

## RISK PROFILE

# *Methyl salicylate*

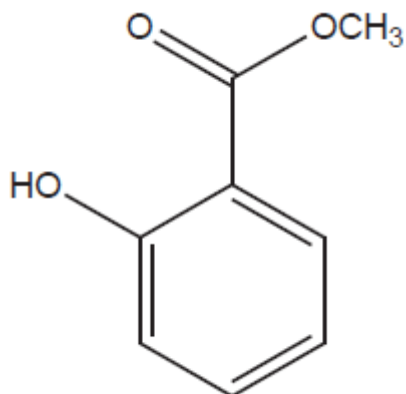
CAS No. 119 -36-8

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### Content of document

1. Identification of substance	p. 1
2. Uses and origin	p. 2
3. Regulation	p. 4
4. Relevant toxicity studies	p. 4
5. Exposure estimates and critical NOAEL/NOEL	p. 9
6. Other sources of exposure than cosmetic products	p. 11
7. Assessment	p. 13
8. Conclusion	p. 14
9. References	p. 15
10. Annexes	p. 18

### 1. Identification of substance

<b>Chemical name (IUPAC):</b>	2-Hydroxy-benzoic acid methyl ester
<b>INCI</b>	Methyl salicylate
<b>Synonyms</b>	Hydroxybenzoic acid, Oil of wintergreen (ca. 98% methyl salicylate)
<b>CAS No.</b>	119-36-8
<b>EINECS No.</b>	204-317-7
<b>Molecular formula</b>	C <sub>8</sub> H <sub>8</sub> O <sub>3</sub>
<b>Chemical structure</b>	
<b>Molecular weight</b>	152.15

Contents (if relevant)	
Physiochemical properties	<p>Appearance: colourless, yellowish or reddish oily liquid; characteristic odour of wintergreen.</p> <p>Boiling point (BP): 220 – 224 °C</p> <p>Melting point (MP): -8.6 °C</p> <p>LogK<sub>ow</sub>: 2.55</p> <p>Solubility: 0.74 g/l at 30°C in water; also soluble in most common organic solvents.</p> <p>VP: The vapor pressure is 0.0343 mmHg at 25°C</p> <p>References: cited in Hansen et al., 2006; IUCLID, 2000)</p>

## 2. Uses and origin

Uses	<p>➤ <b>Cosmetic products:</b></p> <p><i>Functions according to</i></p> <ul style="list-style-type: none"> <li>• CosIng database: <ul style="list-style-type: none"> <li>- Denaturants, Fragrance (Methyl salicylate has the characteristic odor of wintergreen, and is used in perfumery).</li> </ul> </li> <li>• Other: <ul style="list-style-type: none"> <li>- Easing and removing sore muscles and joints caused by increased physical activity level (Hansen et al., 2006).</li> <li>- Flavoring agent</li> </ul> </li> </ul> <p><i>Concentrations of Methyl salicylate being applied</i></p> <p>Methyl salicylate is used in cosmetics as warming-up agent; rubefacient in sport-massage products, at concentrations in the range of <b>3 - 9%</b> in the European (EØS) market. It is used in perfumery as a modifier in blossom fragrance and as a mild antiseptic in oral hygiene products (Gerhartz, 1985, 2000); as a denaturant and flavouring agent at concentrations in the range <b>0.0001% to 0.6%</b> (25 formulations in the FDA voluntary file. CIR, 2003); as a flavouring agent in toothpastes up till <b>1%</b> (Storhagen et al., 2003). The prime purpose of the sports cream/massage products is to alleviate certain discomforts arising occasionally in connection with sports and physical exercises. Although not claimed because this would have placed these products under the medicinal products regulations, they in fact remove aching in the muscles due to anti-inflammatory properties. Saloons providing so-called aroma treatment (aroma-therapy) also use wintergreen oil that contains methyl salicylate up till 98%. Wintergreen oil is an "essential oil"<sup>1</sup>. According to their working codex essential oils are blended with other "base" oils and the concentrations are in the range <b>0.5 - 5%</b>.</p>
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<sup>1</sup> 'Essential' is usually understood as something completely necessary or part of the basic nature of something; e.g. is needed for life or health but not synthesized within the body, as an amino acid or vitamin that must be consumed. Essential also means containing, or having the properties of, a concentrated extract of a plant, drug, food, etc.: an essential oil.

#### *Frequency of use*

The EWG Skin Deep [online] database lists 87 cosmetic products containing methyl salicylate:

- pain relief (27 products)
- mouthwash (20 products)
- muscle/ joint soreness (17 products)
- wound treatment (7 products)
- anti-itch/ rash cream (7 products)

The German Codecheck.info [online] database lists 724 products containing Methyl salicylate.

#### ➤ **Food**

*Flavouring agent.* Methyl salicylate (MS) is used as a flavouring agent in chewing gum, baked goods, syrups, candy, non-alcoholic beverages and ice cream. Besides the compound occur naturally in a series of vegetables and edible berries. According to JECFA the 95th percentile 14-day average daily intake amounts to 0.09 mg/kg bw (JECFA, 2002; Hall et al, 1999). In the age group 2 - 5 years the estimate was 0.15 mg/kg bw. These were not worst-case intake estimates.

