Scientific Committee on Consumer Safety

SCCS

SCIENTIFIC ADVICE – children exposure on Methyl salicylate (methyl 2-hydroxybenzoate)

The SCCS adopted this document
by written procedure on 14 September 2023

ACKNOWLEDGMENTS

Members of the Working Group are acknowledged for their valuable contribution to this Opinion. The members of the Working Group are:

For the preliminary and for the final document

SCCS members

Dr U. Bernauer	
Dr L. Bodin	
Prof. Q. Chaudhry	(SCCS Chair)
Prof. P.J. Coenraads	(SCCS Vice-Chair, Chairperson of the WG)
Prof. M. Dusinska	
Dr J. Ezendam	
Dr E. Gaffet	
Prof. C. L. Galli	
Prof. E. Panteri	
Prof. V. Rogiers	(SCCS Vice-Chair)
Dr Ch. Rousselle	(Rapporteur)
Dr M. Stepnik	
Prof. T. Vanhaecke	
Dr S. Wijnhoven	

SCCS external experts

Dr. E. Benfenati
Dr N. Cabaton
Prof. E. Corsini
Dr A. Koutsodimou
Dr. H. Louro
Prof. W. Uter
Dr N. von Goetz

This scientific advice has exceptionally been subject to a commenting period of four weeks after its initial publication (from 16 May until 19 June 2023). Comments received during this period were considered by the SCCS. For this document, main changes occurred in the following sections: section 3.2.4, Table 4 and conclusions.

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1. ABSTRACT

The SCCS concludes the following:

In the SCCS/1633/21 Opinion, the Committee concluded that Methyl Salicylate in toothpaste is safe for children under 6 years of age when used up to the maximum concentration of 2.52%.

1. In light of the data provided and taking under consideration the conclusions of SCCS/1633/21 and the aggregate exposure, does the SCCS consider Methyl Salicylate safe for children of age 0-3, when used up to a maximum concentration of 0.02% in all of the currently regulated cosmetic products included in Table 1 (except toothpaste in which up to 2.52% can be used)?

   In view of the conclusions of SCCS/1633/21 and the aggregate exposure, the SCCS considers the use of Methyl Salicylate as safe in cosmetic products intended for children of age 0.5-3 years when used up to a maximum concentration of 0.02% in shower gel, hand soap, shampoo, body lotion, face cream, hand cream, lip products and hair conditioner. For toothpaste up to a maximum concentration of 2.52% methyl salicylate is considered safe.

   As no specific data were provided by the applicant for children below 6 months, the SCCS has not considered this age category in this safety assessment.

2. In light of the data provided and taking under consideration the conclusions of SCCS/1633/21 and the aggregate exposure, does the SCCS consider Methyl Salicylate safe for children of age 3-6, when used up to the allowed maximum concentrations for each of the currently regulated cosmetic products included in Table 1 (except toothpaste in which up to 2.52% can be used)?

   In view of the conclusions of SCCS/1633/21 and the aggregate exposure, the SCCS considers the use of Methyl Salicylate as safe in cosmetic products intended for children of age 3-6 years in shower gel, hand soap, shampoo, body lotion, face cream, hand cream, lip products, and hair conditioner up to the allowed maximum concentrations indicated in Table 1. For toothpaste up to a maximum concentration of 2.52% methyl salicylate is considered safe.

Keywords: SCCS, scientific advice, methyl salicylate, methyl 2-hydroxybenzoate, children exposure, Regulation 1223/2009

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Scientific Committee members

Contact

European Commission
Health and Food Safety
Directorate B: Public Health, Cancer and Health security
Unit B3: Health monitoring and cooperation, Health networks
L-2920 Luxembourg
SANTE-SCCS@ec.europa.eu

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2. MANDATE FROM THE EUROPEAN COMMISSION

Background

Methyl Salicylate (CAS/EC No. 119-36-8/204-317-7) is the INCI name of 'methyl 2-hydroxybenzoate' an ingredient used in many fragrance mixtures and as flavouring and soothing agent in oral hygiene products.

Following its classification as 'Toxic for Reproduction Category 2' by the Commission Delegated Regulation (EU) 2021/849 and the submission of an exception dossier by industry, the Commission services mandated the SCCS to assess its safety following the provisions of Article 15(1) of the Cosmetics Regulation (EC). No. 1223/2009. On 27 October 2021, the SCCS concluded on the safety of Methyl Salicylate and Regulation (EU) 2022/1531 restricted its use in cosmetic products. Methyl Salicylate is currently listed in entry 324 of Annex III to the Cosmetic Regulation (EC) No. 1223/2009, with specific concentration limits for various product types and age groups (see Table 1).

Table 1: Currently allowed concentrations of Methyl Salicylate in cosmetic products.

