RISK PROFILE

Podophyllum peltatum extract

CAS No.90063-90-4

Date of reporting 04.02.2012

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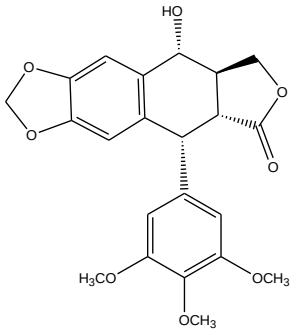
1. Identification of substance

Chemical name (IUPAC):	Not applicable.
INCI	PODOPHYLLUM PELTATUM RHIZOME/ROOT EXTRACT
Synonyms	Extract: Podophyllum resin, Podohylliresina, Podophyllin Plant: mayapple, wild lemon, raccoon berry, wild mandrake and American mandrake.
CAS No.	Extract: 90063-90-4 Podophyllotoxin: 518-25-5
EINECS No.	Extract: 290-050-1
Molecular formula	Podophyllotoxin: $C_{22}H_{22}O_8$
Chemical structure	 Podophyllotoxin

Molecular weight	Podophyllotoxin: 414.40
Contents (if relevant)	Podophyllum peltatum extract is an extract of the rhizomes and roots of the Podophyllum peltatum L., Berberidaceae The Podophyllum peltatum extract (ethanolic) consists of various compounds: water-soluble lignanglycosides (such as podophyllotoxin), α- and β-peltatin and 13 other physiologically active compounds. It also contains significant quantities of the two strongly mutagenic flavonoids quercetin and kampherol, which make up 3 and 6 % of the dry weight of the plant, respectively. The resin of Podophyllum peltatum is often referred to as podophyllin in the literature.
Physiochemical properties	No data found. References: (Council of Europe, 2008).

2. Uses and origin

Uses	➢ **Cosmetic products:** ***Functions according to****:* o CosIng database "Skin conditioning" – Maintains the skin in good condition (CosIng [online]). o Other Podophyllin peltatum is used as a component in Chinese hair preparations (Council of Europe, 2008). ***Concentrations being applied*** No data. ***Frequency of use*** No products containing Podophyllum peltatum showed up in a search at either the database Codecheck.info or EWG's Skin Deep. (EWG's Skin Deep [online]; Codecheck.info [online]). This ingredient - and the ingredient *saccharomyces*/*Podophyllum peltatum ferment filtrate* which may possibly contain the same potentially dangerous substances - are mentioned in the CosIng database of the European Commission, the International Cosmetic Ingredient Dictionary and Handbook of the American branch organization (the CTFA) and also in an branch inventory called the *Cosmetics & Toiletries Bench Reference* (CBR directory) being administrated by the American branch periodical the *Cosmetic & Toiletries Magazine*. The latter inventory also provides addresses to

	manufacturers that offer these ingredients for sale. Offering an ingredient for sale means there are customers. Two products concerning the ferment we occasionally saw being marketed (Wegmans, Taiwantrade). A European firm specializing in development of sophisticated complex ingredients recently launched one consisting of more constituents among which also is *Podophyllum Peltatum Extract*. This complex ingredient is meant to go into ready-to-use cosmetics at a concentration of 25 %. The purpose of product is to reduce growth of hair after depilatory treatment and so to extend time between such treatments (Kalichem). Concentration of *Podophyllum Peltatum Extract* in ready to use hair growth slowing product would be less than 0.4 %. *Podophyllotoxin* possesses keratolytic properties and so seems to find some use in treatment of the disease *seborrhoeic keratosis* also (Shaanxi). One of the great economic players in the branch of cosmetics patented (back in 1996) an antidandruff product that also contains *Podophyllum Peltatum Extract (patsnap).* So, in light of these data we believe that the ingredient in question presently find use in a few special cosmetics products on the single European market (slowing of hair growth, dandruff). ➢ **Medicinal products/applications** Several commercial topical applications containing Podophyllum peltatum extract exists: Posalfilin®: podophyllum resin (20 %) and salicylic acid (10%), meant for use for warts and verrucas; Wartec®: podophyllotoxin cream 0.15 % for treatment of genital warts; and Condyline®: podophyllotoxin 0.5 % solution in ethanol for the topical treatment of external genital warts. Phodophyllotoxin is the main component of *Podophyllum peltatum*, and have properties as an antiviral agent, an antineoplastic drug and a laxative. The mechanism for its effect is as a mitosis-inhibiting agent; it binds the microtubules and causes mitotic arrest. However, because of phodophyllotoxins unacceptable gastrointestinal toxicity, it is not used for the treatment of neoplastic disease in humans (Council of Europe, 2008). Podophyllin resin has been used as a laxative until recently, but has now been banned for oral use due to its potential to induce severe systemic intoxication Longstaff et al., 2001). It is also banned from dietary supplements (Council of Europe, 2008). *Podophyllin peltatum* has been used as a folk remedy for several hundred years for constipation and as an emetic, antihelmentic and cathartic agent (Longstaff et al., 2001). ➢ **Food** The fruit of the plant has a lemon-like flavor and is not toxic. It is therefore used for jams, jellies and marmalade. The fruit can also be dried for later use. The fruit should be eaten only when it is fully ripe, or else it is strongly laxative. In addition, unprocessed raw fruit is only edible in limited quantity, as it can cause colic (Council of Europe, 2008). ➢ **Other** Phodophyllotoxin is used as an insecticide against larvae of

