

HOTLIST INGREDIENT REVIEW
Risk Assessment Division
Consumer and Hazardous Products Safety Directorate (CHPSD)

Polyaminopropyl Biguanide (PHMB)

Date Approved: December 12th, 2023

EXECUTIVE SUMMARY

Purpose

The modernization of Health Canada's Cosmetic Regulations has been identified as an action item under the Government of Canada's Food and Consumer Safety Action Plan. While there are currently no Hotlist conditions restricting or prohibiting the use of PHMB (INCI: Polyaminopropyl Biguanide) in cosmetic products, a cosmetic ingredient review of this substance was initiated in response to potential health and safety concerns relevant to cosmetic use, identified through Chemicals Management Plan (CMP) assessment.

Disclaimer: Please note that recommendations put forward by this document are intended to inform an upcoming Hotlist update, as supported by the currently available evidence. However, the HIR is a dynamic document which may be updated as required, should new information become available.

Recommendations/Conclusions

Sufficient evidence exists to justify classifying PHMB as an inhalation toxicant. Prohibition of PHMB in cosmetic spray formulations is scientifically supported based on toxic effects observed in the respiratory tract in acute and repeat dose toxicity studies. There is some evidence of systemic toxicity of PHMB via the oral route. Results from human repeat insult patch test (HRIPT) studies suggest that exposure of PHMB from cosmetics may cause skin sensitization in humans. However, the Quantitative Risk Assessment (QRA) presented here suggests that a full prohibition of PHMB in cosmetics may not be necessary. Using the QRA methodology, a restriction limit of 0.2% was derived for PHMB in cosmetics (non-spray formulations). Note that in the European Union, PHMB is prohibited in spray products and restricted to 0.1% in non-spray cosmetics.

A full prohibition in spray formulations, and a restriction limit of 0.2% in all other products is recommended.

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1.0 INGREDIENT SUMMARY

INCI Name: Polyaminopropyl Biguanide (PCPC, 2022)

Technical Name: Polihexanide

Synonym(s): Polyhexamethylenebiguanide; Poly(hexamethylenebiguanide) hydrochloride; PHMB

CAS Number(s): 32289-58-0; 27083-27-8; 28757-47-3 (ChemIDplus, 2022; NCIGlobal, 2022; PCPC, 2022; PubChem, 2022)

Note: Three Chemical Abstract Service Registration Numbers (CAS RN) apply. Each describes the polymer from a different perspective.

CAS RN 27083-27-8 expresses PHMB in terms of its starting monomers (N,N''-1,6-hexanediylbis(N'-cyanoguanidine) and 1,6-hexanediamine).

CAS RN 28757-47-3 and 32289-58-0 expresses the PHMB as the resultant polymer and its hydrochloride salt, respectively. (SCCS, 2017, NCI Global, 2022)

For a complete list of synonyms please refer to [Appendix 1](#).

2.0 BACKGROUND ON SUBSTANCE

2.1 Regulatory Status of Substance in Cosmetics

PHMB (INCI: Polyaminopropyl Biguanide) is currently neither prohibited nor restricted in cosmetic products marketed in Canada or the United States. (Health Canada, 2022a; US FDA, 2022a). The European Union¹ and ASEAN² allow the use of PHMB as a preservative up to a maximum concentration of 0.1% in all cosmetic products, except in applications that may lead to exposure of the end-user's lungs by inhalation (CosIng, 2023; ASEAN, 2019). The Eurasian Economic Community (EEC) Customs Union, Switzerland, MERCOSUR³ and New Zealand allow the use of PHMB as a preservative at a maximum allowable concentration of 0.3%, and no additional restrictions on products with potential for inhalation exposure. In Japan, this ingredient is allowed at a maximum amount of 0.1 g per 100 g of product both in leave-on and rinse-off applications, including products that may come in contact with mucous membranes.

Please refer to [Appendix 2](#) for a side-by-side comparison of the cosmetic regulations applicable to these ingredients in other international jurisdictions.

2.1.1 Policy Statements and Decisions Regarding Cosmetics and Cosmetic Regulations

¹ Norway, Iceland, Liechtenstein have the same cosmetic regulations as the EU for this ingredient.

² Association of Southeast Asian Nations (ASEAN) consists of Brunei, Kingdom of Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, Vietnam

³ Mercado Común del Sur is composed of Argentina, Brazil, Paraguay, Uruguay, and Venezuela

No policy statements or decisions regarding cosmetics and cosmetic regulations in Canada have been found.

2.2 Status of Ingredient in Other Cosmetic Lists or Databases

2.2.1 Cosmetics Notifications (Health Canada):

The Cosmetic Notifications search for the timeframe January 1, 2018 - November 7, 2023 revealed a total of 386 cosmetic notifications for INCI name “Polyaminopropyl Biguanide” and 2 notifications for the respective technical name “Polyhexamethylene biguanide”. This ingredient was not notified in cosmetics under any of its other associated synonyms.

