaces that directly contact food. Probable/potential daily intake (PDI) ranging from 0.053 to 0.858 µg/kg bw/day were estimated for the general population. There is no potential for direct food contact if PHMB is used as a component in sanitizers intended for food contact surfaces with a rinse after use of the sanitizer, as a component in additives for treatment of cooling and resort water, or as a component in products intended for hands with a rinse after use of the product (personal communication, email from the Food Directorate, Health Canada, to the New Substances Assessment and Control Bureau, Health Canada, dated August 2018; unreferenced).

Dermal

According to notifications submitted under the *Cosmetic Regulations* to Health Canada, PHMB is used in a variety of cosmetics in Canada, such as cleansers, make-up removers, conditioners, moisturizers, shampoos and hair styling products (personal

communication, emails from the Consumer and Hazardous Products Safety Directorate, Health Canada, to the New Substances Assessment and Control Bureau, Health Canada; dated January 2022; unreferenced). The data indicate that approximately 1.8% of these products contain PHMB at a concentration of 1% to 3%, while approximately 85% of the products contain a maximum concentration of 0.3%.

The high molecular weight (> 1600 g/mol) and very low K_{ow} (- 2.3) of PHMB indicate that the substance likely has limited dermal absorption (WHO 2006; EU 2004; SCCS 2017). In fact, studies have shown that the dermal absorption for PHMB is within the range of 3.5% to 4.1% (CIR 2017; EU 2015; SCCS 2017). For the dermal exposure estimation, and in order to align with international regulations, the concept of systemic exposure dose (SED) is being applied for this risk assessment (SCCS 2015, 2017; CIR 2017). The SED of a cosmetic ingredient is the amount expected to enter the bloodstream (and therefore be systemically available) per kg body weight per day. Generally, the SED of a cosmetic ingredient is estimated by taking into account the amount of the finished cosmetic applied per day, the concentration of the substance in the finished cosmetic, the dermal absorption of that particular substance and a mean human body weight value. In the case of PHMB, dermal absorption is reported as a percentage of the amount of substance applied, and the calculation of SED will be as follows (simplified version):

$$\mathbf{SED = (A \times C \times DA_p)/ bw}$$

Where;

SED: systemic exposure dose (mg/kg bw/day)

A: amount of cosmetic applied daily × retention factor (mg/day)

C: concentration of ingredient in finished product (1 for 100%)

DA_p: absorption through the skin (1 for 100%)

bw: typical body weight of human (kg)

As mentioned above, the concentrations (C) of PHMB in cosmetics are reported to be up to 3% in moisturizers (body, face), styling products (hair), and cleansers (make-up remover). For the purposes of this calculation, the highest potential concentration (or 0.03) was used. For the above-mentioned cosmetics, the amount of product applied daily (A) for adults was estimated as 10 000, 1 280, and 2 600 mg, respectively (SCCS 2015; Ficheux et al. 2015, 2016).

For DA_p, 4% dermal absorption (or 0.04) is chosen.

Typical body weight for an adult is chosen as 75 kg.

From the products considered, only the moisturizer, body spritzer, and certain hair products, such as detanglers, are expected to be used for children, with moisturizer being the highest source of dermal exposure. Accordingly, the values of 2 480 mg/day for A and 11 kg for the body weight of a 1-year-old child are chosen (Ficheux et al. 2015, 2016).

Using the above equation, when moisturizer is used, SEDs for adults and children (1 year old) were calculated to be 0.160 (that is, 10 000 x 0.04 x 0.03/75) and 0.271 mg/kg bw/day (that is, 2480 x 0.04 x 0.03/11), respectively.

Similarly, the SEDs based on dermal exposure from hair styling products and cleansers (only for adults) are calculated to be 0.020 (that is, 1 280 x 0.04 x 0.03/75) and 0.042 mg/kg bw/day (that is, 2 600 x 0.04 x 0.03/75), respectively.

Inhalation

According to notifications submitted under the *Cosmetic Regulations* to Health Canada, PHMB is used in cosmetic spray products in Canada that are expected to result in inhalation exposure. One of two exposure scenarios was derived using a hair detangler containing up to 0.1% PHMB; the second scenario was for a body mist containing 0.3% PHMB. PHMB has very low vapour pressure, and inhalation exposure as a result of volatilization is therefore not expected when the substance is incorporated into non-spray applications. In spray applications, however, the product may be applied to the body or hair within the breathing zone. The second exposure scenario was developed for body spray application of cosmetic toiletries designed for baby care and may contain up to 0.3% PHMB. Its use in pump sprays designed to be sprayed around the head and body may result in incidental inhalation exposure. Theoretically, only a fraction (1% to 5%) of particles with a diameter of less than 10 µm is relevant for deep lung exposure and effects (Rothe 2011). In other words, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters greater than 10 µm (with propellant sprays yielding a greater fraction of droplets/particles below 10 µm, compared with pump sprays) (CIR 2017). Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be expected to reach the deep lung. Bronchial and deep lung exposure to PHMB would present the highest risk of systemic absorption. Aerosol inhalation in infants and toddlers is significantly different from that of adults due to different development stages of nasal and oral cavities. Nasal inhalation is more efficient for aerosol delivery to the lower airways than mouth inhalation in infants and toddlers (Lizal et al. 2020). Irrespective, deposition of this substance in other parts of the respiratory tract may also be harmful to pulmonary function.

The ConsExpo model, version 4.1 (ConsExpo 2016), was used to estimate inhalation exposure to PHMB from use of spray products. ConsExpo is a multi-tiered predictive model used to derive estimates of exposure to substances in products available to consumers. It contains exposure factors for various products and uses, and it is a well-

established model. Concentrations of PHMB in spray products may vary substantially. Accordingly, a range of concentrations of PHMB in pump spray products was used to derive estimates of exposure (see Appendix B for details on the parameters used for each scenario). When pump spray products contain 0.1% to 0.3% PHMB, the mean air concentrations over the day of the event/exposure ranged from 0.0011 mg/m^3 (for adults using pump spray) to 0.0034 mg/m^3 (for children exposed to body spray).

NHPs and NPDs

PHMB is listed with a non-medicinal role for topical use only, up to 0.1%, as a preservative antimicrobial, and is not permitted in sprayable formulations, in the Natural Health Products Ingredients Database (NHPID; [modified 2021]). It is listed as being present as a non-medicinal ingredient in topical, as well as ophthalmic, NHPs in the Licensed Natural Health Products Database (LNHPD [modified 2021]. The concentration of PHMB in NHPs, as well as NPDs, is typically unknown or below 0.1%, although to a maximum of 1% (for example, 0.3% to 0.9% to 1%) (DPD [modified 2018]; personal communication, email from the Therapeutic Products Directorate, Health Canada, to the New Substances Assessment and Control Bureau, Health Canada, dated December 2017; unreferenced; personal communication, email from the Natural and Non-prescription Health Products Directorate, Health Canada, to the New Substances Assessment and Control Bureau, Health Canada, dated December 2017; unreferenced). There was one spray product identified in Health Canada's Drug Product Database (a hospital disinfectant) containing 0.054% PHMB, but it was discontinued in 2008 (DIN 02246830).

3.6.1.2 Indirect exposure

In the event of an unforeseen environmental release, PHMB is expected to become distributed in the aquatic environment given its very high water solubility. PHMB is neither biodegradable nor hydrolyzable. None of the known uses of PHMB (that is, low concentration in products available to consumers) are expected to impact either surface or ground water. Compared to the potential for direct exposure, indirect exposure of the general population to PHMB through environmental media such as drinking water is not expected to be significant.

