

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

**Hotlist Ingredient Review**  
Brucine and its salts

Date Approved: 2023-12-28

## EXECUTIVE SUMMARY

### Purpose

Brucine is one of the main bioactive and toxic constituents of *Strychnos nux-vomica* L. (Loganiaceae) and other species of botanicals under the genus *Strychnos*. In cosmetic preparations, this ingredient or its sulfate salt are used at low concentration as denaturants, to make the products unfit for human consumption.

Brucine is currently described as restricted on the Cosmetic Ingredient Hotlist, with a maximum concentration threshold of 0.1%. The salts of brucine, specifically brucine sulfate, are not captured under the existing entry although they are expected to display a similar hazard profile as the parent compound based on their ability to dissociate into their constituent ions. In the EU, the use of brucine (not including its salts) in cosmetic products has been prohibited since 2010, although a scientific rationale to support this status has not been provided by the European Commission.

This Hotlist Ingredient Review examines the available safety evidence supporting the current restriction level of 0.1% and explores scientific merit of expanding the entry to include the salt forms of brucine.

*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

The presence of brucine on the Hotlist is scientifically supported based on its potential to cause systemic toxicity, primarily central nervous system effects, upon acute oral exposure.

The sulfate salt of brucine is not captured under the present Hotlist entry; however, its acute toxicity is anticipated to be similar to that of brucine based on its ability to dissociate and release brucine ions.

The EU, and other international jurisdictions, apply a full prohibition on brucine when used as an ingredient in cosmetic products. Although no scientific opinions or risk assessments have been identified to justify this particular status. The CIR Expert Panel (2008) was not able to reach a conclusion regarding the safety of denatured alcohol where brucine or brucine sulfate are used as denaturants, due to significant data gaps in the dermal absorption and long-term toxicity database at the time of the opinion.

Animal studies published in years following the CIR (2008) opinion indicate that brucine has significant oral and dermal absorption potentials, with an absolute oral bioavailability as high as 47.15% and absolute transdermal bioavailability of 40.83%.

At this time there is insufficient data to allow a fulsome characterization of the risk to human health that addresses potential long-term adverse health effects from repeated exposure to cosmetic products containing brucine or its sulfate salt.

In light of this available evidence, consideration should be given to prohibiting the use of brucine and its salts as cosmetic ingredients.

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## 1.0 INGREDIENT SUMMARY

### (1) *Brucine*

**INCI Name:** N/A

**Synonym(s):** (-)-Brucine; 10,11-Dimethoxystrychnine; 2,3-Dimethoxystrychnidin-10-one; Brucine alkaloid; Strychnidin-10-one, 2,3-dimethoxy-; (PubChem, 2023)

**CAS Number(s):** 357-57-3 (PubChem, 2021)

### (2) *Brucine Sulfate*

**INCI Name:** Brucine Sulfate

**Synonym(s):** Brucine Sulfate Heptahydrate; 2,3-Dimethoxystrychnidin-10-one Sulfate (2:1); Strychnidin-10-one, 2,3-Dimethoxy-, Sulfate(2:1) (PCPC, 2021; PubChem, 2021)

**CAS Number(s):** 4845-99-2 (PubChem, 2021)

*For a complete list of synonyms of brucine and its salts please see [Appendix 1](#).*

## 2.0 BACKGROUND ON SUBSTANCE

### 2.1 Regulatory Status of Substance in Cosmetics

Brucine is described as restricted on the Cosmetic Ingredient Hotlist with the verbatim entry: “**Brucine** (357-57-3); permitted at concentrations equal to or less than 0.1%” (HC, 2022). Brucine sulfate is not described as prohibited or restricted on the Cosmetic Ingredient Hotlist and it is not currently subject to specific conditions of use in cosmetic products. Both ingredients are not subject to restrictions when sold as part of cosmetic products marketed in the US.

Brucine appears under Annex II/62 “List of substances prohibited in cosmetic products” of Cosmetic Regulations (EC) No. 1223/2009. Brucine sulfate is not captured under this prohibition and is not subject to other restrictions. Several other verified international jurisdictions align with EU regulations for this group of ingredients.

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

[Redacted]

## 2.2 Status of Ingredient in Other Cosmetic Lists or Databases

**2.2.1 Cosmetics Notifications (Health Canada):** As of January 1, 2018, to December 12, 2023, no active notifications were found for cosmetics containing brucine.