Table 1. Total active cosmetic notifications with “Polyaminopropyl Biguanide” and Polyhexamethylene biguanide” between January 1, 2018 and November 7, 2023.

[Redacted for confidentiality]

Table 2. Summary of notifications for “Polyaminopropyl Biguanide” and “Polyhexamethylene biguanide” notified in cosmetics between January 1, 2018 and November 7, 2023.

[Redacted for confidentiality]

2.2.2 Personal Care Products Council (PCPC) INCI Dictionary:

“Polyaminopropyl Biguanide” is listed as a preservative (PCPC, 2023).

2.2.3 International Fragrance Association (IFRA) Standards (51st Amendment):

This ingredient is not listed.

2.3 Status of Ingredient in Other Non-Cosmetic Databases

Domestic Substance List (DSL):

Two relevant entries have been found on the DSL: “Poly(iminocarbonimidoyliminocarbonimidoylimino-1,6-hexanediyl), hydrochloride” (CAS RN 32289-58-0) and “Guanidine, N,N'''-1,6-hexanediylbis[N'-

cyano-, polymer with 1,6-hexanediamine, hydrochloride” (CAS RN 27083-27-8). (ECCC, 2022) As mentioned earlier, these CAS numbers refer to the same substance.

In the initial categorization performed in 2006, this substance met ecological but not human health categorization criteria under CEPA, due to its persistence and inherent toxicity to aquatic organisms; however, it was not considered bioaccumulative (ECCC & HC, 2014). In a subsequent polymer screening (ECCC & HC, 2018), PHMB was identified as having low potential to cause ecological harm. However, it was identified as requiring further assessment due to potential human health risk based on structural alerts, toxicological information and/or uses associated with significant consumer exposure.

A final screening assessment elaborating on the potential of PHMB to cause harm to human health and environment was published in 2023. See section [3.3 Authoritative Opinions and Risk Assessments](#) for additional information.

Drug Product Database (DPD):

“Polyaminopropyl Biguanide” or “Polyhexanide” are listed as active ingredients in 25 Over The Counter (OTC) products classified as “disinfectants”, at strengths ranging between 0.00005% and 0.0001%. All products appear to be cancelled post-market (Health Canada, 2023).

Licensed Natural Health Products Database (LNHPD):

“Polyaminopropyl Biguanide” is listed in the Licensed Natural Health Products Database as a non-medicinal ingredient in 18 active topical NHPs. “Polyhexanide” is listed in the Licensed Natural Health Products Database as a non-medicinal ingredient in 1 active topical NHP. “Polihexanide” is listed as a non-medicinal ingredient in 3 active topical NHPs (Health Canada, 2023).

Natural Health Products Ingredients Database (NHPID):

“Polihexanide” (CAS RN 32289-58-0; 28757-47-3) is listed in the Natural Health Product Ingredient Database as a non-NHP substance. However, it is allowed in NHPs when used as a non-medicinal ingredient, with preservative antimicrobial function. It is allowed in topical use only, up to a maximum concentration of 0.1%, and is not permitted in sprayable formulations. The following proper and common names are also listed: “Poly(iminocarbonimidoyliminocarbonimidoylimino-1,6-hexanediyl), hydrochloride”, “Polyhexamethylene biguanide hydrochloride”, “PHMB”, “Polyaminopropyl biguanide”, “Polyhexanide” (Health Canada, 2023b).

U.S. Code of Federal Regulations, excluding Subchapter G – Cosmetics (FDA):

Title 40 (Protection of the Environment), Chapter I (Environmental Protection Agency), Subchapter E (Pesticide Programs), Part 180 (Tolerances and Exemptions for Pesticide Chemical Residues in Food) lists “Poly(hexamethylenebiguanide) hydrochloride (PHMB)” (CAS Reg. No. 32289-58-0) as exempt from the requirement of a tolerance for residues of the antimicrobial in or on all food commodities when the residues are the result of the lawful application of a food contact surface sanitizer containing PHMB at 550 parts per million (ppm) (US FDA, 2023).

Australian Government Poisons Standard 2021:

“Polihexanide” is listed under Schedule 6: Poison – Substances with a moderate potential for causing harm, the extent of which can be reduced through the use of distinctive packaging with strong warnings and safety directions on the label. Polihexanide may only be used in (a) in cosmetic preparations containing 0.3% or less of polihexanide; or b) preparations containing 5 per cent or less of polihexanide, or c) when packed and labelled for therapeutic use (Australian Government, 2023).

French National Agency for the Safety of Medicines and Health Products (ANSM):

“Polyhexaméthylène biguanide” is listed as an active substance contained in hospital preparations (up to January 2010). The substance is listed as having a maximum allowable concentration of 0.3% in cosmetic products (other than those incriminated by the Committee on Sustainable Development in Health (C2DS), inspected by the Inspection and Establishments Directorate (DIE) of the French Agency for the Safety of Health Products (Agence Nationale de Sécurité du Médicament et des Produits de Santé, ANSM) formerly known as the French Agency for the Safety of Health Products (Agence Française de Sécurité Sanitaire des Produits de Santé, AFSSAPS) (ANSM, 2010).