JECFA has established an Acceptable Daily Intake (ADI) of 0.5 mg/kg body weight.

Methyl salicylate has FDA-specified uses as indirect food additive (CIR, 2003).

*The Council of Europe publications "Plants in Cosmetics Volume III" (2006) and "Active ingredients in cosmetics: safety survey" (2008) present more details.*

#### ➤ **Medicinal products**

Methyl salicylate has anti-inflammatory properties and is still used, incorporated into liniments and ointments for joint and muscle pains and for rheumatic conditions, but apart from this no plant extract with salicylate is now available in western pharmacies. The French BIAM database that shows an overview as to pharmaceutical products, lists 12 different methyl salicylate containing topical products meant to help with muscle pain and that contain **from 3% to 18% MS**.

In the USA methyl salicylate has been present in OTC smoking deterrent drugs, boil treatment, dandruff/ seborrhoea dermatitis/psoriasis, fever blister and cold sore treatment, oral health care and skin protectant-astringent drug products. However, currently FDA has concluded that there are inadequate data to establish general recognition of the safety and effectiveness of these ingredients for the specified OTC uses.

*Labelling:* Any drug containing > 5% MS must bear a label that warns that misdirected use may be dangerous and that the product should be kept out of reach of children (CIR, 2003).

A FDA Advisory Review Panel (OTC products) has concluded that

	<p>methyl salicylate is safe for use up to a concentration of 0.4% in the form of a mouthwash (US EPA, 1997 referring to an assessment made by the FDA OTC panel 25 May 1982). Medicinal product or cosmetics?</p> <p>➤ <b>Other products</b></p>
<p><b>Origin</b> Natural (exo /endo) Synthetic</p>	<p><u>Sources of natural origin:</u> Information is presented in the monograph on methyl salicylate in the Council of Europe publications "<i>Plants in Cosmetics Volume III</i>" (2006) and "<i>Active ingredients in cosmetics: safety survey</i>" (2008).</p> <p><u>Sources of synthetic origin:</u> Structurally, methyl salicylate is the methyl ester of salicylic acid, produced e.g. from the condensation reaction of salicylic acid and methanol.</p> <p>1 ml of oil of wintergreen is equivalent to 1400 mg aspirin; i.e. one teaspoon (5 ml) contains the equivalent of approx. 7000 mg of aspirin. A routine adult aspirin tablet contains 325 mg aspirin.</p>

### 3. Regulation

<b>Norway</b>	Maximum allowed levels: skin cream (1%); mouth wash (0.05%). Regulation to be lifted 11 July 2013
<b>EU</b>	No regulation
<b>Rest of the world</b>	Japanese regulation of methyl salicylate with a maximum limit of 0.1% in any cosmetics <sup>2</sup>

### 4. Relevant toxicity studies

<p><b>Absorption</b> Skin GI tractus</p>	<p>Human data from experiments conducted with methyl salicylate, indicate that the <i>dermal</i> bioavailability is in the range of <b>11.8 – 30.7%</b>. For the assessment of potential oral exposure to salicylates, bioavailability is assumed to be 100% (Belsito et al., 2007).</p> <p><i>Below is a shortened version of relevant toxicity studies contained within monograph of methyl salicylate reported in the Council of Europe publications "<i>Plants in Cosmetics Volume III</i> (2006)" and "<i>Active ingredients in cosmetics: safety survey</i>" (2008).</i></p> <p><u>Absorption (Skin penetration abilities):</u> The use of methyl salicylate as a topical medical product is subject to a</p>
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<sup>2</sup> In Japan, methyl salicylate which conforms to the standards of the Japanese Standards of Cosmetic Ingredients (JSCI) has precedent for use at a maximum concentration of 0.1% in all Comprehensive Licensing Standards of Cosmetics (CLS) categories - except eyeliner preparations, in which it is not used. Methyl (and Ethylhexyl) salicylates are restricted in that the total percentage of UV absorbers in a formulation shall not exceed 10%.