3.6.2 Health effects assessment

No original or primary studies were available. Only industry submissions to the European Union (EU) were available. Therefore, many study details were not available for independent evaluation.

Toxicokinetics

Oral absorption of PHMB ranges from 0.3% to 8%, but a value of 4% is used for the risk characterization based on oral absorption from dietary studies at low doses. Rats fed

^{14}C-PHMB excreted most of the radioactivity in the feces with only 2% excreted in the urine. When administered at 200 ppm, only 4.7% (males) and 3.9% (females) of the dose was bioavailable (SCCS 2017). Dermal absorption is estimated at approximately 8.5% on the basis of data submitted to SCCS (2017) on dermal absorption. Since no information is available on absorption by inhalation, an absorption rate of 100% of substance deposited in the respiratory tract is retained (EU 2015).

Acute oral toxicity

PHMB is of moderate acute toxicity in Sprague-Dawley rats, with an LD_{50} range between 501 and 1 049 mg/kg bw when administered by oral gavage. Sublethal clinical signs included lethargy, ataxia, salivation, laboured breathing, lacrimation, piloerection, ptosis and tiptoe gate (AGDH 2017; SCCS 2017).

Acute dermal toxicity

PHMB has low acute dermal toxicity with an LD_{50} of greater than 5 000 mg/kg bw in rats and an LD_{50} of greater than 2 000 mg/kg bw in rabbits (AGDH 2017). No clinical signs of systemic toxicity were noted. However, local clinical signs included slight to well defined erythema and hemorrhage of dermal capillaries at the treatment site (SCCS 2017).

Acute inhalation toxicity

An acute nose-only inhalation study (4 hours) was performed in Slpk:APfSC rats (5/sex) using a formulation containing 20.6% w/w PHMB with a mass median aerodynamic diameter (MMAD) values of 1.8 to 2.0 µm. A single dose at 1.76 mg/L of the formulation, which corresponds to 0.36 mg/L PHMB, caused the death of 1 animal (out of 10) 3 hours after exposure. All females and most males demonstrated respiratory stress, including breathing irregularities and abnormal respiratory noise.

In another preliminary acute inhalation study performed on rats, both animals exposed to 1.0 mg/L died 1 to 2 hours after exposure. In the main study, Wistar rats (5/sex/dose) were exposed to PHMB at concentrations of 0.1, 0.3 or 0.5 mg/L. None of the animals died when exposed to PHMB at 0.1 mg/L, but laboured respiration, rhonchus, partial ptosis, decreased activity and increased respiratory rate were observed. However, 3 of 5 males died when exposed to 0.3 mg/L and exhibited the same clinical signs in addition to weak body condition. At 0.5 mg/L, all 5 males and 3 females died, with clinical signs including moderate to severe laboured respiration with noisy respiration and gasping, increased respiration and decreased activity. Body weight loss in surviving animals was observed at all doses, but returned to normal 7 to 14 days after treatment. Based on this study, the LC_{50} for PHMB is 0.29 mg/L for males, 0.48 mg/L for females or 0.37 mg/L combined (SCCS 2017; AGDH 2017).

Inhalation exposure of mice to PHMB caused non-reversible fibrosis, squamous metaplasia, pneumonitis and bronchitis in the mice lungs (Song et al. 2018). Although

the mode of action for these non-reversible effects is hypothesized as irritation, cytotoxicity and inflammation, it is possible that these effects are due to hypersensitivity pneumonia (Salisbury et al. 2017). Nevertheless, the lowest NOAEL for inhalation toxicity was 0.025 mg/m^3, which is classified as Category 1 under the Globally Harmonized System of Classification and Labelling of Chemicals (GHS). This is the most sensitive endpoint for the substance.

Dermal irritation

PHMB was considered mildly irritating to New Zealand White rabbit skin after application of 0.5 g neat substance to the intact shaved skin of 3 males for a period of 4 hours. The mean score for erythema and oedema at 24, 48 and 72 hours was 1 or less out of 8 (SCCS 2017; AGDH 2017). Another study found a 20% aqueous solution of PHMB irritating to rabbit skin, with an average score of 2.3 out of a possible 8 for erythema and oedema. Moderate to severe skin irritation also occurred in rats with a 25% aqueous solution applied for 24 hours (CIR 2017). Studies with a 20% solution in both rats and rabbits had variable results, ranging from mildly to moderately irritating. Studies performed in human volunteers with a 20% solution applied at 0.3%, 0.6% and 1.5% a.i. was not irritating to the skin. Therefore, PHMB is considered to be a mild to moderate skin irritant at concentrations of 20% (SCCS 2017).

Eye irritation

PHMB was corrosive to New Zealand White rabbit eyes, causing corneal opacity, iridial inflammation and severe conjunctival irritation after application of 0.1 ml of the neat substance in the conjunctival sac and left unwashed. A 20% solution was also moderately irritating to rabbit eyes (SCCS 2017; AGDH 2017). Therefore, PHMB is considered to be a severe eye irritant at 100% and a moderate eye irritant at 20.2% concentration. In clinical case reports, 0.02% of aqueous PHMB solution was well tolerated by human corneal and conjunctival epithelium (AGDH 2017).

Dermal sensitization

Both animal and human summary data are available for dermal sensitization. However, both have limitations for performing a quantitative risk assessment of dermal sensitization.

In one guinea pig maximization test (GPMT), PHMB was found to be a moderate dermal sensitizer. Intradermal induction with 0.06% a.i. and a dermal induction with 20.2%, followed by a challenge with 20.2%, caused scattered redness or moderate diffuse redness in 18 of 20 and 16 of 20 guinea pigs at 24 and 48 hours, respectively. Challenge with 6% PHMB caused reactions in 5 of 20 animals at 24 hours and 2 of 20 animals at 48 hours (AGDH 2017). Another GPMT with intradermal injections of 1%, topical inductions of 20% and challenge with 20% PHMB elicited a moderate erythema in 14 of 20 test animals at 24 hours and in 15 of 20 animals at 48 hours and is

considered a moderate to strong sensitizer under the conditions of this assay. Not all GPMT reported were positive for sensitization. A GPMT with intradermal of 0.15%, a topical induction of 20% PHMB and challenge with 20% or 10% PHMB elicited erythema in only 1 of 10 test animals and was not considered a dermal sensitizer under the conditions of the test. PHMB was also positive for sensitization in Buehler assays performed in guinea pigs. Topical induction of 10% (2% a.i.) and challenge at 10% and rechallenge with 20%,10% and 1% (4, 2 and 0.2 a.i.) elicited mild erythema in 6 of 10 test animals. Rechallenge with 20% resulted in moderate erythema in 8 of 9 test animals and faint erythema in 3 of 10 controls. No reactions were observed with 1%. However, PHMB was considered a moderate sensitizer at 10%. Another Buehler assay where a range of induction and challenge concentrations were tested concluded that the threshold for eliciting sensitization in guinea pigs is approximately 1% and that PHMB is a strong sensitizer at concentrations greater than 1.2% (SCCS 2011). PHMB was a weak sensitizer or non-sensitizer in the LLNA. However, no study details were provided to substantiate the results (CIR 2017).