The ingredient was not found in the following sources:

List of all Challenge Substances, Chemicals Management Plan (CMP);
Food and Drug Regulations (C.R.C, c. 870);
Lists of Permitted Food Additives (HC);
New Drugs List (aka Listing of Drugs Currently Regulated as New Drugs) (TPD)
Prescription Drug List (HC);
List of chemicals known to the state to cause cancer or reproductive toxicity (California EPA);
Danish List of Undesirable Substances;
International Agency for Research on Cancer (IARC) Classes of Carcinogens List

3.0 SCIENTIFIC JUSTIFICATION

3.1 Background

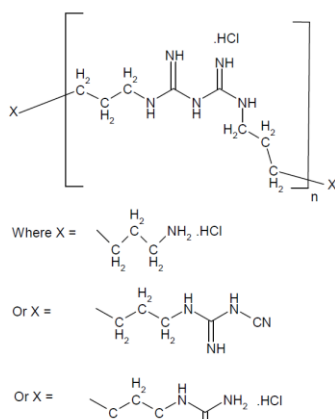


Figure 1 Chemical structure of PHMB (ECHA RAC, 2011)

PHMB (INCI: Polyaminopropyl Biguanide) is a polymeric substance with a molecular weight ranging from 700 to 4200 g/mole (Figure 1). It is an off-white to pale yellow powder with a strong ammonia smell at room temperature. It is freely soluble in water and its aqueous solution is stable for several weeks.

PHMB is used as a preservative and as an antimicrobial agent in cosmetics. It has excellent biocidal activity against a wide spectrum of microorganisms including bacteria, fungi, and yeasts.

Note on substance identity: The Cosmetic Ingredient Review (CIR) describes PHMB as an amino polymer containing propyl biguanide repeat units (polyaminopropyl biguanide (PABA)), hexyl biguanide repeat units (polyhexamethylene biguanide), or their hydrochloride salts (CIR, 2017). The INCI name for PHMB is stated as Polyaminopropyl Biguanide (SCCS, 2015). The Scientific Committee for Consumer Safety (SCCS) considers all these substances toxicologically equivalent and refers to them as PHMB (SCCS, 2015).

3.2 Relevant Toxicokinetics

Absorption of PHMB through the oral route is low and it distributes to some extent in liver and kidney tissues (SCCS, 2015). It is still unclear how PHMB is metabolised in humans and animals. However, the available data suggest that it is poorly metabolised and mainly excreted through feces. An oral absorption rate of 8.5% was derived from a toxicokinetic study carried out in Alpk:APfSD rats (Lythgoe et al. 1995).

An in-vitro dermal absorption study was carried out by applying 0.1% or 0.3% of [14C]-PHMB (at a rate of about 2.0 mg/cm²) on to human split-thickness skin membrane samples mounted on a static cell. At the end of 24 hours, the receptor fluid, epidermis, and dermis contained 0.03 % ± 0.01 %, 11.47 % ± 5.69 % and 1.56 % ± 2.49 % of [14C]-PHMB. Overall mass balance of > 90% was observed in 24 h (the post-dose period). Moreover, by extending the monitoring time for up to 72 hours, this study has demonstrated that there was negligible increase in the absorbed dose from 24 h to 72 h. Hence, the SCCS opined that the PHMB found in epidermis should be excluded from the total absorbed dose. The SCCS derived a dermal absorption value of 4.09% (= % found in dermis (1.56) + 1 SD (2.49) + receptor fluid (0.03))(SCCS, 2015).

No information on absorption through the inhalation route is available.

3.3 Authoritative Opinions and Risk Assessments

Most of the toxicity data for PHMB were submitted by industry stakeholders to EU/US regulators, and only a limited number of relevant scientific studies are available from primary sources such as peer-reviewed journal articles. The Cosmetic Ingredient Review (CIR), the Scientific Committee on Consumer Safety (SCCS), European Chemicals Agency, US Environmental Protection Agency, and the Australian Pesticides and Veterinary Medicines Authority have reviewed the toxicity of PHMB. The data presented in the aforementioned reviews are summarized in [Appendix 3](#).

Additionally, Environment and Climate Change Canada and Health Canada jointly assessed the human health risks of PHMB under the CMP program. The assessment concluded that PHMB posed minimal ecological harm. However, the potential human health risks for PHMB were evaluated on the basis of structural alerts, toxicological information and/or uses associated with significant consumer exposure. The calculated MOE⁴ for cosmetic spray products is considered inadequate to address uncertainties in the health effects and exposure databases. Overall, the CMP assessment concluded that PHMB 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.

3.4 Hazard Assessment

Results from the acute and chronic toxicity studies carried out in animals indicate that the systemic toxicity of PHMB is of low concern via oral and dermal exposure routes. However, PHMB elicited skin irritation and skin sensitization reactions in animals and in humans. Given that these endpoints are of relevance for exposure to PHMB via cosmetic products use, these endpoints were considered further for risk analysis.