In the same timeframe, a total of ten active notifications were identified for cosmetic products containing brucine sulfate. These products include **[redacted for confidentiality]**, with a notified concentration of  $\leq 0.1\%$  brucine sulfate. Historical notifications also include **[redacted for confidentiality]**. The notified product forms include oily or non-oily liquids, semi-solid gels and semi-solid lotions.

**[Redacted for confidentiality]** and several recently notified sunless-tanning products are applied via mist dispensers.

**Table 1.** Summary of cosmetic products containing brucine sulfate notified from January 1, 2018, to December 12, 2023.

### **[Redacted for confidentiality]**

A supplemental Cosmetic Notification Search revealed an additional 33 cosmetic products notified since January 1, 2018, containing SD Alcohol 40 which *may*<sup>1</sup> use brucine or brucine sulfate as denaturant. The concentration range of SD Alcohol 40 in these products ranges from 10-30% to 0.1% or less. Since the functional concentration of brucine or brucine sulfate is not expected to exceed 0.011%<sup>2</sup> in the specially denatured (SD) alcohol, the level of denaturant in the finished product would not exceed 0.0033% assuming SD Alcohol 40 was notified at the upper limit of the 10-30% range.

Approximately 30% of the total notifications containing SD Alcohol 40 are leave-on products such as moisturizers. Additional uses in products such as antiperspirant/deodorant, fragrance and make-up (non-permanent) are reported.

It is important to note that SD Alcohol 40 may also be notified more broadly as “Alcohol Denat.”<sup>3</sup> which is intended to capture ethyl alcohol that is denatured with one or more denaturing agents. Since compositional information of individual ingredients is not provided at the time of notification, the total number of products containing brucine or brucine sulfate as part of their cosmetic formulation could be higher. Additionally,

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<sup>1</sup> According to CosIng, SD Alcohol 40 is ethyl alcohol denatured with t-butyl alcohol and any combination of one or more of the following: brucine (alkaloid), brucine sulfate, or quassin in accordance with 27CFR21.

<sup>2</sup> According to the US Bureau of Alcohol, Tobacco, Firearms and explosives formulary: To every 100 gallons of alcohol add 1/8 gallon of tert-butyl alcohol, and: One and one-half avoirdupois ounces of either (1) brucine alkaloid, (2) brucine sulfate, N.F. IX, (3) quassin, or (4) any combination of two or of three of those denaturants (CFR Title 27, 2022)

<sup>3</sup> All EU Member States recognize denaturing methods applied by any of the other EU-Member States. This INCI name may also be used in the United States for ethyl alcohol denatured in accordance with the regulations of the Alcohol and Tobacco Tax and Trade Bureau, U.S. Department of the Treasury, as found in 27CFR20 and 27CFR21.

denatured alcohol (INCI: Alcohol Denat.) has been notified at concentration ranges as high as 30-100% in cosmetic products (data not shown).

**Table 2.** Summary of cosmetic products containing SD Alcohol 40 notified from January 1, 2018, to December 12, 2023.

**[Redacted for confidentiality]**

**2.2.2 Personal Care Products Council (PCPC) INCI Dictionary:** Brucine is not listed. Brucine sulfate (CAS 4845-99-2) is listed with the reported function as denaturant.

(PCPC, 2023)

**2.2.3 International Fragrance Association (IFRA) Standards (51<sup>st</sup> ed.):** The ingredients are not listed.

### ***2.3 Status of Ingredient in Other Non-Cosmetic Databases***

#### **Domestic Substance List (DSL):**

Brucine (CAS 357-57-3, as “Strychnidin-10-one, 2,3-dimethoxy-”) is specified on the DSL. The substance was determined to be environmentally persistent and inherently toxic to aquatic organisms. It was found to meet the environmental criteria but not human health criteria for categorization under subsection 73(1) of the Canadian Environmental Protection Act, 1999 (CEPA),

Brucine sulfate (CAS 4845-99-2, as “Strychnidin-10-one, 2,3-dimethoxy-, sulfate (2:1)”) is listed on the DSL. The substance was determined to be environmentally persistent but not bioaccumulative or inherently toxic to aquatic organisms. Overall, it was not found to meet the environmental or human health categorization criteria under subsection 73(1) of the Canadian Environmental Protection Act, 1999 (CEPA).

