

RISK PROFILE

Extract and Essential oil of SASSAFRAS OFFICINALE

CAS No. 84787-72-4 (extract)
CAS No. 8006-80-2 (essential oil)

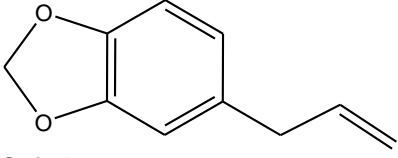
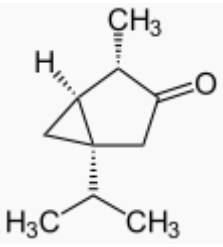
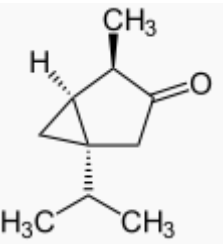
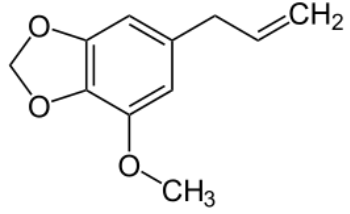
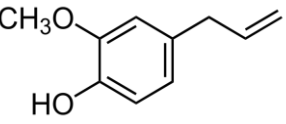
Date of reporting 23.04.2012

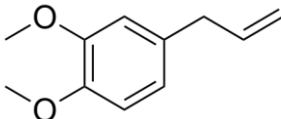
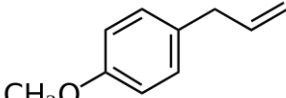
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1. Identification of substance

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| Chemical name (IUPAC): | 5-allyl-1,3-benzodioxole (safrole) is one of the main components of <i>Sassafras officinale</i> essential oil |
| INCI | <i>Sassafras officinale</i> root oil |
| Synonyms | <i>Sassafras officinale</i> , <i>Sassafras albidum</i> |
| CAS No. | <i>Sassafras officinale</i> essential oil: 8006-80-2 <i>Sassafras officinale</i> extract: 84787-72-4 <i>Some contents of Sassafras officinale with potentially harmful effects:</i> Safrole: 94-59-7 Thujone: 546-80-5 (α -thujone), 471-15-8 (β -thujone) Myristicine: 607-91-0 Eugenol: 97-53-0 Methyleugenol: 93-15-2 β -asarone: 5273-86-9 |

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| | Estragole: 140-67-0 |
| EINECS No. | <p><i>Sassafras officinale</i> essential oil: 284-113-2 <i>Sassafras officinale</i> extract: 284-113-2</p> <p><i>Some contents of Sassafras officinale with potentially harmful effects:</i> Safrole: 202-345-4 Thujone: 208-912-2 (α-thujone) Myristicine: 210-146-9 Eugenol: 202-589-1 Methyleugenol: 202-223-0 β-asarone: 226-096-6 Estragole: 205-427-8</p> |
| Molecular formulas | <p>Safrole: $C_{10}H_{10}O_2$ Thujone: $C_{10}H_{16}O$ Myristicine: $C_{11}H_{12}O_3$ Eugenol: $C_{10}H_{12}O_2$ Methyleugenol: $C_{11}H_{14}O_2$ β-asarone: $C_{12}H_{16}O_3$ Estragole: $C_{10}H_{12}O$</p> |
| Chemical structure |  <p>Safrole</p> <div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;">  <p>(+)-α-thujone</p> </div> <div style="text-align: center;">  <p>(-)-β-thujone</p> </div> </div>  <p>Myristicine</p>  <p>Eugenol</p> |

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| |  <p>Methyleugenol</p>  <p>Estragole</p> |
| Molecular weight | <p>Safrole: 162.19 Thujone: 152.23 Myristicine: 192,21 Eugenol: 164.20 Methyleugenol: 178,23 β-asarone: 208.25 Estragole: 148.20</p> |
| Contents (if relevant) | <p>The essential oil contains a number of constituents which have potentially harmful effects; i.a. safrole, cineol, thujone, anethol, myristicine, methyleugenol, β-asarone, estragole. The content of the different constituents varies considerably, depending on time and method of harvesting, soil conditions, climate, etc. The safrole content is reported to range from 75 to 92% (Council of Europe 2008).</p> <p>One source report about the following typical composition of the essential oil obtained from the bark of the root as concerns the named harmful constituents (two different analysis %) (ventakataramna industries¹)</p> <ul style="list-style-type: none"> • Safrol: 85, 90 • methyleugenol: 1.1 , 3 • beta asarone: < 1, 1.8 • eugenol < 1 , traces • estragol < 1, • thujone < 1, traces • myristicin < 1, traces |
| Physiochemical properties | <p>Sassafras oil: Boiling point 236 °C Density 1.09 g/ml at 25 °C (Chemical Book)</p> |