Both acute and repeat dose toxicity studies demonstrate that PHMB exposure via inhalation exposure route could produce significant toxic effects to the respiratory system.

3.4.1. Dermal Sensitization

The CIR report indicates that PHMB did not induce sensitization in the local lymph node assay, although no study details were provided (CIR, 2017). However, the SCCS classifies PHMB as a moderate to strong sensitizer based on the results from skin sensitization studies in guinea pigs. We estimated an acceptable exposure level (AEL) of 8.53 µg/cm² based on the results available from Human Repeat Insult Patch Test (HRIPT) studies (see [Appendix 4](#)).

⁴ In the discussion above, Margin of Safety (MOS) and Margin of Exposure (MOE) have equivalent meaning and represent risk characterization metrics with an acceptable value of 100 or more. Note that the term MOE is used in CMP assessment whereas SCCS opinions uses MOS in cosmetic ingredients evaluations.

3.4.2. Inhalation irritation

No chronic inhalation toxicity studies are available. Therefore, a 28-d inhalation toxicity study carried out in Alpk:APfSD rats is considered to be the critical study to estimate acceptable exposure levels for PHMB. In that study, rats were subjected to nose-only exposure to 19.2% aqueous solution of PHMB at a dose level of 0, 0.000025, 0.00025, 0.0025 mg/L for 28 days. Treatment-related irritation effects in the respiratory system were observed at 0.25 and 2.5 mg/m³ dose levels. Pneumonitis and bronchitis in the lungs were observed at 2.5 mg/m³ group. Based on these findings, NOAEC of 0.025 mg/m³ was estimated (SCCS, 2017; CIR, 2017).

3.5 Exposure Assessment

The CIR panel has reviewed the exposure data as well as toxicity of PHMB in 2017. PHMB was reported to be used at concentrations up to 0.5% in both leave-on and rinse-off formulations. Furthermore, the CIR report suggests that PHMB is also used in pump hair sprays (0.000002% - 0.27%) and aerosol hair sprays (0.00025% - 0.0004%).

3.5.1. Dermal exposure estimation

There were 388 cosmetic products notified between January 1, 2017 and November 7, 2023 containing PHMB. Exact concentrations of PHMB used in these products are not available. However, based on the upper limit of the concentration range codes submitted in the Cosmetics Notification Form, a maximum concentration of 3% (12 products), 1% (51 products), 0.3% (130 products), 0.1% (195 products) could be deduced (see Table 2).

PHMB is used as a preservative in leave-on and rinse-off products (Table 2). Given that preservatives are used in several leave-on and rinse off products by consumers daily, the Scientific Committee on Cosmetic Products and Non-Food Products (SCCNFP) recommends the use of aggregate exposure scenario for ingredients used as preservatives – i.e., exposure from the use of various products that a person may apply daily (SCCNFP, 2000).

From an exposure assessment perspective, use of body lotion/moisturizer containing PHMB is expected to produce maximum consumer exposure (Ficheux et al. 2016). To account for the use of other daily use cosmetic products containing PHMB, we used a maximum product use of 2 mg/cm²/application. Other default parameters used to estimate the PHMB exposure from the use of cosmetic products are provided in *Appendix 4*. We derived the consumer exposure level (CEL) of 120 µg/cm² based on the maximum concentration of PHMB (3%) found in the products in the Canadian market, (See [Appendix 4](#) for calculation).

3.5.2. Inhalation exposure estimation

[Redacted for confidentiality]. Although the exact concentration of PHMB in this product is not notified, the maximum concentration, based on the range code, is expected to be 0.3% **[Redacted for confidentiality]**. Using ConsExpo Web tool, the mean PHMB concentration on day of exposure for hair spray products containing 0.3% PHMB is estimated to be 3.5 X 10⁻⁴ mg/m³.

3.6 Risk Characterization

Risk characterization matrix for PHMB via dermal and inhalation route is presented in **Table 3**.

Between January 01, 2017, to November 7, 2023, PHMB was notified in 388 cosmetic products up to a maximum concentration of 3%. For dermal exposure, we used aggregate exposure scenario and estimated the consumer exposure level (CEL) of 120 µg/cm². Comparing the CEL to the AEL of 8.53 µg/cm² suggest that the use of PHMB in dermal care products may pose skin sensitization risk to consumers in Canada.

[Redacted for confidentiality] containing PHMB at a potential maximum concentration of 0.3% was identified. A mean PHMB inhalation exposure concentration of 3.5 X 10⁻⁴ mg/m³ was estimated using ConsExpo Web tool. Comparing this exposure concentration to the NOAEC of 0.025 mg/m³, a margin of exposure of 71 was estimated and is not considered acceptable. Similarly, the SCCS has concluded that it is not safe to use PHMB in spray formulations (SCCS, 2017).