Product type, Body parts	**Maximum concentration in ready for use preparation**	**Other**
(a) Leave-on skin products (except face makeup, spray/aerosol body lotion, spray/aerosol deodorant and hydroalcoholic-based fragrances) and leave on hair products (except spray/aerosol products)	(a) 0.06 %	Not to be used in preparations for children under 6 years of age, with the exception of (k) "Toothpaste"
(b) Face makeup (except lip products, eye makeup and makeup remover)	(b) 0.05 %	
(c) Eye makeup and makeup remover	(c) 0.002 %	
(d) Leave-on hair products (spray/aerosol)	(d) 0.009 %	
(e) Deodorant spray/aerosol	(e) 0.003 %	
(f) Body lotion spray/aerosol	(f) 0.04 %	
(g) Rinse-off skin products (except hand wash) and rinse-off hair products	(g) 0.06 %	
(h) Hand wash	(h) 0.6 %	
(i) Hydroalcoholic-based fragrances	(i) 0.6 %	
(j) Lip products	(j) 0.03 %	
(k) Toothpaste	(k) 2.52 %	
(l) Mouthwash intended for children aged 6–10 years	(l) 0.1 %	
(m) Mouthwash intended for children above 10 years of age and adults	(m) 0.6 %	
(n) Mouth spray	(n) 0.65 %	

In November 2022, industry submitted additional data to support the use of Methyl Salicylate in cosmetic products intended for children (age groups 0-3 and 3-6) considering that the combined exposure to Methyl Salicylate from oral and non-oral products is above the Margin of Safety (MoS), when used:

- for children of age 0-3, up to a maximum concentration of 0.02% in all of the currently regulated cosmetic products included in Table 1 (except toothpaste in which up to 2.52% can be used)?

- for children of age 3-6, up to the allowed maximum concentrations for each of the currently regulated cosmetic products included in Table 1 (except toothpaste in which up to 2.52% can be used)?

The Commission, therefore, requests the SCCS to carry out a safety assessment on Methyl Salicylate in view of the information provided.

Terms of reference

In the SCCS/1633/21 Opinion, the Committee concluded that Methyl Salicylate in toothpaste is safe for children under 6 years of age when used up to the maximum concentration of 2,52%.

1. In light of the data provided and taking under consideration the conclusions of SCCS/1633/21 and the aggregate exposure, does the SCCS consider Methyl Salicylate safe for children of age 0-3, when used up to a maximum concentration of 0.02% in all of the currently regulated cosmetic products included in Table 1 (except toothpaste in which up to 2.52% can be used)?

2. In light of the data provided and taking under consideration the conclusions of SCCS/1633/21 and the aggregate exposure, does the SCCS consider Methyl Salicylate safe for children of age 3-6, when used up to the allowed maximum concentrations for each of the currently regulated cosmetic products included in Table 1 (except toothpaste in which up to 2.52% can be used)?

3. SCIENTIFIC ADVICE

3.1 CHEMICAL AND PHYSICAL SPECIFICATIONS

Taken from the discussion of SCCS/1633/21

Methyl salicylate (methyl 2-hydroxybenzoate; CAS 119-36-8 as 99% pure) is the ester of methyl alcohol and salicylic acid. Different studies have shown that salicylic acid is the main metabolic product of methyl salicylate by hydrolysis. The SCCS issued an Opinion on the safety of salicylic acid in 2018 (Corrigendum 2019).

Methyl salicylate is also the main component of the natural 'oil of wintergreen'.

After having reviewed the data provided in the dossier, SCCS considers that salicylic acid and dimethyl 4-hydroxyisophthalate are organic impurities in methyl salicylate. A full report in terms of impurity tests in representative batches of the test substance should be provided and the validity of the analytical methodologies used must be shown. Identity and concentration of any impurities that may be present must also be stated.

Methyl salicylate should be considered as very slightly soluble according to the table in NoG.

Data on the stability of the test substance under the experimental conditions of the reported studies and under conditions of use and information on any hydrolysis products must be provided.

3.2 EXPOSURE ASSESSMENT & TOXICOKINETICS

3.2.1 Function and uses

Methyl Salicylate (CAS/EC No. 119-36-8/204-317-7) is the INCI name of 'methyl 2-hydroxybenzoate', an ingredient used in many fragrance mixtures and as flavouring and soothing agent in oral hygiene products. It can also be used as a denaturant (CosIng data base).

Following its classification as 'Toxic for Reproduction Category 2' by the Commission Delegated Regulation (EU) 2021/849 and the submission of an exception dossier by industry, the Commission services mandated the SCCS to assess its safety following the provisions of Article 15(1) of the Cosmetics Regulation (EC). No. 1223/2009. On 27 October 2021, the SCCS concluded on the safety of methyl salicylate and Regulation (EU) 2022/1531 restricted its use in cosmetic products. Methyl salicylate is currently listed in entry 324 of Annex III to the Cosmetic Regulation (EC) No. 1223/2009, with specific concentration limits for various product types and age groups (see Table 1).

