Scientific Committee on Consumer Safety

SCCS

SCIENTIFIC ADVICE – children's exposure to Methyl Salicylate (methyl 2-hydroxybenzoate)

- Revision of SCCS/1654/23 -

The SCCS adopted this document
by written procedure on 30 April 2025

ACKNOWLEDGMENTS

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This scientific advice has been exceptionally subject to a commenting period of 4 weeks after its initial publication (from 20 January to 17 February 2025). Comments received during this period were considered by the SCCS. For this final document, main changes occurred in the following sections: Table 2, exposure assessment (in particular section 3.2.4), section 3.4 as wall as related conclusion 1 and the reference list.

All Declarations of Working Group members are available on the following webpage:
Register of Commission expert groups and other similar entities (europa.eu)

1. ABSTRACT

The SCCS concludes the following:

1. *Taking under consideration the conclusions of SCCS/1658/23 and the aggregate exposure, the SCCS is requested to re-assess the maximum concentration of Methyl Salicylate that is considered safe when used in products intended for children of age 0-3.*

   The SCCS is of the view that, to be considered safe, the concentration of Methyl Salicylate should not exceed 0.4% in toothpaste and 0.02% in other products when used in products intended for children of age 0-3 years.

2. *Does the SCCS have any further scientific concerns with regard to the use of Methyl Salicylate in cosmetic products and children's exposure?*

   The SCCS mandates do not address environmental aspects. Therefore, this assessment did not cover the safety of Methyl Salicylate for the environment.

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

Document to be cited as: SCCS (Scientific Committee on Consumer Safety), Scientific Advice on Methyl Salicylate (methyl 2-hydroxybenzoate) – children exposure, version of 17 January 2025, final version of 30 April 2025, SCCS/1676/25.

About the Scientific Committees

Two independent non-food Scientific Committees provide the Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention to the new or emerging problems which may pose an actual or potential threat.
These Committees are the Scientific Committee on Consumer Safety (SCCS) and the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER), and they are made up of scientists appointed in their personal capacity.

In addition, the Commission relies upon the work of the European Food Safety Authority (EFSA), the European Medicines Agency (EMA), the European Centre for Disease prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

SCCS

The Committee shall provide Opinions on questions concerning health and safety risks (notably chemical, biological, mechanical and other physical risks) of non-food consumer products (for example cosmetic products and their ingredients, toys, textiles, clothing, personal care and household products such as detergents, etc.) and services (for example: tattooing, artificial sun tanning, etc.).

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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).

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). On 14 September 2023, the SCCS concluded in their Opinion SCCS/1654/23[1] on the safety of Methyl Salicylate in cosmetic products intended for children of age 0.5-3 and 3-6 years in specific types of cosmetic products and with defined concentration limits.

On 29 July 2024, the SCCS published a preliminary Opinion (addendum to SCCS/1658/23)[2] on the safety of Hexyl Salicylate, where the scientific committee noted that the amount of toothpaste ingested by children below 3 years old (considered in the calculation of the margin of safety) has been adapted based on available data and is much higher than the one used in previous opinions including their Opinion on Methyl Salicylate (*i.e.*, SCCS/1654/23). The SCCS concluded that this may raise concerns on the safety of such substances, where the MoS is close to 100. In view of this, the Commission, requests the SCCS to re-assess the safety of Methyl Salicylate in cosmetic products intended for children.

Terms of reference

1. *Taking under consideration the conclusions of SCCS/1658/23 and the aggregate exposure, the SCCS is requested to re-assess the maximum concentration of Methyl Salicylate that is considered safe when used in products intended for children of age 0-3.*

2. *Does the SCCS have any further scientific concerns with regard to the use of Methyl Salicylate in cosmetic products and children's exposure?*

[1] https://health.ec.europa.eu/publications/sccs-scientific-advice-children-exposure-methyl-salicylate-methyl-2-hydroxybenzoate_en

[2] https://health.ec.europa.eu/publications/sccs-addendum-scientific-opinion-hexyl-salicylate-sccs165823-casec-no-6259-76-3228-408-6-children_en

3. SCIENTIFIC ADVICE

This Scientific Advice only addresses exposure assessment to Methyl Salicylate in cosmetic products (see section 3.2): for the chemical and physical specifications and for the toxicological evaluation, it relies on the previous SCCS Opinion (SCCS/1633/21). Therefore, for the sake of the readers, only a short summary of the SCCS conclusions is included in this advice for these 2 sections (3.1 and 3.3).