A human repeated insult patch test (HRIPT) was performed on 191 volunteers (3 panels) using PHMB at concentrations of 2% and 4% for induction and challenged with 0.05%, 0.1%, 0.2%, 0.5%, 1% or 2% a.i. Volunteers were exposed for 24 hours on the dorsal surface of the upper arm 3 times a week for 10 applications total. In panel 1, at challenge, 8 of 49 subjects had skin reactions at 2.0% a.i., 7 of 49 at 1.0% and 0.5%, and 2 of 49 at 0.1%. In a second panel, 114 subjects were induced at 4% and challenged with 0.05%, 0.1%, 0.2% and 0.5%. Of the 114 subjects, 19 showed reactions at 0.5% and 8 showed reactions at 0.2%. No reactions were observed at 0.1% or 0.05%. A third panel was induced at 2% and challenged with 0.05%, 0.1%, 0.2% and 0.5%. One of 28 subjects reacted at the highest challenge concentration of 0.5% and all other subjects gave negative results (Smith 1981, as cited in SCCS 2017). It was determined that PHMB HCl (2% a.i.) was not capable of causing primary skin irritation, but was capable of causing sensitization. It was also determined that skin sensitization in humans can be elicited at concentrations beginning at 0.2% a.i. (CIR 2017; SCCS 2017). The Australian Government of Health concluded that PHMB is a possible skin sensitizer in humans in products at a concentration of 0.5%, with potential for causing dermal sensitization at 0.2% in sensitive individuals (AGDH 2017).

In a HRIPT using a modified Draize procedure, a group of 26 volunteers were exposed to an aqueous solution containing 1% PHMB (v/v) and 0.01% sodium lauryl sulfate 3 times per week for 3 or 4 weeks (total number of applications of 9 or 12). Each patch was applied for 24 hours, and after removal of the patch, the test site was exposed to natural sunlight for one hour. After a 2- to 3-week rest period, a challenge dose of 1% was applied to the test site. Skin reactions were evaluated at 48 and 96 hours after application. No sensitization reactions were observed in any individuals following challenge exposure, and the study concluded that dermal exposure of 1% PHMB did not elicit sensitization in humans (Hink 1976, as cited in ECHA 2011).

Overall, human sensitization studies carried out in healthy humans suggest that 1% PHMB did not induce skin irritation. However, sensitization may occur.

In addition to the immunological responses which cause dermal sensitization in experimental animals and humans, there are 3 reported cases of anaphylaxis following dermal exposure to PHMB during hospitalization (Kautz et al. 2010; Olivieri et al. 1998; Schunter et al. 2017) showing the potential for a more systemic effect rather than a local dermal response.

Subchronic toxicity

Several repeated-dose studies, both subchronic and chronic have been performed with PHMB. A 28-day range finding study for a 2-year drinking water study in rats at concentrations of 0.1, 0.5, 1.0, or 2.0 mg/ml generated a lowest-observed-adverse-effect level of 0.1 mg/ml (equivalent to approximately 10 mg/kg bw/day) with liver and kidney effects (SCCS 2017).

A range finding drinking water study was also performed in mice (8/sex/dose). They were given 0.1. 0.3. 0.6 or 1.2 mg/ml of PHMB in their drinking water for 28 days. Decreases in body weight were attributed to a decrease in water and food consumption as a result of the palatability of the substance. The decrease in alanine aminotransferase activity and reduced liver weights were attributed to poor nutritional status. Since body weight changes were observed at all doses, no NOAEL was established and 0.3 mg/ml was recommended as the high dose for a 2-year chronic drinking water study (SCCS 2017).

A 90-day subchronic range-finding dietary study was performed in CD-1 mice and Wistar rats. The mice (12/sex/group with an additional 4/sex/group used for sacrifice at day 29) were dosed at concentrations of 1 000, 2 000 or 4 000 ppm a.i., corresponding to 162, 328, or 736 mg/kg bw/day in males and 224, 445, or 963 mg/kg bw/day in females, respectively. The rats (12/sex/group with an additional 4/sex/group used for sacrifice at day 29) were dosed at concentrations of 1 000, 2 000, 4 000 or 6 000 ppm a.i., corresponding to 83.9, 171.5, 373.0, or 556.1 mg/kg bw/day in males and 92.3, 192.9, 409.8, or 617.4 mg/kg bw/day in females, respectively (SCCS 2017). Rats showed a reduced body weight at doses of 2 000 ppm and higher, with a poor nutritional state, increased haemoglobin and hematocrit seen in males at these doses. The kidneys were affected in the form of decreased urine volume and increased specific gravity. An increase in kidney weight was apparent at 4 000 and 6 000 ppm. Treatment-related increases in plasma alkaline phosphatase, alanine transaminase and/or aspartate transaminase were seen at all dose levels in both males and females. The authors considered 1 000 ppm (83.9 mg/kg bw/day in males and 92 mg/kg bw/day in females) as the NOAEL. In mice, reduced body weights were seen in males at 2 000 ppm, and a marked effect on body weight was seen in both sexes at 4 000 ppm. No treatment-related effects were noted in the liver or kidneys. The authors considered

1 000 ppm (162 mg/kg bw/day for males and 224 mg/kg bw/day for females) as the NOAEL.

A 30-day dermal study was performed in Wistar rats (5/sex/dose). A 20.2% aqueous solution of PHMB was applied to the shaved intact skin of the animals 5 days/week at doses of 20, 60, or 200 mg/kg bw/day under an occlusive dressing for 6 hours/day. At 60 mg/kg bw/day, there was a slight dermal irritation, which regressed by the end of the study. At 200 mg/kg bw/day, all animals showed a moderate dermal irritation, which persisted until the end of the study. However, no clinical signs or changes in gross pathology or histopathology were observed. The NOAEL for systemic toxicity was 200 mg/kg bw/day and 20 mg/kg bw/day for local irritation (SCCS 2017).

A 28-day nose-only inhalation study (6 hours/day, 5 days/week) was performed in Wistar rats (5/sex/dose). The animals were exposed to PHMB at concentrations of approximately 0.025, 0.25 or 2.5 µg/L (mg/m^3) with MMAD values of 0.3 to 1.30 µm, 0.48 to 5.06 µm, and 0.67 to 1.67 µm, respectively, for 28 days with the addition of a recovery group which was sacrificed 13 weeks after high-dose treatment. There were no mortalities at any of the doses. A lower body weight was observed at the mid and high dose which mostly recovered after cessation of treatment. Lung weights were slightly elevated at the highest dose and showed signs of irritation. Squamous metaplasia of the larynx and tracheal inflammation were seen in the mid- and high-dose animals. Pneumonitis and bronchitis were seen in the lungs of high-dose animals which did not recover after termination of treatment. The NOAEL for this study was considered to be 0.025 mg/m^3, which is classified as Category 1 under GHS (SCCS 2017). The experimental concentration NOAEL of 0.025 mg/m^3 from the 28-day study in the rat is a benchmark for inhalation exposure.

Kim et al. (2016) suggest that the mechanism of PHMB-induced respiratory effects is via irritation, cytotoxicity and inflammation (that is, via activation of the NF-κB signaling pathway). As observed with polyhexamethylene guanidine phosphate (PHMG-p) in humans, repeated insult may lead to fibrosis and respiratory distress.

Chronic oral toxicity

A 1-year chronic diet study was performed in Beagle dogs (4/sex/dose) fed PHMB at concentrations of 300, 1 500, or 4 500 ppm (corresponding to 11, 54, or 169 mg/kg bw/day for both sexes, respectively). The high dose was reduced to 3 000 ppm (108 mg/kg bw/day) after 11/12 weeks due to signs of toxicity, such as marked reddening/peeling of scrotal skin, loss of appetite, body weight loss or indications of liver impairment as noted by elevated plasma alanine transaminase and/or aspartate transaminase activities. Treatment-related histopathological findings were present in the skin, as well as the liver and kidneys only at the highest dose. The authors considered 1 500 ppm (54 mg/kg bw/day) to be the NOAEL (CIR 2017).