	<p>series of studies showing that the substance has a pronounced ability to penetrate the skin upon dermal administration (Cross et al., 1997; Megwa et al., 1995; Morra et al., 1996; Yano, 1991; Pratzel et al., 1990; Pratzel, 1987; Danon et al., 1986).</p> <p>Part 2: <i>Humans:</i> Morra et al. (1996) carried out a study involving 12 healthy volunteers, ages 21-44 years, who applied 5 g of an ointment containing 12.5% methyl salicylate twice daily for 4 days. The recovery in the urine in the first 24 h after application was 15.5%. When being used in sports massage creams methyl salicylate is often applied together with a vehicle like for example menthol or camphor - which enhances its skin penetration ability (Yano et al., 1991). In humans approximately <b>12 to 20%</b> of topically applied methyl salicylate is systemically absorbed within 10 hours of application (EMEA, 1999). CIR (2003) points out that the available data describe the following percutaneous absorption patterns: rate of penetration is proportional to concentration applied; absorption is dependent on the vehicle (e.g., ethanol &gt; water); absorption varies as a function of pH; and absorption is greater through damaged skin compared to normal skin.</p> <p>An in vivo study indicated that l-menthol and dl-camphor enhances the skin penetration of methyl salicylate and slows down the hydrolysis of it markedly (Yano et al., 1991).</p> <p>Aqueous chlorhexidine (Aq-C, 0.1% w/v) and alcoholic chlorhexidine (Al-C, 0.5% w/v) have in Thoroughbred geldings shown to increase the penetration of methyl salicylate and its analyte, salicylate. Compared with control skin, significantly more methyl salicylate penetrated through skin prepared with Al-C or Aq-C, and significantly more salicylate was recovered in the receptor phase from skin prepared with Aq-C and Al-C (Mills et Cross, 2006).</p>
<b>Distribution</b>	<p>After absorption, salicylate is distributed throughout most body tissues and most transcellular fluids, primarily by pH dependent passive processes. Salicylate is actively transported by a low-capacity, saturable system out of the CSF (cerebrospinal fluid?) across the choroid plexus. The salicylate readily crosses the placental barrier. The plasma half-life for salicylate is 2 to 3h in low doses and about 12h at usual anti-inflammatory doses. The half-life of salicylate may be as long as 15 to 30 h at high therapeutic doses or when there is intoxication (Gilman et al., 1990).</p>
<b>Metabolism</b>	<p>Orally administered methyl salicylate is nearly completely hydrolysed to salicylic acid/salicylate within 1 hour in rats and dogs. Salicylate levels in plasma and brain reached about the same level as the one obtained when administering salicylic acid. In 6 healthy adults 21% of the intact ester was found in plasma 90 min after oral exposure (Davidson C et al., 1961).</p> <p>For small doses 80% of the hepatic metabolism results from conjugation with glycine to form salicyluric acid and with glucuronic acid to form salicyl acyl and phenolic glucuronide. The two parallel pathways (glycine, glucuronide conjugation) have limited capacity and saturate easily above therapeutic doses (Ellenhorn et al., 1988).</p> <p>The biotransformation of salicylates takes place in many tissues, but particularly in the hepatic endoplasmic reticulum and mitochondria. The</p>

	<p>three main metabolic products are salicylic acid (the glycine conjugate), the ether or phenolic glucuronide, and the ester or acyl glucuronide. In addition, a small fraction is oxidized to gentisic acid (2,5-dihydroxybenzoic acid) and to 2,3-dihydroxybenzoic and 2,3,5-trihydroxybenzoic acids; gentisuric acid, the glycine conjugate of gentisic acid, is also formed (Gilman et al., 1990).</p> <p>Methyl salicylate was extensively metabolised to salicylic acid in the dermal and sc tissues after topical application (Cross et al., 1997; Pratzel, 1987).</p>
<b>Excretion</b>	<p>Salicylates are excreted in the urine as free salicylic acid (10%), salicylic acid (75%), salicylic phenolic (10%) and acyl (5%) glucuronides, and gentisic acid (less than 1%). However, excretion of free salicylate is extremely variable and depends upon both the dose and the urinary pH. In alkaline urine, more than 30% of the ingested drug may be eliminated as free salicylate, whereas in acidic urine this may be as low as 2% (Gilman, 1990).</p>
<b>Local toxic effects</b> Irritation Sensitivity	<p><b>Skin irritation:</b> Methyl salicylate has skin-irritating properties of the primary irritation type (Arts et al., 1997). When applied at a concentration as low as 1% (vehicle being 70% ethanol + emollient), it is a moderate irritant and may elicit necrosis and intradermal and subcutaneous haemorrhage. When in propylene glycol methyl salicylate produced no or little irritation up to 6% (Yankell, 1972). When applied in a closed patch test at a concentration of 8% in petrolatum, it has been found to be non-irritant at 48 hours. (Opdyke, 1978). Application of sweet birch oil - that consists almost wholly of methyl salicylate – undiluted to the skin of rabbits, mice and pig show methyl salicylate to be an irritant. However, at a concentration of 4% in petrolatum it was proven to be non-irritant when applied to human skin (Opdyke, 1979). In 20 patients with eczema or contact dermatitis, methyl salicylate at 67% is reported to cause irritation in 8 subjects; at 40%, 2 subjects; and at 38%, 15% and 3.75%, no irritation in any subject (ref in CIR, 2003).</p> <p><b>Mucous membranes irritation:</b> Severe irritant to guinea pig skin and eyes (Opdyke, 1978).</p> <p><b>Skin sensitivity:</b></p> <p><i>Animals:</i> Murine local lymph node assay of methyl salicylate at higher concentrations (&gt; or = 50%) show a dose-response relationship and clearly positive results (Montelius et al., 1998).</p> <p><i>Humans:</i> No sensitisation could be demonstrated in 25 volunteers subjected to a maximisation test with 4% sweet birch oil in petrolatum (Opdyke, 1979). Patch tests with 2% methyl salicylate produced 3 positive reactions in 183 eczema patients (Rudner, 1977).</p>
<b>Systemic toxic effects</b> Acute	<p><b>Acute toxicity:</b> Salicylates uncouple oxidative phosphorylation (ref. in for example Beynen et al., 1982) and as regards methyl salicylate there is evidence of high acute toxicity in man – but only moderate acute toxicity in most experimental animals.</p>