Table 1. Currently allowed concentrations of methyl salicylate in cosmetic products.

Product type, Body parts	**Maximum concentration in ready for use preparation**	**Other**
(a) Leave-on skin products (except face makeup, spray/aerosol body lotion, spray/aerosol deodorant and hydroalcoholic-based fragrances) and leave-on hair products (except spray/aerosol products)	(a) 0.06 %	Not to be used in preparations for children under 6 years of age, with the exception of (k) "Toothpaste"
(b) Face makeup (except lip products, eye makeup and makeup remover)	(b) 0.05 %	
(c) Eye makeup and makeup remover	(c) 0.002 %	
(d) Leave-on hair products (spray/aerosol)	(d) 0.009 %	
(e) Deodorant spray/aerosol	(e) 0.003 %	
(f) Body lotion spray/aerosol	(f) 0.04 %	
(g) Rinse-off skin products (except hand wash) and rinse-off hair products	(g) 0.06 %	
(h) Hand wash	(h) 0.6 %	
(i) Hydroalcoholic-based fragrances	(i) 0.6 %	
(j) Lip products	(j) 0.03 %	
(k) Toothpaste	(k) 2.52 %	
(l) Mouthwash intended for children aged 6–10 years	(l) 0.1 %	
(m) Mouthwash intended for children above 10 years of age and adults	(m) 0.6 %	
(n) Mouth spray	(n) 0.65 %	

SCCS comments

In Table 1, SCCS notes that for some dermally applied products intended to be used by adults such as: (c) Eye makeup and makeup remover (0,002%) (d) Leave-on hair products (spray/aerosol) (0,009%) and (e) Deodorant spray/aerosol (0,003%), the currently allowed concentrations are much lower than the concentration supported by industry for products intended to be used by children (0.02%). Therefore, the SCCS will not include these products in this assessment, and in any case, these products are unlikely to be used regularly by children below 6 years old.

The following categories will therefore be considered depending on age categories:

Table 2. Cosmetic products considered by SCCS for Safety Assessment in children between 6 months and 6 years

Children between 6 months and 1 year	Children between 1 and 6 years
Shower gel Hand soap Shampoo Body lotion Face cream Hand cream Lip products	Shower gel Hand soap Shampoo Body lotion Face cream Hand cream Lip products Hair conditioner
Toothpaste (RF 40%)	Toothpaste (RF 40%)

Moreover, in light of potential differences in metabolism between newborns/infants up to six months and adults, it is worth giving extra consideration to the ingredients used in any cosmetic product intended for use for all ages. As no specific data were provided by the applicant for children below 6 months, the SCCS will exclude this age category and only perform a safety assessment for children above 6 months.

Exposure assessment in children

Daily exposure rates to methyl salicylate for the different age categories were based on data for daily exposures in adults and the body surface area of adults and children. Body surfaces for children were estimated from the body weights (according to EFSA) based on Sharkey *et al*. (2001). E.g. the exposure to methyl salicylate used in shower gel is considered to be 190 mg/day on a surface of 17 500 cm^2 for an adult. For a toddler (1-3 years of age) with a total body surface area 5 600 cm^2, the daily exposure would then result in 190 mg/d *5 600 cm^2/17 500 cm^2 = 61 mg/day.

Table 3. Amount of cosmetic products dermally applied on children by age groups in mg/kw bw/d

Product type[1]	Age category (yrs)	Mean bodyweight[2] (kg)	body surface	Adult surface area for application[4] (cm^2)	Calculated child surface area for application[5] (cm^2)	Adult daily exposure[4] (g/d)	Calculated child exposure[6] (g/d)	Calculated child exposure (mg/kg bw/d)
Shower gel								
Infants	0.5 -1	8.8	4 400	17 500	4 400	0.19	0.048	5.43
Toddlers	1-3	11.9	5 600	17 500	5 600	0.19	0.061	5.11
Children	3-6	14	6 200	17 500	6 200	0.19	0.067	4.81
Hand soap								
Infants	0.5 -1	8.8		860	216	0.2	0.050	5.71
Toddlers	1-3	11.9		860	275	0.2	0.064	5.38
Children	3-6	14		860	305	0.2	0.071	5.06
Shampoo								
Infants	0.5 -1	8.8		1 440	362	0.11	0.028	3.14
Toddlers	1-3	11.9		1 440	461	0.11	0.035	2.96
Children	3-6	14		1 440	510	0.11	0.039	2.78
Hair conditioner								
Toddlers	1-3	11.9		1 440	461	0.04	0.013	1.08
Children	3-6	14		1 440	510	0.04	0.014	1.01
Body lotion								
Infants	0.5 -1	8.8		15 670	3 940	7.82	1.966	223.43
Toddlers	1-3	11.9		15 670	5 014	7.82	2.502	210.29
Children	3-6	14		15 670	5 552	7.82	2.771	197.89
Face cream								
Infants	0.5 -1	8.8		565	142	1.54	0.387	44.00
Toddlers	1-3	11.9		565	181	1.54	0.493	41.41
Children	3-6	14		565	200	1.54	0.546	38.97
Hand cream								
Infants	0.5 -1	8.8		860	216	2.16	0.543	61.71
Toddlers	1-3	11.9		860	275	2.16	0.691	58.08
Children	3-6	14		860	305	2.16	0.765	54.66
Lipstick								
Infants	0.5 -1	8.8		4.8	1	0.06	0.015	1.71
Toddlers	1-3	11.9		4.8	2	0.06	0.019	1.61
Children	3-6	14		4.8	2	0.06	0.021	1.52
Aggregated								
Infants	0.5 -1							345.14
Toddlers	1-3							325.92
Children	3-6							306.71