2. Uses and origin

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| Uses | <p>Cosmetic products: Function according to CosIng database: -Skin conditioning and tonic (extract)</p> |
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¹ <http://www.venkatramna-perfumers.com/Products.aspx?Category=Natural%20Essential%20Oils%20&&Title=Sassafras%20Oil>

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| | <p>-Masking (root oil)</p> <p>The essential oil has been used as an aromatic and fragrance material, e.g. for scenting soaps and in aroma treatment (Council of Europe 2008).</p> <p>In total, approximately 10 products were identified at Codecheck.info and EWG's Skin Deep databases. These comprise i.e. the following product categories:</p> <ul style="list-style-type: none"> -Facial cleanser -Moisturizer -Toners/astringents -Mask -Body spray/oil -Muscle/joint soreness <p>Medicinal products:</p> <p>Sassafras leaves, roots and bark have been used medicinally for centuries. Sassafras oil has rubefacient properties and was formerly used to treat lice (pediculicide) (Martindale). It has also been traditionally as a diuretic and as a remedy against urinary tract disorders or kidney problems (Dietz and Bolton, 2007).</p> <p>Food:</p> <p>The extract has been used as an aromatic in American root beer (Council of Europe 2008).</p> <p>Other:</p> <p>Safrole is used as a raw material for the production of some illegal drugs, e.g. ecstasy (MDMA – methylenedioxy-methamphetamine) (Council of Europe 2008).</p> |
| <p>Origin</p> <p>Natural (exo /endo) Synthetic</p> | <p><i>Sassafras officinale</i> essential oil is a volatile oil extracted by steam distillation from the bark and roots of the tree <i>Sassafras officinale</i> (Dietz and Bolton, 2007).</p> |

3. Regulation

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| <p>Norway</p> | <p>Norway has the same regulation as the EU. Safrol is not allowed in any cosmetic products, except in essences, provided the concentration does not exceed 100 ppm in the finished product. Maximum allowed concentration in products for dental and oral hygiene is 50 ppm. Safrole is not allowed in toothpaste for children (FOR 1995-10-26 nr 0871).</p> <p>The herb <i>Sassafras officinale</i> is classified as a drug, prescription only (FOR 1999-12-27 nr 1565).</p> |
| <p>EU</p> | <p>In the EU, the constituent safrole but not the oil has been banned in cosmetics since years. According to the CosIng database (based on Eu Directive 76/768 Annex II N. 360) the maximum allowed concentration of safrole can not exceed 100 ppm in the finished</p> |

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| | <p>cosmetic product, 50 ppm in products for dental and oral hygiene, and can not be present in toothpastes intended specifically for children. Hence, it is not the Sassafras oil per se with all its constituents which are regulated, but the safrole constituent in particular.</p> <p>This regulation implies that an essential oil which contains for example 80% safrole can be present in a cosmetic product on sale in Europe, provided that the concentration is kept below 0.0125% (Council of Europe 2008).</p> <p>Safrole is classified as a carcinogen category 1b and as a mutagen category 2 (European chemical Substances Information System, ESIS).</p> <p>Sassafras oils (as safrole) are controlled under the EU Regulation 3677/90 as amended by Council Regulation 900/92, as a Category 1 substance. This implies that safrole cannot be bought or traded without authorisation from customs. Regulation 3677/90 lays down measures to be taken to monitor trade with substances used for the illicit manufacture of narcotic drugs and psychotropic substances.</p> |
| Rest of the world | <p>FDA banned the use of sassafras oil and safrole in commercially produced foods and drugs in 1976. However, "safrole-free" sassafras extracts are allowed and are used commercially in e.g. herb teas and root beers (FDA 2012, Council of Europe 2008, Wikipedia 2011).</p> <p>Australia has a corresponding requirement for import authorisation of safrole as the EU (Australian Customs 2004).</p> |