	Drosophila melanogaster Meigen (Council of Europe, 2008).
Origin Natural (exo /endo) Synthetic	Natural, plant-derived.

3. Regulation

Norway	No regulation[1].
EU	No regulation.
Rest of the world	No regulation.

4. Relevant toxicity studies

Absorption Skin GI tractus	GI tractus: podophyllin is absorbed rapidly after ingestion. Oral bioavailability in dogs after high doses of podophyllotoxin (1.0 mg/kg bw) is up to 63 %. Skin: podophyllin can be absorbed through skin when applied topically. (Council of Europe, 2008).
Distribution	No data available.
Metabolism	The serum half-life of podophyllotoxin is between 1-4.5 hours. Metabolism of the other constituents is not known (Council of Europe, 2008).
Excretion	A podophyllic acid preparation was eliminated predominantly in the urine. Podophyllotoxin is eliminated in the bile (Council of Europe, 2008).
Local toxic effects Irritation Sensitivity	Skin irritation: podophyllin produces an acute inflammatory reaction with necrosis of the treated area with some degree of irritation (Council of Europe, 2008). Skin sensitivity: Allergic hypersensitivity to podophyllin resin has been reported. However, the hypersensitivity is usually related to the vehicle (benzoin) or other contaminants (Council of Europe, 2008). Mucous irritation: podophyllum resins and podophyllotoxin may cause severe irritation and burns to the mucous membranes and the respiratory tract (Council of Europe, 2008).
Systemic toxic effects Acute	In humans, severe systemic toxicity has been seen after ingestion and local applications to large areas or in excessive amounts (Longstaff et al., 2001). A fatal case was described after topical application to the vulva of a 25 % podophyllin ointment, and after application of 90 ml of a 17.5 % podophyllin solution to the vulva. When taken podophyllum orally, small amounts, such as 350 mg, can be fatal (Council of Europe, 2008). Fatal outcome is generally due to the CNS effects that cause coma, respiratory depression and cardiovascular crisis (Council of Europe, 2008).

[1] The Norwegian medicinal products agency considered podophyllum peltatum extracts medicinal remedies. Because of that up till 2008 topical products containing these extracts were considered medicines – meaning a topical product containing the extract were automatically classified a medicine. This regime has since been lifted.