Table 3: Risk estimates for PHMB exposure from cosmetic products sold in Canada

Exposure route	Critical effect	No observed adverse effects level	Risk Characterization	Conclusion
Dermal	Sensitization (SCCS, 2017)	NESIL: 768 µg/cm ²	$MOS = \frac{NESIL}{Exposure}$ $MOS = \frac{768}{120}$ $MOS = 6.4$	Unacceptable sensitization risk to consumers
Inhalation	Squamous metaplasia in the larynx and tracheal inflammation (SCCS, 2017)	NOAEC: 0.025 mg/m ³	$MOS = \frac{NOAEC}{Exposure}$ $MOS = \frac{0.025}{3.5 \times 10^{-4}}$ $MOS = 71$	Unacceptable metaplasia and respiratory irritation risk to consumers

Restriction limit for PHMB in cosmetics non-spray formulation

There are currently no specific conditions for use of PHMB in cosmetics sold in Canada. Between January 01, 2017, and November 07, 2023, PHMB was notified in cosmetics up to a maximum concentration of 3%. As indicated earlier, PHMB is a moderate to strong skin sensitizer based on laboratory results and clinical studies. Based on the QRA methodology for skin sensitization, a maximum permissible concentration of PHMB in skin care cosmetics is estimated to be 0.2 % for cosmetics. The detailed methodology is included in [Appendix 5](#).

4.0 CONCLUSION

Overall the dermal and oral absorption of PHMB were estimated to be 4% (in-vitro study) and 8.5% (rat study), respectively. Acute oral and dermal toxicity of PHMB is of low concern; however, it is highly toxic via the inhalation route during both acute and repeated exposure scenarios. PHMB is a mild skin irritant. Exposure to undiluted PHMB produces severe toxic effects in rabbit eyes. PHMB is categorized as a moderate to strong skin sensitizer. Available evidence suggests that the systemic toxicity of PHMB via oral or dermal route is of low concern. The weight of evidence is not strong enough to classify PHMB as a carcinogen, and it is neither mutagenic nor genotoxic. PHMB did not exhibit any adverse changes on reproduction and development parameters.

Sufficient evidence exists to justify classifying PHMB as an inhalation toxicant. Prohibition of PHMB in cosmetic spray formulation is scientifically supported based on the toxic effects observed in the respiratory tract in acute and repeat dose toxicity studies. Results from HRIPT studies suggest that exposure of PHMB from the use of cosmetics may cause skin sensitization in humans. As such, our analysis suggests that a full prohibition of PHMB is warranted in spray products that might be inhaled. A restriction limit of 0.2% in all other products is proposed to protect from the risk of sensitization following topical administration of PHMB.

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APPENDIX 1 – Ingredient Summary of PHMB

INCI NAME	CAS RN	SYNONYM(S)
Polyaminopropyl Biguanide	32289-58-0; 27083-27-8; 28757-47-3 (ChemIDplus, 2022; NCIGlobal, 2022; PCPC, 2022; PubChem, 2022)	Polihexanide (INN); Polyhexanide; Polyhexamethylenebiguanide; Poly(hexamethylenebiguanide) hydrochloride; PHMB; 1-Hexylbiguanide; Poly(iminocarbonimidoyliminocarbonimidoylimino-1,6-hexanediyl), hydrochloride; polyhexamethylene biguanide hydrochloride; Poly(iminoimidocarbonyl-iminoimidocarbonyl-iminohexamethylene), hydrochloride; Poly(iminoimidocarbonyliminoimidocarbonyliminohexamethylene) hydrochloride; polyhexamethylene guanidine hydrochloride (ChemIDplus, 2022; NCIGlobal, 2022; PCPC, 2022; PubChem, 2022)

Return to Section [1.0 Ingredient Summary](#).

APPENDIX 2 - Comparison of Regulatory Status of PHMB in Cosmetics across Different International Jurisdictions

	Canada ¹	USA ²	European Union ^{3,9}	Other Jurisdictions ⁴⁻⁸
Status	No conditions	No conditions	Restricted	EEC: Restricted Switzerland: Restricted ASEAN: Restricted New Zealand: Restricted MERCOSUR: Restricted Japan: Restricted
Max.	-	-	0.1%	EEC: 0.1% Switzerland: 0.3% ASEAN: 0.1% New Zealand: 0.3% MERCOSUR: 0.3% Japan: 0.1g/100g
Product Type	-	-	-	-

	Canada ¹	USA ²	European Union ^{3,9}	Other Jurisdictions ⁴⁻⁸
Product Form	-	-	Prohibited in products with potential for inhalation exposure.	ASEAN: Prohibited in products with potential for inhalation exposure.
Label Requirements	-	-	-	-
Other	-	-	-	-

¹HC, 2022; ²US FDA, 2022; ³EU-Annex V, 2023; ⁴FDHA, 2015; ⁵(EEC, 2011), ⁶ASEAN, 2022; ⁷MERCOSUR- GMC n°7/11, 2012; ⁸Japan, 2000; ⁹Norway, Iceland, and Liechtenstein have the same cosmetic regulations as the EU for this ingredient.