A 2-year chronic diet study was performed in Wistar rats (64/sex/dose). The animals were fed PHMB at doses of 200, 600 or 2 000 ppm (corresponding to 12.1, 36.3 or 126.1 mg/kg bw/day in males and 14.9, 45.3 or 162.3 mg/kg bw in females, respectively). At 2 000 ppm, there was a reduction in body weight in both sexes, but it was more pronounced in females. There were no treatment-related clinical signs. Hematological and histopathological changes included slightly raised plasma alkaline phosphatase activity and a slightly increased incidence of hepatocyte fat and spongiosis hepatitis in males at the high dose. There was also a slight increase in the incidence of hemangiosarcomas in high-dose females. The authors established a NOAEL of 600 ppm (36 and 45 mg/kg bw/day in males and females, respectively) (SCCS 2017).

Genotoxicity

PHMB was not genotoxic in a number of bacterial reverse mutation assays in any of the bacterial strains tested in either the presence or absence of metabolic activation. However, this assay is not reliable as PHMB is bactericidal in nature and is expected to be cytotoxic to the bacterial strains (CIR 2017). It was also not genotoxic in an *in vitro* mouse lymphoma assay using either L5178Y TK +/- or P388 (tk +/-) cells. It was not clastogenic in a micronucleus test using cultured human peripheral blood lymphocytes or *in vivo* when tested in CD-1 mice at doses of 350 and 400 mg/kg bw (CIR 2017; SCCS 2017). It was also negative in an *in vivo* unscheduled DNA synthesis in rats dosed at 750 and 1 500 mg/kg bw.

Carcinogenicity

Induction of vascular tumours was reported following long-term oral exposure of rats and mice to high doses of PHMB (AGDH 2017). In Wistar rats (64/sex/dose), a diet containing PHMB at doses of 200, 600 or 2 000 ppm, corresponding to 12.1, 36.3 or 126.1 mg/kg bw/day in males and 14.4, 45.3, or 162 mg/kg bw/day in females, respectively, was administered for 2 years. There were no overt signs of toxicity or abnormal behaviour during the study, although high-dose females had a 13% lower survival rate. This group also had a decrease in body weight and increased alkaline phosphatase activity. There was an increase in hemangiomas (2/64 males and 2/64 females) and hemangiosarcomas (1/64 female) in the liver of animals exposed to the high dose (APVMA 2011). A NOAEL of 600 ppm (36.3 mg/kg bw/day) was established on the basis of these observed effects.

CD-1 mice were given a diet containing 400, 1 200, or 4 000 ppm PHMB (corresponding to 54.7, 167, or 715 mg/kg bw/day in males and 69, 216.5, or 855.5 mg/kg bw/day in females, respectively) for 2 years. The high-dose animals had an increased incidence of hemangiosarcomas in the liver of both males and females and gall bladder papillomas in two males. There was also an increased incidence of squamous cell carcinoma at the recto-anal junction (males and females) as well as an adenocarcinoma at the recto-anal junction in one male. Although PHMB is not genotoxic or clastogenic, it has the potential to cause liver tumours at high doses in rodents.

Developmental and reproductive toxicity

A two-generation diet study in Wistar rats (26/sex/dose) fed PHMB at 200, 600 or 2 000 ppm (corresponding to 23–24, 70–71 or 239–249 mg/kg bw/day in males and 25–26, 77–79, or 258–270 mg/kg bw/day in females, respectively) did not show any treatment-related effects on reproductive parameters or on offspring growth and development at any of the doses tested. However, adults treated at the highest dose showed decreased body weight and decreased food efficiency. A systemic NOAEL of 600 ppm (70–79 mg/kg bw/day) and a reproductive NOAEL of 2 000 ppm (239–270 mg/kg bw/day) were established.

In another diet study (similar to OECD 414), Alderley Park rats (20/group) were given a diet containing PHMB at doses of 200, 1 000, or 2 000 ppm (13, 54 or 112 mg/kg bw/day, respectively) from gestational day (GD) 1 to 20. There were no mortalities or adverse clinical effects at any of the doses tested. Maternal weight gain and food consumption were reduced at 1 000 and 2 000 ppm. There were no effects on reproductive parameters. There was an increase in extra ribs at the high dose, which was considered an effect of maternal toxicity. Based on reduced food consumption and body weight, a maternal NOAEL of 200 ppm (13 mg/kg bw/day) and a developmental NOAEL of 1 000 ppm (54 mg/kg bw/day) were established.

Another developmental study (similar to OECD 414) was performed whereby Alderley Park mice (47 to 49 in dose groups, 25 controls) were dosed by oral gavage at 10, 20 or 40 mg/kg bw/day from GD 6-15. There were some mortalities of dams in the highest dose group. The animals that died showed macroscopic changes in the stomach and caecum consistent with irritation and inflammation at the site of contact. There were no reproductive, developmental or teratogenic effects in surviving animals. Increases in pre- and post-implantation loss in the mid- and high-dose groups as well as unossified 5th sternebrae were either not dose related or occurred at maternally toxic doses and were not considered substance related. The authors established a maternal NOAEL of 20 mg/kg bw/day and a developmental NOAEL of 40 mg/kg bw/day (SCCS 2017). Based on the available data from several animal studies, PHMB is not expected to exhibit reproductive or developmental toxicity (AGDH 2017).

Additional Information

In Korea, the related substance, PHMG-P, was suspected to be the substance responsible for adverse health effects in at least 258 people from use of the substance as a humidifier disinfectant, including 113 fatalities (Kim 2016). At the time of this event, no inhalation data of PHMG-P were available, and public health authorities in Korea based their conclusions on animal toxicity data for PHMB (Kim et al. 2016; Kim et al. 2017). Given the similarities in the toxicological mode of action between PHMG-P and PHMB, public health authorities felt that they could extrapolate the known inhalation hazard of PHMB to support a ban on uses of PHMG-P that could result in inhalation exposure (Kim et al. 2016; Kim et al. 2017). Both experimental animals and humans

exposed to PHMB or PHMG-P via inhalation show similar pathological features, that is, inflammatory cell infiltration in peribronchiolar, perivascular, and subpleural areas of the lungs, hyperplasia and apoptosis/necrosis of bronchiolar and alveolar epithelial cells, mucus plug in the bronchiole, and collagen deposition in the lung parenchyma (Song et al. 2018; Kim et al. 2017). Given the similarities between these two substances, it is likely that inhalation of PHMB by humans would have a similar effect to that seen with PHMG-P.

3.6.3 Characterization of risk to human health

During the second phase of polymer rapid screening (ECCC, HC 2018), PHMB (CAS RN 32289-58-0) was identified as requiring further assessment as a result of the presence of toxicological data suggesting inhalation toxicity and restrictions by other domestic and international jurisdictions on concentrations for some applications. A second CAS RN from the second phase of polymer rapid screening (CAS RN 27083-27-8) was added to this assessment as it was found to be synonymous with PHMB.