(ECCC, 2006, 2023)

#### **Specially Denatured Alcohol Regulations:**

In Canada, specifications for denatured alcohols are outlined in the Denatured and Specially Denatured Alcohol (SDA) Regulations under the Excise Act (2001), administered by the Canadian Revenue Agency (CRA).

Since these alcohols are not intended for human consumption, the SDA regulations were designed with the intent of preventing fraud and protecting consumers from the serious health risks of drinking illegal alcoholic drinks, but also to provide relief from excise duties.

Alcohol SD 40 is not listed on the Schedule 2, which outlines the specifications for various authorized grades of specially denatured alcohol. Additionally, brucine or brucine sulfate are not present on the list of authorized denaturants.

(Justice Canada, 2006)

#### **Drug Product Database (DPD):**

Brucine was listed in the Drug Product Database (DPD) of the Therapeutic Products Directorate (TPD) as part of a homeopathic product for human use. The product was cancelled post-market in 1996. No authorized drug products were found to contain either brucine or brucine sulfate.

(HC, 2023a)

#### **Licensed Natural Health Products Database (LNHPD):**

Brucine sulfate (CAS 4845-99-2) is listed as a non-medicinal ingredient in a hand sanitizer product licensed as of 2020-04-19.

(HC, 2023b)

#### **Natural Health Products Ingredients Database (NHPID):**

Brucine is listed in the Natural Health Product Ingredient Database (NHPID) as a homeopathic ingredient.

Brucine sulfate (CAS 4845-99-2) is listed as a chemical substance and denaturant, permitted at up to 0.1% (brucine eq.) for topical use only.

SD Alcohol 40 is not listed. The Natural and Non-prescription Health Products Directorate (NNHPD) has clarified in the past that the absence of an ingredient from the NHPID does not imply the ingredient is considered unsafe. It is strictly a indication of whether or not an application for a product containing that ingredient has been submitted to the NNHPD.

Based on interim guidance established by the US Food and Drug Administration (US FDA) during the COVID-19 pandemic, the NNHPD encouraged the use of the formulas SD Alcohol 3-C, 40-A and 40-B in hand sanitizers, as these specially denatured alcohols appeared to have the best safety profiles.

(HC, 2023c)

#### **US Code of Federal Regulations (CFR):**

As per 27 CFR 21.151, brucine alkaloid and brucine sulfate are denaturants authorized for specially denatured (SD) alcohols. As per 27 CFR 21.74, SD Alcohol 40 is formulated as follows: To every 100 gallons of alcohol add 1/8 gallon of tert-butyl alcohol, and: 1.5 ounces of either (1) **brucine alkaloid**, (2) **brucine sulfate**, (3) quassin, or (4) any combination of two or of three of those denaturants.

SD Alcohol 40 is authorized as solvent in: Hair and scalp preparations; Bay rum; Lotions and creams (hand, face, and body); Deodorants (body); Perfumes and perfume tinctures; Toilet waters and colognes; Shampoos; Soaps and bath preparations; External pharmaceuticals, not U.S.P. or N.F.; Disinfectants, insecticides, fungicides, and other biocides; Cleaning solutions (including household detergents); Theater sprays, incense, and room deodorants; Miscellaneous.

(CFR, 2023)

#### **Australian Government Poisons Standard 2023:**

Brucine is listed under Schedule 7 “Dangerous Poison” of the Poisons Standard 2023 *except* in alcohol containing 0.02 per cent or less of brucine as a denaturant.

(TGA, 2023)