[1] Calculation of daily exposure to toothpaste and mouthwash are shown in Table 14.

[2] Default values from EFSA 2012, for children from 3 to 6, as no specific data for this age category were available, the P5 of body weight for children from 3 to 10 was taker

[3] Values from Sharkey *et al.* 2001.

[4] Default values from SCCS Notes of Guidance 11th version (SCCS/1628/21).

[5] Calculated child surface area for application = (surface area for application for adults * child body surface area)/adult body surface area.

[6] Calculated child daily exposure = (mg/d for adults * body surface are for age category)/ surface area for adults. SCCS 2011 (SCCS/1446/11).

3.2.2 Dermal / percutaneous absorption

Taken from the discussion of SCCS/1633/21

As no reliable data are available to properly assess skin absorption, the SCCS considers that a default value of 50% skin absorption, based on the data reported in humans and on the physicochemical properties of methyl salicylate, can be used to estimate systemic exposure following skin application.

Metabolism *vi*a the dermal route is rapid, with maximal absorption between 1-4 h, and mostly as salicylic acid and its secondary metabolites. Some studies indicate that methyl salicylate conversion to salicylic acid systemically could be assumed to be 50% as it passes through the skin, but then any parent material that enters the blood is hydrolysed rapidly in blood and by the liver such that within only a few hours, no parent substance can be detected except, only free salicylate/salicylic acid.

3.2.3 Other studies on toxicokinetics

Taken from the discussion of SCCS/1633/21

Limited studies are available on the ADME properties and kinetics of methyl salicylate via the oral route in animals and humans. However, available data provide evidence that methyl salicylate is rapidly and extensively absorbed across the gut and is completely hydrolysed to its primary metabolites, salicylic acid and methanol. An oral absorption value of 100% can be used in risk assessment.

Based on the available data, an absorption value by inhalation of 100% can also be used in the risk assessment.

3.2.4 Calculation of SED/LED in children

Dermal exposure

The Systemic Exposure Doses (SED) of methyl salicylate following dermal application of cosmetic products were calculated by age category, taken into account the amount of products applied as reported in Table 3.

Table 4. SED calculations for methyl salicylate in dermally applied **cosmetic products** at the maximum use level of 0.02% for children between 6 months and 3 years and when used up to the allowed maximum concentrations for each of the currently regulated cosmetic products included in Table 1 for children between 3 and 6 years.

Product type [1]	Age category (yrs)	Calculated child exposure (mg/kg bw/d)	Concentration MeSC %	Dermal absorption DAp %	SED [2] (µg/kg bw/d)
Shower gel					
Infants	0.5 -1	5.43	0.02	50	0.54
Toddlers	1-3	5.11	0.02	50	0.51
Children	3-6	4.81	0.06	50	1.44
Hand soap					
Infants	0.5 -1	5.71	0.02	50	0.57
Toddlers	1-3	5.38	0.02	50	0.54
Children	3-6	5.06	0.6	50	15.18
Shampoo					
Infants	0.5 -1	3.14	0.02	50	0.31
Toddlers	1-3	2.96	0.02	50	0.30
Children	3-6	2.78	0.06	50	0.84
Hair conditioner					
Toddlers	1-3	1.08	0.02	50	0.11
Children	3-6	1.01	0.06	50	0.30
Body lotion					
Infants	0.5 -1	223.43	0.02	50	22.34
Toddlers	1-3	210.29	0.02	50	21.03
Children	3-6	197.89	0.04	50	39.58
Face cream					
Infants	0.5 -1	44.00	0.02	50	4.40
Toddlers	1-3	41.41	0.02	50	4.14
Children	3-6	38.97	0.05	50	9.74
Hand cream					
Infants	0.5 -1	61.71	0.02	50	6.17
Toddlers	1-3	58.08	0.02	50	5.81
Children	3-6	54.66	0.06	50	16.40
Lipstick					
Infants	0.5 -1	1.71	0.02	100	0.34
Toddlers	1-3	1.61	0.02	100	0.32
Children	3-6	1.52	0.03	100	0.46
Aggregated					
Infants	0.5 -1	345.14			34.69
Toddlers	1-3	325.92			32.75
Children	3-6	306.71			83.94