Based on the available data, PHMB has a moderate acute oral toxicity (LD_{50} of 501 to 1 049 mg/kg bw), a low acute dermal toxicity (LD_{50} > 2 000 mg/kg bw) and a high acute inhalation toxicity (LC_{50} < 0.5 mg/L). It is a dermal sensitizer in both animals and humans and has been linked to three case reports of anaphylaxis. It has moderate subchronic and chronic oral toxicity (NOAELs of 30–300 and 10–100 mg/kg bw/day, respectively), low subchronic dermal toxicity (NOAEL > 200 mg/kg bw/day) and high subchronic inhalation toxicity (NOAEL < 0.06 mg/L). It is not genotoxic or clastogenic, but does increase the risk of hemangiomas in the liver of rodents at high doses likely via a threshold mode of action. It is not a developmental or reproductive toxicant.

Direct exposure to the polymer could occur through ingestion, dermal absorption or inhalation.

<u>Oral route</u>

The lowest NOAEL from any subchronic oral study was 13 mg/kg bw/day. It was derived from a rat developmental study and is used as the point of departure (POD) for systemic toxicity. Since carcinogenicity is expected to occur at doses higher than 13 mg/kg bw/day (that is, greater than 36 mg/kg bw/day), using the NOAEL from the subchronic oral study is considered protective of carcinogenic effects. The potential for chronic exposure through the oral route due to food residues is conservatively estimated to be between 21 and 23 µg/kg bw/day for adult males and females and less than 20 µg/kg bw/day for children 7 to 14 years of age. The MOEs for this exposure are 619-565 and > 650, respectively. Therefore, PHMB is not expected to pose a human health risk to adults or children from oral ingestion.

If released into the environment, PHMB is expected to distribute readily through the environment as a result of its high water solubility. PHMB is not manufactured in

Canada, and current known use patterns in Canada are not expected to cause significant amounts of the polymer to be released into environmental media. Therefore, there are no human health risks anticipated as a result of indirect exposure through environmental media, such as air, soil or drinking water.

Dermal route

Systemic toxicity through repeated dermal exposure in experimental animals is low to moderate (SCCS 2017). The dermal NOAEL is considered to be 200 mg/kg bw/day, the highest dose tested in rats, and showed only local skin effects in a 28-day repeated-dose test. Toxicokinetic experiments show that only 4% of the substance is expected to be dermally absorbed. Given a dermal application of body lotion containing PHMB at a concentration of 3% with a SED of 0.160 mg/kg bw/day for adults and 0.271 mg/kg bw/day for children, the MOEs would be 1250 and 738, respectively. Given the low absorption, absence of systemic effects from dermal applications in experimental animals and the above MOE values, the health risk for systemic toxicity from repeated dermal application is low.

Although the risk for systemic health effects from dermal exposure is considered low, PHMB is a dermal sensitizer in experimental animals and humans and there have been three reported cases of more serious anaphylactic reactions to PHMB with products containing the substance (Kautz et al. 2010; Olivieri et al. 1998; Schunter et al. 2017). Dermal irritation studies in humans showed that the a.i. at concentrations up to 1.5% was not a dermal irritant (SCCS 2017), but in one human study the substance caused skin sensitization at concentrations of 0.2% or higher (AGDH 2017), while in another human study there was no sensitization reaction at 1% (Hink 1976 as cited in ECHA 2011). Results from both animal and human studies are variable, and sensitive individuals may develop an allergic response at lower concentrations; however, 1% was used as the POD for sensitization. Appendix C shows calculations which convert the 1% concentration to a dose per unit of exposed skin surface. The No Expected Sensitization Induction evel (NESIL) using a 1% threshold is equivalent to a dose of 768 $\mu g/cm^2$ and the Acceptable Exposure evel (AEL) is 8.53 $\mu g/cm^2$. The estimated Consumer Exposure evel (CEL) from dermally applied products containing 3% PHMB is 120 $\mu g/cm^2$, which is less than the NESIL but higher than the AEL and therefore considered inadequate to address uncertainties in the health effects and exposure databases. The estimated CEL from dermally applied products containing 1% PHMB is 40 $\mu g/cm^2$, which is still higher than the AEL. The estimated CEL from dermally applied NHPs containing the limit of PHMB at 0.1% as outlined in the NHPID [modified 2021] is 4 $\mu g/cm^2$, which is below the NESIL and the AEL, and therefore is considered adequate to address uncertainties in the health effects and exposure databases.

Inhalation route

A concentration of 0.1% PHMB in a cosmetic spray product, such as a hair detangler, produces a predicted exposure of 0.0011 mg/m^3 for adults and 0.0034 mg/m^3 for

children based on use in pump sprays. Using the inhalation NOAEL of 0.025 mg/m^3 as a POD, MOEs of 22.7 and 7.4, respectively, are estimated. Further refinement of these inhalation scenarios for these products in order to account for reduced proportions of inhaled and retained fractions of the substance, limited exposure times, representative body weights and adjusted ventilation capacity resulted in MOEs of 61 and 26 (see Appendix B).

The calculated MOEs for cosmetic spray products are considered inadequate to address uncertainties in the health effects and exposure databases. In establishing the acute, medium-term and long-term inhalation AEL for PHMB, the EU considered the same principal study, the same POD and MOEs of 25, 75 and 150, respectively (EU 2015). These MOEs, which were derived by other jurisdictions, are similar to the MOE values indicated for inhalation exposures in this screening assessment. In addition, the CIR (2018) obtained an MOE of 11 for cosmetic pump sprays containing PHMB at a concentration of 0.053%.

4. Soya alkyd resin and polyurethane-33

4.1 Discussion regarding the polymer of low concern status for the substances

Various jurisdictions, including the United States, Australia and Canada, recognize that polymers that meet predetermined and established physical-chemical and toxicological criteria generally possess low ecological and human health hazard. As outlined in detail below, polymers that meet these sets of criteria are known internationally as Polymers of Low Concern (PLC). In Canada, as they are known as Reduced Regulatory Requirement (RRR) polymers under the NSNR (C&P) (Canada 2005) as outlined in the ‘Guidelines for the Notification and Testing of New Substances: Chemicals and Polymers’ (Environment Canada, Health Canada 2005). To study the applicability of PLC, the Organisation for Economic Co-operation and Development (OECD) analyzed over 100 polymers that meet the criteria for PLC in various OECD member countries.[4] Based on the available information submitted by participating jurisdictions (that is, Canada, Australia, United States, and Korea), polymers that met the PLC criteria generally showed low human health and ecological concerns. For that reason, the use of the PLC criteria, such as those described in the NSNR (C&P) (Canada 2005) for screening of polymers, is recognized as appropriate (OECD 2009).

[4] The term “polymer of low concern” is used in other countries to describe polymers that share the same structural characteristics as polymers that meet RRR in Canada.

Polymers that meet the RRR polymer criteria and that are therefore considered to present low human health concern (Canada 2005) include:

(a) a polymer that is not one of the types listed in items 1 to 4 of Schedule 7 in section 9 of the NSNR (C&P) (Canada 2005) and that has a Mn greater than 10,000 daltons, with less than 2% of its components having molecular weights of less than 500 daltons and less than 5% of its components having molecular weights of less than 1 000 daltons;
(b) a polymer that is not one of the types listed in Schedule 7 in section 9 of the NSNR (C&P) (Canada 2005) and that has a Mn greater than 1 000 daltons and equal to or less than 10 000 daltons, with less than 10% of its components having molecular weights of less than 500 daltons and less than 25% of its components having molecular weights of less than 1 000 daltons; or
(c) a polymer that is a polyester manufactured solely from reactants listed in Schedule 8 in section 9 of the NSNR (C&P) (Canada 2005), or an anhydrous form of those reactants, other than the reactants or their anhydrous forms that include both 1-butanol and fumaric or maleic acid.