#### 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, and:

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

International Agency for Research on Cancer (IARC) Classes of Carcinogens List

## **3.0 SCIENTIFIC JUSTIFICATION**

### **3.1 Background**

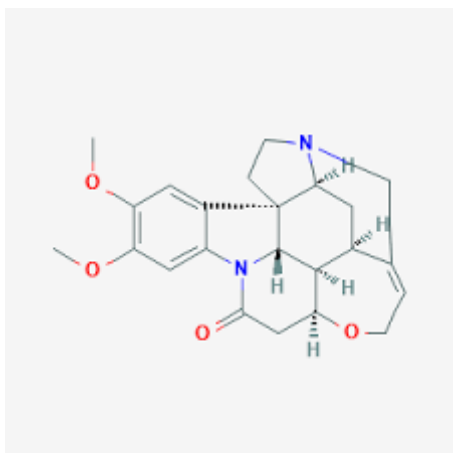


Figure 2 Chemical Structure of Brucine

Brucine (2,3-dimethoxystrychnine), a derivative of strychnine, is an alkaloid neurotoxin found naturally in the seeds and bark of several flowering plants of the *Strychnos* genus (Achappa et al., 2012; Metaxas & Cort, 2013). In botanical sources, it is often present alongside strychnine (a potent rodenticide) and other indole alkaloids (Teske, et al., 2011). Brucine is the 2<sup>nd</sup> most abundant alkaloid constituent in *Semen Strychni* (also known as *Nux Vomica*) a botanical commonly used in Chinese traditional medicine for its claimed analgesic, anti-diarrheal, antioxidant, anti-inflammatory, anti-microbial and anti-neoplastic properties. Unlike strychnine, brucine is considered significantly less toxic and has also been shown to possess pharmacological activities and therapeutic properties that have been investigated pre-clinically to develop novel drug

candidates (Chen et al., 2013; Lu et al., 2020; Mak et al., 2021).

Brucine and brucine sulfate are the only substances of relevance to cosmetics. Brucine is permitted at a concentration equal to or less than 0.1% while brucine sulfate is not captured on the Hotlist. Both ingredients are used as alcohol denaturants due to their intense bitterness, which may lead to very low concentrations in the finished cosmetic formulations (CIR, 2008). Prior to dermal and oral bioavailability data becoming available, Arena and Drew (1986) had noted that the quantities present in denatured alcohol do not create any great hazard, unless an unusually large quantity is ingested.

Brucine *sulfate* specifically, has been identified as an ingredient in a limited number of cosmetic products marketed in Canada including: sunless tanning products (non-SPF) and teeth-whitening gels all with notified concentrations  $\leq 0.1\%$  (see [section 2.3](#)), although it may be a potential component of products notified Alcohol SD 40 or other denatured alcohols of unspecified composition (INCI: "Alcohol denat.").

Based on the cosmetic functions in the notified products, form and area of application, the potential of exposure to brucine and brucine sulfate is expected mainly via the dermal and oral/buccal routes. Most products are notified as semi-solid gels or oily/non-oily liquids. Although brucine is considered a non-volatile substance based on its low vapor pressure<sup>4</sup>, some sunless tanning products and hair styling products are applied as mists or aerosol sprays which create the potential for inhalation exposure during the anticipated use of these products.

In the US, the addition of denaturant ingredients is prescribed by federal regulations.

The Code of Federal Regulations (CFR) authorized use of SD Alcohol 40 covers various cosmetic product categories with dermal application. However, oral care products (e.g., toothpastes, tooth whiteners) are not listed as part of the authorized product categories. According to the CFR specifications, the final concentration of brucine or brucine sulfate in

<sup>4</sup> <https://pubchem.ncbi.nlm.nih.gov/compound/Brucine>

the SD Alcohol 40 formulation is not expected to exceed a maximum functional level of 0.011% (CFR, 2023).

### 3.2 Relevant Toxicokinetics

Brucine showed a high intestinal permeability in an *in-vitro* study using a human Caco-2 cell monolayer model that has the best correlation with oral absorption *in vivo* (Ma et al., 2009). Similar to strychnine, brucine can be easily ionized under gastrointestinal (GI) pH conditions but the main site for absorption is the intestine. A pharmacokinetic study of brucine upon oral administration (via gavage) in rats indicates that the absolute oral bioavailability of brucine compared to its intravenous administration is 40.31-47.15% (Chen et al., 2013; Talcott, 2018).

Two skin permeation investigations of brucine were conducted by Chen et al. (2013) to assess the extent of its dermal absorption potential *ex vivo* and *in vivo*. They are summarized below.