Oral exposure

Toothpaste

Taken from the Opinion SCCS/1633/21

Intakes for 1-6 years of age:

Toothpaste use starts with the first erupted teeth and occurs with a high percentage of dentifrice ingestion. Therefore, the amount of toothpaste to be used by children ages 6 and under, as implemented for fluoride toothpastes, is generally set at a pea-size amount. The SCCNFP (2003) defined this as 0.25 grams when assessing the safety of fluoridated oral care products for children. Furthermore, a retention factor of 40% for children 7 months to 8 years of age was explicitly stated to be "already an overestimate" when these exposure calculations were revisited (SCCP 2005).

Taking the above intake values from product-use scenarios, and dividing by the EFSA default body weights (EFSA 2012b)(P5; lowest 5th percentile body weight) for specific age ranges, the following conservative intakes in mg/kg/day are calculated in Table 5.

Table 5: Intake of methyl salicylate by children 1-6 years old using toothpaste

Product type	Age categories	Amount used (g/use)	Frequency (uses/day)	Retention factor	Oral bioavailability (%)	Systemic Exposure (mg/person/day)	Body weight (kg)	Relative daily exposure (mg/kg bw/d)	MeS content (%)	SED (mg/kg bw/d)
Toothpaste	Toddlers (1-3)	0.25	2	0.4	100	200	11.9	16.81	2.56	0.43
	Children (3-6)	0.25	2	0.4	100	200	14	14.29	2.56	0.37

Exposure by inhalation

As the exposure *via* inhalation is limited compared to dermal absorption, the SCCS did not consider it for children.

Aggregated exposure

An overview on the aggregated SEDs for methyl salicylate as an ingredient in cosmetic products is shown in Table 6

Table 6. SED calculations **for aggregated exposure** to methyl salicylate when used in dermally applied cosmetic products and oral products at the maximum use level of 0.02% for children between the ages of 6 months and 3 years and when used up to the allowed maximum concentrations for each of the currently regulated cosmetic products included in Table 1 for children between 3 and 6 years.

Age categories		Dermal MeS in products (µg/kg bw/d)	ToothPaste (µg/kg bw/d)	Aggregated (µg/kg bw/d)
Infants	0.5 -1	34.7	0	34.7
Toddlers	1-3	32.7	430	463
Children	3-6	83.9	370	454

3.3 TOXICOLOGICAL EVALUATION

Taken from the discussion of SCCS/1633/21

Methyl salicylate (MeS) and acetylsalicylic acid (ASA, aspirin) are related substances, both are esters of salicylic acid (ortho-hydroxy benzoic acid), which is characterised by a carboxyl group and a hydroxyl group. Salicylic acid (SA) is the common hydrolysis product of both substances.

Irritation and corrosivity

Based on the data available, the SCCS considers that there is no evidence of a skin irritation potential of methyl salicylate in humans at concentrations up to 12%. Relevant signs of irritation may only be observed at higher doses. The SCCS considers that methyl salicylate is non irritating to the skin at a concentration up to 12%, but it may cause severe eye damage.

Skin sensitisation

Methyl salicylate is identified as a skin sensitiser in different LLNA studies using high (>25%) concentrations. This is further supported by clinical data showing that methyl salicylate is a skin sensitiser in humans. The incidence in unselected and selected patients is low. Taking all data together, methyl salicylate is a weak skin sensitiser in the LLNA and humans, which is in line with the classification as a 1B skin sensitiser.

Acute toxicity

The available LD50 values by oral route range from 580 mg/kg bw (mice) to doses higher than 2 000 mg/kg bw in rats, rabbits and dogs. Based on the available data, methyl salicylate should be considered as harmful if swallowed (Acute Tox. 4; H302).

By the other routes of exposure, methyl salicylate does not warrant any classification for acute toxicity.

Repeated dose toxicity

Since the early 1960's, methyl salicylate has been studied in repeated dose toxicity studies of varying duration in different species. Repeated dose toxicity studies ranging in duration from 4 weeks to 2 years have been conducted in rats, rabbits and dogs.

The SCCS notes that the repeated dose toxicity studies are mostly old studies that were not performed following the current guidelines. It should also be noted that limited endpoints were evaluated, and a limited number of animals were examined. Furthermore, it is not indicated if a statistical analysis was performed on histopathological findings. Therefore, it cannot be excluded that effects can occur at lower doses in organs that were not examined. In addition, considering the small number of animals examined at histopathology, only the effects occurring at a high incidence could have been detected in these studies.