In summary, polymers that meet the criteria noted above are polymers with a high Mn, that have a limited percentage of low-molecular-weight components (<1 000 daltons), are chemically stable and do not contain certain reactive or cationic moieties (Environment Canada, Health Canada 2005). During the second phase of polymer rapid screening, polymers with sufficient evidence to determine that they are of low concern were concluded as not meeting criteria in section 64 of CEPA, and did not undergo further assessment. Polymers with insufficient or conflicting information that suggested the polymer may be synthesized in different forms that may not meet these criteria were identified for further evaluation (ECCC, HC 2018).

Inspection of properties of the polymer, such as those shown in Table 4-1, suggests that the criteria describing polymers of low concern are applicable to these substances for the purpose of determining low human health concern. The two remaining polymers in the Other Polymers Group were further assessed against criteria describing polymers of low concern, as described above. On the basis of additional information (see Table 3-1), two polymers (CAS RNs 125826-44-0 [polyurethane-33] and 67762-15-6 [soya alkyd resin]) were identified as meeting criteria describing polymers of low concern. Any toxic monomer or cationic, or potentially cationic, groups in these polymers (such as hydrazine or isocyanate) are expected to be reacted into the polymer backbone and not likely to be readily released from the polymer and are therefore considered to be unavailable for uptake in their neat form (personal communication, emails from manufacturers, August 2017; unreferenced). It is therefore concluded that these two polymers are of low concern for human health.

Table 4-1. Molecular weight information and PLC status for soya alkyd resin and polyurethane-33

Substance name (CAS RN)	Soya alkyd resin (67762-15-6)	Polyurethane-33 (125826-44-0)
Weight average molecular weight (Mw)(daltons)	60 000 to 78 000	800 000 to 18 500 000
Number average molecular weight (Mn)(daltons)	3 300 to 3 700	10 000 to 697 000
Components having molecular weight < 1 000 daltons (%)	2 to 8	0 to 0.5
Components having molecular weight < 500 daltons (%)	1 to 3	0 to 0.2
References	ECCC 2015 Canada 2015	ECCC 2015 Canada 2015

4.2 Potential to cause ecological harm

Critical data and considerations used during the second phase of polymer rapid screening to evaluate the substance-specific potential to cause ecological harm are presented in ECCC (2016).

Soya alkyd resin was identified as having low water extractability/solubility in the second phase of polymer rapid screening (ECCC, HC 2018). Therefore, this substance was characterized as having a low potential for ecological risk. It is unlikely that this substance is resulting in concerns for the environment in Canada.

Polyurethane-33 was classified as having moderate hazard potential according to information considered in the second phase of polymer rapid screening (ECCC, HC 2018). On the basis of low exposure potential, this substance was characterized as having a low potential for ecological risk. It is unlikely that this substance is resulting in concerns for the environment in Canada.

4.3 Potential to cause harm to human health

Soya alkyd resin and polyurethane-33 meet the criteria that describe polymers of low concern and, as a result, they are not a concern for human health. Therefore, detailed exposure and hazard assessments of these substances are not warranted. Both of these substances are used in coatings, such as paints. Because of the high molecular weight of the substances, the low quantity of small molecular components, and the fact that they are used in cured form, exposure and hazard are mitigated.

In summary, it is concluded that the two polymers, soya alkyd resin and polyurethane-33, are unlikely to pose a human health risk.

5. Uncertainties in evaluation of risk to human health

DGEBA-DA resin (CAS RN 55818-57-0) contains a significant proportion of DGEBA-DA (CAS RN 4687-94-9), since its polymerization number is low, that is, $n \leq 0.1$. The two substances are structurally very similar such that DGEBA-DA can be used as a surrogate for DGEBA-DA resin. However, the minor variation in composition between the two results in some uncertainty.

There were also uncertainties associated with the toxicity of DGEBA-DA resin as only one reference was identified and the studies were not available for a detailed review. Considering that conservative assumptions were used throughout the human health risk assessment for DGEBA-DA resin, the uncertainties associated with structural representation and lack of toxicity data are not expected to influence the outcome of this human health risk assessment.

For PHMB, four almost equivalent CAS RNs can be allocated, depending on how the polymer is described. Consequently, there are some inconsistencies in the literature as to how this substance was identified.

An inhalation exposure scenario from use of spray products containing PHMB was estimated using the ConsExpo model with pump spray concentrations of 0.1% and 0.3%. However, other products available to consumers with higher concentrations and potential other uses were not used in the exposure scenarios.

Other uncertainties are the absence of long-term dermal studies as well as the absence of the full toxicological studies.

Despite the above uncertainties, it is believed that the risk conclusions made for the substances are accurate.

6. Conclusion

Considering all available lines of evidence presented in this screening assessment, there is low risk of harm to the environment from PHMB (CAS RNs 32289-58-0 and 27083-27-8), DGEBA-DA resin, soya alkyd resin, and polyurethane-33. It is concluded that these substances 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.

Considering all the information presented in this screening assessment, it is concluded that DGEBA-DA resin, soya alkyd resin, and polyurethane-33 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 to human life or health in Canada. However, it is concluded that PHMB (CAS RNs 32289-58-0 and 27083-27-8) meets the criteria under paragraph 64(*c*) of CEPA as it is entering or may enter 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 DGEBA-DA resin, soya alkyd resin, and polyurethane-33 do not meet any of the criteria set out in section 64 of CEPA, but that PHMB (CAS RNs 32289-58-0 and 27083-27-8) does meet the criteria under section 64 of CEPA.

It is also concluded that PHMB (CAS RNs 32289-58-0 and 27083-27-8) meets the persistence criteria but not the bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations* of CEPA.

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Appendix A. Ecological assessment approaches applied during the second phase of polymer rapid screening

The approach applied for ecological assessment during the second phase of polymer rapid screening is outlined in this section.

Characterization of ecological risk for PHMB, DGEBA-DA resin, soya alkyd resin, and polyurethane-33

The ecological risks of PHMB, DGEBA-DA resin, soya alkyd resin, and polyurethane-33 were characterized using the approach outlined in the report titled “Second Phase of Polymer Rapid Screening: Results of the Screening Assessment” (ECCC, HC 2018).

The ecological component of the second phase of polymer rapid screening approach consisted of four main steps to identify polymers that warrant further evaluation of their potential to cause harm. The first step involved identifying polymers that are not likely to be of ecological concern based on low import and manufacture quantities reported under Phase Two of the *Domestic Substances List* (DSL) Inventory Update (Canada 2012), a voluntary survey (ECCC 2015) and a mandatory survey issued pursuant to section 71 of CEPA (Canada 2015). Polymers with import and/or manufacture volumes less than 1 000 kg per year are not likely to be of ecological concern. This is consistent with the notifying trigger quantity of 1 000 kg for polymers under section 7 of the *New Substances Notification Regulations (Chemicals & Polymers)* [NSNR (C&P)] (Canada 2005).

The second step involved determining whether the polymer will likely have water extractability greater than 2% by weight. Water extractability greater than 2% by weight indicates that the polymer may be more bioavailable to aquatic organisms. The increased potential for exposure to aquatic organisms may present higher ecological risk. Literature, online safety data sheet databases, the internal New Substances database for polymers, data gathered through a voluntary survey (ECCC 2015) and a mandatory survey issued pursuant to section 71 of CEPA (Canada 2015), and other reliable sources and databases (for example, QSAR toolbox, ECHA chemical database) were searched for water extractability and solubility information.