Return to [Section 2.1 Regulatory Status of Ingredient\(s\) in Cosmetics](#).

APPENDIX 3 – Summary of Toxicological Data Reviewed in the Authoritative Opinions and Risk Assessments on PHMB

Acute Toxicity

PHMB has low to moderate oral toxicity (LD50: 500 to 1000 mg/kg bw in rats) and low dermal toxicity (LD50: > 5000 mg/kg bw in rats) (SCCS, 2017). However, inhalation of PHMB even at low mg/L concentrations could be fatal, based on the results from an acute inhalation toxicity study in Wistar CRL rats (SCCS, 2017). Animals (5/sex/concentration) were exposed to PHMB aerosols at 0.1, 0.3 and 0.5 mg/L of for 4 hours (note: no control group was apparent). While no fatality was noted in the 0.1 mg/L group, 3/5 males died in 0.3 mg/L group and 5/5 males and 3/5 females died 0.5 mg/L group. Observed clinical signs in surviving animals include laboured respiration, rhonchus, decreased activity, hunched back and increased respiration rate. A lethal concentration (LC50) value of 0.37 mg/L (males and females combined) was estimated (SCCS, 2017).

Skin/eye irritation

PHMB caused skin irritation when applied on intact (mild irritation) and abraded (moderate) skin areas of rabbits (SCCS, 2017). The European Chemical Agency classifies PHMB as an eye irritant based on the results from two eye irritation studies carried out in rabbits. In both studies, irreversible ocular damage including, translucent corneal opacity, and vascularization, ulceration of the nictating membrane and cornea, were observed when undiluted PHMB was instilled in the conjunctival sac (ECHA RAC, 2011).

Skin Sensitization

Several skin sensitization studies have been described in guinea pigs, using both Magnusson and Kligmann (with Freund's complete adjuvant) and Buehler (without adjuvant) methods (ECHA RAC, 2011). Frequency of sensitization was observed in 10% to 60% of animals, dependent on the induction and challenge concentrations.

Jackson and Oliver (1983) studied the effect of induction concentration on the sensitization frequency according to Buehler method. Groups of 10 guinea pigs were treated with PHMB at concentration range of 0.3% to 5% (induction phase) and challenged with 0.03% to 15%. Results showed that between 30% and 75% of animals exhibited positive reactions above an induction concentration of 1.2%.

Two HRIPT studies with PHMB were reported. In the first study, 209 subjects participated, of which 191 subjects completed the study. The subjects were divided into three panels (panel 1: 49 subjects; panel 2: 114 subjects; panel 3: 28 subjects). Induction phase consisted of applying PHMB patches for 3 times per week for a total of 10 applications. After approximately 2 weeks rest period, challenge patches were applied. Skin reactions were scored using a pre-defined grading scale during the induction phase and at 48 and 96 h after the challenge.

The PHMB concentrations applied to participants during the indication phase was adjusted based on the level of skin irritation observed. Subjects in panel 1 were exposed first to 2% PHMB for 6 patches, and then to 4% PHMB. Due to high level of skin reactions, the induction concentration was reduced to 2% again. In panel 2, an induction concentration of 4% was first chosen, but due to the skin reactions observed, it was reduced to 2% from the 4th patch onward. In panel 3, induction was performed with 2% for first 4-5 patches and for the rest of the patches distilled water was used.

The challenge concentrations used in panels 1, 2 and 3 ranged from 2% to 0.1%, 0.5 to 0.05% and 0.5 to 0.05% respectively. Elicitation reactions in panels 1, 2 and 3 were observed in 16% to 4%, 16% to 0%, 3.6% to 0% of individuals, respectively (SCCS, 2017).

In a second study, photosensitization of PHMB was studied in 26 individuals using a modified repeat insult patch test using a Draize-type protocol (Draize et al. 1944). The study subjects were exposed to an aqueous solution containing 1% PHMB (v/v) and 0.01% sodium lauryl sulfate three 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 the test site was exposed to natural sunlight for one hour. After a 2 to 3 weeks rest period, a challenge dose of 1% was applied to the test site on week 6. Skin reactions were evaluated at 48 and 96 h after the challenge application. No sensitization reactions were observed in any individuals and the study concluded that dermal exposure of 1% PHMB did not elicit sensitization in humans (Hink, 1976, as cited in ECHA RAC 2011).

The Australian Government's Department of Health conducted a detailed evaluation of the available skin sensitisation studies; however, the study report was never published in the public domain. Nevertheless, in 2018, a Tier-2 risk assessment on polyhexanide was published that included the conclusions from the evaluation of the skin sensitization studies (Australian Government, 2018). As per that report, PHMB is a possible skin sensitizer in humans in product formulations at 0.5%, with a potential for causing sensitisation at 0.2% in sensitive individuals. The CHPSD staff were not able to obtain the unpublished Australian report.

In summary, publicly available information on sensitization in guinea pigs and the HRIPT studies referenced above suggest that induction of skin sensitization with PHMB occurs above a concentration of 1% PHMB. The HRIPT study results indicate that skin irritation as well as skin sensitization occurs during dermal exposure to PHMB at or above 2% concentration. Taken together, these results indicate that sensitization induction threshold in humans is between 1% and 2%.