Based on the data available for the calculation of the MoS; the following values could be identified:

- For oral exposure (Webb and Hansen, 1963): a NOAEL of 50 mg/kg bw/day (LOAEL = 150 mg/kg bw/day)
- For dermal exposure (Webb and Hansen, 1963): a LOAEL of 585 mg/kg bw/day
- For exposure by inhalation (Gage,1970): A NOAEL of 700 mg/m^3 (120 ppm)

Reproductive toxicity

Concerning fertility and reproductive function, there is insufficient evidence that methyl salicylate exhibits adverse effects on sexual function and fertility. Therefore, the SCCS concurs with the proposal by RAC that no classification is justified for methyl salicylate for adverse effects on sexual function and fertility.

Concerning effects on development, a CMR category 2 classification was agreed by the RAC on September 2019 for methyl salicylate. The CMR category 2 classification for methyl salicylate is consistent with the 2016 CMR category 2 classification decision for salicylic acid. Salicylic acid is the principal primary metabolite of methyl salicylate via the dermal and oral routes: systemically the body is exposed to more salicylic acid metabolite than to the parent compound.

The lowest developmental NOAEL are < 60 mg/kg bw/d in rats exposed subcutaneously from GD6 to LD21 (FDA, 2006b) and 75 mg/kg bw/d in a 3-generation study in rats by oral route (Collins *et al.*, 1971). The NOAEL of 75 mg/kg bw/d is used by SCCS for the calculation of the MoS.

Mutagenicity / genotoxicity

The genotoxicity of methyl salicylate was investigated with valid *in vitro* genotoxicity tests for bacterial gene mutations and chromosomal aberrations with negative results. Additionally, a valid *in vivo* micronucleus in rats with negative result was provided. Based on the results, methyl salicylate can be considered to pose no genotoxic hazard.

Carcinogenicity

The overall totality of evidence, even if limited, indicates that methyl salicylate did not reveal any carcinogenic effects.

Photo-induced toxicity

The UV absorption maximum of a methanol solution of methyl salicylate is 305nm, which indicates that methyl salicylate can undergo direct photolysis. CIR (2003) concluded that salicylic acid is not a photo sensitiser, nor is it phototoxic. There is no evidence from over a century of human use of products containing methyl salicylate c that photo-mediated toxicity is an issue.

Special investigation: endocrine disrupting effects

The only endocrine pathway that was investigated by the applicant is the estrogenic pathway: no information on the androgen, thyroid and steroidogenesis pathways were provided.

Methyl salicylate is not, however, identified at EU level as an SVHC substance for its endocrine properties, either for human health or for the environment.

Methyl salicylate is not on the ED-list (https://edlists.org/the-ed-lists) of endocrine disrupters, meaning that it is not a substance identified as an endocrine disruptor at EU level (List I), a substance under evaluation for endocrine disruption under an EU legislation (List II) or a substance considered, by the evaluating National Authority, to have endocrine disrupting properties (List III).
Therefore, the SCCS has no specific concern regarding the endocrine disrupting potential of methyl salicylate. Moreover, the SCCS considers that *in vitro* data provided by the applicant are not useful for calculating a maximum dose.

3.4 SAFETY EVALUATION (including calculation of the MoS)

Methyl salicylate can be used in different product categories of cosmetic products that could lead to exposure depending on age by dermal or oral routes – therefore, aggregated exposure has to be taken into consideration.

In this section to answer the mandate addressed to SCCS and in complement to opinion *SCCS/1633/21,* to assess the risk of methyl salicylate by systemic exposure, the MOS was calculated separately for children between 0.5 to 1, 1 to 3 and 3 to 6 years old. The SCCS has used the NOAEL of 75 mg/kg bw/d derived from the 3-generation study in rats by oral route (Collins *et al.*, 1971). Because of the evidence for rapid and almost complete absorption of methyl salicylate from the oral route, the SCCS has not applied any adjustment for oral bioavailability to this NOAEL value.

Details of the calculation of systemic exposure dose (SED) are presented in the Tables in section 3.2.4. A generic maximal value for skin penetration of methyl salicylate of 50% (see section 3.2.1) has been used for all products in these calculations where dermal absorption needs to be factored in to calculate a systemic exposure dose (SED). For oral care products, a worst-case value of 100% absorption is used for passage across the oral mucosa. The calculations of MoS for different product types are given in Tables below.

