

RISK PROFILE

Symphytum officinale extracts

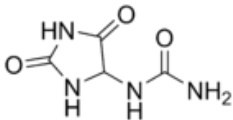
CAS No. 84696-05-9

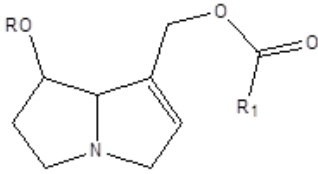
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1. Identification of substance

Chemical name (IUPAC):	Allantoin: 5-ureidohydantoin, 5-ureidoimidazolidine-2,4-dione, 2,5-dioxoimidazolidine-4-ylurea
INCI	<i>Symphytum officinale</i> leaf extract, <i>Symphytum officinale</i> leaf powder, <i>Symphytum officinale</i> root extract, <i>Symphytum officinale</i> root cell extract
Synonyms	Comfrey, (<i>valurt</i> in Norwegian)
CAS No.	<i>Symphytum officinale</i> : 84696-05-9 Allantoin: 97-59-6
EINECS No.	<i>Symphytum officinale</i> : 283-625-3 Allantoin: 202-592-8
Molecular formula	Allantoin: C ₄ H ₆ N ₄ O ₃
Chemical structure	Allantoin:  Pyrrolizidine alkaloids (general structural formula):

	
Molecular weight	Allantoin: 158.1
Contents (if relevant)	<p>The herb contains i.a. allantoin, mucilage, tannins, steroidal saponins, pyrrolizidine alkaloids, inulin and proteins (Sigma-Aldrich Co).</p> <p>Comfrey consists of the dried root and rhizome of <i>Symphytum officinale</i> (Boraginaceae); the leaf has also been used. It contains about 0.7% of allantoin, large quantities of mucilage, and some tannin. It also contains different hepatotoxic pyrrolizidine alkaloids. The total content of pyrrolizidine alkaloids is approximately 0.3% of the dry weight of the root, usually lower in the leaves. The amount of pyrrolizidine alkaloids in the fresh plant may not be very high, but the ready-to-use preparations often have high levels, e.g. 270-2900 mg/kg (Martindale, Toxnet, Council of Europe 2008, Cornell University).</p>
Physiochemical properties	Allantoin: A white or almost white, crystalline powder. Slightly soluble in water; very slightly soluble in alcohol (Martindale).

2. Uses and origin

Uses	<p>Cosmetic products:</p> <p><i>Symphytum officinale</i> extract is used as a soothing agent, as an emollient and against skin impurities, in concentrations of 0.5-4% (Council of Europe 2008).</p> <p>The defined functions of comfrey according to CosIng are:</p> <ul style="list-style-type: none"> -skin conditioning -abrasive -antidandruff -soothing <p>Several products (>100) were identified containing <i>Symphytum officinale</i> in the databases EWG's Skin Deep and Codecheck. These comprise i.a. the following product categories:</p> <ul style="list-style-type: none"> -Cream -Moisturizer -Facial moisturizer -Facial cleanser -Shampoo -Hair colour and bleaching -Mask -Body wash/cleanser -Toners <p>Medicinal products:</p>
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	<p><i>Symphytum officinale</i> has been used as a medicinal plant for years, in the form of e.g. extracts and physically modified derivatives such as tinctures, concretes, absolutes, essential oils, etc. (ESIS, Cornell University).</p> <p>Comfrey was formerly used as an application to wounds and ulcers to stimulate healing and was also given systemically for gastric ulceration and respiratory tract disease. It has been applied topically in the treatment of i.a. broken bones and inflammatory disorders. The healing action of comfrey has been attributed to the presence of allantoin and mucilage. Absorption through the skin of pyrrolizidine alkaloids is lower compared to oral administration (Council of Europe 2008, Martindale, Cornell University).</p> <p>Allantoin is an astringent and keratolytic, and it is used in preparations intended for various skin disorders. It is also used for the treatment of haemorrhoids and other anorectal disorders due to its astringent properties. FDA in the US has decided that allantoin should be removed from lotions indicated for psoriasis, as it was considered to be ineffective (Martindale).</p> <p>Food: For vegetarians, numerous recipes are available for different food with comfrey; salads, soufflés, soups, bread, rolls and root beverages. The consumption of food with comfrey is widespread (Council of Europe 2008).</p>
Origin Natural (exo /endo) Synthetic	Comfrey is a common wild plant in parts of the USA and is cultivated in much of the world. It is a perennial herb with deep roots. The leaves are large, rough and prickly and the flowers are bell-like with pinkish or creamy colour. Comfrey can often be confused with foxglove (<i>Digitalis spp.</i>) when it is not flowering (Cornell University)
Contraindications / Interactions	<i>Symphytum officinale</i> is not recommended for internal use because of the hepatotoxic pyrrolizidine alkaloid content. Use is contraindicated during pregnancy and lactation, in infants, and in patients with kidney or liver disease. Interactions are not well documented (Drugs). In general plant extracts have the potential of causing severe drug interactions.