Repeated dose	Several cases of poisoning have been reported after ingestion of Chinese herbal products containing *Podophyllum peltatum* (Ramirez et al., 1970). LDLO (lowest published lethal dose), oral, woman: 6 mg/kg bw LDLO, oral, man: 156 mg/kg bw LD_{50}, intraperitoneal, rat: 15 mg/kg bw LD_{50}, oral, mouse: 68 mg/kg bw LD_{50}, subcutaneous, mouse: 58 mg/kg bw (Council of Europe, 2008). Humans: Repeated exposure to lower doses of podophyllin can affect highly proliferative tissues, such as bone marrow and intestinal mucosa. Non-lethal damage is clinically fully reversible within days or weeks, except peripheral neuropathy (Cassidy et al., 1982), which may persist for several months (Filley et al., 1982). Animals: No repeated dose studies with Podophyllum peltatum extract was found. However, several studies with repeated doses of podophyllotoxin have been performed. The no-adverse-effect levels (NOAELs) are summarized below: - Rat, dermal: 0.25 mg/kg bw/day - Rat, oral: 0.3 mg/kg bw/day - Dog, oral: 0.3 mg/kg bw/day (Council of Europe, 2008).
Mutagenicity /genotoxicity	Podophyllin causes chromosomal changes in hamster, leads to increased mutation rate in Salmonella typhimurium, induces chromosomal defects in mammalian cell cultures, and induces a high incidence of chromatid and chromosome deletions, chromatid exchanges, and cells with multiple aberrations in human lymphocytes (Longstaff et al., 2001).
Carcinogenicity	Podophyllin is classified as non-carcinogenic by IARC in animal studies. However, it has been reported to be co-carcinogenic when applied together with estrogen in mice (Kaminetzky et al., 1965). Several studies with podophyllotoxin have been conducted, with equivocal results. For details, see the assessment done by Council of Europe (2008).
Reproductive toxicity / Teratogenicity	Podophyllin has been used to terminate pregnancy, which indicates that it is teratogenic (Council of Europe, 2008). An intrauterine death of a fetus was reported in a woman treated with podophyllum for vulvar warts during week 32 of pregnancy (Chamberlain et al., 1972). Skin tags and malformations were reported for a newborn whose mother had been treated with podophyllum (Council of Europe, 2008). In mice, podophyllin has been shown to cause a high frequency of fetal mortality following single intraperitoneal doses of 5-15 mg/kg bw. In addition, one fetus in the podophyllin-treated group developed abnormalities (Council of Europe, 2008). In the literature, it has been stated that podohyllin is embryotoxic but not teratogenic in the rat (Council of Europe, 2008).

5. Exposure estimate and critical NOAEL / NOEL

NOAEL/NOEL critical	NOAEL: 0.25 mg/kg bw (based on repeated dermal doses in rat).
Exposure cosmetic products	The data available are not sufficient to assess the systemic exposure to *Podohyllum peltatum*. The below calculation is for illustrative purposes only. *Leave-on products (tentative hair regrowth slowing product used in conjunction with depilating treatment)* Area of skin exposed (female legs): 5530 cm^2 (default value – RIVM 2006). Amount of product per cm^2: 1 mg (default, SCCS) Concentration of Podophyllum peltatum extract in products: 0,1 % (for illustrative purposes) Skin penetration rate: 100 % (dermal data for NOAEL) Body weight: 60 kg (default value SCCS guidelines). SED (per application): 5530 x 1 x 0.001 / 60 = 0,092 mg/kg bw/day Frequency of depilating treatment is 17 times a year (RIVM 2006). A single daily dose of **0,0043** mg/kg bw gives a accumulated yearly dose equalizing17 times the SED per application. *Rinse-off products (tentative dandruff shampoo):* Amount of product per day: 110 mg (default value for shampoo, SCCS guidelines) Concentration of Podophyllum peltatum extract in products: 0,1 % (for illustrative purposes) Skin penetration rate: 100 % (dermal data for NOAEL) Body weight: 60 kg (default value SCCS guidelines). SED: 110 x 0.001 / 60 = **0,0018 mg/kg bw/day**
Margin of Safety (MoS)	As the data available was not sufficient to assess the systemic exposure to Podophyllum peltatum, the MoS calculated below is for illustrative purposes only. NOAEL: 0.25 mg/kg bw/day ***MoS for use of tentative hair regrowth slowing product*** SED: 0.0043mg/kg bw/day MoS: 0.25/ 0.0043 = 58 ***MoS for use of tentative dandruff shampoo*** SED: 0.0018 mg/kg bw/day MoS: 0.25/ 0.0018 = 139

6. Other sources of exposure than cosmetic products

Food stuffs	No data found.
Pharmaceuticals	Products containing purified podophyllotoxin are available in concentrations of 0.5 % in ethanol and 0.15 % in cream and gel and

	are designed for topical self-treatment in one or several 3-day cycles for genital warts (Council of Europe, 2008). The potential fatal toxicity from excess topical podophyllin has led to recommended volumes of 0.9-1.2 and 0.4-0.5 ml for freshly made, respectively.
Other sources	No data.
Adverse side effects - from uses other than cosmetics	

7. Assessment

Podophyllum peltatum extract is used in several topical applications meant for removal of warts. At present the substance does not, however, find much use in cosmetic products. That could possibly change inventive undertakings making more use of this *plant derived* ingredient in different borderline products. Generally, plant extracts enjoy increasing popularity in todays' market of cosmetic products.