The *ex vivo* mouse skin permeation of brucine was investigated using a Franz diffusion cell. The effective permeation area was 2.27 cm<sup>2</sup>, with abdominal skin excised from ICR<sup>5</sup> mice. Normal saline was used as receptor solution and incubated at 37 ± 0.2 °C. A volume of 0.1 mL brucine solution (5 or 10 mg/mL)<sup>6</sup> was spread on the surface of the skin and samples (0.25 mL) were withdrawn from the receptor fluid at different time intervals (0.25, 0.5, 1, 2, 4, 6, 8 and 10 h). Receptor fluid samples were analyzed by HPLC to quantify the brucine content. The cumulative amounts of brucine at 10 h were determined to be 96.22 ± 9.67% and 91.42 ± 5.97% respectively for the two applied solutions, demonstrating that brucine penetrated through mouse skin completely in the *ex vivo* assay. The author reports that in a previous *in vitro* study, the cumulative amount of brucine absorbed from an applied hydrogel formulation, was 40.05 ± 3.65% at 12 hours (Chen et al., 2012)

In the *in vivo* pharmacokinetic study, nine groups of mice (six mice per group) were topically administered a brucine solution at a dose of 40 mg/kg, while seven groups of mice (six mice per group) were intravenously injected brucine at a dose of 4 mg/kg. The study showed that brucine was absorbed rapidly, with a T<sub>max</sub> of 15 min. The absolute transdermal bioavailability of brucine was determined to be 40.83%. The results indicate that skin permeability *in vivo* may be lower than *ex vivo*. The authors suggested that a possible explanation for the significant difference between *ex vivo* and *in vivo* permeation behavior is the precipitation of brucine on the surface of the skin before it has a chance to be absorbed, following solvent (water and ethanol) evaporation upon dermal application. A previous study conducted by Yang et al (2011) had also found evidence of rapid dermal absorption upon topical application, during *in vivo* animal testing; however, the finding was applicable to liposome-encapsulated<sup>7</sup> brucine, as part of a pre-clinical investigation of its analgesic and anti-inflammatory properties.

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<sup>5</sup> Strain of albino mice named after the initial letters of the Institute of Cancer (ICR)

<sup>6</sup> Due to the poor solubility of brucine in pH 7.4 phosphate buffer solution (PBS), 20% ethanol was added as solvent to increase solubility when preparing the 10 mg/mL brucine solution

<sup>7</sup> Liposomal encapsulation provides a trans-dermal drug delivery method designed to enhance absorption, facilitate targeted and sustained release active pharmaceutical agents while reducing their systemic toxicity.

In terms of tissue distribution, regardless of the route of administration, brucine was shown to accumulate primarily in the kidneys, an indication that the kidney is the primary excretion organ for this substance. The lowest level was detected in the brain, suggesting a potential to cross the blood-brain barrier, according to Chen et al. (2013). A previous study conducted by Chen et al. (2011) in rats had shown that both strychnine and brucine administered intravenously (1 mg/kg) possess similar tissue distribution, with no long-term accumulation of either substance found in rat tissues. Highest values were detected in tissues with abundant blood supply such as the kidney, small intestine, liver, spleen and lung, suggesting that the distribution of these alkaloids is dependent on the blood flow and perfusion rate of the organ.

No available toxicokinetic data is available for the inhalation route of exposure.

### 3.3. Evidence of Acute Toxicity in Humans

Although brucine has been studied pre-clinically for a wide range of pharmacological activities including anti-tumor, anti-inflammatory and analgesic effects, its central nervous system toxicity has been the primary obstacle to its clinical study. At toxic doses<sup>8</sup>, brucine may cause convulsions, increased blood pressure, renal failure and in cases of severe intoxication, death (Lu et al., 2020).

Its mechanism of action resembles that of strychnine, acting as antagonist of the inhibitory neurotransmitter glycine, which increases the excitability of neurons. The excitatory effect cause muscle spasms and seizures which can result in life-threatening complications like rhabdomyolysis<sup>9</sup> which results in acute kidney injury due to the precipitation of myoglobin in the renal tubules. Death typically results from respiratory failure (asphyxia) (Achappa et al., 2012; Arena, JM and Drew, 1986; Lu et al., 2020) .

Although there are many case reports of fatal strychnine poisoning, case reports from brucine (only) poisoning are poorly documented, often because strychnine and brucine are consumed simultaneously as part of herbal preparations of *Strychnos nux-vomica* and the observed adverse effects are often attributed to strychnine, due to its high acute toxicity.

A fatal case was reported in India upon a ritualistic ingestion of a herbal decoction prepared from the bark of the *Strychnos nux-vomica* tree. Subsequent analysis flagged the presence of brucine but the absence of strychnine in the herbal preparation, thus the ensuing symptoms were directly attributed to brucine intoxication.