Repeated dose	<p>K: LD50 values (mg/kg bw): Rat (oral): 887; rabbit (oral): 2 800; guinea pig (oral): 1 060; dog (oral): 2 100; guinea pig (dermal): 700 (Clayton et Clayton, 1981). According to the IUCLID database, <u>oral</u> toxicity is 880 to 2100 mg/kg for various types of animals. For <u>dermal</u> toxicity, LD50 is from 700 to more than 5000 mg/kg (IUCLID, 2000; Hansen et al., 2006).</p> <p><i>Humans:</i> LD50 values in mg/kg bw: Man; adult (oral): 500; child (oral) 170 (LD<sub>low</sub>) (Clayton et Clayton, 1981). Probable oral lethal dose in human: 50 – 500 (Gosselin et al., 1984). The average lethal dose of methyl salicylate for children is 10 ml (Clayton et al., 1981). As little as 4 ml (4 700 mg) taken orally may be fatal (Gilman et al., 1990).</p> <p><i>Short term toxicity:</i> <i>Animals:</i> Rat feeding studies (10-12 weeks) showed development of increased bone density. The no effect level (NOAEL) was high; 450 mg/kg bw (Harrison et al., 1963). In a sub-acute 13-day toxicity study in rats, methyl salicylate induced alterations of microbodies in hepatocytes at dietary level of approximately 50 mg/kg bw (EMEA, 1999).  A 6-month feeding study involving beagle dogs revealed a no effect level (NOEL) of 170mg/kg bw/day, pertaining to the influence on liver and kidney weight (Abbott et Harrison, 1978).  When methyl salicylate was administered topically to rabbits for 90 days (0.5, 1, 2 and 4ml/kg bw/day), early deaths and kidney damage were observed at all doses tested. As only summary information was available no NOAEL could be established (EMEA, 1999). Conversion ml to (mg/kg bw).<sup>3</sup></p> <p><u>NOAEL</u> A NOAEL 50mg/kg bw has been established on the basis of long-term studies only. Considering the safety of methyl salicylate in food (oral intake), JECFA made use of the NOAEL 50 mg/kg bw observed by Webb et Hansen (1963) and a conventional safety factor of 100 which implies an acceptable daily intake (ADI) of 0.50 mg/kg bw. Already in 1967 JECFA set this ADI value. It was not changed when JECFA evaluated the safety of use in the year 2002.</p> <p><i>Mutagenicity/genotoxicity:</i> <i>In vitro tests :</i> Methyl salicylate tested negative in the Salmonella/microsome preincubation assay, when using the standard protocol approved by the National Toxicology Program (NTP) (Mortelmans et al., 1986). Also other authors reported negative reverse mutation tests (Ames) – confer overview given by JECFA (2002) they referring to tests performed by Ishidate et al., (1984) and Kawachi et al., (1980). However, another Ames test study demonstrated mutagenicity when applying the TA98 strain upon addition of hamster S-9 mixture. Weak mutagenicity was also found using the TA100 strain with hamster S-9 mixture for methyl salicylate (Kuboyama et Fujii, 1992 – a study not mentioned in the JECFA overview).</p> <p><i>In vivo tests are not available – and apparently have not been performed</i></p>
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<sup>3</sup> Conversion: 4 ml methyl salicylate equals 4 700 mg

<p>Mutagenicity /genotoxicity</p>	<p>(JECFA, 2002).</p> <p>EMEA concluded that salicylic acid and methyl salicylate can be considered not to possess genotoxic properties (EMEA, 1999).</p> <p>No studies have been performed with the primary purpose of determining the carcinogenicity of methyl salicylate. Chronic exposure studies with two-year exposure durations that included extensive pathology did not indicate any dose dependent increases in incidences of benign or malignant tumors.</p>
<p>Carcinogenicity</p>	<p>Also corroborating the view that methyl salicylate is devoid of carcinogenic properties is the finding that acetyl salicylic acid apparently does not possess such a property. Carcinogenicity studies have been performed to assess the carcinogenic potential of acetyl salicylic acid in mice at 1 and 5% and in rats at 0.25% and 2% in drinking water. The results were negative in both studies. Considering these results, salicylic acid, a metabolite of acetyl salicylic acid (and of methyl salicylate), was considered to be devoid of such a potential (SCCNFP, 2002).</p>
<p>Reprotoxicity / teratogenicity</p>	<p><i>Animals:</i> Drug-induced renal abnormality is apparent in offspring of rats exposed to methyl salicylate on days 10 and 11 of gestation. It also caused retarded renal development in fetuses (Gibson, 1976). Methyl salicylate was administered topically to pregnant hamsters (days 7 – 9) and the teratogenic results were compared with those obtained following oral treatment with the same compound. A daily dose of 1 750mg/kg bw was applied in both the dermal (dose on the skin) and oral study. Both treatments produced the same defect in embryos recovered at day 9: failure of fusion of the neural tube, especially in the area of the developing brain. Analysis of serum salicylate levels following both treatments produced similar curves and indicated that teratogenic levels of salicylate can reach the maternal circulation after topical exposure (Overman, 1983).</p> <p>In two 3-generation studies in rats at 25, 50, 150 and 250 mg/kg bw no adverse effects were observed at 50 mg/kg bw (NOAEL). Salicylate, but not its metabolites, was found to be primarily or solely responsible for the teratogenic effects in rats (EMEA, 1999).</p> <p>Methyl salicylate is teratogenic in animals and can be absorbed in toxic quantities by the dermal route. Consequently, the dermal absorption and teratogenic potential of a petroleum-based grease (PBG) manufactured using methyl salicylate (3%) was assessed. The test material (petroleum based grease/methyl salicylate) was dermally applied at doses of either 0, 1, 3, or 6 g/kg/day to groups of pregnant rats on gestational days 6-15. The maternal and developmental No-Observable-Adverse-Effect-Level for petroleum based grease/methyl salicylate was greater than 6 g/kg/day (Infurna R et al, Teratology 41 (5): 566, 1990, cited in Hansen et al., 2006).</p> <p><i>Humans:</i> There is no evidence that moderate therapeutic doses of salicylates cause foetal damage in human beings; however, babies born to women who ingest salicylates for long periods may have significantly reduced weights at birth. In addition, there is an increase in perinatal mortality, anemia, antepartum and postpartum haemorrhage, prolonged gestation, and complicated deliveries (Gilman et al., 1990).</p>
<p>Other effects</p>	