There are limited data on the adverse effects of exposure to Podophyllum peltatum extract. However, there are indications that the extract is genotoxic, co-carcinogenic and teratogenic. When dealing with a possible genotoxic and teratogenic compound, we think it pertinent to apply a MoS of 10,000 (BfR 2005).

MoS for tentative leave-on product	58	(when usage limit is 0.1 %).
MoS for tentative rinse-off product	139	(when usage limit is 0.1 %).

To consider the use of Podophyllum peltatum extract to be safe to use in cosmetics, the MoS ought to be above 10,000, we think. The MoS values estimated are, however, much lower; even about 3 orders of magnitude lower applying cautiously set premises for illustrative purposes. Thus, the use of this extract in cosmetic products can not be considered safe. Data on dermal absorption, reproductive toxicology and carcinogenicity is necessary.

8. Conclusion

In conclusion, we propose to prohibit the use of Podophyllum peltatum extract in all cosmetic products.

9. References

BfR 2005 is for the following paper produced by the German "Bundesinstitut für Risikobevertungden" - that also refer to EFSA considerations: *"Risk assessment of genotoxic and carcinogenic substances to be harmonized in the EU"* (BfR Expert Opinion No. 029/2005 of 18 May 2005)

Cassidy DE, Drewry J, Fanning JP. Podophyllum toxicity: a report of a fatal case and a review of the literature. J Toxicol Clin Toxicol. 1982 Mar;19(1):35-44.

CBR directory to be accessed at https://dir.cosmeticsandtoiletries.com/login.do
Click: *Cosmetic Bench Reference*
http://dir.cosmeticsandtoiletries.com/detail/tradeName.html?id=11054

Chamberlain MJ, Reynolds AL, Yeoman WB. Medical memoranda. Toxic effect of podophyllum application in pregnancy. Br Med J. 1972 Aug 12;3(5823):391-2.

Council of Europe. Active ingredients used in cosmetics: safety survey. Council of Europe Publishing. Strasbourg, March 2008.

Filley CM, Graff-Richard NR**, Lacy JR,** Heitner MA, Earnest MP. Neurologic manifestations of podophyllin toxicity. Neurology. 1982 Mar;32(3):308-11.

Kaminetzky HA, Swerdlow M. Podophyllin and the mouse cervix: assessment of carcinogenic potential. Am J Obstet Gynecol. 1965 Oct 15;93(4):486-90.

Longstaff E, von Krogh G. Condyloma eradication: self-therapy with 0.15-0.5% podophyllotoxin versus 20-25% podophyllin preparations--an integrated safety assessment. Regul Toxicol Pharmacol. 2001 Apr;33(2):117-37.

Ramirez B, Marieb NJ. Hypokalemic metabolic alkalosis due to Carter's little pills. Conn Med. 1970 Mar;34(3):169-70.

RVM 2006: Report produced by the Dutch research institute RIVM; report 32014001

Online:
Codecheck © 2011. Available at: http://www.codecheck.info/ (accessed 29th November 2011).

CosIng, European Commission, Health and Consumers, Cosmetics. Available at: http://ec.europa.eu/consumers/cosmetics/cosing/) (accessed 29th November 2011).

EWG's Skin Deep © Cosmetic Safety Database. Environmental Working group. Available at: http://www.ewg.org/skindeep/ (accessed 29th November 2011).

Wegman:

http://www.wegmans.com/webapp/wcs/stores/servlet/ProductDisplay?langId=-1&storeId=10052&catalogId=10002&productId=722690 (accessed 31 January 2012)
Taiwantrade:
http://www.taiwantrade.com.tw/EP/twskincare/specialoffers-detail/en_US/1828159 (accessed 31 January 2012)
Kalichem:
http://www.kalichem.it/genera_pdf_categ_V_red_en.php (accessed 2 February 2012)
http://www.kalichem.it/allegati/MIX%20OXI%20STOP%20-%20BROCHURE.pdf (accessed 2 February 2012)
Shaanxi stands for the company Shaanxi Sciphar Hi-Tech Industry Co., Ltd.
http://www.alibaba.com/product-gs/323352508/Podophyllotoxin.html (accessed 2 February 2012)
Patsnap.
http://www.patsnap.com/patents/view/JP08113516.html (accessed 2 January 2012)