Within an hour from the time of consumption, the 29 year old male experienced an episode of tonic clonic seizure, followed by a series of convulsions. Other family members who had consumed the same preparation (likely lower doses) experienced less severe symptoms primarily mild muscle spasms and nausea. In the case of the 29 year old male, cardio-pulmonary arrest and renal failure developed within hours, resulting in his ultimate demise.

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<sup>8</sup> Toxic doses are not well-characterized.

<sup>9</sup> Breakdown of striated muscle and necrosis causing leakage of intracellular constituents into the circulation and extracellular fluid

A quantification of brucine levels post-mortem was not available; however, brucine was detected in the liver and kidneys of the deceased (Achappa et al., 2012).

A similar case is reported by Naik & Chakrapani (2009), where a 24-year old male presented with a history of consuming the decoction made from the *Strychnos nux vomica* tree. Initial symptoms included muscle spasms and convulsions; however within days from hospital admission he developed features of rhabdomyolysis and acute renal failure. Other members of the family experienced a range of symptoms including mild muscular spasms and stiffness. Two fatalities were reported in two young children who had consumed the same decoction (Naik & Chakrapani, 2009).

The findings of a 2015 *in vitro* study, suggest that the brucine-mediated cytotoxicity may be the cause for necrosis in the renal tubular epithelium, thus offering another possible explanation for the observed renal toxicity in brucine poisoning cases (Liu et al., 2015).

Based on animal studies, the reported oral medial lethal dose (LD50) is 1 mg/kg in rats, 150 mg/kg in male Swiss-Webster mice and 4 mg/kg in rabbits (Malone et al., 1992; WHO/IPCS, 1990). Please see [Appendix 3](#) for a table summarizing the LD50 values derived from animal studies. For comparison, the reported oral LD50 values for strychnine are 2.3 mg/kg in rats, 2 mg/kg in mice and 0.5 mg/kg in dogs (Guo et al., 2018). A lethal amount of 1000 mg for brucine has been reported in humans compared to a lethal amount of 30-120 mg for strychnine. The lethal dose for these alkaloid substances is suspected to vary depending on the age, sex and the health condition of the individual (Gosselin & Gleason, 1976; Teske et al., 2011).

### 3.4 Authoritative Opinions and Risk Assessments

#### *CIR, 2008*

In 2008, the Cosmetic Ingredient Review (CIR) Expert Panel published a safety assessment of Alcohol Denat., including SD Alcohol 3-A, SD Alcohol 30, SD Alcohol 39, SD Alcohol 39-B, SD Alcohol 39-C, SD Alcohol 40, SD Alcohol 40-B, and SD Alcohol 40-C, and the Denaturants, Quassin, Brucine Sulfate/Brucine, and Denatonium Benzoate. The Panel considered that the safety data on the denaturant ingredients is relevant to the safety assessment of the alcohols formulated with these denaturants.

Overall, there were no reported adverse local effects (skin irritation, sensitization, phototoxicity, or photosensitization) following exposure to products formulated with SD Alcohol 40 denatured with brucine sulfate. However, the Panel did not consider the available safety data sufficient to support the safety of brucine or brucine sulfate, or the alcohols denatured with these ingredients in cosmetics. The CIR (2008) concluded that additional genotoxicity, reproductive toxicity, and dermal absorption data were required for further assessment.

### 3.5 Risk Characterization of Cosmetic Exposure to Brucine in Cosmetic Products Sold in Canada

Based on the available notification data, brucine sulfate is present in products that may be used daily, over extended periods. No long-term repeated dose toxicity data are available to allow an investigation of the dose-response relationship to its observed effects, the identification of a critical effect level and the selection of a point of departure (PoD) for further risk characterization. To address data gaps in long-term toxicity data, a read-across approach was considered to identify a potential suitable analogue for the target substance. Results of read-across modelling using the OECD QSAR Toolbox confirmed strychnine as the analogue candidate with the highest degree of structural similarity. Due to its extremely high acute toxicity, long-term toxicity studies have not been conducted. Other possible analogue substances were identified with a structural similarity of 30-40% to the target substance, and available chronic or sub-chronic toxicity data. However, after a closer inspection and comparison of their structures with the target substance, they were dismissed as acceptable candidates for read-across.