4. Relevant toxicity studies

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| Absorption Skin GI tractus | Sassafras oil may be absorbed (to an unknown degree) through the skin (DrugDigest 2011). |
| Distribution | No data available |
| Metabolism | No data available |
| Excretion | No data available |
| Local toxic effects Irritation Sensitivity | No skin sensitization was observed in a small study where safrole was tested in a concentration of 8% in petrolatum (Opdyke, D.L.J. (1979). |
| Systemic toxic effects Acute | <p>The evaluation on toxicity of extracts or essential oils of Sassafras officinale has primarily been focused on safrole. This substance is the main constituent in such preparations and has carcinogenic properties. Some of the other possible harmful substances in Sassafras officinale are also mentioned.</p> <p><u>Acute</u> Clinical poisoning due to sassafras oil has indicated that safrole induces i.a. nausea, vomiting, shock, cyanosis, delirium, circulatory collapse</p> |

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| | <p>vertigo, hallucinations, respiratory depression and probably convulsions. The toxic dose in adult amount is 5 ml (Ford MD 2001).</p> |
| Skin penetration | <p><u>Skin penetration</u> Safrole is assumed to penetrate skin as easily as do the structurally closely related compound methyleugenol: 40 % skin penetration rate (Council of Europe 2008)</p> |
| Repeated dose | <p><u>Repeated dose</u> Council of Europe refer to an WHO Inchem monograph as to this endpoint</p> |
| Mutagenicity /genotoxicity Carcinogenicity | <p><u>Mutagenicity /genotoxicity</u> <u>Carcinogenicity</u></p> <p>In the European chemical Substances Information System (ESIS), safrole is classified as a substance which should be regarded as it is carcinogenic to man (category 1b) and a substance which causes concern for man owing to possible mutagenic effects (category 2).</p> <p>Safrole (and isosafrole) is carcinogenic in mice and rats, producing liver tumours when administered orally. Safrole also produced liver and lung tumours in male infant mice following subcutaneous injection (IPCS INCHEM, 1998). No case reports or epidemiological studies are available with human data. In the INCHEM database safrole is classified as an agent possibly carcinogenic to humans (category 2B).</p> <p>Corresponding information is available from Toxnet, National Library of Medicine in the US. The Human Health Assessment Group in US Environment Protection Agency has evaluated safrole and concluded it is carcinogenic in animals and probably carcinogenic to humans. The TD₅₀ value (standardized measure of carcinogenic potency inducing tumors in half of the test animals) for safrole is 441 and 51.3 mg/kg/day in rats and mice respectively. These figures are reported in the Carcinogenic Potency Database, accessed via Toxnet.</p> <p>According to US Department of Health and Human Services, safrole and methyleugenol are <i>reasonably anticipated to be a human carcinogen</i> (Report on Carcinogens 2012). The TD₅₀ for methyleugenol is 19.7 mg/Kg bw/day in the rat (liver) and 19.3 mg/Kg bw /day in the mouse (liver) whereas the LTD₁₀ for estragole in mouse is 6.38 mg/Kg bw (Carcinogenic Potency Database at Berkley). Studies indicate that the carcinogenic potency of estragole is similar to that of safrole (Council of Europe 2006).</p> <p>Besides also beta asarone is recognized as a carcinogen that even show cardiotoxic effects (Council of Europe 2008, Council of Europe 2006).</p> |
| Reprotoxicity / teratogenicity | <p><u>Reprotoxicity / teratogenicity</u> Council of Europe refer to an WHO Inchem monograph as to this endpoint</p> |
| Other effects | <p><u>Other effects</u></p> |

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| | <p>Hallucinations and abortion have also been reported with safrole, and large doses of the oil may have narcotic effects. Myristicine and thujone have psychotropic and neurotoxic properties (Council of Europe 2008, Council of Europe 2006).</p> <p>Thujone rich essential oils should be avoided during pregnancy. Thujone can cause convulsions when taken by mouth and is suspected of being particularly toxic to the CNS. Relatively low-doses of thujone have been shown to affect nervous tissue. This strongly suggests that it has the ability to cross the blood-brain barrier and to enter the CNS after systemic absorption (Council of Europe 2006).</p> <p>Neither sassafras nor the oil should be ingested and the use of herb teas of sassafras may lead to a large dose of safrole.</p> |
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5. Exposure estimate and critical NOAEL / NOEL