Limited information on three patch test studies carried out in dermatology patients were provided in ECHA RAC (2011). In the first study, exposure to 2.5% aqueous solution of PHMB caused positive reactions in 0.4% patients. In the second study, 0.5% and 0.8% of the patients reacted to PHMB when exposed to a concentration of 2.5% and 5% respectively. In the third study, exposure to 2.5% concentration of PHMB caused reactions in 0.5% of the patient population. However, it is unknown if these patients were previously sensitized to PHMB or its analogs.

Repeat Dose Toxicity

In a 28-d inhalation toxicity study, AlpK:ApfSD rats (5/sex/dose) were subjected to nose-only exposure to 19.2% aqueous solution of PHMB at a dose levels of 0, 0.000025, 0.00025, 0.0025 mg/L for 28 days (5d/wk; 6h/d). Treatment-related microscopic changes in larynx, trachea, and lungs, including, squamous metaplasia in the larynx and tracheal inflammation and transient histopathological changes characteristics of exposure to respiratory irritant, were observed at 0.25 and 2.5 mg/m³ dose levels. Pneumonitis and bronchitis in the lungs were observed at 2.5 mg/m³ group. A no-observed-adverse-effect-concentration (NOAEC) of 0.025 mg/m³ was derived. It has been concluded that PHMB is a severe inhalation toxicant (SCCS, 2017; CIR, 2017).

A 30-d repeat dose dermal toxicity study of PHMB in AlpK:ApfSD rats was reported (Lees and Leah, 1993). PHMB at dose levels of 0, 20, 60, or 200 mg/kg/d was applied on the shorn back of animals (5/sex/dose) using an occlusive patch for 6 hours per

treatment. Animals were treated for 21 study days over a period of 30 days. No mortality or overt clinical signs of toxicity were observed in animals in treatment groups. However, local skin irritation was observed in animals in 200 and 60 mg/kg/d group. NOAELs of 200 and 20 mg/kg bw/d, respectively were reported for systemic toxic effects and local skin irritation effects after dermal application.

In a 1-year chronic study in beagle dogs, animals (4/sex/dose) were exposed to 11, 54, 108 mg/kg/d of PHMB in diet. Toxicity to liver, kidney, and testis as well as skin dermatitis were observed in animals only in the highest dose group. A NOAEL of 54 mg/kg bw was reported.

Genotoxicity and Mutagenicity

In an in-vitro study, PHMB did not induce chromosomal aberrations in human lymphocytes. It did not produce micronucleated polychromatic erythrocytes in a mouse bone marrow micronucleus test and did not produce damage to DNA in the unscheduled DNA synthesis assay in rats (ECHA RAC, 2011).

Carcinogenicity

In a carcinogenicity study, Alpk:APfSD rats (64/sex/dose) were fed a diet containing 0, 200, 600, or 2000 ppm of Vantocil P (20.2% aqueous PHMB solution) for 104 weeks (Horner, 1996). Dose-related reduction in body weight was observed in females in the 2000 ppm dose group. A slight increase in alkaline phosphatase activity in females and a slight increase in the incidence of hepatocyte fat and spongiosis hepatitis in males were also observed at this dose. Although 4% of animals in this group had developed vascular tumours (haemangiomas and haemangio-sarcomas), the results were re-evaluated by an expert group which concluded that these vascular neoplasms were not treatment-related. No other clinical signs of toxicity attributable to treatment were observed in any animals. A NOAEL of 600 ppm corresponding to 36 mg/kg bw/d (males) and 45 mg/kg bw/d (females) of PHMB was reported.

In another oral carcinogenicity study, C57Bl/10J/CD-1 Alpk mice (55/sex/dose) were fed diets containing 0, 400, 1200, or 4000 ppm PHMB with a mean daily dose of 55, 167, or 715 mg/kg bw (males) and 69, 217, or 856 mg/kg bw (females) for 104 weeks (ECHA, 2011). The highest dose (4000 ppm) was considered to exceed the maximum tolerated dose (MTD). At this dose, increased mortality and a significant decrease in the bodyweight in animals in treatment group compared to control were observed. Moreover, increased incidence of vascular tumors (haemangiosarcoma), anal swelling, an increase in haemoglobin, haematocrit and red blood cell counts were observed. In addition, several non-neoplastic changes in the liver, gall bladder and recto-anal junction and changes in hematology and clinical chemistry parameters were also noted. At 1200 ppm, a small increase in haemangiosarcoma was observed. Main non-neoplastic changes included inflammation of the recto-anal junction and gall bladder. At 400 ppm, only minimal inflammation of the recto-anal junction was observed.