In the absence of long-term toxicity data, the risk characterization would have to focus on the potential for acute systemic toxicity resulting from exposure to cosmetic products with active notifications, e.g., tooth whiteners, sunless tanning products and hair styling products. However, based on the expected use patterns of these products, a risk characterization relying on acute toxicity as point of departure (PoD) would not appropriately address the potential for chronic health effects that may arise at significantly lower doses upon repeated cosmetic use. Therefore, based on the available database of toxicological information, a *quantitative* risk assessment to derive a safe exposure level in cosmetic products is not feasible at this time.

Brucine has demonstrated a range of neurotoxic effects in humans upon oral exposure at toxic doses through known botanical sources such as *Strychnos nux vomica*. While a probable human lethal dose has been reported in scientific literature, along with several case reports of fatal and non-fatal human poisonings, a no-observed-adverse-effect threshold is yet to be identified. Evidence of significant systemic absorption observed in animal models upon dermal exposure raises concerns regarding the unquantified risk of long-term health effects that may result from repeated cosmetic exposure consistent with the available notification data. In light of these considerations, a conservative approach to risk mitigation in cosmetic products is presently warranted.

## 4.0 CONCLUSION

Brucine is currently restricted on the Cosmetic Ingredient Hotlist to concentrations of 0.1% or less. At this time, the entry does not capture the salts of brucine, such as brucine sulfate, which is present in cosmetic notifications for products such as tooth whiteners, sunless tanning products and other historically notified products at concentrations  $\leq 0.1\%$ . Several international jurisdictions including the EU, Switzerland, New Zealand and ASEAN and MERCOSUR countries, prohibit the use of brucine in cosmetics, although a scientific basis for the prohibitions has not been provided. These jurisdictions do not apply any restrictions on the use of brucine salts in cosmetic formulations.

Based on the available evidence, the presence of brucine on the Hotlist is scientifically supported due to its well documented acute systemic toxicity, particularly to the central nervous system. However, the scientific basis for the existing 0.1% restriction could not be established.

Due to significant safety data gaps at the time of the opinion, the Cosmetic Ingredient Review (CIR) Expert Panel (2008) was unable to reach a conclusion on the safety of brucine, brucine sulfate or SD Alcohol 40 denatured with these ingredients. The noted data gaps at the time included a lack of data on dermal absorption<sup>10</sup> as well as chronic toxicity data such as reproductive and developmental toxicity. However, based on the available studies reviewed by the CIR, cosmetic products formulated with variable concentrations of SD Alcohol 40 (undisclosed concentration) did not display potential for skin irritation, skin sensitization, phototoxicity or photosensitization. No dermal or inhalation toxicity data were available for brucine or its salts at the time of the opinion.

Studies published after the CIR (2008) opinion indicate that brucine displays significant oral and dermal bioavailability which bring additional concerns regarding its potential to cause both acute and long-term toxicity in response to cosmetic exposure.

Data gaps in long-term toxicity data involving brucine and its salts do not allow for an adequate assessment of the potential of brucine or its salts to cause long-term health effects that may result from current patterns of cosmetic use. In light of its high acute toxicity, known neurotoxic properties and significant potential for dermal absorption, a prohibition on brucine may be justified at this time.

Based on the ability of brucine salts to dissociate and release the parent compound, they are considered functionally and toxicologically equivalent to brucine. Therefore, consideration should be given to expanding the Hotlist entry to “Brucine and its salts”.

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<sup>10</sup> Data on dermal absorption became available after the opinion was published

## 5.0 REFERENCES

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## APPENDIX 1 – Ingredient summary of associated complexes of brucine and its salts used in cosmetics