3. Regulation

Norway	<p>Comfrey is classified as a drug, prescription only (FOR 1999-12-27 nr 1565).</p> <p>The Norwegian cosmetics regulation (FOR 1995-10-26 nr 0871, Annex 3), which is in force until 11th June 2013, states that <i>Symphytum officinale</i> is allowed in cosmetics provided it does not contain pyrrolizidine alkaloids.</p>
EU	Neither comfrey nor allantoin is listed in any EU Directive/Regulation Annexes, and there are no known restrictions to the use of this substance.
Rest of the world	The US Food and Drug Administration has banned the sale of oral comfrey products in the USA due to i.a. the risk of severe liver damage (Toxnet, FDA 2001).

4. Relevant toxicity studies

Absorption Skin GI tractus	<p>Data on absorption of pyrrolizidine alkaloids are limited and different values are found. The absorption of pyrrolizidine alkaloids through skin in the form of free base may amount to 5% compared to after oral intake (Council of Europe 2008).</p> <p>In an animal study, topical application of an extract resulted in very low absorption of pyrrolizidine alkaloids and 0.1-0.4% was recovered in the urine over the next 24 hours (Sigma-Aldrich).</p>
Distribution	No data available
Metabolism	Pyrrolizidine alkaloids are metabolised in the liver and converted to necines and other metabolites. Depending on the structure of the original pyrrolizidine alkaloids, this may eventually lead to end products which can cause alkylation of DNA (Council of Europe 2008).
Excretion	No data available
Local toxic effects Irritation Sensitivity	No data available
Systemic toxic effects Acute Repeated dose Mutagenicity /genotoxicity Carcinogenicity Reprotoxicity / teratogenicity Other effects	<p>Ingestion of comfrey has been associated with hepatotoxicity. Toxic pyrrolizidine alkaloids have been isolated from several species of comfrey plants. Ingestion of plants containing such alkaloids can cause severe liver damage, liver cancer, mutagenicity and even death. The alkaloids are common cause of hepatic veno-occlusive disease in developing countries. Hepatotoxicity likely due to pyrrolizidine alkaloid from comfrey has been reported in North America and Europe. Pulmonary endothelial hyperplasia and carcinogenic activity have also been reported in animals. (Martindale, Toxnet, Cornell University).</p> <p>Pyrrolizidine alkaloids are potent poisons which can give rise to poisoning in grazing livestock. There are species differences in susceptibility to pyrrolizidine alkaloids, and horses and cattle are most commonly poisoned. Liver damage is the main adverse effect, likely due to pyrrole derivatives which are produced when the alkaloids are metabolized, and the effects of the alkaloids are cumulative at very low intake rates. The alkaloids can also give rise to tumours. The typical chronic liver lesion observed in experimental animals is a progressive enlargement of parenchymal cells and their nuclei due to antimitotic action (Samuelsson 1992, Cornell University, Council of Europe 2008).</p>

5. Exposure estimate and critical NOAEL / NOEL

NOAEL/NOEL critical	<p>In one case a dose of 0.015 mg/kg body weight/day from intake of a supplement led to obliteration of the smaller hepatic veins. In most of the non-fatal cases of veno-occlusive disease, the total dosage of pyrrolizidine alkaloids was 2-27 mg/kg bodyweight (Council of Europe 2008).</p> <p>Clear information on the NOAEL/NOEL has not been found.</p>
Exposure cosmetic products	A lifetime cancer risk of approximately 10^{-4} has been calculated when using aftershave products containing 5% comfrey extracts. The risk