	<p><i>Other toxicity:</i> Human dermal toxicity according to the case literature: severe urticaria and angioedema with methyl salicylate exposure (ref in CIR, 2003).</p> <p><i>Phototoxic effects:</i> The phototoxic properties of methyl salicylate seem not to have been investigated. One should observe, however, that the UV absorption maximum of a methanol solution of methyl salicylate is 305nm, which indicates that methyl salicylate can undergo direct photolysis. One photolysis study was performed which yielded a half-life of methyl salicylate in solution of about 48min (Kondo, 1978). The degradation products may possibly be harmful to skin causing irritation and or other toxic effects. <i>CIR (2003) concluded that salicylic acid is not a photo sensitizer, nor is it phototoxic.</i></p> <p>SCCNFP (2002), on the other hand, states that no information is available concerning the phototoxicity or photo allergenic potential of salicylic acid in animals.</p> <p><i>Interactions:</i> Methyl salicylate, like other salicylates, interferes with vitamin K metabolism thereby decreasing the blood clotting ability.</p>
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## 5. Exposure estimate and critical NOAEL / NOEL

<b>NOAEL/NOEL critical</b>	For risk assessment of methyl salicylate in cosmetic products, we have used the NOAEL value of <b>50 mg/kg bw/day</b> for salicylates identified in sub-chronic and chronic toxicity studies (Belsito et al., 2007) <sup>4</sup> . Cf. also Cosmetic Ingredient review of various salicylates, including methyl salicylate (CIR, 2003).
<b>Exposure cosmetic products</b>	<p>Although a global exposure scenario cannot be performed because of lack of data, among cosmetic products giving rise to highest systemic exposure of methyl salicylate are probably sport massage products (see e.g. Hansen et al., 2006).</p> <ul style="list-style-type: none"> <li>• <b>Sport massage products</b> (lower limbs)</li> </ul> <p><i>Alt 1:</i> (according to Council of Europe, 2008) <u>Premises:</u> Skin surface treated - legs: 3240 cm<sup>2</sup> (18% of total body area; use the "rule of 9" principle – see "References"). Amount of product per area (cm<sup>2</sup>): 1.0 (default; SCCNFP guidelines) Concentration of methyl salicylate in product: 9.0%<sup>5</sup> Skin penetration rate: 20% (worst case scenario).<sup>6</sup> Body weight: 60 kg (default female; SCCNFP guidelines)</p> <p>SED (single use): 3240 x 1 x 0.09 x 0.20 /60 = <b>0.97 mg /kg bw/day</b>. SED (corrected; footnote 5) = <b>1.5 mg/kg bw/day</b></p> <p><i>Alt 2:</i> <u>Premises:</u></p>

<sup>4</sup> The RIFM Expert Panel, 2007.

<sup>5</sup> Letter from Norwegian Medicines Agency to distributor of a cosmetic product containing 9% methyl salicylate, which exceeds the current limit of 1% set by SNT/MT as the maximum safe level of this ingredient (SLV, 2000).

<sup>6</sup> Human data indicate dermal bioavailability of methyl salicylate in the range of 12 – 30.7% (Belsito et al., 2007).