- Dermally applied products

Table 7: MoS calculation for dermally applied products containing methyl salicylate in children between 0.5 and 6 years old

Product type [1]	Age category (yrs)	Calculated child exposure (mg/kg bw/d)	Concentration MeSC %	Dermal absorption DAp %	SED [2] (µg/kg bw/d)	NOAEL Adj (µg/kg bw/d)	MOS
Shower gel							
Infants	0.5 -1	5.43	0.02	50	0.54	75000	**138158**
Toddlers	1-3	5.11	0.02	50	0.51	75000	**146793**
Children	3-6	4.81	0.06	50	1.44	75000	**51995**
Hand soap							
Infants	0.5 -1	5.71	0.02	50	0.57	75000	**131250**
Toddlers	1-3	5.38	0.02	50	0.54	75000	**139453**
Children	3-6	5.06	0.6	50	15.18	75000	**4940**
Shampoo							
Infants	0.5 -1	3.14	0.02	50	0.31	75000	**238636**
Toddlers	1-3	2.96	0.02	50	0.30	75000	**253551**
Children	3-6	2.78	0.06	50	0.84	75000	**89809**
Hair conditioner							
Toddlers	1-3	1.08	0.02	50	0.11	75000	**697266**
Children	3-6	1.01	0.06	50	0.30	75000	**246976**
Body lotion							
Infants	0.5 -1	223.43	0.02	50	22.34	75000	**3357**
Toddlers	1-3	210.29	0.02	50	21.03	75000	**3567**
Children	3-6	197.89	0.04	50	39.58	75000	**1895**
Face cream							
Infants	0.5 -1	44.00	0.02	50	4.40	75000	**17045**
Toddlers	1-3	41.41	0.02	50	4.14	75000	**18111**
Children	3-6	38.97	0.05	50	9.74	75000	**7698**
Hand cream							
Infants	0.5 -1	61.71	0.02	50	6.17	75000	**12153**
Toddlers	1-3	58.08	0.02	50	5.81	75000	**12912**
Children	3-6	54.66	0.06	50	16.40	75000	**4574**
Lipstick							
Infants	0.5 -1	1.71	0.02	100	0.34	75000	**218750**
Toddlers	1-3	1.61	0.02	100	0.32	75000	**232422**
Children	3-6	1.52	0.03	100	0.46	75000	**164651**
Aggregated							
Infants	0.5 -1	345.14			34.69	75000	**2162**
Toddlers	1-3	325.92			32.75	75000	**2290**
Children	3-6	306.71			83.94	75000	**893**

For systemic effects, considering all dermally applied products include in the table above taken individually and also the aggregated dermal exposure, the margin of safety is above 100.

- Oral products

Table 8: MoS calculation for oral products (toothpaste) containing methyl salicylate in children between 0.5 and 6 years old

Product type	Age categories	SED (mg/kg bw/d)	NOAEL (mg/kg bw/d)	Oral bioavailability (%)	MoS
Toothpaste	Toddlers (1-3)	0.43	75	100	174
	Children (3-6)	0.37	75	100	205

For systemic effects, considering exposure to methyl salicylate via toothpastes, the margin of safety is above 100.

- Aggregated exposure

Table 8: MoS calculation for dermally applied and oral products (toothpaste) containing methyl salicylate in children below between 0.5 and 6 years old

Age categories		Dermal MeS in products (µg/kg bw/d)	ToothPaste (µg/kg bw/d)	Aggregated (µg/kg bw/d)	NOAEL Adj (µg/kg bw/d)	MOS
Infants	0.5 -1	34.7	0	35	**75000**	**2161**
Toddlers	1-3	32.7	430	463	**75000**	**162**
Children	3-6	83.9	370	454	**75000**	**165**

For systemic effects, considering all products taken individually and also the aggregated exposure, the margin of safety is above 100.

3.5 DISCUSSION

Methyl salicylate (CAS/EC No. 119-36-8/204-317-7) is the INCI name of 'methyl 2-hydroxybenzoate' an ingredient used in many fragrance mixtures and as flavouring and soothing agent in oral hygiene products.

Following its classification as 'Toxic for Reproduction Category 2' by the Commission Delegated Regulation (EU) 2021/849 and the submission of an exception dossier by industry, the Commission services mandated the SCCS to assess its safety following the provisions of Article 15(1) of the Cosmetics Regulation (EC). No. 1223/2009. On 27 October 2021, the SCCS concluded on the safety of Methyl Salicylate and Regulation (EU) 2022/1531 restricted its use in cosmetic products. Methyl Salicylate is currently listed in entry 324 of Annex III to the Cosmetic Regulation (EC) No. 1223/2009, with specific concentration limits for various product types and age groups (see Table 1).

In November 2022, industry submitted additional data to support the use of Methyl Salicylate in cosmetic products intended for children (age groups 0-3 and 3-6) considering that the combined exposure to Methyl Salicylate from oral and non-oral products is above the Margin of Safety (MoS), when used:

- for children of age 0-3, up to a maximum concentration of 0.02% in all of the currently regulated cosmetic products included in Table 1 (except toothpaste in which up to 2.52% can be used)?