	<p>may be considerably higher or lower, depending on the content of pyrrolizidine alkaloids in the extracts. Only risks below 10^{-5} should be accepted (Council of Europe 2008).</p> <p>Rough estimates of the systemic exposure dose (SED) for leave-on face, body lotion and body wash products are given below:</p> <p>For leave-on face products the surface area is estimated to 565 cm² (face surface area) Amount of product per cm²: 1 mg (SCCS guidelines 2011, assumed leave-on, not rinse-off) Number of applications per day: 2 Concentration of <i>Symphytum officinale</i> in products: 4 % (no specific information on concentration, 4 % is an assumption) Skin penetration rate: assumed 100 % (worst case) as no data are available (SCCS guidelines) Body weight: 60 kg (SCCS guidelines) SED face product: $565 \times 1 \times 2 \times 0.04 \times 1/60 = 0.75 \text{ mg/kg bw/day}$</p> <p>For body lotion products the surface area is estimated to 15670 cm² (body and hand area, female) Amount of product per cm²: 1 mg (SCCS guidelines 2011) Number of applications per day: 2.28 (SCCS guidelines 2011) Concentration of <i>Symphytum officinale</i> in products: 4 % (no specific information on concentration, 4 % is an assumption) Skin penetration rate: assumed 100 % (worst case) as no data are available (SCCS guidelines) Body weight: 60 kg (SCCS guidelines) SED body lotion: $15670 \times 1 \times 2.28 \times 0.04 \times 1/60 = 23.8 \text{ mg/kg bw/day}$</p> <p>For body wash products the calculated daily exposure is 2.79 mg/kg bw/day (SCCS guidelines 2011) Skin penetration rate: assumed 100 % (worst case) as no data are available (SCCS guidelines) Concentration of <i>Symphytum officinale</i> in products: 4 % (no specific information on concentration, 4 % is an assumption) SED body wash: $2.79 \text{ mg/kg bw/day} \times 1 \times 0.04 = 0.11 \text{ mg/kg bw/day}$</p>
<p>Margin of Safety (MoS)</p>	<p>As an example, a NOEL for <i>Symphytum officinale</i> of 100 mg/kg bw, gives the following MoS values:</p> <p>Face product: SED: 0.18 mg/kg bw/day MoS = $100/0.75 = 133$</p> <p>Body lotion: SED: = 5.95 mg/kg bw/day MoS = $100/23.8 = 4$</p> <p>Body wash: SED: 0.03 mg/kg bw/day MoS = $100/0.11 = 909$</p>

6. Other sources of exposure than cosmetic products

Food stuffs	Available in over-the-counter herbal remedies.
Pharmaceuticals	No data
Other sources	No data
Adverse side effects - from uses other than cosmetics	In general, intake of herbs may cause transient adverse effects such as nausea, vomiting, and GI distress due to a variety of chemical constituents.

7. Assessment

The safety concerns over comfrey are primarily due to the pyrrolizidine alkaloids. These alkaloids have been shown to have a hepatotoxic effect, in addition to being mutagenic and carcinogenic. Norway has therefore prohibited comfrey extracts in cosmetics if it contains pyrrolizidine alkaloids. The risk of getting cancer because of cosmetics adds to the risk from exposure of pyrrolizidine alkaloids through the diet. FDA has advised manufacturers that herbal products containing comfrey should be removed from the market.

Although a lower amount of pyrrolizidine alkaloids are absorbed systemically when *Symphytum officinale* is administered topically compared to orally, we consider the potential of severe health effects to be sufficient to warrant a restrictive regulation. In addition, the complete absence of pyrrolizidine alkaloids in *pyrrolizidine free extracts* might be problematic to guarantee and control.

8. Conclusion

The toxicity and carcinogenicity of pyrrolizidine alkaloids in humans warrants a very restrictive use of products which might contain such substances. The exposure to pyrrolizidine alkaloids should be kept as low as practically possible, and comfrey extracts should therefore not be used in cosmetics..

9. References

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10. Annexes

Council of Europe's Committee of Experts on Cosmetic Products. *Symphytum officinale* extracts, monograph no. 38. Active ingredients used in cosmetics: safety survey, Council of Europe Publishing. 2008; 369-374.