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| NOAEL/NOEL critical | <p>A daily dose of about 10 µg safrole/kg bw has been considered hazardous to humans (Council of Europe 2008).</p> <p>Not possible to estimate a NOEL/NOAEL based on the current existing data.</p> |
| Exposure cosmetic products | Unknown |
| Margin of Safety (MoS) | <p>Not calculated, see above.</p> <p>A rough worst-case calculation using the 100 ppm limit, skin penetration rate of 40% (equal to safrole's closely related molecule methyleugenol) and a TD₅₀ value of 51.3 mg/kg bw gives a theoretical lifetime risk of cancer of about 10⁻⁴. Acceptable risks would be below 10⁻⁵ only (Council of Europe 2008).</p> <p>Studies have shown that even "safrole-free" extracts/oils produce tumours in two-thirds of the animals tested. This indicates that other constituents in the extracts/oils than safrole are responsible for the carcinogenic activity (Council of Europe 2008).</p> |

6. Other sources of exposure than cosmetic products

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| Food stuffs | Herb teas, flavouring of root beers, filé powder. |
| Pharmaceuticals | No data available |
| Other sources | No data available |
| Adverse side effects - from uses other than cosmetics | Neither <i>Sassafras officinale</i> nor the oil should be taken internally, and the use of safrole in food has been banned because of carcinogenic and hepatotoxic risks (Martindale). |

7. Assessment

The evaluation of *Sassafras officinale* (*Sassafras albidum*) has been focused on safrole, as this is the main constituent in the essential oil. Both EU and World Health Organization (IPCS) have classified safrole as a substance which should be regarded as being carcinogenic to man (category 1b and 2B respectively). Further, EU has classified safrole as a substance which causes concern for man owing to possible mutagenic effects (category 2).. The FDA in USA has corresponding evaluations and regulations.

In addition to safrole, *Sassafras officinale* contains several other substances which have potentially harmful effects, e.g. asarone, methyleugenol and estragol. These substances, as safrole, are recognised as (i.a.) being carcinogenic. They may all be considered more potent than safrole in that respect.

As extracts and oils of *Sassafras officinale* contain safrole and other substances with harmful effects, e.g. carcinogenic, mutagenic and neurotoxic, the use of such substances in cosmetic products can not be considered safe.

8. Conclusion

One of the main constituents in *Sassafras officinale* (*Sassafras albidum*), safrole, has been shown to have both a carcinogenic and mutagenic potential. It should therefore be prohibited to use extracts, oils, etc. of the plant *Sassafras officinale* in cosmetics.

Despite "safrole-free" extracts and oils are on the market, these should neither be used as data indicate that such products also may have a carcinogenic potential.

Based on the available data, the ban on using safrole in cosmetic products should be enforced. In addition, the use of *Sassafras officinale* extracts and oils should be prohibited, due to a high content of safrole and other harmful constituents which are incompatible with use in cosmetic products.

9. References

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Opdyke, D.L.J. (ed.). Monographs on Fragrance Raw Materials. New York: Pergamon Press, 1979., p. 669

Report on Carcinogens 12th edition, 2011: US Department of Health and Human Services: Methyleugenol 267-8, Safrole 374-5; <http://ntp.niehs.nih.gov/ntp/roc/twelfth/roc12.pdf> (accessed 27th Jan 2012)

The Carcinogenic Potency Project (CPDB): Safrole; <http://potency.berkeley.edu> (accessed 1st Jul 2011 via Toxnet).

The International Programme on Chemical Safety (IPCS INCHEM): Safrole, 22nd Mar 1998; <http://www.inchem.org/> (accessed 3rd Aug 2011).

US Food and Drug Administration (FDA): *Sassafras*, Safrole; <http://www.fda.gov/> (accessed 3rd Aug 2011).

US National Library of Medicine, Toxnet: Safrole; <http://toxnet.nlm.nih.gov/> (accessed 1st Jul 2011).

Wikipedia: *Sassafras albidum* 27th Jul 2011; http://en.wikipedia.org/wiki/Sassafras_albidum (accessed 8th Aug 2011).

TOXNET: <http://toxnet.nlm.nih.gov/cgi-bin/sis/search/a?dbs+hsdb:@term+@DOCNO+2653>

10. Annexes

None