



HOTLIST INGREDIENT REVIEW

Risk Assessment Division

Consumer and Hazardous Products Safety Directorate (CHPSD)

Hotlist Ingredient Review

Symphytum spp., with the exception of Symphytum officinale

Date Approved: 2024-08-07

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EXECUTIVE SUMMARY

Purpose:

For over 2000 years, the *Symphytum* (comfrey) genus has been used by humans for several purposes. Certain comfrey species have been cultivated as feed for animals, used in fertilizers, or consumed as a vegetable. Most notably, comfrey has been used externally to treat inflammatory disorders and bone fractures, and consumed based on claims of treating gastritis and arthritis.

The present Hotlist Ingredient Review (HIR) has been undertaken to address questions surrounding the current *Symphytum spp.* entry on the Cosmetic Ingredient Hotlist. *Symphytum spp.* is described as prohibited from use in cosmetics, except for one of its species, *Symphytum officinale* (*S. officinale*). The prohibition appears to be based on potential for hepatotoxic effects in humans following oral consumption. This review will investigate if the available scientific evidence supports the prohibition of *Symphytum spp.*, and assess if the exemption for *S. officinale* is justified.

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:

All members of the *Symphytum* genus commonly known as comfrey, with the exception of *S. officinale*, are prohibited from use in cosmetic products.

Based on the available evidence, the genus-wide prohibition of *Symphytum spp.* is scientifically justified. However, the exemption for *S. officinale* from the existing prohibition was found to be unsupported.

Multiple international jurisdictions have banned or severely restricted the use of comfrey in oral and respectively topical natural health products and/or certain foodstuffs due to serious safety concerns regarding the presence of pyrrolizidine alkaloids (PAs), such as echimidine, lasiocarpine, lycopsamine and others. Certain PAs have been identified as genotoxic carcinogens and long-term exposure can increase the risk of developing cancer, particularly in the liver.

While *S. officinale* is not considered to be an official source of echimidine, it is not devoid of other PAs of concern such as lasiocarpine. Documented as one of the most toxic 1,2-unsaturated PAs, lasiocarpine was classified by IARC as a class 2B carcinogen, thus possibly carcinogenic in humans. EFSA concluded it may act as genotoxic carcinogen via DNA-adduct formation. In spite of the structural diversity across PAs, the present knowledge on

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lasiocarpine has been used by EFSA to assess the health impacts of pyrrolizidine alkaloids as a class, and derive a daily exposure level that is considered to pose a low cancer risk (Margin of Exposure or MoE $\geq 10,000$) and would also be protective of non-cancer effects.

This level however should not be equated with being “harmless” from a toxicological perspective. Within the European Union, the general recommendation is to minimise the exposure to mutagenic and carcinogenic substances as low as reasonably achievable (ALARA principle), recognizing that even low intake quantities can result in an increased health risk with regular, repeated exposure.

To maintain an MoE $\geq 10,000$ in cosmetics, it was determined that the concentration of *Symphytum spp.* extract in a leave-on product with full body application, would need to be at least 100 fold lower than 0.1%. Since these ingredients are alleged to have a skin-conditioning function (according to the INCI monographs), it is unlikely that such low concentration would be functional in a cosmetic product.

In light of the available evidence, it is recommended that the existing prohibition for *Symphytum spp.* be expanded to include *S. officinale*.

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1.0 INGREDIENT(S) SUMMARY

Symphytum spp. species, including but not limited to:

(1) *Symphytum officinale*

INCI Name(s): Symphytum Officinale Leaf Extract, Symphytum Officinale Callus Culture Extract, Symphytum Officinale Callus Culture Lysate, Symphytum Officinale Extract, Symphytum Officinale Leaf Powder, Symphytum Officinale Rhizome/Root Extract, Symphytum Officinale Root Cell Extract, Symphytum Officinale Root Extract (PCPC, 2024)

Synonym(s): Comfrey, boneset, consound, healing herb, knitbone, slippery-root, common comfrey (GRIN, 2024)

CAS Number(s): 84696-05-9 (PCPC, 2024)

(2) *Symphytum asperum*

INCI Name(s): None

Synonym(s): Prickly comfrey; Persian comfrey; rough Comfrey (GRIN, 2024)

CAS Number(s): None

(3) *Symphytum x uplandicum*

INCI Name(s): None

Synonym(s): Russian Comfrey; blue comfrey (GRIN, 2024)

CAS Number(s): None

Refer to [Appendix 1](#), Table 1 for a list of some *Symphytum spp.* species and their synonyms.

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2.0 BACKGROUND ON THE SUBSTANCE(S)

2.1 Regulatory Status of the Ingredient(s) in Cosmetics

In Canada, *Symphytum spp.* is listed as prohibited on the Cosmetic Ingredient Hotlist except for the species *S. officinale*. Other verified international jurisdictions such as the EU, EEC Customs Union, ASEAN, MERCOSUR, and New Zealand do not limit the use of *Symphytum spp.-derived* ingredients in cosmetic products.

Please refer to [Appendix 2, Table 3](#) for a detailed comparison of the cosmetic regulations applicable to *Symphytum spp.-derived* ingredients in other international jurisdictions.

2.1.1 Policy Statements and Decisions Regarding Cosmetics and Cosmetic Regulations

A record of decision regarding comfrey was identified in a Health Canada advisory issued in 2003, which states “Health Canada is advising Canadian consumers not to use the herb comfrey or any health products that contain comfrey because they might contain a compound called echimidine, which may cause liver damage.” This advisory also recommended avoiding topical application to broken skin.

However, in a 2004 response to a consumer concerning Health Canada’s advisory on comfrey, it was clarified that comfrey species, such as *S. officinale* which are not known to contain echimidine, are not subject to this ban.

At the time of the 2003 advisory, it was indicated that some comfrey products do not specify the species in the product representation and out of an abundance of caution consumers were advised to avoid all products containing comfrey. However, according to section 21.2 (3) of the *Cosmetic Regulations*, botanicals must be listed by specifying at least the genus and species portions of the INCI name. Therefore, listing an ingredient solely as “comfrey” on the label would not be compliant with the *Cosmetic Regulations* and it would be required to identify, at a minimum, the *Symphytum* species present in the product on the label.

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2.2 Status of Ingredient(s) in Other Cosmetic Lists or Databases

Cosmetics Notifications (Health Canada): Between January 1st 2019 and May 29 2024, 1355 active notifications were found for cosmetic products containing *Symphytum* and/or comfrey.

(I) Symphytum officinale

Only one species of *Symphytum spp.* was identified in the active cosmetic notifications: ***Symphytum officinale***.

The majority of notifications include moisturizers, cleansers, exfoliants and hair products (styling products, hair dyes). The notified skincare and hair products covered all concentration ranges, however the most common notified concentration for these products was less than 0.1%.

Potential cases of non-dermal exposure:

A number of notified products (n=44) with a maximum concentration range of 3-10% are notified as loose powders and aerosols thus presenting the potential for inhalation exposure. Some notifications (n=40) with a maximum reported concentration range of 30-100% indicate the lips as one of the areas of application; **[Redacted for confidentiality]** with a maximum reported concentration range of 10-30% present the potential for ingestion exposure.

(II) Comfrey

Twenty-six products notified to contain “comfrey” will be flagged for follow-up and clarification on the species identification.

Please refer to Tables 4 and 5 in [Appendix 3](#), for the full cosmetic notification reports on *Symphytum officinale*. and comfrey.

Personal Care Products Council (PCPC) INCI Dictionary:

S. officinale is present in the INCI dictionary under the following INCI names:

Symphytum Officinale Callus Culture Extract
Symphytum Officinale Callus Culture Lysate
Symphytum Officinale Extract
Symphytum Officinale Leaf Extract
Symphytum Officinale Leaf Powder
Symphytum Officinale Rhizome/Root Extract
Symphytum Officinale Root Cell Extract
Symphytum Officinale Root Extract

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Reported functions include skin-conditioning and abrasive.

No other *Symphytum* species are reported to have cosmetic function, according to the INCI database.

(PCPC, 2024)

International Fragrance Association (IFRA) Standards (51st ed.): The ingredients are not listed.

2.3 Status of Ingredient(s) in Other Non-Cosmetic Databases

Domestic Substance List (DSL):

Comfrey, *Symphytum officinale* ext. (CAS: 84696-05-9) is listed on the DSL. It did not meet the criteria for categorization under subsection 73(1) of the *Canadian Environmental Protection Act, 1999* (CEPA).

(ECCC, 2023)

Food and Drug Regulations (C.R.C, c. 870)

Symphytum spp. in a drug for human use is considered adulterated if it contains any of the following species or extracts or tinctures thereof:

- (i) *Symphytum asperum*,
- (ii) *Symphytum x uplandicum*, or
- (iii) echimidine or any of its salts
- (iv) any other plant species containing echimidine.

Symphytum asperum, *Symphytum x uplandicum* and the pyrrolizidine alkaloid echimidine have been prohibited in drugs since 1988. *S. officinale* and other comfrey species or pyrrolizidine alkaloids are not prohibited under section C.01.038 of the Food and Drug Regulations.

(Justice Canada, 2019)

Natural Health Products Ingredients Database (NHPID)

Symphytum officinale and *Symphytum x uplandicum* are listed in the Natural Health Product Ingredient Database.

Symphytum officinale is listed as a non-medicinal skin-conditioning agent for external/topical use and a medicinal agent classified as an NHP under Schedule 1

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item 1 of the NHP regulations. Topical non-medicinal use is intended for short term use, in adults only, and testing must be performed to ensure that the amount of pyrrolizidine alkaloids does not exceed 0.35 micrograms per day.

In medicinal use, testing must be performed to ensure the absence of pyrrolizidine alkaloids (e.g., echimidine) in *Symphytum officinale*.

Symphytum x uplandicum is classified as a NHP under Schedule 1 item 1 of the NHP regulations. Testing must be performed to ensure the absence of pyrrolizidine alkaloids in *Symphytum x uplandicum*.

(HC, 2024)

Licensed Natural Health Products Database (LNHPD)

Symphytum spp. (*Symphytum officinale*, *Symphytum*, *Symphytum x uplandicum*) are listed as medicinal ingredients in 98 active licensed natural health products for oral or topical use (e.g. oil, lip balm, chest rub, masque, cleanser). *Symphytum officinale* or “comfrey” (no species descriptor) are listed as non-medicinal ingredients in 47 active licensed natural health products for topical use (e.g. sunscreen, medicated wipes, toner, cream, lip balm).

(HC, 2023b)

Drug Product Database (DPD):

“Comfrey” (no species descriptor) is listed as an active ingredient in 11 over the counter (OTC) products, and 54 homeopathic products cancelled post-market.

(HC, 2023a)

Drugs.com®

Internal use of comfrey is not recommended due to pyrrolizidine alkaloid content that can cause hepatotoxicity. Externally applied alkaloids can be absorbed and detected in the urine, therefore the use of topical comfrey should not exceed 100 µg/day. The use is also contraindicated during pregnancy and lactation, in infants and in patients with liver or kidney disease.