	<p>The exposure scenarios are from Hansen et al. (2006). The maximum content of methyl salicylate was 76 mg per gram product (i.e. 7.6%).</p> <ul style="list-style-type: none"> <li>- Concentration of methyl salicylate in product: 7.6% (illustrative example; Hansen et al., 2006) = 0.076</li> <li>- Calculated relative daily exposure of product: <math>123.20 \times 0.20 = 24.64</math> mg/kg bw/day<sup>7</sup></li> <li>- Dermal absorption: 31% = 0.31 (worst case, experimental data).</li> </ul> <p>SED = A (mg/kg bw/day) x C(%) / 100 x Dap (%) / 100  = 24.64 mg/kg bw/day x 0.076 x 0.31 = <b>0.5 mg/kg bw/day</b></p> <p><b>SED (corrected): 0.5 * 3.2 = 1.6 mg/kg bw/day</b></p> <ul style="list-style-type: none"> <li>• <b>Mouthwash</b></li> </ul> <p>0.2% methyl salicylate (mouth wash) as illustrative example - maximum amount used according to FDA (CIR, 2003).</p> <p>Calculated relative daily exposure of product: 32.54 mg/kg bw/day  Concentration of ingredient in product: 0.2% = 0.002  Dermal absorption (SCCS default value): 100% = 1</p> <p>SED = A (mg/kg bw/day) x C(%) / 100 x Dap (%) / 100  = 32.54 mg/kg bw/day x 0.002 x 1 = <b>0.07 mg/kg bw/day</b></p> <ul style="list-style-type: none"> <li>• <b>Face cream</b></li> </ul> <p>2.0% methyl salicylate (face cream) as illustrative example  Calculated relative daily exposure of product: 24.14 mg/kg bw/day  Concentration of ingredient in product: 2.0% = 0.02  Dermal absorption (experimental value): 31% = 0.31 (worst case)</p> <p>SED = A (mg/kg bw/day) x C(%) / 100 x Dap (%) / 100  = 24.14 mg/kg bw/day x 0.02 x 0.31 = <b>0.15 mg/kg bw/day</b></p> <ul style="list-style-type: none"> <li>• <b>Hand cream</b></li> </ul> <p>2.0% methyl salicylate (hand cream) as illustrative example  Calculated relative daily exposure of product: 32.70 mg/kg bw/day  Concentration of ingredient in product: 2.0% = 0.02  Dermal absorption (SCCS default value): 100% = 1</p> <p>SED = A (mg/kg bw/day) x C(%) / 100 x Dap (%) / 100  = 32.70 mg/kg bw/day x 0.02 x 0.31 = <b>0.20 mg/kg bw/day</b></p> <p>Total systemic exposure (cosmetics): overall use of sport massage products + mouthwash + face cream + hand cream:</p>
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<sup>7</sup> Application of sport massage product was estimated to be 7.82 g daily for total body area (- face) (SCCS, 2010). The ratio of area two legs (3240 cm<sup>2</sup>) / total body lotion area (15670 cm<sup>2</sup>): 0.20. Theoretically this amounts to daily application of 7.82 \* 0.20 = 1.564 g sports cream. Because experimental data determined that 5 g cream was applied per day (Hansen et al., 2006), as opposed to 1.564 g according to SCCS default value, the estimated exposure is multiplied with a correction factor of 3.2 (5/1.564). Alt1: amount of applied product: 1 mg/cm<sup>2</sup> \* 3240 cm<sup>2</sup> = 3200 mg = 3.2 g. Assuming that 5g sport massage cream is applied, the correction factor is 5/3.2 = 1.5; SED (corrected) = 0.97 \* 1.5 = 1.5 mg/kg bw/day.

	SED (total) $1.60 + 0.07 + 0.15 + 0.20 = 2.02 \text{ mg /kg bw/day}$
<b>Margin of Safety (MoS)</b>	<p>MoS (NOAEL / SED):</p> <p><b>MoS for sport massage cream (limbs):</b>  SED = 1.6 mg/kg bw/day  MoS = <math>50/1.6 = 31.25</math></p> <p><b>MoS for mouthwash:</b>  SED = 0.07 mg/kg bw/day  MoS = <math>50 / 0.07 = 714</math></p> <p><b>MoS for face cream:</b>  SED = 0.15 mg/kg bw/day  MoS = <math>50 / 0.15 = 333</math></p> <p><b>MoS for hand cream:</b>  SED = 0.20 mg/kg bw/day  MoS = <math>50 / 0.20 = 250</math></p> <p><b>MoS for overall use of cosmetics:</b>  SED = 2.02 mg/kg bw/day  MoS = <math>50 / 2.02 = 25.0</math></p>

## 6. Other sources of exposure than cosmetic products

<b>Food stuffs</b>	<p>The (oral) dietary intake of methyl salicylate as a flavouring ingredient amounts to 0.09mg/kg bw/day (95<sup>th</sup> percentile; average over a period of 14 days), see Council of Europe reports (2006 and 2008).</p> <p>A NOAEL of 0.1% methyl salicylate in the diet, equivalent to 50 mg/kg bw/day, has been identified (Tobacco information [online]). JECFA used the NOAEL 50 mg/kg bw observed by Webb et Hansen (1963) and a conventional safety factor of 100 to establish an acceptable daily intake (ADI) of 0.50 mg/kg bw/day.</p>
<b>Pharmaceuticals</b>	<p>The Procter and Gamble Company (1999a) developed a risk assessment of facial cosmetic products containing <math>\leq 2\%</math> Salicylic Acid using oral studies on acetyl salicylic acid ASA (aspirin).</p> <p>Using the premise that oral intake of a low-dose regimen (81 mg) “baby” aspirin by a 58-kg female would result in an exposure of <math>\sim 1.4</math> mg/kg/day and that this exposure level is not considered to present any reproductive or developmental toxicity risk, the CIR Expert Panel considered that a representative exposure to a <i>cosmetic product containing Salicylic Acid</i> could result in exposure to <math>\sim 0.4 - 0.5</math> mg/kg/day and would not present a risk of developmental or reproductive toxicity (CIR, 2003).</p>
<b>Other sources</b>	
<b>Adverse side effects - from uses other than cosmetics</b>	<p>Prominent features of poisoning by methyl salicylate similar to those described for aspirin (acetylsalicylate): central excitation, intense hyperpnea, and hyperpyrexia (Gilman et al., 1990).</p> <p>Generally, ingestion of salicylates at doses larger than 150mg/kg bw can produce toxic symptoms such as tinnitus, nausea, and vomiting. Salicylates have been linked with Reye’s syndrome in children and can cause retention of salt and water as well as acute reduction of renal function in-patients with congestive heart failure or hypovolemia (Gilman et al., 1990).</p>