- for children of age 3-6, up to the allowed maximum concentrations for each of the currently regulated cosmetic products included in Table 1 (except toothpaste in which up to 2.52% can be used)?

The Commission, therefore, requests the SCCS to carry out a safety assessment on methyl salicylate in view of the information provided.

The SCCS has considered in this opinion cosmetic products that are prone to be used by children between 6 month and 1 year and between 1 year and 6 years (see Table 2). In light of potential differences in metabolism between newborns/infants up to six months and adults, the question may indeed be raised whether cosmetic ingredients could require extra consideration. As no specific data were provided by the applicant for children below 6 months, the SCCS will exclude this age category and only perform a safety assessment for children above 6 months.

Daily exposure to methyl salicylate for the different age categories were based on data for daily exposures in adults and the body surface area of adults and children. Body surfaces for children were estimated from the body weights (according to EFSA) based on Sharkey *et al*. (2001).

As no reliable data are available to properly assess skin absorption, the SCCS has used the default value of 50% skin absorption, based on the data reported in humans and on the physico-chemical properties of methyl salicylate, to estimate systemic exposure following skin application. For oral care products, a worst-case value of 100% absorption is used for passage across the oral mucosa.

The Systemic Exposure Doses (SED) of methyl salicylate following dermal application and oral uses of cosmetic products were calculated by age categories taken into account the amount of products applied as reported in table 2. Aggregated exposure has also been considered.

To assess the risk of methyl salicylate by systemic exposure and in complement to opinion *SCCS/1633/21,* the MOS was calculated separately for children between 0.5 to 1, 1 to 3 and 3 to 6 years old. The SCCS has used as PoD the NOAEL of 75 mg/kg bw/d derived from the 3-generation study in rats by oral route (Collins *et al.*, 1971). Because of the evidence for

rapid and almost complete absorption of methyl salicylate from the oral route, the SCCS has not applied any adjustment for oral bioavailability to this NOAEL value.

For systemic effects, considering all dermally applied products include in the table 2 above and oral exposure via toothpastes, the MOS is above 100 for individual exposure as well as for aggregated exposure.

4. CONCLUSION

In the SCCS/1633/21 Opinion, the Committee concluded that Methyl Salicylate in toothpaste is safe for children under 6 years of age when used up to the maximum concentration of 2.52%.

1. In light of the data provided and taking under consideration the conclusions of SCCS/1633/21 and the aggregate exposure, does the SCCS consider Methyl Salicylate safe for children of age 0-3, when used up to a maximum concentration of 0.02% in all of the currently regulated cosmetic products included in Table 1 (except toothpaste in which up to 2.52% can be used)?

   In view of the conclusions of SCCS/1633/21 and the aggregate exposure, the SCCS considers the use of Methyl Salicylate as safe in cosmetic products intended for children of age 0.5-3 years when used up to a maximum concentration of 0.02% in shower gel, hand soap, shampoo, body lotion, face cream, hand cream, lip products and hair conditioner. For toothpaste up to a maximum concentration of 2.52% methyl salicylate is considered safe.

   As no specific data were provided by the applicant for children below 6 months, the SCCS has not considered this age category in this safety assessment.

2. In light of the data provided and taking under consideration the conclusions of SCCS/1633/21 and the aggregate exposure, does the SCCS consider Methyl Salicylate safe for children of age 3-6, when used up to the allowed maximum concentrations for each of the currently regulated cosmetic products included in Table 1 (except toothpaste in which up to 2.52% can be used)?

   In view of the conclusions of SCCS/1633/21 and the aggregate exposure, the SCCS considers the use of Methyl Salicylate as safe in cosmetic products intended for children of age 3-6 years in shower gel, hand soap, shampoo, body lotion, face cream, hand cream, lip products and hair conditioner up to the allowed maximum concentrations indicated in Table 1. For toothpaste up to a maximum concentration of 2.52% methyl salicylate is considered safe.

5. MINORITY OPINION

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6. REFERENCES

- SCCS (2021). The SCCS Notes Of Guidance For The Testing Of Cosmetic Ingredients And Their Safety Evaluation, 11th revision. https://ec.europa.eu/health/sites/default/files/scientific_committees/consumer_safety/docs/sccs_o_250.pdf (SCCS/1628/21). Adopted 30-31 March 2021.
- SCCS (2022) opinion on methyl salicylate
- Sharkey *et al*., 2001, Body surface area estimation in children using weight alone: application in paediatric oncology; Br J Cancer. 2001 Jul 6;85(1):23-8. doi: 10.1054/bjoc.2001.1859

7. GLOSSARY OF TERMS

See SCCS/1647/22, 12th Revision of the SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation – Appendix 15 - from page 158

8. LIST OF ABBREVIATIONS

MeS = methyl salicylate

See SCCS/1647/22, 12th Revision of the SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation – Appendix 15 - from page 158