(Drugs.com®, 2024)

Drugs and Lactation Database (LactMed®)

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The Drugs and Lactation Database flags the topical use of comfrey preparations during breastfeeding to be contraindicated. If used nonetheless, it should only be applied to intact skin, away from the breast on the smallest area of skin as possible for a limited duration. It is recommended that an infant does not come into direct contact with the treated area as ingestion may cause severe liver damage.

(LactMed®, 2021)

List of chemicals known to the state to cause cancer or reproductive toxicity (California EPA)

As of 1988, lasiocarpine, a pyrrolizidine alkaloid constituent of comfrey is specified on the list of chemicals known to the State of California to cause cancer. Echimidine and other pyrrolizidine alkaloids quantified in *S. officinale* are not listed.

(CA EPA, 2023)

Australian Government Poisons Standard

Symphytum spp. (Comfrey) is listed under **Schedule 5**: Caution - substances with a low potential for causing harm, the extent of which can be reduced using appropriate packaging with simple warnings and safety directions on the label. This caution is for dermal therapeutic or dermal cosmetic use.

Symphytum spp. is listed as **Schedule 10**: Substances of such danger to health as to warrant prohibition of supply and use - Substances which are prohibited for the purpose or purposes listed for each poison. This is for preparations for human or animal use except when in Schedule 5.

In **Appendix F, clause 4** – Poisons that must be labelled with warning statements and safety directions *Symphytum spp.* must be labelled with the following directions:

- (i) Do not use on broken skin.
- (ii) Do not use under occlusive dressing.

(TGA, 2024)

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

Symphytum spp. is not mentioned in the IARC, however lasiocarpine, a pyrrolizidine alkaloid constituent of comfrey has been classified as possibly carcinogenic to humans (Group 2B).

Two additional PAs that have not been quantified in *Symphytum spp.*, monocrotaline and riddelliine, have also been classified as possibly carcinogenic to humans (Group 2B).

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Echimidine has not been classified by IARC with respect to its carcinogenic potential.

(IARC, 1987)

The ingredient(s) were not found in the following sources:

Lists of Permitted Food Additives (HC);

New Drugs List (aka *Listing of Drugs Currently Regulated as New Drugs*) (TPD)

Prescription Drug List (HC);

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

Danish List of Undesirable Substances, and;

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

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3.0 SCIENTIFIC JUSTIFICATION

3.1 Background

3.1.1 *Symphytum spp.*

Symphytum spp. (*Boraginaceae* family), is a diverse genus of perennial flowering plants that contains around 36 species – not including hybrids (Salehi et al., 2019; Tropicos, 2024). Members of the *Symphytum* genus are found all over Europe, Siberia, North America, and Asia, and have reported uses since 50 AD as herbal medicines (Frost et al., 2013).

In Canadian cosmetics, *S. officinale* extracts sourced from various plant parts (roots, callus, leaves, rhizomes) are reported to be used for their skin-conditioning properties (PCPC, 2023). Products containing *S. officinale* are notified across all concentration ranges; however, 90% of notifications are found at a concentration of less than 3%. The notified products present potential for dermal, oral, inhalation, and mucous membrane exposure.

In addition to its use in cosmetic products, *S. officinale* has been marketed for internal and external use in traditional medicine. Specifically, it has been used *externally* in the form of ointments and compresses to treat joint disorders, bruises, sprains, pulled muscles and ligaments, and *internally* in the form of tea or tinctures for bone and joint pain. The alleged anti-inflammatory effects are induced via several constituents, such as allantoin that inhibits mitogen-activated protein kinases (MAPKs), nuclear factor kappa B (NF- κ B), and potentially cyclooxygenase 2 (COX-2) expression (Seigner et al., 2019).

As the Cosmetic Ingredient Hotlist entry exempts *S. officinale* from the scope of the prohibition, our review will also take into consideration studies referencing this species specifically. Lastly, since the pyrrolizidine alkaloid content of *Symphytum spp.* appears to be at the core of the *Symphytum spp.* prohibition, relevant toxicity data on these constituents of concern will also make the focus of this review.

Please see [Appendix 1](#), Table 2 for a list of the chemical constituents quantified in *S. officinale*.

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3.1.2 Pyrrolizidine Alkaloids

Pyrrolizidine alkaloids (PAs) are a diverse group of naturally occurring pro-toxins¹ that are present at low levels in the *Symphytum* genus. Over 6000 plant species are known to contain PAs. Although PAs encompass more than 400 different compounds from various plant lineages, as many as 23 different PAs have been identified in *S. officinale*² (Avula et al., 2015; Kruse et al., 2019). Depending on the plant part, the PA concentration ranges from 0.04-0.6%, with the concentration in the roots being 100-fold higher than the aerial parts (Salehi et al., 2019; Stickel & Seitz, 2000). However, their content also varies with each season, with small young leaves often storing a higher alkaloid content than older leaves (EMA, 2011). Besides exposure to PAs via cosmetic ingredients and medicinal products for external use, consumers may also be exposed to these alkaloids via food products (e.g. honey, herbal teas, herbal supplements) (Dalefield et al., 2016).

Three essential criteria are generally responsible for the observed hepatotoxicity of the pyrrolizidine alkaloid molecule: 1) the double bond of the 1,2-unsaturated necine base, 2) esterification of the hydroxy group in positions 9 and 7, and 3) a branched carbon chain in at least one of the ester side chains (Stickel & Seitz, 2000).

The toxicity of 1,2-unsaturated PAs is almost exclusively associated with their metabolites. Upon ingestion, their biotransformation by hepatic microsomal enzymes (P450 cytochrome monooxygenases) results in the formation of reactive pyrrolic compounds that can interact as powerful alkylating agents with cellular molecules such as DNA and proteins (Fig 1) (Kruse et al., 2019; Stickel & Seitz, 2000).

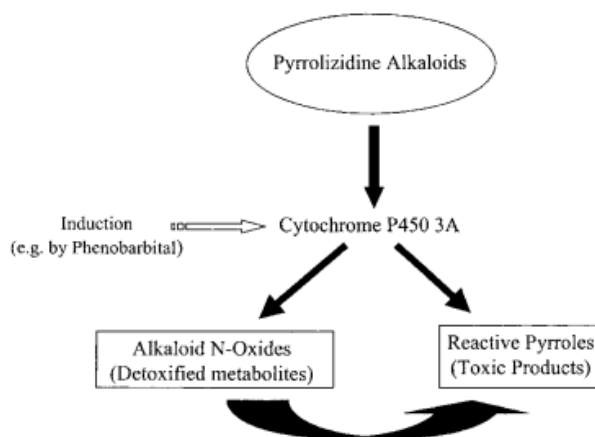


Figure 1. Metabolic transformation of 1,2-unsaturated pyrrolizidine alkaloids found in Comfrey by cytochrome P450 3A enzymes (Stickel & Seitz, 2000)

¹ Precursors of toxins that require metabolic conversion to achieve their active form

²Notable quantities of echimidine are often reported, because other species that are morphologically close may be mistaken for *S. officinale*, however small quantities of echimidine have been reported in *S. officinale* samples.

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Structurally, 1,2-unsaturated PAs are mono- or diesters of necine acids with a necine base. Based on their necine base, they are classified generally into **3 main types**: retronecine-type, otonecine-type and heliotridine-type. Retronecine, otonecine, and heliotridine-type PAs contain the 1,2-unsaturated necine base, allowing hepatic activation of toxic metabolites (Fig 2) (Ebmeyer et al., 2020).

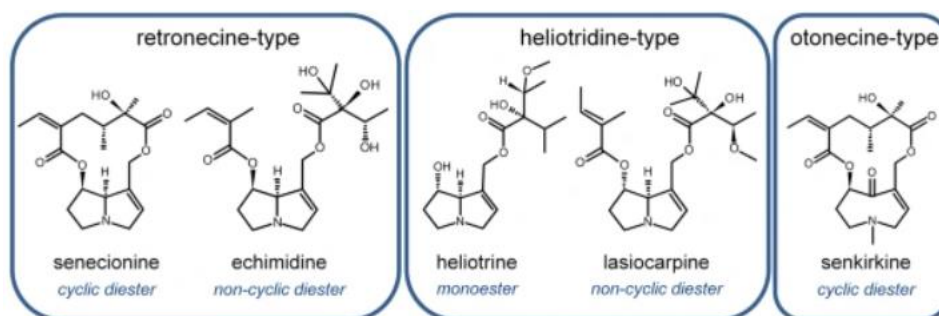


Figure 2 Structure of 1,2-unsaturated PA representatives (Ebmeyer et al., 2020)

Although **echimidine** (retronecine-type) and **lasiocarpine** (heliotridine-type) have been reported as having the highest toxic potentials (Ebmeyer et al., 2020), several PAs known to lead to hepatotoxicity in humans and carcinogenesis in rats have been identified. In the quality control of herbal medicinal products, 28 PAs are considered, including but not limited to echimidine, lasiocarpine, lycopsamine, intermidine as well as their respective N-oxides (Giera et al., 2022).

Due to their high toxicity even in small quantities, stringent limits for the presence of PA contaminants have been set by the European Union member states for certain commodities such as tea & herbal infusions, and certain food items such as honey (Food Supplements Europe, 2020).

Since the presence of PAs hinders the therapeutic applications of comfrey-based preparations, recent research efforts have been devoted to identifying cost-effective strategies to improve the safety profile of comfrey. While there are no officially recognized methods for the complete removal of PAs, some experimental reduction strategies have been successful in depleting or completely eradicating the PA content (Giera et al., 2022; Kopp et al., 2020; Kruse et al., 2019; Trifan et al., 2023; Zakaria et al., 2021).

A recent method described by Zakaria and colleagues (2021) proposed a CRISPR/Cas9-mediated genome editing approach to silence the gene expression underlying the PA biosynthetic pathway. Upon the introduction of detrimental mutations in the *hss* gene encoding homospermidine synthase (HSS), an enzyme that plays a key role in PA biosynthesis, the level of PAs in the *S. officinale* hair roots became undetectable.

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In 2023, Trifan and colleagues (2023), subjected various *S. officinale* root PA depleted extracts (PAs <2 ppm) to a rigorous phytochemical characterization and bioactivity evaluation, and demonstrated that PA depletion does not significantly affect the antioxidant (radical scavenging) properties and pharmacological activities of the extracts. The authors went on to conclude that PA-depleted extracts represent a safer alternative to raw comfrey extracts.

3.1.3 Echimidine in Comfrey species

Numerous documented case reports showing that the internal use of comfrey extracts is associated with severe hepatotoxicity, in particular cirrhosis and ascites, prompted various jurisdictions, including Canada, US, UK, Australia and Germany to implement a full ban on the inclusion of comfrey in dietary supplements intended for oral consumption.

In Canada, the rationale for the *Symphytum* spp. prohibition with an exemption for *S. officinale* on the Cosmetics Ingredient Hotlist may have been based on the expectation that the pyrrolizidine alkaloid echimidine is not present in *S. officinale*. Until 1988, when Canada's *Food and Drug Regulations* were amended to prohibit the sale of any products containing echimidine, this PA had been flagged as a key alkaloid involved in cases of acute toxicity associated with *Symphytum* spp. consumption in humans (FSANZ, 2001).