| INCI Name                    | CAS RN                        | Synonym(s)                                                                                                                                                                                                                                                                                                                   |
|------------------------------|-------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Brucine                      | 357-57-3<br>(PubChem, 2021)   | (–)-Brucine; 10,11-Dimethoxystrychnine; 10,11-Dimethoxystrychnine; 2,3-Dimethoxy-strychnine; 2,3-Dimethoxystrychnidin-10-one; 2,3-Dimethoxystrychnine; Brucine alkaloid; Brucinum; Bruzin; Dimethoxy strychnine; Strychnidin-10-one, 2,3-dimethoxy-; Strychnine, 2,3-dimethoxy- (ChemIDplus, 2021) l-Brucine (PubChem, 2021) |
| Brucine sulfate              | 4845-99-2<br>(PubChem, 2021)  | Brucine Sulfate Heptahydrate; 2,3-Dimethoxystrychnidin-10-one Sulfate (2:1); Strychnidin-10-one, 2,3-Dimethoxy-, Sulfate (2:1); Strychnidin-10-one, 2,3-Dimethoxy-, Sulfate(1:1), Heptahydrate (PCPC, 2021) Brucine sulphate; Brucine sulfate [NF] (PubChem, 2021)                                                           |
| Brucine tetrahydrate         | 5892-11-5<br>(PubChem, 2021)  | Brucine, tetrahydrate; Brucine tetrahydrate [MI]; Strychnidin-10-one, 2,3-dimethoxy-, hydrate (1:4); Strychnidin-10-one, 2,3-dimethoxy-, tetrahydrate (ChemIDplus, 2021) 2,3-dimethoxystrychnidin-10-onewater (1/4) (PubChem, 2021)                                                                                          |
| Brucine nitrate              | 5786-97-0<br>(PubChem, 2021)  | N/A                                                                                                                                                                                                                                                                                                                          |
| Brucine hydrochloride        | 5786-96-9<br>(PubChem, 2021)  | Brucine HCl; Strychnidin-10-one, 2,3-dimethoxy-, hydrochloride (1:1); Strychnidin-10-one, 2,3-dimethoxy-, monohydrochloride (ChemIDplus, 2021) Brucine hydrochloride; Brucinhydrochlorid (PubChem, 2021)                                                                                                                     |
| Brucine sulfate heptahydrate | 60583-39-3<br>(PubChem, 2021) | 2,3-Dimethoxystrychnidin-10-one sulfate (1:1) heptahydrate; Strychnidin-10-one, 2,3-dimethoxy-, sulfate (1:1), heptahydrate (ChemIDplus, 2021)<br>Brucine sulphate (PubChem, 2021)                                                                                                                                           |

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

## APPENDIX 2 - Comparison of regulatory status of brucine and its salts in certain jurisdictions

|                    | Canada <sup>1</sup> | USA <sup>2</sup>             | European Union <sup>3,10</sup>                           | Other Jurisdictions <sup>4-9</sup>                                                                                                                                                                                              |
|--------------------|---------------------|------------------------------|----------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Status             | Restricted          | Not Prohibited or Restricted | Prohibited (Brucine)<br>Not Restricted (Brucine sulfate) | <b>EEC:</b> Prohibited (Brucine), Not Restricted (Brucine sulfate)<br><b>ASEAN:</b> Prohibited (Brucine), Not Restricted (Brucine sulfate)<br><b>New Zealand:</b> Prohibited (Brucine)<br><b>MERCOSUR:</b> Prohibited (Brucine) |
| Max.               | 0.1%                | -                            | -                                                        | -                                                                                                                                                                                                                               |
| Product Type       | -                   | -                            | -                                                        | -                                                                                                                                                                                                                               |
| Product Form       | -                   | -                            | -                                                        | -                                                                                                                                                                                                                               |
| Label Requirements | -                   | -                            | -                                                        | -                                                                                                                                                                                                                               |
| Other              | -                   | -                            | -                                                        | -                                                                                                                                                                                                                               |

<sup>1</sup>HC, 2022; <sup>2</sup>US FDA, 2023; <sup>3</sup>EU-Annex II, 2021; <sup>4</sup>FDHA, 2017; <sup>5</sup>EEC, 2011, <sup>6</sup>ASEAN, 2023; <sup>7</sup>MERCOSUR-N° 62/14, 2014; <sup>8</sup>Japan, 2000; <sup>9</sup>New Zealand, 2017, <sup>10</sup>Norway, 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 – Acute toxicity data in animal models

| Route                                           | Species | LD50 (mg/kg) | Reference                    |
|-------------------------------------------------|---------|--------------|------------------------------|
| Oral                                            | Rat     | 1            | WHO/IPCS, 1990               |
| Oral                                            | Rabbit  | 4            | WHO/IPCS, 1990               |
| Oral                                            | Mouse   | 150          | Malone et al., 1992          |
| Intraperitoneal                                 | Rat     | 91           | WHO/IPCS, 1990               |
| Intraperitoneal<br>62<br>Malone et al.,<br>1992 | Mouse   | 50.10        | Li et al., 2014              |
| Subcutaneous                                    | Mouse   | 60           | Sandberg & Kristianson, 1970 |
| Intravenous                                     | Mouse   | 12           | Malone et al., 1992          |