	<p>Serious toxicity in humans at doses greater than 400 mg/kg bw, with severe vomiting, hyperventilation, hyperthermia, confusion, coma, convulsions, hyper- or hypoglycemia, and acid-base disturbances e.g. respiratory alkalosis or metabolic acidosis (Amdur et al., 1991).</p> <p>One death incident has been related to excessive use of a sports cream containing high amounts of methyl salicylate<sup>8</sup>. Associated Press reported June 13, 2007, that a 17 years old girl from New York died because of an overdose of methyl salicylate caused by long term use of sport cream "BenGay" produced by Johnson &amp; Johnson. The cause of the death was established by health authorities in New York.</p>
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<sup>8</sup> <http://www.msnbc.msn.com/id/19208195>  
<http://voices.yahoo.com/death-bengay-toxic-dose-muscle-treatment-kills-401068.html?cat=70>

## 7. Assessment

As stated in the monograph of methyl salicylate in the Council of Europe publication "Plants in Cosmetics Volume III (2006)": "Taking into account data on hepatotoxicity, the toxic effect on reproduction, the ability to cause severe malformation in the unborn, the ability to irritate skin and mucous membranes and the skin penetration, the concentration of methyl salicylate should not exceed 2% in finished cosmetic products. Due to irritation potential when combined with ethanol the maximum authorized concentration in products high in that vehicle should not exceed 0.4%. Methyl salicylate should be forbidden in products near the eyes. Further data on mutagenicity (in vivo) and photo toxicity should be provided".

### *General toxicity:*

In the period after publication of the two Council of Europe monographs on methyl salicylate (2006, 2008), no further evidence for mutagenic or carcinogenic effects of the ingredient has been found. In the present updated report, the Council of Europe monographs have been extended by estimating MoS of methyl salicylate in cosmetics (see below).

### *Cosmetics:*

#### Systemic:

Among cosmetic products, sport massage products contribute most to the systemic exposure dose (SED) of methyl salicylate. The following premises were used to estimate SED: sports massage cream containing maximum 7.6% (Hansen et al., 2006) or 9% methyl salicylate (worst case), dermal bioavailability of 20% (Council of Europe reports, 2006, 2008) or 31% (present risk profile), and application of 5g sport massage product to both legs (corresponding to an area of 3240 cm<sup>2</sup>). A NOAEL value of 50 mg/kg bw/day is based on oral intake of methyl salicylate (CIR, 2003; Belsito et al, 2007). Critical effect: kidneys

Thus, the estimated margin of safety (MOS) for sports massage creams and other products types (illustrative concentrations of ingredient)<sup>9</sup> amounts to:

**MoS (sport massage cream):** SED = 1.6 mg/kg bw/day; MoS = 50/1.6 = **31.25**

**MoS (mouthwash):** SED = 0.07 mg/kg bw/day; MoS = 50 / 0.07 = **714**

**MoS (face cream):** SED = 0.15 mg/kg bw/day; MoS = 50 / 0.15 = **333**

**MoS (hand cream):** SED = 0.20 mg/kg bw/day; MoS = 50 / 0.20 = **250**

**MoS (overall use of cosmetics):** SED = 2.02 mg/kg bw/day; MoS = 50 / 2.02 = **25.0**

#### Local:

MoS is not used for describing sensitizing effects as these effects do not have a lower concentration limit. Methyl salicylate has skin-irritating properties at concentrations greater than 50% (CIR, 2003). When applied at a concentration as low as 1% with a 70% ethanol + emollient) it is a moderate irritant, but produces little or no irritation at methyl salicylate concentrations up to 6%.

#### *Food:*

The average daily intake of methyl salicylate as a flavouring substance amounts to 0.09 mg/kg bw/day, whereas safe long-term use in food is established by an ADI of 0.5 mg/kg bw/day.

#### *Medicinal products:*

- Pharmacological effects (pain relief; analgesic) of methyl salicylate have been reported at concentrations in the range of 15-20 mg/kg bw/day. However, the exposure of this ingredient from drugs is generally short-term, and smaller than expected from cosmetics and dietary products.