The European Medicines Agency (2015) assessment report on *S. officinale* reports that in theory, this species does not contain echimidine. Often, its reported presence is the result of mistaking the plant for other species that are morphologically similar, such as *S. asperum*, or the falsification of the herbal substance with *S. pergrinum* roots (EMA, 2015). Using PAs as chemotaxonomical markers, Huizing and colleagues (1982) demonstrated that in isolated alkaloids from several extracts of *Symphytum* taxa, echimidine was not detected in *S. officinale* extracts. However, in crossing experiments of *S. officinale* and *S. asperum*, echimidine was found in all the interspecies hybrids (Huizing et al., 1982). These authors indicate that the possibility that hybrids were used in other analyses where echimidine was found in *S. officinale* must not be overlooked. Other reports state that the presence of echimidine may also indicate the hybridization of *S. officinale* with *S. x uplandicum* (Avula et al., 2015).

Although *S. officinale* is not expected to have echimidine, several investigations have shown that the chemotaxonomic classification that distinguishes certain *Symphytum* species from *S. officinale* based on their echimidine absence can no longer be applied strictly.

- (I) *S. officinale* plants were collected from their natural habitats all over Europe and thin-layer chromatography was performed to compare relevant compounds. Six extracts from fresh *S. officinale* specimens³ contained echimidine, albeit in small quantities (Jaarsma et al., 1989)

³Derived from root material; a total of 26 *S. officinale* samples were used in this analysis.

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- (II) In 13 comfrey products purchased from retail stores in the Ottawa area, with some using the label designation '*S. officinale*', echimidine was detected using thin-layer chromatography and gas chromatography-mass spectrometry (Awang et al., 1993)
- (III) Using high-speed countercurrent chromatography to isolate PAs from an alkaloid extract from the roots of *S. officinale*, purchased from Richters (Ontario, Canada), echimidine was found within the alkaloid extract (Kim et al., 2001)
- (IV) A thin-layer chromatogram of crude alkaloids extracted with methanol from dried, milled roots of *S. officinale* (5 kg), revealed the presence of both symphytine (2.8 g) and echimidine (2.7 g) in fraction (Furuya & Araki, 1968)

3.2 Relevant Toxicokinetics

There is limited data on the dermal absorption potential of *Symphytum spp.* extracts or specific PAs, but some studies have investigated dermal penetration in animals and humans and they are summarized below.

- (I) A crude alcoholic extract of *S. officinale* root, corresponding to a dose of 194 mg alkaloid-N-oxides/kg bw was applied dermally to Sprague Dawley derived/SIV 50 male rats (200g each) (n=2). The application area measured about 3 cm² and the sample was applied immediately after shaving with an electric clipper. After treatment, the skin was covered with aluminum foil and fixed with an elastic bandage, with a total contact time of 44 hours. The urine of the treated animals was collected daily, and quantitation and identification of the alkaloids were done through GC-FID and GC-MS. Over 2 days, the excretion of the alkaloids in the urine was in the range of 0.1-0.4% of the applied dose (Brauchli et al., 1982). No conclusions regarding dermal absorption can be drawn from this study as no mass balance loss assessment is reported in this publication.
- (II) In a membrane diffusion and permeability study via a vertical Franz diffusion cell, 3.03 µg of lycopsamine PA isolated from comfrey extracts was applied to a synthetic membrane (Porafil membrane filter) and on heat-separated human epidermis excised from 2 male Caucasian patients (*ex vivo*) supported with Porafil membrane filter. Distilled water thermostated to 37 ± 0.5 C was used as acceptor phase. After 24 hours, the cumulative amount of diffused lycopsamine ranged between 0.11% and 0.72% in the synthetic membrane and between 0.04% and 0.22% through the human epidermis (Jedlinszki et al., 2017)
- (III) A recent *ex vivo* study conducted by Plaza et al. (2022) as per OECD guidelines and GLP, investigated the propensity of PAs to become bioavailable following topical application to split thickness human skin consisting of the epidermis and a portion

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of the dermis, excised from the abdomen of donors aged 27-61 years old. The biological sex of the human donors was not reported. Comfrey root cream formulation spiked with echimidine (purity 93.13%), lycopsamine (purity 99%), and retrorsine (purity 99%) at 0.006 mg/g was applied evenly over the stratum corneum. The skin was either occluded with aluminum foil or left open to the atmosphere. PBS with bovine serum albumin (5% w/v) receptor fluid fractions were collected at 2, 6, 12, and 24 hours post-dose. The exposed skin was then heat separated into dermis and epidermis samples and retained for analysis via LC-MS/MS. The Scientific Committee for Consumer Safety (SCCS) considers the amounts measured in the dermis, epidermis (without stratum corneum) and the receptor fluid as dermally absorbed in their risk assessment calculations. Thus, based on SCCS guidance (2023), the dermally absorbed amounts derived from this experiment are 4.14%, 3.61% and 5.80% for echimidine, lycopsamine and retrorsine respectively.

Upon the oral ingestion, PAs are absorbed from the gastrointestinal tract, with a large proportion (80%) excreted unchanged in the urine and feces. Using ¹⁴C-labeled monocrotaline, it was shown that a fraction of ~10% is metabolized and that the ¹⁴C-labeled carbons are exhaled as CO₂. A small fraction of toxic pyrroles is hypothesized to remain bound to cellular components or retained as cellular adducts that are slowly recycled overtime (Stegelmeier et al., 2016).

Based on the study performed by Brauchli and colleagues (1982) in Sprague Dawley derived/SIV 50 male rats, oral administration via gavage (194 mg alkaloid-N-oxides/kg b.wt) led to a 20-50 times higher excretion of alkaloids in the urine (3.4-9.4%) when compared to dermal administration (0.1-0.4%). According to EMA (2021), these findings suggest that the systemic absorption of PAs via oral route could be 20-50 times higher than via the dermal route, at least in the rat model.

Studies have revealed the rat as being the most sensitive species to PA toxicity. While the toxicokinetic behaviors of each pyrrolizidine alkaloid present in *Symphytum spp.* have not been investigated systematically upon oral administration, a comparative pharmacokinetic study of lasiocarpine⁴ and heliotrine⁵ in rats showed absolute oral bioavailabilities of 0.5% and 23.3% respectively (Lin et al., 2023). A pharmacokinetic study of senescione, another hepatotoxic, genotoxic and tumorigenic PA found in *Symphytum spp.* found an absolute oral bioavailability of 8.2 ± 2.7% in Sprague-Dawley rats (C. Wang et al., 2011).

As described by Moreira et al., (2018), bioactivation of orally ingested PAs occurs primarily in the liver, causing this organ to be the main target of toxicity caused by PA exposure. Three principal pathways for metabolic activation of PAs in the liver have been identified:

- I) Hydrolysis to produce necines and necic acids
- II) N-oxidation to form pyrrolizidine alkaloid N-oxides (PANO)

⁴ Quantified in *Symphytum spp.*

⁵ Not quantified in *Symphytum spp.*

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- III) Oxidation to form pyrrolic esters or dehydropyrrolizidine alkaloids (DHPAs) which can be oxidized to toxic, highly reactive didehydropyrrolizidine derivatives (pyrroles)

The first two pathways are important detoxification routes promoting clearance of these compounds. However, PANO can reverse back to PAs which can be oxidized to DHPAs; these metabolites are primarily involved in the observed acute, sub-acute and chronic effects associated with PA exposure due to their ability to form DNA adducts. The isoforms of CYP450 that are responsible for PA metabolism leading to DHPA formation are generally CYP3A and CYP2B. (Moreira et al., 2018).

In addition to the liver, where their levels are most prominent, cutaneous expression of these enzymes has been identified in keratinocytes and fibroblasts, granted their constitutive levels are too low to be measured without exogenous inducers (Slominski et al., 2014; Smith et al., 2018).

Upon bioactivation, DHPAs are distributed to other target organs, with the lungs being the 2nd most affected organ by pyrrole formation, after the liver (Moreira et al., 2018). According to Stegelmeier and colleagues (2016) extrahepatic damage has been reported in the lungs, kidneys and the gastrointestinal tract. In addition to their known systemic toxicity, recent studies have also shown evidence of PA-induced secondary (hepatogenous) phototoxicity and photogenotoxicity, whereby pyrrolic metabolites generated in the liver may be transported to the skin where they can induce photosensitization reactions and possibly contribute to skin cancer formation (C. C. Wang et al., 2014; Zhao et al., 2011).

3.3 Authoritative Opinions and Risk Assessments

Norwegian Food Safety Authority (Mattilsynet), 2013

The Norwegian Cosmetics Regulation (FOR 1995-10-26 nr 0871, Annex 3), which was in force up until June 11th, 2013, stated that *S. officinale* was allowed in cosmetics provided it did not contain pyrrolizidine alkaloids. However, in the “*Risk Profile of Symphytum Officinale extracts*” published November 2013, the Norwegian Food Safety Authority (Mattilsynet) stated that while lower amounts of PAs are expected to be absorbed systemically as a result of the topical use of *S. officinale* when compared to oral exposure, the potential for severe health effects warrants a restrictive approach. Since the complete absence of PAs may be difficult to achieve, Mattilsynet recommended a full prohibition of comfrey extract in cosmetics (Mattilsynet, 2013).

In their review of systemic toxicity, Mattilsynet focused on the hepatotoxic effects associated with the ingestion of comfrey, including hepatic veno-occlusive disease (HVOD), severe liver damage and liver cancer.

HVOD initially presents with fatigue, abdominal distension, and signs of portal hypertension, and can rapidly progress to hepatomegaly and multiorgan failure (LiverTox,

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2012). Liver histology often shows occlusion of small hepatic venules (Allgaier & Franz, 2015). To this day, there are no effective clinical therapies for PA-induced HVOD cases (Q. Wang et al., 2021).

The lowest known dose associated with long-term toxicity (HVOD) in humans is reported to be 0.015 mg PA/kg bw/day, with an exposure period of 6 months. In most non-fatal cases of HVOD, the total dosage of PAs was 2-27 mg/kg body weight (Mattilsynet, 2013).

A lifetime cancer risk of 10^{-4} was calculated when using aftershave products containing 5% comfrey extracts although the Authority acknowledged that the risk could be higher or lower depending on the PA content in the extracts. According to the Council of Europe (2008) the lifetime cancer risk must be below 10^{-5} to be considered acceptable.

In their Margin of Safety (MoS)⁶ calculations, a NOEL of 100 mg/kg bw for *Symphytum officinale* was used (no reference study provided), resulting in MoS values⁷ of 133 for face products, 4 for body lotions and 909 for body washes, based on a maximum assumed concentration of 4% *S. officinale* extracts in cosmetic product and an assumed dermal absorption of 100% as a worst case scenario since no adequate data were available at the time of the opinion. The Authority did not endorse the current levels of exposure as safe and it did not follow up with a recommendation for alternate safe levels of comfrey extract in cosmetic products. Instead, the risk profile concluded that due to toxicity and carcinogenicity concerns, the exposure to PAs should be kept as low as practically possible. Therefore, prohibiting the use of comfrey extracts in cosmetics is warranted.