In a dermal carcinogenicity study in mice, PHMB was applied to the shorn backs of Alpk:APfCD-1 mice (50/sex/dose) at dose levels of 0, 15, 150, or 750 mg/kg bw/d for

80 weeks. The highest dose exceeded the MTD due to excessive mortality and reduced bodyweight gain. A high incidence of skin irritation and a slight increase in liver tumours were observed in animals at this dose level. There were no carcinogenic effects observed at other dose levels (ECHA RAC, 2011).

The European Chemical Agency concluded that the overall weight of evidence was not considered strong enough for the classification of PHMB as carcinogen (ECHA RAC, 2011).

Reproductive and Developmental Toxicity

One 2-generation and one 3-generation feeding studies in rats were carried out to evaluate the reproductive effects of PHMB (SCCS, 2017). No effect on the reproductive parameters, sex ratios or on the growth and development of offspring was observed. Two feeding studies were presented to evaluate the developmental effects of PHMB. The results indicate that PHMB is neither embryotoxic nor teratogenic.

Case Reports

A few case reports from patients using wet wipes containing PHMB were reported (CIR, 2017). Symptoms observed include angioedema, pruritus, itchy dermatitis, and severe anaphylaxis reactions.

Return to section [3.3 Authoritative Opinions and Risk Assessments](#).

APPENDIX 4 - A Modified Quantitative Risk Assessment Methodology for PHMB

Photosensitization of PHMB was studied in 26 individuals using a modified repeat insult patch test using a Draize-type protocol. The study concluded that dermal exposure of 1% PHMB did not induce sensitization in humans (Hink, 1976, as cited in ECHA RAC 2011). Following a methodology similar to the Quantitative Risk Assessment (QRA) for skin sensitization (Api et al. 2008), No Expected Sensitization Induction Level (NESIL) for PHMB in cosmetics could be derived as follows:

STEP 1: Conversion of NESIL in appropriate dose metrics

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

$$\text{Relative density of PHMB} = 1,20 \frac{g}{mL} \text{ (ECHA RAC 2011)}$$

$$\begin{aligned} \text{Concentration of PHMB in } 1\% \frac{v}{v} \text{ solution} &= 0,01 \times 1,2 \frac{g}{mL} \\ &= 0,012 \text{ g/mL} \end{aligned}$$

$$\text{Exposure threshold} = 0,012 \frac{g}{ml}$$

$$\text{Exposure Volume} = 0,4 \text{ mL}$$

$$\text{Exposure area} = 6,25 \text{ cm}^2 \text{ (1 square inch)}$$

$$\text{Exposure dose} = \frac{0,012 \frac{\text{g}}{\text{mL}} \times 0,4 \text{ mL}}{6,25 \text{ cm}^2} = 0,000768 \frac{\text{g}}{\text{cm}^2}$$

$$\boxed{\text{No Expected Sensitization Induction Level (NESIL)} = 768 \frac{\mu\text{g}}{\text{cm}^2}}$$

Step 2: Safety Assessment Factors

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 Acceptable Exposure Level (AEL). To account for the differences in individual susceptibility for skin sensitisation within the human population a factor of 10 is included. The 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 which 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 safety assessment factor of 90 (10 x 3 x 3) is proposed.

$$\text{Inter – individual variability} = 10$$

$$\text{Matrix effects} = 3$$

$$\text{Use consideration} = 3$$

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

Step 3: Acceptable Exposure Level

$$\text{Acceptable Exposure Level (AEL)} = \frac{\text{NESIL}}{\text{SAF}}$$

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

$$\boxed{\text{AEL} = 8,53 \frac{\mu\text{g}}{\text{cm}^2}}$$

Step 4: Consumer Exposure Level

$$\text{Consumer Exposure Level (CEL)} \mu\text{g}/\text{cm}^2 = \frac{\text{SL} \times 1000 \times C \times F \times \text{RF}}{100}$$

Where

$$SL = \text{Surface Loading} = 2 \frac{mg}{cm^2} \text{ (Body Lotion scenario; conservative)}$$

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

$$F = \text{Frequency of application} = 2/\text{day}$$

$$RF = \text{Retention Factor} = 1 \text{ (Leave – on scenario; conservative)}$$

Substituting,

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

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

Step 5: Comparison of AEL and CEL

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

Return to section [3.5 Hazard Assessment](#).

APPENDIX 5 - Restriction Limit for PHMB

Sensitization risk is considered acceptable only when the consumer exposure level (CEL) is less than or equal to the acceptable exposure level (AEL).

$$\text{Consumer Exposure Level (CEL)} \mu \frac{g}{cm^2} = \frac{SL \times 1000 \times C \times F \times RF}{100}$$

Rearranging,

$$C = \frac{CEL \times 100}{SL \times 1000 \times F \times RF}$$

By substituting CEL = AEL in the above equation the maximum allowable concentration of PHMB is calculated as follows:

$$C = \frac{AEL \times 100}{SL \times 1000 \times F \times RF}$$

Substituting,

$$C = \frac{8.53 \times 100}{2 \times 1000 \times 2 \times 1}$$

$$C = 0.213\%$$

$$C = 0.2\%$$

Return to section [3.6. Risk Characterization](#)