#### *Total exposure:*

The systemic dose resulting from the usage of methyl salicylate in cosmetics come on top of the daily "background" dose due to dietary intake (0.5 + 0.09 = approx. 0.6 mg/kg bw/day), i.e. 30% (0.6/2) of the total exposure from cosmetics.

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<sup>9</sup> Fragrances: at concentrations of salicylates typically used in fragrances (perfume), MoS = 125 - 2500000, based on an oral NOAEL of 50 mg/kg/day (The RIFM Expert Panel, 2007). Thus, all use of methyl salicylate in fragrances is considered safe. Typical use levels of fragrances: 0.5% .

## 8. Conclusion

Maximum use levels of methyl salicylate according to current regulations/practice: Norway: maximum 1%; other EU (EØS) countries: 3 – 9%.<sup>10</sup> In Norway, methyl salicylate is allowed only in specified cosmetic product categories at the following maximum concentrations:

Skin creams: 1%  
Mouth water: 0.05%

In the present updated risk profile, the following maximum usage limits (%) were calculated for methyl salicylate, corresponding to an acceptable margin of safety (MoS) of 100 (based on animal data):

- Sport massage products:  $(7.6\% \times 31.25) / 100 = 2.4\%$  <sup>11</sup>
- Mouth wash:  $(0.2\% \times 714) / 100 = 1.5\%$
- Face cream:  $(2\% \times 333) / 100 = 6.7\%$
- Hand cream:  $(2\% \times 250) / 100 = 5.0\%$
- Overall exposure to methyl salicylate from cosmetics:  $(7.6\% \times 25) / 100 = 1.9\%$  <sup>12</sup>

Other product categories (e.g. body lotion) not assessed.

Thus, the following upper use levels are recommended for methyl salicylate, when only exposure from cosmetic products is considered:<sup>13</sup>

**Sport massage products, face cream and hand cream – 2%**  
**Mouth water – 0.2%**  
**Not allowed in products near the eyes**

### Remarks:

Due to irritation potential when combined with ethanol, the maximum allowed concentration of methyl salicylate in products high (70%?) in ethanol should not exceed 0.4%.

Interactions: Patients must be aware of the potential hazard of using topical methyl salicylate in combination with warfarin.

<sup>10</sup> **N:** Authorised up to 0.05% in oral care products and up to 1% in skin creams (methyl salicylate as such).

**CH:** Max. 3.0% of essential oils and its main ingredient in products which remain on the skin.

**S:** Sport-massage products – only acceptable claims are warming or cooling.

Although there is no maximal concentration set up of how much methyl salicylate cosmetic and hygienic products can contain in Sweden, a content of 8% methyl salicylate is with margin far too much compared with well-established practice.

**A:** Maximum 0.5% as fragrance

**D:** Recommendation: maximum 1% in leave on products; max. 2.5% in rinse off products.

<sup>11</sup>  $C2 (\%) [SED2] = (C1 (\%) [SED1] \times MoS1) / MoS2$

<sup>12</sup> With the premise that the cosmetic product contains 7.6% methyl salicylate; i.e. the maximum amount of the ingredient found by Hansen et al (2006) in a Danish survey of sports cream products.

<sup>13</sup> The recommendation is largely in agreement with a previous risk assessment of salicylic acid by SCCNFP concluding that: "The SCCNFP considers that salicylic acid is safe for "other uses" than as a preservative, at a concentration up to 2.0 % for the leave-on and rinse-off cosmetic products ..." (REF: SCCNFP opinion 4 June 2001), and two previous monographs on methyl salicylate published by the Council of Europe (September 2006, March 2008): ISBN-19: 92-871-5912-2 and ISBN 978-92-871-6298-4.

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## 10. Annexes

### Annex 1: Examples of uses for methyl salicylate in cosmetic products

Product Name	Distributor /Manufacturer	Markets –retail trade	Cosmetic category (intended use)	References /internet links

(Tabell i Annex 1: fyll inn)

### Annex 2: Ingredient usage as a function of product type (taken from CIR, 2003)

TABLE 3  
Ingredient usage as a function of product type (*Continued*)

Product type (Total number reported to FDA 1998)	Number of formulations with the ingredient (FDA 1998)	Concentration of use (CTFA 2000) (%)
<b>Methyl Salicylate</b>		
Dentifrices (38)	4	0.03
Mouthwashes and breath fresheners (49)	10	0.08–0.2
Other oral hygiene products (6)	—	0.2
Bath soaps and detergents (385)	—	0.0001
Bath oils, tablets, and salts (124)	1	—
Body and hand preparations (excluding shaving) (796)	1	0.05
Skin cleansing (653)	1	—
Douches (5)	2	—
Foot powders and sprays (35)	—	0.02
Hair conditioners (636)	1	—
Shampoos (noncoloring) (860)	1	—
Tonics, dressings, and other hair-grooming aids (549)	1	—
Paste masks (mud packs) (255)	1	0.6
Skin fresheners (184)	1	0.1
Other skin care preparations (692)	1	0.02
Suntan gels, creams, and lotions (136)	—	0.2
<b>Total Methyl Salicylate uses and concentration ranges</b>	<b>25</b>	<b>0.0001–0.6</b>