Apart from Mattilsynet, the safety of comfrey and/or its pyrrolizidine alkaloids in cosmetic products has not been addressed as part of a formal scientific opinion or safety assessment by other international expert panels (e.g. SCCS & CIR).

Other international opinions/public statements:

Although not directly relevant to cosmetics, the safety of pyrrolizidine alkaloids has been reviewed by other international expert panels and dietary limits have been derived. These are summarized in Table 1 below, along with the Point of Departure (PoD) and target Margin of Exposure (MoE) that lead to these daily intake values. Due to their potential genotoxic and carcinogenic effects, it is unanimously accepted by different international authorities that the exposure to PAs should be kept as low as reasonably achievable (ALARA principle) and not exceeding the daily intake values summarized below.

Table 1. Summary of the maximum daily intakes for PA dietary limits available internationally and their points of departure

⁶ Note: The Margin of Safety (MoS) calculation described by Mattilsynet is consistent with a Margin of Exposure (MoE) calculation i.e. uses a no-observed-effect-level (NOEL) as the point of departure rather than a health-based guidance value (HBGV)

⁷ No target MoS provided.

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International Authority	Maximum daily intake for pyrrolizidine alkaloids (PAs)	PoD and Target MoE	Critical Study
European Medicines Agency (EMA, 2021)	0.0237 µg/kg bw/day Or: Max. 1 µg/day PAs in adults ⁸ , updated from 0.35 µg/day published in 2014 Max. 0.5 µg/day in children ⁹	BMDL ₁₀ = 237 µg/kg bw (Riddelliine) Target MoE ≥ 10,000	NTP, 2003
German Federal Institute for Risk Assessment (BfR, 2016)	Max. 0.0237 µg/kg bw/day Or: Max. 1 µg/day in adults ⁷ If use duration > 6 weeks, max. 0.1 µg/day For oral products: Not to be used during pregnancy or lactation	BMDL ₁₀ = 237 µg/kg bw (Riddelliine) Target MoE ≥ 10,000	NTP, 2003
European Food Safety Authority (EFSA, 2017)	Max. 0.0237 µg/kg bw/day ----- Previously: Max. 0.007 µg/kg bw/day	BMDL ₁₀ = 237 µg/kg bw (Riddelliine) Target MoE ≥ 10,000 ----- Previously: BMDL ₁₀ = 73 µg/kg bw (Lasiocarpine) Target MoE ≥ 10,000	NTP, 2003

⁸Based on a body weight value of 50 kg for an adult individual. The choice of default value is explained by EMA (2021) as follows: “For ~18% (average) of the European population the body weight is given with less than 60 kg (EUROPEAN COMMISSION 2006). This number would increase to up to 30%, if only taking into account women. Therefore, the calculation is linked to a body weight of 50 kg. This is in accordance with ICH M7”

⁹Based on a body weight of 20 kg, the default body weight value used by EMA (2021)

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Food Standards Australia New Zealand (FSANZ, 2001)	Max. 1 µg/kg bw/day (Provisional Tolerable Daily Intake, non-cancer effects)	Tentative NOEL = 10 µg/kg ¹ Target MoE = 10	(Ridker et al., 1985)
National Institute for Public Health and the Environment (RIVM, 2015)	Max. 0.1 µg/kg bw /day	NOAEL = 0.01 mg/kg bw (Riddelliine) Target MoE ≥ 100	NTP, 2003
UK Committee on Toxicity (COT), 2008	Max. 0.1 µg/kg bw/day (non-cancer unlikely) ----- Max. 0.007 µg/kg bw/day (cancer unlikely) Max 0.35 µg/day in adults ⁷	BMDL ₁₀ = 237 µg/kg bw (Riddelliine) Target MoE ≥ 10,000 ----- BMDL ₁₀ = 73 µg/kg bw (Lasiocarpine) Target MoE ≥ 10,000	NTP, 2003 ----- NTP, 1978

¹No-observed-effect-level (NOEL) value based on available data on cases of veno-occlusive disease in humans

The initial 2011 opinion published by the European Food Safety Agency (EFSA) on the risk assessment of toxic unsaturated PAs, used an MoE approach to estimate the potential cancer risk in response to dietary PA exposure (EFSA, 2011).

A number of 1,2-unsaturated PAs from different structural classes were deemed to be of particular importance to food and feed, including but not limited to lasiocarpine, monocrotaline, echimidine and riddelliine. Some, but not all of the identified PAs have been quantified in the *Symphytum* genus (*Boraginacea* family). Irrespective of its botanical source, lasiocarpine was reported in the EFSA (2011) opinion as one of the most toxic PAs¹⁰ tested, along with riddelliine.

Since 1,2-unsaturated PAs are genotoxic and carcinogenic, the EFSA's Panel on Contaminants in the Food Chain (CONTAM) decided that applying a Margin of Exposure approach (MoE) rather than establishing a Tolerable Daily Intake (TDI) would be more appropriate. This is aligned with the ALARA principle ("as low as reasonably achievable").

As a conservative approach, EFSA based the risk characterization of 1,2-unsaturated PAs on the BMDL₁₀ value of 73 µg/kg bw/day for lasiocarpine. Rather than correcting for individual

¹⁰ Relative toxic potencies according to lasiocarpine > senecionine > seneciphylline ≥ retrorsine > heliotrine (?) echimidine ≥ europine ≈ indicine ≈ lycopsamine ≈ monocrotaline (Gao & Schrenk, 2023)

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potencies of different PAs, EFSA considered the occurrence of all 1,2-unsaturated PAs as a sum and assumed equivalent potency in terms of their carcinogenic potentials.

The BMDL₁₀ value for lasiocarpine was derived from an NTP carcinogenicity study conducted by the National Toxicology Program (NTP, 1978). In the NTP carcinogenicity study, doses of 7, 15, and 30 mg lasiocarpine/kg (equivalent to 0.35, 0.75 and 1.5 mg/kg bw/day) were administered orally to Fischer 344 rats over 104 weeks. Liver angiosarcomas were observed in 13 out of 23 male and 2 out of 23 female rats in the highest dose, 11 out of 23 male and 7 out of 24 female rats in the medium dose, and 5 out of 24 male and 8 out of 22 female rats in the lowest dose.

EFSA considers that for substances that are both genotoxic and carcinogenic, an MoE of 10,000 (10⁵) or higher would be of low concern from a public health point of view. Therefore, doses up to 0.007 µg/kg bw/day PA from dietary exposure were deemed unlikely to pose a chronic health concern. This dose translates into a daily dose of 0.35 µg for an adult with a body weight of 50 kg. However, doses up to 0.007 µg/kg bw/day PA may be of possible concern in juveniles (toddlers and children) who were identified by EFSA as high consumers of honey.

In 2014, in the context of elaborating a monograph on *Symphytum*, the Herbal Medicinal Products Committee (HPMC) at the European Medicines Agency (EMA) issued a public statement setting a limit of 0.35 µg toxic unsaturated PA per day over a maximum of 14 days of consumption. This limit was informed by EFSA's conclusion that a lifetime exposure dose of up to 0.007 µg/kg bw/day (based on lasiocarpine) is of low concern to human health. The limit of 0.35 µg/day aligns with the quality specifications applied by the NNHPD when *S. officinale* extracts are used as NMIs in products with topical application on intact skin.

In 2017, EFSA revised the dose-response analysis used to inform the previous 2011 opinion regarding the risk for chronic effects posed by dietary PA exposure. Due to weaknesses and limitations in the NTP (1978) study conducted with lasiocarpine, EFSA selected a more recent study conducted with riddelliine (NTP, 2003), which in spite of some technical limitations, was considered an overall more suitable study for performing BMD modelling (EFSA, 2017). It is important to note that unlike lasiocarpine, riddelliine has not been identified in *Symphytum spp.*

Taking into account uncertainties in the available studies used for the dose response analysis and the fact that riddelliine and lasiocarpine are among the most toxic PAs, EFSA concluded that updating the reference point would not impact the conservative nature of the previous risk assessment.

Consequently, the BMDL₁₀ of 238 µg/kg bw day, derived for the incidence of liver haemangiosarcoma in female rats exposed to riddelliine replaced the previous reference point of 73 µg/kg bw day derived for lasiocarpine in the chronic risk assessment of PAs. In response to their updated characterization of chronic risk, and based on a target MoE of

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10,000, a maximum level of 0.0237 µg/kg bw/day would be considered of low concern in terms of chronic health risk.

The most recent statement issued by EMA's Committee on Herbal Medicinal Products (HMPC) in 2021 reflects the updated evaluation of the PA carcinogenicity data, and endorses 1.0 µg/day (adult) as an acceptable limit for oral intake of PAs, based on a maximum level of 0.0237 µg/kg bw/day calculated for riddelliine. This oral intake limit would be reduced to 0.5 µg/kg in children (BW=20 kg) as well as pregnant and breastfeeding women. Due to uncertainties regarding dermal absorption potential, the same limits apply to cutaneous use, on intact skin only (EMA, 2021).

3.4 Supplemental Toxicological Review

Given the limited number of international scientific opinions addressing the safety or acceptability of comfrey and its species in the context of cosmetics, a supplemental toxicological review was conducted to further explore the potential for unintended local effects such as skin irritation and sensitization.

Overall, there is an absence of data addressing the local tolerability of *S. officinale*-derived extracts in relation to cosmetic formulations. However, some clinical trials have reported adverse events following the application of comfrey-containing topical products for various medicinal uses. A few of them are summarized below:

- (I) A single-blind, controlled, randomized clinical trial, compared the efficacy of a comfrey (*S. officinale*) root extract (99%-PA reduced, 1:2 ethanol 60% (V/V) ointment to a Diclofenac gel for the treatment pain associated with acute ankle sprains (n = 82 in each treatment group). A total of four adverse events were reported in the comfrey group, including headache (n=1), heartburn (n=1), bronchitis (n=1) and redness of the skin (n=1). No irritation or skin sensitization reactions were reported (Predel et al., 2005).
- (II) A two-centre, double-blind, parallel-group, placebo-controlled, randomized trial compared the efficacy of topical 4Jointz (standardized *S. officinale* extract (200 mg/g) and pharmaceutical grade tannic acid (100 mg/g) plus other ingredients including aloe vera gel (300 mg/g), eucalyptus oil (40 mg/g), and frankincense oil (1.0 mg/g)) to an identical but inert placebo¹¹ in reducing knee pain (n=133). The prevalence of rash was significantly higher in the 4Jointz group (n=69), with severity high enough to discontinue the study drug in four participants (Laslett et al., 2012). However, it is possible that the other ingredients could have contributed to the rash.