The third step in the ecological component involved identifying polymers with reactive functional groups (RFGs). RFGs are groups with chemical functionality that are considered to be reactive and may have damaging effects on the biological community. These groups are well described in Schedule 7 of the NSNR (C&P) (Canada 2005) and polymers containing RFGs may be of increased ecological concern, and require further screening. The RFGs include, among others, potentially cationic or cationic functionalities, alkoxy silanes, and phenols with unsubstituted ortho or para positions. To determine the presence of RFGs, structural information was gathered through a voluntary survey (ECCC 2015) and a mandatory survey issued pursuant to section 71 of

CEPA (Canada 2015). For polymers where no representative structures were provided, structural representations were derived from information available for similar polymers: 1) obtained from the internal New Substances program database; 2) from the Chemical Abstract Services name; or 3) based on professional knowledge on likely polymerization mechanisms.

The final step for ecological considerations involved applying environmental release scenarios to estimate environmental exposure. Two generic aquatic exposure scenarios were applied to identify potential concerns near the point of discharge of a polymer into the environment. These scenarios involved comparing conservative (that is, ecologically protective) estimates of exposure in receiving waters (predicted environmental concentrations [PEC]) with an effects threshold (predicted no-effect concentration [PNEC]) in order to evaluate whether a polymer is likely to cause harm to the local aquatic environment. The approaches made use of quantity information from each reporting company gathered under Phase Two of the DSL Inventory Update (Canada 2012) and import and/or manufacture volumes obtained through a voluntary survey (ECCC 2015) and a mandatory survey issued pursuant to section 71 of CEPA (Canada 2015). The aquatic PNEC for each of the scenarios was derived from the critical toxicity value (CTV), which was divided by an assessment factor (AF) as shown:

$$\text{Aquatic PNEC (mg/L)} = \text{CTV} / \text{AF}$$

CTVs were based on empirical or modelled data (where appropriate). Experimental ecotoxicity data were gathered through the voluntary survey and mandatory survey issued pursuant to section 71 of CEPA, from literature information, as well as from read-across data from polymers that have been assessed by the New Substances program. If the scenarios indicated a low likelihood of harm to aquatic organisms (that is, ratio of PEC/PNEC is less than 1), the polymer is anticipated to present low ecological concern.

It is recognized that conclusions resulting from the use of the second phase of polymer rapid screening have associated uncertainties, including commercial activity variations. However, the use of a wide range of information sources (relating to both exposure potential and hazard concerns identified for a polymer) and conservative exposure scenarios increases confidence in the conclusion that the polymers identified as not requiring further assessment are unlikely to be of concern.

Information on the decision taken at each step for each polymer is presented in a document titled “Information on the Decision Taken at Each Step for Rapid Screening II of Polymers” (ECCC 2016).

Based on available information, PHMB, DGEBA-DA resin, soya alkyd resin, and polyurethane-33 were identified in ECCC, HC (2018) as being unlikely to be causing ecological harm.

Appendix B. Estimates of inhalation exposure to PHMB

Product available to consumer type	Assumptions[a]	Mean concentration on day of inhalation exposure (mg/m^3)
Pump spray (hair detangler for adults and children)	Weight fraction compound: 0.001 (fraction) Exposure duration: 5 minute Room volume: 10 m^3 Ventilation rate: 0.6 L/hr Mass generation rate: 0.4 g/sec Spray duration: 0.24 minute Airborne fraction: 0.2 (fraction) Weight fraction non-volatile: 0.03 (fraction) Density non-volatile: 1.2 g/cm^3 Room height: 2.5 m Inhalation cut-off diameter: 15 µm Cloud volume: 0.0625 m^3 Non-respirable uptake fraction: 1 (fraction) Spraying towards exposed person Body weight: 61 kg Use frequency: 2 per day	1.1×10^{-3}
Pump spray (body spritzer for babies)	Weight fraction compound: 0.003 (fraction) Exposure duration: 5 minute Room volume: 10 m^3 Ventilation rate: 0.6 L/hr Mass generation rate: 0.4 g/sec Spray duration: 0.24 minute Airborne fraction: 0.2 (fraction)	3.4×10^{-3}

	Weight fraction non-volatile: 0.03 (fraction) Density non-volatile: 1.2 g/cm^3 Room height: 2.5 m Inhalation cut-off diameter: 15 µm Cloud volume: 0.0625 m^3 Non-respirable uptake fraction: 1 (fraction) Spraying towards exposed person Body weight: 11 kg Use frequency: 2 per day	

[a] Based on the default exposure scenarios in ConsExpo (RIVM 2009) with minor modification(s). For PHMB, the following properties were considered: molecular weight (1600 g/mol), log K_{ow} (-2.3), vapour pressure (10^{-7} Pa), and application temperature (20 °C).

Summary of inhalation risk assessment scenario:

PHMB in cosmetic spray products produce predicted exposures ranging from 0.0034 and 0.0011 mg/m^3 when used in pump sprays with concentrations of 0.3% and 0.1% concentrations, respectively.

Using the experimental concentration no-observed-adverse-effect level (NOAEL) of 0.025 mg/m^3 from a 28-day study in the rat as a benchmark for the margin of exposure (MOE), MOEs of 22.7 and 7.4 are estimated.

NOAEL 0.025 mg/m^3 divided by 0.0011 mg/m^3 in 0.1% pump spray = MOE 22.7

NOAEL 0.025 mg/m^3 divided by 0.0034 mg/m^3 in 0.3% pump spray = MOE 7.4

In establishing their acute, medium-term and long-term inhalation acceptable exposure levels (AELs) for PHMB, the European Union considered the same principal study, the same point of departure and similar MOEs of 25, 75 and 150, respectively (EU 2015).

In addition, the CIR (2018) obtained an MOE of 11 for a cosmetic pump sprays containing PHMB at a concentration of 0.053%. The magnitude of the MOEs for cosmetic spray products is considered to result in an unacceptable risk to human health.

Refined comparison of experimental NOAEL to use pattern scenarios specific to children:

The following scenarios for human exposure have been refined so that duration of exposure is 15 minutes, percent of respirable substance is 10%, and the default for retained dose of the substance inhaled is 50%. In addition, body weights and ventilation rates have been adjusted for the age specific groups.

The daily average inhalation rates for long-term exposures for children (males and females combined, unadjusted for body weight) range from 3.5 m^3/day (0.15 m^3/hour) for children from 1 to < 3 months to 9.0 m^3/day (0.38 m^3/hour) for children aged 1 to 6 years. Mean values for adults average about 16.0 m^3/day (0.67 m^3/hour) for people 16 to 51 years (US EPA 2011).