¹¹ Same formulation of topical 4Jointz minus the standardized comfrey extract (200 mg/g) and pharmaceutical grade tannic acid (100 mg/g)

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- (III) In a critical scoping review of external uses of comfrey, Frost and colleagues, (2013) identified twenty-one clinical studies that assessed adverse events or tolerability to topical comfrey (*S. officinale* and *Symphytum x uplandicum* - Nyman¹²) products. Inclusion criteria consisted of the evaluation of an external preparation of any comfrey species, alone or with any combination of herbs, for any indication and outcome and against any comparator. Exclusion criteria were evaluations of homeopathic doses of comfrey, either internally or externally. Among them, 12 of the studies identified mild and transient adverse events that included skin redness, itching, burning, pain, chafing, rash, and eczema.

Since all studies evaluated developing or established commercial creams formulations containing comfrey extract along with other co-formulants, it is not possible to conclusively correlate the reported adverse events with the presence of a specific ingredient.

As discussed in [section 3.2.](#), upon metabolic activation, 1,2-unsaturated PAs can generate biologically reactive pyrrolic metabolites (dehydropyrrolizidine alkaloids or DHPAs) that are capable of inducing tumors through a genotoxic mechanism mediated by the formation of DHPA-derived DNA adducts. Malignant tumors have been reported in F-344 male rats fed lasiocarpine (50 ppm) in their diets for 55 weeks. Out of a total of 20 animals in the treatment group, a combined 85% (n=17) developed angiosarcoma of the liver and/or hepatocellular carcinoma, while one rat developed a malignant adnexal¹³ tumor of the skin and one rat developed lymphoma (Rao & Reddy, 1978). Another study reports that topical doses of dehydromonocrotaline (DHM), a primary toxic metabolite of the PA monocrotaline¹⁴, followed by repeated treatments with croton oil, caused malignant tumors of the skin in LACA mice (Mattocks & Cabral, 1982). The mechanism responsible for the observed skin malignancies has not been fully elucidated, however, Zhao et al. (2011) proposed that when highly reactive dehydro-PAs circulate to the skin, they can lead to photosensitization or if they are metabolically formed *in* the skin, they can elicit skin tumors by a phototoxic effect. More specifically, the authors conducted a series of experiments showing that UVA irradiation of certain PA metabolites, such as dehydrolasiocarpine, generates reactive oxygen species (ROS) that mediate the initiation of lipid peroxidation, a phenomenon that underlies skin damage. Therefore, the UVA-induced phototoxic activity exerted by dehydro-PAs when present in the skin, may enhance skin damage and over time could increase the risk of skin cancer.

These findings are further supported by Wang and colleagues (2014) who found that UVA irradiation of the pyrrolic metabolites dehydromonocrotaline and dehydroriddelliine induced DNA adducts in HaCaT skin keratinocytes.

¹² Hybrid species obtained by crossing *Symphytum officinale* with *Symphytum asperum*

¹³ A type of appendageal tumor that arises from the adnexal structures of the skin e.g. hair follicles, sebaceous glands, sweat glands

¹⁴ Not quantified in *Symphytum spp.*

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While no reports of cancer cases in humans have been identified as a direct consequence of PA consumption or dermal application of comfrey extracts, the potential photogenotoxic effects associated with the presence of unquantified levels of PAs raises health concerns from topically applied cosmetics.

3.5 Risk Characterization of *Symphytum Officinale* Extract in Cosmetics

Presently, all ingredients derived from *Symphytum spp.* with the exception of *S. officinale* are prohibited from use in cosmetic products marketed in Canada, as per the Hotlist.

As noted in [section 2.2](#) the highest reported concentration for *S. officinale*-derived ingredients in leave-on products is in the range of 30-100%.

Since a further refinement of the maximum concentration of *S. officinale* extract is not possible based on the available notification data, a concentration of 100% was assumed to allow the exposure calculations and limit derivation captured in [Appendix 4](#), Tables 6, 7 and 8.

Published literature indicates that the roots of *S. officinale*, the part of the plant reported to carry the highest concentration of PAs, consist of maximum 0.6% total PAs. It is important to note that this concentration corresponds to the PA level in the raw, unprocessed root material. Depending on the process of extraction and any additional purification steps, the level of PAs could become more concentrated or more dilute in the final extract. Based on the expected variability across *S. officinale* extracts, and the lack of quality specification data in the public domain, the concentration range of PAs in the *S. officinale* extracts remains a source of uncertainty.

In our exposure modelling, it is assumed that the occurrence of all 1,2-unsaturated PA constituents in *S. officinale* extract are considered as a sum and assumed to have equivalent in potency in terms of their carcinogenic potentials to lasiocarpine. This is in line with EFSA's approach (see [section 3.3](#)).

The maximum daily intake value was adjusted from 0.35 µg PA/day (based on a 50 kg adult) to 0.518 µg PA/day for a 74 kg adult in the exposure modelling calculations.

In the absence of experimental dermal absorption data directly relevant to lasiocarpine, a default absorption value of 50% was assumed. This approach aligns with the most recent (2023) recommendation of the SCCS notes of guidance for testing of cosmetic ingredients, when no experimentally determined dermal absorption values are available. The use of echimidine, a close structural analogue of lasiocarpine, with available dermal absorption data was considered as a potential refinement. However, upon careful consideration, this approach was dismissed largely due to uncertainties regarding the dermal penetration enhancement effects of certain cosmetic formulations. The use of transdermal delivery systems in cosmetics is an extensive topic, that goes far beyond the scope of this HIR; however, it is important to acknowledge that various dermal penetration enhancement methods are presently used in cosmetics to help overcome the barrier function of the skin

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and more effectively deliver certain ingredients into the deeper skin layers. To account for these uncertainties, particularly when both substance-specific or formulation-specific dermal absorption data are lacking, the use of a conservative default value of 50% is defensible.

Exposure modelling in adults (19+) indicates that a theoretical systemically absorbed daily amount (30,000 µg/day), based on the assumptions described above, exceeds the maximum daily intake value of 0.518 µg/day by > 50,000 times. Assuming a 0.6% PA content in *Symphytum spp.* extracts, the maximum acceptable concentration of *Symphytum spp.* extracts in a leave-on product with full body application, would need to be as low as 0.002% for adults, and less for younger populations. The limit could also be potentially even lower if the PA content has become more concentrated upon extraction and purification of the plant raw material.

The presence of *S. officinale* extract has also been identified in mouthwash products, at a concentration range of 10-30%. Exposure modelling calculations show that the theoretical systemically absorbed amount (~1500 µg/day) from the incidental ingestion of a mouthwash product with a concentration corresponding to the upper limit of the notified concentration range, exceeds the maximum daily intake value of 0.518 µg/day by over 2,000 times. Assuming the PA concentration in the extract remains within 0.6%, the acceptable concentration of *S. officinale* extract in the finished product should not exceed 0.01% in adults (19+), or less if the product is available for use by younger populations.

4.0 CONCLUSION

Based on the evidence reviewed here, the presence of *Symphytum spp.* on the Cosmetic Ingredient Hotlist is scientifically supported. However, the exemption of *S. officinale* is not supported.

The existing evidence has highlighted the toxicity of pyrrolizidine alkaloids which are a common feature across all members of the *Symphytum* genus. Among them, echimidine was previously identified by Health Canada as the hepatotoxic alkaloid responsible for the reported incidents of liver damage upon consumption of health products containing the medicinal herb comfrey.

In theory, *S. officinale* does not contain echimidine, which was the basis for its exemption. However, multiple studies have shown that *S. officinale* extracts contains echimidine at very low concentrations. Its presence may be explained by interspecies hybridization or misidentification during collection.

Furthermore, *Symphytum spp.*, including *S. officinale* contain other 1,2-unsaturated PAs such as lasiocarpine, which has been demonstrated to be carcinogenic in rodents via oral route, and has been classified as possibly carcinogenic in humans.

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Although exposure to PAs occurs predominantly through contaminated foodstuffs and herbal preparations, dermal exposure may also pose a concern, particularly in individuals with liver or kidney disease.

Absorption upon dermal application may be enhanced with application to broken skin, impaired skin barrier function or absorption enhancers. Furthermore, there is a paucity of dermal absorption data across all the identified PAs in *S. officinale*; the experimental values that are available showcase a high degree of variability across different individual PAs. It is also important to consider that certain co-formulants in cosmetic products may enhance the dermal penetration potential of PAs. The calculated acceptable concentration of *Symphytum spp.* extract would have to be significantly lower than 0.1% in order to meet a maximum daily intake level of 0.518 µg/day in adults and even lower for younger, more vulnerable populations.

Other international jurisdictions do not presently regulate the use of comfrey in cosmetics; there is however an international consensus regarding the significant adverse effects associated with chronic exposure to pyrrolizidine alkaloids leading to maximum daily exposure limits being recommended for other consumer products such as certain foods, herbal teas and health supplements.

In light of the evidence available at this time, it is recommended that the prohibition on *Symphytum spp.* be expanded to include the species *S. officinale*.

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5.0 REFERENCES

- ASEAN. (2023). *Association of Southeast Asian Nations (ASEAN) Cosmetic Directive. Annexes of the ASEAN Cosmetic Directive*. <https://www.hsa.gov.sg/cosmetic-products/asean-cosmetic-directive>
- Avula, B., Sagi, S., Wang, Y.-H., Zweigenbaum, J., Wang, M., & Khan, I. A. (2015). Characterization and screening of pyrrolizidine alkaloids and N-oxides from botanicals and dietary supplements using UHPLC-high resolution mass spectrometry. *Food Chemistry*, 178, 136–148. <https://doi.org/10.1016/j.foodchem.2015.01.053>
- Awang, D. V. C., Dawson, B. A., Fillion, J., Girad, M., & Kindack, D. (1993). Echimidine Content of Commercial Comfrey (*Symphytum* spp.-Boraginaceae). *Journal of Herbs, Spices & Medicinal Plants*, 2(1), 21–34. https://doi.org/10.1300/J044V02N01_04
- BfR. (2016). *BfR (Bundesinstitut für Risikobewertung). Announcement on the Test of the Content of Pyrrolizidine Alkaloids to Ensure the Quality and Safety of Medicinal Products that Contain Herbal Substances or Herbal Preparations or Homeopathic Preparations Made of Herbal Starting Materials as Active Substances*. https://www.bfarm.de/SharedDocs/Bekanntmachungen/DE/Arzneimittel/besTherap/bm-besTherap-20160301-pa-pdf.pdf;jsessionid=458AAF61F1254F4122155357D3650307.1_cid319?_blob=publicationFile&v=3
- Brauchli, J., Lüthy, J., Zweifel, U., & Schlatter, C. (1982). Pyrrolizidine alkaloids from *Symphytum officinale* L. and their percutaneous absorption in rats. *Experientia*, 38(9), 1085–1087. <https://doi.org/10.1007/BF01955382>
- CosIng. (2024). *European Commission Cosmetic Ingredient Database*. <https://ec.europa.eu/growth/tools-databases/cosing/>
- Dalefield, R. R., Gosse, M. A., & Mueller, U. (2016). A 28-day oral toxicity study of echimidine and lasiocarpine in Wistar rats. *Regulatory Toxicology and Pharmacology*, 81, 146–154. <https://doi.org/10.1016/J.YRTPH.2016.08.006>
- Drugs.com®. (2024). *Comfrey*. <https://www.drugs.com/>
- Ebmeyer, J., Rasinger, J. D., Hengstler, J. G., Schaudien, D., Creutzenberg, O., Lampen, A., Braeuning, A., & Hessel-Pras, S. (2020). Hepatotoxic pyrrolizidine alkaloids induce DNA damage response in rat liver in a 28-day feeding study. *Archives of Toxicology*, 94(5), 1739–1751. <https://doi.org/10.1007/S00204-020-02779-2/FIGURES/6>
- ECCC. (2023). *Environment and Climate Change Canada (ECCC). Domestic Substance List (DSL) Search Engine*. <https://pollution-waste.canada.ca/substances-search/Substance?lang=en>
- EEC. (2011). *Eurasian Economic Community Union (EEC) TR TC 009/2011 “On the safety of perfumery and cosmetic products”*.
- EFSA. (2011). *European Food Safety Agency. Panel on Contaminants in the Food Chain (CONTAM). Scientific Opinion on Pyrrolizidine alkaloids in food and feed*. <https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2011.2406>
- EFSA. (2017). *European Food Safety Agency. Panel on Contaminants in the Food Chain (CONTAM). Risks for human health related to the presence of pyrrolizidine alkaloids in honey, tea, herbal infusions and food supplements*. <https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2017.4908>

HOTLIST INGREDIENT REVIEW
Risk Assessment Division
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- EMA. (2015). *European Medicines Agency. Committee on Herbal Medicinal Products. EMA/HMPC/572844/2009. Assessment report on Symphytum officinale L., radix.*
- EMA. (2021). *European Medicines Agency. Committee on Herbal Medicinal Products. Public statement on the use of herbal medicinal products¹ containing toxic, unsaturated pyrrolizidine alkaloids (PAs) including recommendations regarding contamination of herbal medicinal products with PAs.*
https://www.ema.europa.eu/en/documents/public-statement/public-statement-use-herbal-medicinal-products-containing-toxic-unsaturated-pyrrolizidine-alkaloids-pas-including-recommendations-regarding-contamination-herbal-medicinal-products-pyrrolizidine_en.pdf
- European Commission (2006). Commission Regulation (EC) No 401/2006 of 23/02/2006 laying down the methods of sampling and analysis for the official control of the levels of mycotoxins in foodstuffs. <https://eur-lex.europa.eu/eli/reg/2006/401/oj>.
- FDHA. (2017). *Federal Department of Home Affairs. Ordinance on the Use of Swiss Indications of Source for Cosmetic Products. RO 2017 1597.*
<https://www.fedlex.admin.ch/eli/cc/2016/737/en>
- Food Supplements Europe. (2020). *Guidelines and recommendations to reduce the presence of pyrrolizidine alkaloids in food supplements.* https://foodsupplementseurope.org/wp-content/themes/fse-theme/documents/publications-and-guidelines/Pyrrolizidine_Guidelines-June2020.pdf
- Frost, R., MacPherson, H., & O'Meara, S. (2013). A critical scoping review of external uses of comfrey (*Symphytum* spp.). *Complementary Therapies in Medicine*, 21(6), 724–745.
<https://doi.org/10.1016/J.CTIM.2013.09.009>
- FSANZ. (2001). *Food Standards Australia New Zealand. Pyrrolizidine Alkaloids in Food. A Toxicological Review and Risk Assessment. TECHNICAL REPORT SERIES NO. 2.*
<https://www.foodstandards.gov.au/sites/default/files/publications/Documents/TR2.pdf>
- Furuya, T., & Araki, K. (1968). Studies on Constituents of Crude Drugs. I. Alkaloids of *Symphytum officinale* LINN. *Chemical and Pharmaceutical Bulletin*, 16(12), 2512–2516.
<https://doi.org/10.1248/CPB.16.2512>
- Gao, L., & Schrenk, D. (2023). Structure-dependent relative toxic potencies of selected pyrrolizidine alkaloids. *Lebensmittelchemie*, 77(S2), S2-062.
<https://doi.org/10.1002/LEMI.202352223>
- Giera, D. S., Preisitsch, M., Brevard, H., & Nemetz, J. (2022). Quantitative Removal of Pyrrolizidine Alkaloids from Essential Oils by the Hydrodistillation Step in Their Manufacturing Process. *Planta Medica*, 88(7), 538–547. <https://doi.org/10.1055/A-1534-6928>
- GRIN. (2024). *USDA-ARS Germplasm Resources Information Network (GRIN).*
<https://www.ars-grin.gov/>
- HC. (2022). *Health Canada. Cosmetic Ingredient Hotlist.* <https://www.canada.ca/en/health-canada/services/consumer-product-safety/cosmetics/cosmetic-ingredient-hotlist-prohibited-restricted-ingredients/hotlist.html>
- HC. (2023a). *Health Canada. Drug Products Database (DPD).* <https://health-products.canada.ca/dpd-bdpp/index-eng.jsp>
- HC. (2023b). *Health Canada. Licensed Natural Health Products Database (LNHPD).*
<https://health-products.canada.ca/lnhpd-bdpsnh/index-eng.jsp>

HOTLIST INGREDIENT REVIEW
Risk Assessment Division
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- HC. (2024). *Health Canada. Natural Health Products Ingredients Database (NHPID)*.
<https://webprod.hc-sc.gc.ca/nhp-id-bdipsn/search-rechercheReq.do>
- Huizing, H. J., Gadella, T. W. J., & Kliphuis, E. (1982). Chemotaxonomical investigations of the *Symphytum officinale* polyploid complex and *S. asperum* (Boraginaceae): The pyrrolizidine alkaloids. *Plant Systematics and Evolution*, 140(4), 279–292.
<https://doi.org/10.1007/BF02418897/METRICS>
- Jaarsma, T. A., Lohmanns, E., Gadella, T. W. J., & Malingré, T. M. (1989). Chemotaxonomy of the *Symphytum officinale* agg. (Boraginaceae). *Plant Systematics and Evolution*, 167(3–4), 113–127. <https://doi.org/10.1007/BF00936400/METRICS>
- Jedlinszki, N., Balázs, B., Csányi, E., & Csupor, D. (2017). Penetration of lycopsamine from a comfrey ointment through human epidermis. *Regulatory Toxicology and Pharmacology*, 83, 1–4. <https://doi.org/10.1016/J.YRTPH.2016.11.015>
- Justice Canada. (2019). *Food and Drug Regulations (C.R.C., c. 870)*. http://laws-lois.justice.gc.ca/eng/regulations/c.r.c.,_c._870/FullText.html
- Kim, N. C., Oberlies, N. H., Brine, D. R., Handy, R. W., Wani, M. C., & Wall, M. E. (2001). Isolation of symplandine from the roots of common comfrey (*Symphytum officinale*) using countercurrent chromatography. *Journal of Natural Products*, 64(2), 251–253.
<https://doi.org/10.1021/NP0004653/ASSET/IMAGES/LARGE/NP0004653C00001.JPG>
- Kopp, T., Abdel-Tawab, M., & Mizaikoff, B. (2020). Extracting and Analyzing Pyrrolizidine Alkaloids in Medicinal Plants: A Review. *Toxins*, 12(5).
<https://doi.org/10.3390/TOXINS12050320>
- Kruse, L. H., Kruse, L. H., Jensen-Kroll, J., Engelhardt, A., Wesseling, A. M., Ober, D., Lippert, A., & Ludwig-Müller, J. (2019). Reduction of Pyrrolizidine Alkaloid Levels in Comfrey (*Symphytum officinale*) Hairy Roots by RNAi Silencing of Homospermidine Synthase. *Planta Medica*, 85(14–15), 1177–1186. <https://doi.org/10.1055/A-0998-5125>
- LactMed®. (2021, May 17). *Comfrey*. Drugs and Lactation Database (LactMed®); National Institute of Child Health and Human Development.
<https://www.ncbi.nlm.nih.gov/books/NBK501773/>
- Laslett, L. L., Quinn, S. J., Darian-Smith, E., Kwok, M., Fedorova, T., Körner, H., Steels, E., March, L., & Jones, G. (2012). Treatment with 4jointz reduces knee pain over 12 weeks of treatment in patients with clinical knee osteoarthritis: a randomised controlled trial. *Osteoarthritis and Cartilage*, 20(11), 1209–1216.
<https://doi.org/10.1016/J.JOCA.2012.07.019>
- Lin, F., Zhao, L., Wang, Y., Ye, Y., & Liu, J. (2023). Comparative Pharmacokinetic Study of Two Pyrrolizidine Alkaloids Lasiocarpine and Heliotrine in Rats. *Planta Medica*, 89(5), 571–579. <https://doi.org/10.1055/A-1915-5456>
- Mattilsynet. (2013). *Norwegian Food Safety Authority (Mattilsynet). Risk Profile: Symphytum officinale extracts CAS No. 84696-05-9*. https://mattilsynet-xp7prod.enonic.cloud/api/_/attachment/inline/7cb89b3c-d9dc-491c-8ca4-a75b9bae1cf0:a7d93e342cedbbe0d01b8a11f51bf6b21656c10/Risk%20Profile%20Symphytum%20officinale.pdf
- Mattocks, A. R., & Cabral, J. R. P. (1982). Carcinogenicity of some pyrrolic pyrrolizidine alkaloid metabolites and analogues. *Cancer Letters*, 17(1), 61–66.
[https://doi.org/10.1016/0304-3835\(82\)90109-4](https://doi.org/10.1016/0304-3835(82)90109-4)