Inhalation exposure for human child (1-6 years) using hair detangler with 0.1% substance:
(FQ x C x R x IR x D x P) / BW = (2 x 0.001 mg/m^3 x 0.1 x 0.38 m^3/hour x 0.25 hour x 0.5) / 16 kg

= 5.9 x 10^{-7} mg/kg bw/day exposure for 16 kg (~3 year old) human child exposed to 0.1% substance in hair detangler

FQ: frequency of use (use/day) = 2 use per day
C: air concentration (mg a.i./m^3) = 0.001 mg/m^3 (0.1% pump scenario)
R: percent respirable (10%) = 0.1
IR: inhalation rate (m^3/hour) = 0.38 m^3/hour
D: duration of exposure (hours) = 0.25 hour(15 minutes)
BW: mean body weight = 16 kg
P: inhaled dose retained = 0.5 (default)
where: 1 000 L = 1 m^3 = 1 000 000 ml

Inhalation exposure for human baby (1-3 months) exposed to body spritzer with 0.3% substance:
(FQ x C x R x IR x D x P) / BW = (2 x 0.003 mg/m^3 x 0.1 x 0.15 m^3/hour x 0.25 hour x 0.5) / 8 kg

= 1.4 x 10^{-6} mg/kg bw/day exposure for 8 kg (~3 month old) human child exposed to 0.3% substance in body spritzer

FQ: frequency of use (use/day) = 2 use per day
C: air concentration (mg air/m^3) = 0.003 mg/m^3 (0.1% pump scenario)
R: percent respirable (10%) = 0.1
IR: inhalation rate (m^3/hour) = 0.15 m^3/hour (ventilation rate of human ~3 months)
D: duration of exposure (hours) = 0.25 hour(15 minutes)
BW: mean body weight = 8 kg

P: inhaled dose retained = 0.5 (default)
where: 1 000 L = 1 m^3 = 1 000 000 ml

The no adverse effects inhalation dose based the 28-day experimental NOAEL concentration was determined:
(FQ x C x R x IR x D x P) / BW = (1 x 0.025 mg/m^3 x 0.01 x 0.0144 m^3/hour x 6 hour x 0.5) / 0.3 kg

= 3.6 x 10^{-5} mg/kg bw/day exposure for rat to at the NOAEL determined experimentally

NOAEL 3.6 x 10^{-5} mg/kg bw/day divided by 5.9 x 10^{-7} mg/kg bw/day from 0.1% pump spray = MOE 61

NOAEL 3.6 x 10^{-5} mg/kg bw/day divided by 1.4 x 10^{-6} mg/kg bw/day from 0.3% pump spray = MOE 26

When the no adverse effects inhalation dose determined from a 28-day study was compared to estimated dose levels from potential human exposures, the magnitude of the MOEs for cosmetic spray products were considered inadequate to address uncertainties in the health effects and exposure databases.

Appendix C. Dermal quantitative risk assessment methodology for PHMB

Step 1: Conversion of the no expected sensitization induction level (NESIL) in appropriate dose metrics

$$Exposure\ threshold = 1\%\ \left(\frac{v}{v}\right)$$

$$Relative\ density\ of\ PHMB\ \ = 1.20\frac{g}{mL}(ECHA\ RAC\ 2011)$$

$$Concentration\ of\ PHMB\ in\ 1\%\frac{v}{v}\ solution\ = 0.01\ \times 1.2\frac{g}{mL}$$

$$= 0.012\ g/mL$$

$$Exposure\ threshold\ \ \ = 0.012\frac{g}{ml}$$

$$Exposure\ volume\ \ \ = 0.4\ mL$$

$$Exposure\ area\ \ \ \ \ = 6.25\ cm^2\ (1\ square\ inch)$$

$$Exposure\ dose\ \ \ = \frac{0.012\frac{g}{mL} \times 0.4\ mL}{6.25cm^2} = 0.000768\frac{g}{cm^2}$$

$$\boxed{NESIL\ \ \ = 768\frac{\mu g}{cm^2}}$$

Step 2: Safety Assessment Factors (SAFs)

$$Inter - individual\ variability\ \ \ = 10$$

$$Matrix\ effects\ \ \ \ = 3$$

$$Use\ consideration\ \ \ = 3$$

$$\boxed{Total\ SAFs\ \ \ = 90\ (= 10\ x\ 3\ x\ 3)}$$

Step 3: Acceptable Exposure Level (AEL)

$$AEL = \frac{NESIL}{SAF}$$

$$AEL = \frac{768}{90}\frac{\mu g}{cm^2}$$

$$\boxed{AEL = 8.53\frac{\mu g}{cm^2}}$$

Step 4: Consumer Exposure Level (CEL)

$$CEL\ ug/cm^2 = \frac{SL \times 1000 \times C \times F \times RF}{100}$$

Where

$SL = Surface\ loading = 2\frac{mg}{cm^2}\ (Body\ lotion\ scenario; conservative)$

$C = Concentration\ of\ PHMB\ in\ the\ product = 3\%\ (maximum\ concentration\ notified)$

$F = Frequency\ of\ application = 2$

$RF = Retention\ factor = 1\ (Leave - on\ scenario; conservative)$

Substituting,

$$CEL = \frac{2 \times 1000 \times 3 \times 2 \times 1}{100}$$

$$\boxed{CEL = 120\frac{\mu g}{cm^2}}$$

Step 5: Comparison of AEL and CEL

The AEL <<< CEL indicating that the current level of exposure is unacceptable.

There are two human repeated insult patch test (HRIPT) studies on PHMB reported in dossiers prepared by the European Chemical Society and the Scientific Committee on Consumer Safety. The study by Hink (1976; as cited in ECHA 2011) suggests that PHMB did not induce skin sensitization at a concentration of 1%. Sensitization induction was observed when the induction concentration is 2% or more (Smith 1981, as cited in SCCS 2017). Taken together, these results indicate that sensitization induction threshold in humans is between 1% and 2%. Following a methodology similar to that of

the quantitative risk assessment (QRA) for skin sensitization (Api et al. 2008), the NESIL for PHMB in cosmetics was estimated to be 768 µg/cm^2.

The NESIL is adjusted with a set of safety assessment factors (SAFs) to account for inter-individual variability, matrix effects and use considerations to estimate the AEL. To account for the differences in individual susceptibility for skin sensitization within the human population, a factor of 10 is included. PHMB is notified in several product types, such as deodorants, bath products, cleansers, moisturizers, nail care products. The vehicle used in HRIPT studies is distilled water, whereas cosmetic formulations contain complex vehicles containing various aqueous and non-aqueous substances that are likely to affect the dermal absorption of PHMB. To account for the differences in the composition of the vehicles, a factor of 3 is included. Finally, to account for the differences in the use patterns of cosmetics containing PHMB, an additional factor of 3 is included. Overall, a SAF of 90 (10 x 3 x 3) is proposed. By incorporating the SAF, the AEL is estimated to be 8.53 µg/cm^2.

Based on notifications submitted under the *Cosmetic Regulations* to Health Canada, the maximum concentration of PHMB in moisturizers in the Canadian market is 3%. Assuming 3% PHMB in a product available to consumers, the CEL is estimated to be 120 µg/cm^2. The estimated CEL from dermally applied products containing 1% PHMB is estimated to be 40 µg/cm^2. Comparison of the AEL with the CEL suggests that the current exposure levels from products containing 1% and 3% PHMB are not acceptable.

Assuming 0.1% PHMB in a dermally applied natural health product (NHP), the CEL is estimated to be 4 µg/cm^2. Comparison of the AEL with the CEL suggests that the current exposure level from NHPs containing the limit of PHMB at 0.1% as outlined in the Natural Health Products Ingredients Database are acceptable.

Several uncertainties exist in the HRIPT studies. These studies were submitted by the industry to the European and United States regulators and provide only secondary sources of information. The number of study subjects who completed the study is lower than the generally acceptable number of subjects for HRIPT (Politano and Api 2008). Moreover, complete study design, grading scales, and endpoints measured were not available to evaluate the study quality. There are several deviations, including the changes in the induction concentrations and the administration of multiple challenge concentrations during the course of the study, which increase the ambiguity of the study outcome.