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

- MERCOSUR. (2024). *Productos de Higiene Personal y Cosméticos Perfumes Portal*.
<https://dinavisa.gov.py/productos-higiene-personal-cosmeticos-perfumes/>
- MHLW. (2000). *Japan's Ministry of Health, Labour, and Welfare. Standards for Cosmetics (Ministry of Health and Welfare Notification No. 331 of 2000)*.
<http://www.mhlw.go.jp/english/dl/cosmetics.pdf>
- Moreira, R., Pereira, D. M., Valentão, P., & Andrade, P. B. (2018). Pyrrolizidine Alkaloids: Chemistry, Pharmacology, Toxicology and Food Safety. *International Journal of Molecular Sciences*, 19(6). <https://doi.org/10.3390/IJMS19061668>
- NTP. (1978). *Bioassay of Lasiocarpine for possible carcinogenicity. NTP Technical Report. NCI-CG-TR-39*.
https://ntp.niehs.nih.gov/sites/default/files/ntp/htdocs/lt_rpts/tr039.pdf
- NTP. (2003). *Toxicology and carcinogenesis studies of riddelline. NTP Technical Report 508*.
https://ntp.niehs.nih.gov/sites/default/files/ntp/htdocs/lt_rpts/tr508.pdf
- NZ EPA. (2017). *New Zealand Environment Protection Authority (EPA). Cosmetic Products Group Standard 2017 - HSR002552*. <https://www.fedlex.admin.ch/eli/oc/2017/165/fr>
- PCPC. (2023). *Personal Care Products Council. Cosmetic Ingredient Identification Database: International Nomenclature of Cosmetic Ingredients (INCI) Dictionary*.
<http://gov.personalcarecouncil.org/jsp/gov/GovHomePage.jsp>
- PCPC. (2024). *Personal Care Products Council Cosmetic Ingredient Identification Database: International Nomenclature of Cosmetic Ingredients (INCI) Dictionary*.
<http://gov.personalcarecouncil.org/jsp/gov/GovHomePage.jsp>
- Plaza, A., Toner, F., Harris, J., Ottersbach, P., Roper, C., & Mahony, C. (2022). Support for Regulatory Assessment of Percutaneous Absorption of Retronecine-type Pyrrolizidine Alkaloids through Human Skin. *Planta Medica*, 88(2), 144–151.
<https://doi.org/10.1055/A-1505-8524>
- Predel, H. G., Giannetti, B., Koll, R., Bulitta, M., & Staiger, C. (2005). Efficacy of a comfrey root extract ointment in comparison to a diclofenac gel in the treatment of ankle distortions: results of an observer-blind, randomized, multicenter study. *Phytomedicine : International Journal of Phytotherapy and Phytopharmacology*, 12(10), 707–714. <https://doi.org/10.1016/J.PHYMED.2005.06.001>
- Rao, M. S., & Reddy, J. K. (1978). Malignant neoplasms in rats fed lasiocarpine. *British Journal of Cancer*, 37(2), 289. <https://doi.org/10.1038/BJC.1978.38>
- Ridker, P. M., Ohkuma, S., Mcdermott, W. V., Trey, C., & Huxtable, R. J. (1985). Hepatic venoocclusive disease associated with the consumption of pyrrolizidine-containing dietary supplements. *Gastroenterology*, 88(4), 1050–1054.
[https://doi.org/10.1016/S0016-5085\(85\)80027-5](https://doi.org/10.1016/S0016-5085(85)80027-5)
- RIVM. (2015). *National Institute for Public Health and the Environment Ministry of Health, Welfare and Sport. Adequate limit value for pyrrolizidine alkaloids in herbal tea and herbal preparations*. <https://www.rivm.nl/en/news/adequate-limit-value-for-pyrrolizidine-alkaloids-in-herbal-tea-and-herbal-preparations>
- Salehi, B., Sharopov, F., Tumer, T. B., Ozleyen, A., Rodríguez-Pérez, C., Ezzat, S. M., Azzini, E., Hosseinabadi, T., Butnariu, M., Sarac, I., Bostan, C., Acharya, K., Sen, S., Kasapoglu, K. N., Daşkaya-Dikmen, C., Özçelik, B., Baghalpour, N., Sharifi-Rad, J., Fokou, P. V. T., ... Martins, N. (2019). Symphytum Species: A Comprehensive Review on Chemical Composition, Food Applications and Phytopharmacology. *Molecules*, 24(12).
<https://doi.org/10.3390/MOLECULES24122272>

HOTLIST INGREDIENT REVIEW

Risk Assessment Division

Consumer and Hazardous Products Safety Directorate (CHPSD)

- SCCS. (2023). *Scientific Committee for Consumer Safety. Notes of guidance for the testing of cosmetic ingredients and their safety evaluation - 12th revision - European Commission.* https://health.ec.europa.eu/latest-updates/sccs-notes-guidance-testing-cosmetic-ingredients-and-their-safety-evaluation-12th-revision-2023-05-16_en
- Seigner, J., Junker-Samek, M., Plaza, A., D'Urso, G., Masullo, M., Piacente, S., Holper-Schichl, Y. M., & De Martin, R. (2019). A symphytum officinale root extract exerts anti-inflammatory properties by affecting two distinct steps of NF- κ B signaling. *Frontiers in Pharmacology*, 10(APR). <https://doi.org/10.3389/FPHAR.2019.00289/FULL>
- Slominski, A. T., Zmijewski, M. A., Semak, I., Zbytek, B., Pisarchik, A., Li, W., Zjawiony, J., & Tuckey, R. C. (2014). Cytochromes P450 and Skin Cancer: Role of Local Endocrine Pathways. *Anti-Cancer Agents in Medicinal Chemistry*, 14(1), 77. <https://doi.org/10.2174/18715206113139990308>
- Smith, S. A., Colley, H. E., Sharma, P., Slowik, K. M., Sison-Young, R., Sneddon, A., Webb, S. D., & Murdoch, C. (2018). Expression and enzyme activity of cytochrome P450 enzymes CYP3A4 and CYP3A5 in human skin and tissue-engineered skin equivalents. *Experimental Dermatology*, 27(5), 473–475. <https://doi.org/10.1111/EXD.13483>
- Stegelmeier, B. L., Colegate, S. M., & Brown, A. W. (2016). Dehydropyrrolizidine Alkaloid Toxicity, Cytotoxicity, and Carcinogenicity. *Toxins*, 8(12). <https://doi.org/10.3390/TOXINS8120356>
- Stickel, F., & Seitz, H. K. (2000). The efficacy and safety of comfrey. *Public Health Nutrition*, 3(4A), 501–508. <https://doi.org/10.1017/S1368980000000586>
- Symphytum asperum* - Plant Finder. (2024). <https://www.missouribotanicalgarden.org/PlantFinder/PlantFinderDetails.aspx?taxonid=277976>
- Symphytum officinale* (Black wort, Boneset, Bruise wort, Comfrey, Common Comfrey, Consound, Cultivated Comfrey, Knitbone, Quaker Comfrey, Slippery-Root, True Comfrey) | North Carolina Extension Gardener Plant Toolbox. (n.d.). Retrieved January 31, 2024, from <https://plants.ces.ncsu.edu/plants/symphytum-officinale/>
- TGA. (2024). *Therapeutic Goods Administration. Australian Government. The Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP).* <https://www.tga.gov.au/how-we-regulate/ingredients-and-scheduling-medicines-and-chemicals/poisons-standard-and-scheduling-medicines-and-chemicals/poisons-standard-susmp>
- Trifan, A., Czerwińska, M. E., Zengin, G., Esslinger, N., Grubelnik, A., Wolfram, E., Skalicka-Woźniak, K., & Luca, S. V. (2023). Influence of pyrrolizidine alkaloids depletion upon the biological activity of *Symphytum officinale* L. extracts. *Journal of Ethnopharmacology*, 303, 116010. <https://doi.org/10.1016/J.JEP.2022.116010>
- Tropicos. (2024). *Search results for query: "Symphytum."* <https://www.tropicos.org/home>
- UK Committee on Toxicity (COT). (2008). *COT Statement on Pyrrolizidine Alkaloids in Food.* <https://cot.food.gov.uk/sites/default/files/cot/cotstatementtpa200806.pdf>
- US FDA. (2023). *U.S. Food & Drug Administration. Code of Federal Regulations (CFR) Title 21.* <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/cfrsearch.cfm>
- Wang, C. C., Xia, Q., Li, M., Wang, S., Zhao, Y., Tolleson, W. H., Yin, J. J., & Fu, P. P. (2014). Metabolic activation of pyrrolizidine alkaloids leading to phototoxicity and photogenotoxicity in human HaCaT keratinocytes. *Journal of Environmental Science and Health. Part C, Environmental Carcinogenesis & Ecotoxicology Reviews*, 32(4), 362–384. <https://doi.org/10.1080/10590501.2014.969980>

HOTLIST INGREDIENT REVIEW

Risk Assessment Division

Consumer and Hazardous Products Safety Directorate (CHPSD)

- Wang, C., Li, Y., Gao, J., He, Y., Xiong, A., Yang, L., Cheng, X., Ma, Y., & Wang, Z. (2011). The comparative pharmacokinetics of two pyrrolizidine alkaloids, senecionine and adonifoline, and their main metabolites in rats after intravenous and oral administration by UPLC/ESIMS. *Analytical and Bioanalytical Chemistry*, 401(1), 275–287. <https://doi.org/10.1007/S00216-011-5075-3/FIGURES/7>
- Wang, Q., Huang, A., Wang, J. B., & Zou, Z. (2021). Chronic Drug-Induced Liver Injury: Updates and Future Challenges. *Frontiers in Pharmacology*, 12, 627133. <https://doi.org/10.3389/FPHAR.2021.627133/BIBTEX>
- Zakaria, M. M., Schemmerling, B., & Ober, D. (2021). CRISPR/Cas9 -Mediated Genome Editing in Comfrey (Symphytum officinale) Hairy Roots Results in the Complete Eradication of Pyrrolizidine Alkaloids. *Molecules (Basel, Switzerland)*, 26(6). <https://doi.org/10.3390/MOLECULES26061498>
- Zhao, Y., Xia, Q., Yin, J. J., Lin, G., & Fu, P. P. (2011). Photoirradiation of dehydropyrrolizidine alkaloids—Formation of reactive oxygen species and induction of lipid peroxidation. *Toxicology Letters*, 205(3), 302–309. <https://doi.org/10.1016/J.TOXLET.2011.06.020>

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APPENDIX 1 – Ingredient Summary

Table 1. Species associated with the *Symphytum* genus include but are not limited to:

Symphytum spp.	INCI Names	Synonym(s)/Common names
<i>Symphytum officinale</i> ¹	Symphytum Officinale Callus Culture Extract; Symphytum Officinale Callus Culture Lysate; Symphytum Officinale Extract; Symphytum Officinale Leaf Extract; Symphytum Officinale Leaf Powder; Symphytum Officinale Rhizome/Root Extract; Symphytum Officinale Root Cell Extract; Symphytum Officinale Root Extract	Black wort; Boneset; Bruise wort; Comfrey; Common Comfrey; Consound; Cultivated Comfrey; Knitbone; Quaker Comfrey; Slippery-Root; True Comfrey (North Carolina Extension Gardener Plant Toolbox, 2024)
<i>Symphytum asperum</i> ²		prickly comfrey, Persian comfrey (Missouri Botanical Garden, 2024)
<i>Symphytum × uplandicum</i> ¹ (<i>S. asperum</i> × <i>S. officinale</i> , synonym: <i>S. peregrinum</i>)		Russian comfrey Missouri Botanical Garden, 2024)
<i>Symphytum bulbosum</i>		bulbous comfrey
<i>Symphytum brachycalyx</i>		Palestine comfrey
<i>Symphytum caucasicum</i>		Caucasian comfrey
<i>Symphytum grandiflorum</i>		creeping comfrey
<i>Symphytum ibericum</i>		Iberian comfrey
<i>Symphytum orientale</i>		white comfrey
<i>Symphytum tauricum</i>		Crimean comfrey
<i>Symphytum tuberosum</i>		tuberous comfrey

¹Only species with a reported cosmetic function according to the INCI Dictionary

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²Specified in the Food and Drug Regulations C.R.C., c. 870 (Section C.01.038)

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

Table 2. Chemical constituents identified in *S. officinale* ([Stickel, 2000](#))

Compound	Content (%)
Allantoin	0.6-0.8
Pyrrolizidine Alkaloids	0.04-0.6
Tannins	4-6
Fructanes	15-30
Starch	25
Triterpenes	
Triterpenoid saponins	
Hederagenin hexasaccharide	
Oleanolic acid	
Sitosterole	
Lithospermic acid	
Asparagine	1-3
Amino acids	Variable

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APPENDIX 2 - Regulatory Status of *Symphytum spp.*, including *Symphytum officinale* in cosmetics

Table 3. Comparison of Regulatory Status of *Symphytum spp.*, including *Symphytum officinale* in Certain Jurisdictions

	Canada ¹	USA ²	European Union ^{3,4}	Other Jurisdictions ⁵⁻⁹
Status	Prohibited on the Hotlist since December 2004, except for <i>Symphytum officinale</i>	Not restricted	Not restricted	Not restricted
Max.	-	-	-	-
Product Type	-	-	-	-
Product Form	-	-	-	-
Label Requirements	-	-	-	-

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	Canada ¹	USA ²	European Union ^{3,4}	Other Jurisdictions ⁵⁻⁹
Other	-	-	-	-

¹HC, 2022; ²US FDA, 2023; ³CosIng, 2024; ⁴Switzerland (FDHA, 2017); ⁵Eurasian Economic Community Union (EEC, 2011); ⁶Association of Southeast Asian Nations (ASEAN, 2023); ⁷Mercado comun del sur (MERCOSUR, 2024); ⁸New Zealand (NZ EPA, 2017); ⁹Japan ((MHLW, 2000).

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APPENDIX 3 –*Symphytum officinale*-derived Ingredients in Other Cosmetic Databases

Table 4. Total active cosmetic notifications for *Symphytum officinale* from Jan 1, 2019 to May 29, 2024.

Ingredients	Number of Notifications
Comfrey Extract	
COMFREY LEAF EXTRACT	19
Comfrey Root	
Comfrey root powder	
Symphytum Officinale	268
Symphytum Officinale (Comfrey) Leaf Extract	
Symphytum Officinale (Comfrey) Leaf Powder	
symphytum officinale callus culture extract	17
Symphytum Officinale Extract	166
Symphytum officinale huile/oil	
Symphytum officinale leaf and root	
Symphytum Officinale Leaf Extract	569
Symphytum Officinale Leaf Powder	29
SYMPHYTUM OFFICINALE RHIZOME/ROOT EXTRACT	64
Symphytum Officinale Root Cell Extract	10
symphytum officinale root extract	189
Symphytum Officinals	
Grand Total	1355

[Entries with limited product counts redacted for confidentiality]

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Table 5. Summary of the cosmetic purpose and concentration ranges of *Symphytum officinale* in products notified from Jan 1, 2019 to May 29, 2024.

[Redacted for confidentiality]

Return to Section [2.2 Status of Ingredients in Other Cosmetic Databases](#).

APPENDIX 4 – Exposure Modelling Calculations and Limit Derivation for *Symphytum officinale* Extracts

Table 6. Oral exposure scenario and limit derivation for a non-fluoride toothpaste formulated with *Symphytum officinale* extract

	Age groups				
Product (Toothpaste)	19+	14 to 18	9 to 13	4 to 8	2 to 3
Product amount (mg) – ingested ¹	80	80	140	210	210
Concentration (%/100) of <i>Symphytum</i> ²	0.1	0.1	0.1	0.1	0.1
Concentration PA (%/100) ³	0.006	0.006	0.006	0.006	0.006

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Frequency⁴	2.5	2.6	2.6	2.9	2.9
Bioavailability (%/100)⁵	0.5	0.5	0.5	0.5	0.5
BW (kg)⁶	74	62	42	23	15
Daily systemic exposure amount(mg/day)⁷	0.1	0.1	0.1	0.2	0.2
Maximum daily intake amount (mg/day)⁸	0.00051800	0.000434	0.000294	0.000161	0.000105
% Acceptable conc. Symphytum extract⁹	0.086%	0.070%	0.027%	0.009%	0.006%

¹Default values for mean/median product amount (g/application) for toothpaste across different age groups, as recommended by the Personal Care Products Workbook (internal reference)

²Based on a notified maximum concentration range of 3-10%. The upper bound limit of 10% was assumed to be the concentration of *S. officinale* extract in the product.

³Assuming a 0.6% lasiocarpine content based on a typical chemical composition of *S. officinale* root according to Stickel & Seitz (2000)

⁴Default values for frequency of use per day for a toothpaste across different age groups, as recommended by the Personal Care Products Workbook (internal reference)

⁵Based on the SCCS Notes of Guidance (2023), a 50% oral bioavailability will be assumed in the absence of empirically derived data for *S. officinale* extract or lasiocarpine

⁶Default body weight (kg) across different age groups, as recommended by the Personal Care Products Workbook (internal reference)

⁷Calculated daily systemic exposure amount: Product amount (mg) corresponding to incidental ingestion x Concentration (%/100) x PA concentration (%/100) x Frequency

⁸Maximum daily intake of PAs should not exceed 0.35 µg/day (for a 50 kg adult) corresponding to 0.007 µg/kg bw day. This value is derived based on a BMDL₁₀ of 73 µg/kg bw day for lasiocarpine as the point of departure (POD), and a target Margin of Exposure (MoE) of 10,000. This value was adjusted to 0.518 µg/day for an adult body weight of 74 kg.

⁹Maximum concentration of *S. officinale* extract permitted in a toothpaste to ensure that a maximum daily intake amount (mg/day) is not exceeded. Derived as: Maximum daily intake (mg/day) / (Amount ingested (mg) x Concentration of PA (%/100) x Frequency x Oral Bioavailability (%/100))

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Table 7. Oral exposure scenario and limit derivation for a mouthwash formulated with *Symphytum officinale* extract

	Age groups				
Product (Mouthwash)	19+	14 to 18	9 to 13	4 to 8	2 to 3
Product amount (mg) – ingested ¹	1700	1700	1000	1000	-
Concentration (%/100) of Symphytum ²	0.3	0.3	0.3	0.3	-
Concentration PA (%/100) ³	0.006	0.006	0.006	0.006	-
Frequency ⁴	1	1	0.85	0.85	-
Bioavailability (%/100) ⁵	0.5	0.5	0.5	0.5	-
BW (kg) ⁶	74	62	42	23	-
Daily systemic exposure amount(mg/day) ⁷	1.5	1.5	0.8	0.8	-
Maximum daily intake amount (mg/day) ⁸	0.00051800	0.000434	0.000294	0.000161	-
% Acceptable conc. Symphytum extract ⁹	0.010%	0.0085%	0.0115%	0.006%	-

¹Default values for mean/median product amount (g/application) for mouthwash across different age groups, as recommended by the Personal Care Products Workbook (internal reference)

²Based on a notified maximum concentration range of 10-30%. The upper bound limit of 30% was assumed to be the concentration of *S. officinale* extract in the product.

³Assuming a 0.6% lasiocarpine content based on a typical chemical composition of *S. officinale* root according to Stickel & Seitz (2000)

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⁴Default values for frequency of use per day for a mouthwash across different age groups, as recommended by the Personal Care Products Workbook (internal reference)

⁵Based on the SCCS Notes of Guidance (2023), a 50% oral bioavailability will be assumed in the absence of empirically derived data for *S. officinale* extract or lasiocarpine

⁶Default body weight (kg) across different age groups, as recommended by the Personal Care Products Workbook (internal reference)

⁷Calculated daily systemic exposure amount: Product amount (mg) corresponding to incidental ingestion x Concentration (%/100) x PA concentration (%/100) x Frequency

⁸Maximum daily intake of PAs should not exceed 0.35 µg/day (for a 50 kg adult) corresponding to 0.007 µg/kg bw day. This value is derived based on a BMDL₁₀ of 73 µg/kg bw day for lasiocarpine as the point of departure (POD), and a target Margin of Exposure (MoE) of 10,000. This value was adjusted to 0.518 µg/day for an adult body weight of 74 kg.

⁹Maximum concentration of *S. officinale* extract permitted in a mouthwash to ensure that a maximum daily intake amount (mg/day) is not exceeded. Derived as: Maximum daily intake (mg/day) / (Amount ingested (mg) x Concentration of PA (%/100) x Frequency x Oral Bioavailability (%/100))

Table 8. Dermal exposure scenario and limit derivation for a body lotion formulated with *Symphytum officinale* extract

	Age groups							
Product (body lotion)	19+	14 to 18	9 to 13	4 to 8	2 to 3	1	6 to 11 mo	0 to 5 months
Amount applied (mg) ¹	10000	10000	7700	5200	4100	3200	2700	2100
Concentration (%/100) of <i>Symphytum</i> ²	1	1	1	1	1	1	1	1
PA concentration (%/100)	0.006	0.006	0.006	0.006	0.006	0.006	0.006	0.006

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Frequency⁴	1	0.8	0.8	0.8	0.8	0.8	0.8	0.8
Retention factor⁵	1	1	1	1	1	1	1	1
Dermal absorption⁶	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
BW (kg)⁷	74	62	42	23	15	11	9.1	6.3
Daily systemic exposure amount (mg/day)⁸	30.0000	24.0000	18.4800	12.4800	9.8400	7.6800	6.4800	5.0400
Maximal daily intake amount (mg/day)⁹	0.00051800	0.00043400	0.00029400	0.00016100	0.00010500	0.00007700	0.00006370	0.00004410
Acceptable conc. of <i>S. officinale</i> extract¹⁰	0.002%	0.002%	0.002%	0.001%	0.001%	0.001%	0.001%	0.001%

¹Default values for mean/median product amount (mg/application) for a body lotion across different age groups, as recommended by the Personal Care Products Workbook (internal reference)

²Based on a notified maximum concentration range of 30-100%. The upper bound limit of 100% was assumed to be the concentration of *S. officinale* extract in the body lotion.

³Assuming a 0.6% lasiocarpine content based on a typical chemical composition of *S. officinale* root according to Stickel & Seitz (2000)

⁴Default values for frequency of use per day for a body lotion across different age groups, as recommended by the Personal Care Products Workbook (internal reference)

⁵Default values for the retention factor of a body lotion, as recommended by the Personal Care Products Workbook (internal reference)

⁶Based on the SCCS Notes of Guidance (2023), a 50% dermal absorption value will be assumed in the absence of empirically derived data for *S. officinale* extract or lasiocarpine

⁷Default body weight (kg) across different age groups, as recommended by the Personal Care Products Workbook (internal reference)

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⁸Calculated daily systemic exposure amount (mg/day): Product amount applied (mg) x Concentration of *S. officinale* extract (%/100) x PA concentration (%/100) x Frequency x Retention factor x Dermal absorption (%/100)

⁹Maximum daily intake of PAs should not exceed 0.35 µg/day (for a 50 kg adult) corresponding to 0.007 µg/kg bw day. This value is derived based on a BMDL₁₀ of 73 µg/kg bw day for lasiocarpine as the point of departure (POD), and a target Margin of Exposure (MoE) of 10,000

⁹Maximum concentration of *S. officinale* extract permitted in a body lotion to ensure that the maximum daily intake amount (mg/day) is not exceeded. Derived as: Maximum daily intake (mg/day) / (Amount applied (mg) x Concentration of PA (%/100) x Frequency x Retention Factor x Dermal Absorption (%/100))

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