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 %	

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, requested the SCCS to carry out a safety assessment on Methyl Salicylate in view of the information provided.

In its previous scientific advice – children exposure on Methyl Salicylate (SCCS/1654/23), the SCCS concluded:

- 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.

- 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.

On 25th October 2024, SCCS published an Addendum to the Scientific Opinion on hexyl salicylate SCCS/1658/23 (CAS/EC No. 6259-76-3/228-408-6) - Children exposure 0-3 years old, where the scientific committee noted that the amount of toothpaste ingested by children below 3 years old (considered in the calculation of the margin of safety) has been adapted based on available data and is much higher than the one used in previous opinions including their Opinion on Methyl Salicylate (*i.e.*, SCCS/1654/23). The SCCS concluded that this may raise concerns on the safety of such substances, where the MoS is close to 100.

In view of this, and based on a request from the Commission, the SCCS re-assess the safety of Methyl Salicylate in cosmetic products intended for children below 3 years old, taking into account the updated value for toothpaste and for other dermally applied products whenever needed. The products categories considered in this advice are the same than the ones included in the previous scientific advice (SCCS/1654/23). They are listed in Table 2 below. The amount of products used by children under 3 years is taken from the SCCS Addendum to the Scientific Opinion on Hexyl Salicylate SCCS/1658/23 – children exposure 0-3 y.o. (SCCS/1668/24, Table 5).

Table 2. Cosmetic products intended for children of age 0-3 years considered by SCCS in this scientific advice

Children up to 1 year	Children between 1 and 3 years
Shower gel Hand soap Shampoo Body lotion Face cream Hand cream Lip products Fragrance products	Shower gel Hand soap Shampoo Body lotion Face cream Hand cream Lip products Hair conditioner Fragrance products
Toothpaste (RF 40%)	Toothpaste (RF 40%)

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 *via* 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 2.

The SCCS has recalculated the aggregate dermal exposure by relying on the available children-specific data when available, and if not, was based on Skin Surface Area (SSA) approach as explained also in the recent hexyl salicylate Opinion (SCCS/1668/24).

The SCCS assessments should consider the European population. In this regard the data sparsity for children data represents a methodological challenge. Data for children are currently only available for France and Switzerland, whereas for adults, data are available that are considered representative for the EU. Regarding children's data, for France the most comprehensive, consistent, methodologically sound and recent data on cosmetics use have been collected by Ficheux et and Roudot, 2017. Therefore, this study was selected over other French studies (*e.g.,* Gomez-Berrada *et al.*, 2017 who included a smaller number of 78 children aged 0-2 years old and Gomez-Berrada *et al.,* 2013 who reviewed clinical studies performed under less realistic conditions). Comparing the data from Ficheux and Roudot, 2017 to data from Switzerland (Garcia-Hidalgo *et al*., 2017), the French data are considered more reliable by the SCCS from a methodological perspective. This is because the sample size is larger in the French study (395 parents, in Ficheux and Roudot, 2017) and the reported

data specifically target the age group of 0-3 years old, whereas the Swiss data refers to an age group of 0-5 years (participants 3% of 759, *i.e.*, 23, Garcia-Hidalgo *et al*., 2017). Also, the amount data in the study by Ficheux and Roudot, 2017 was determined by weighing the personal cosmetic items before and after use, whereas *e.g*., Garcia-Hidalgo *et al.*, 2017 used pictures in a self-administered questionnaire to assess use amounts.

Still, since Ficheux and Roudot, 2017 have investigated only children in France and not the whole of Europe, the data for Switzerland is considered as important supporting evidence and the fact that the Swiss data are in a similar order of magnitude as the French data supports the extrapolation from French data to the whole of Europe.

Table 3. SED calculations for Methyl Salicylate in dermally applied cosmetic products intended for children of age 0-3 years at the maximum use level of 0.02%

Product type	Data source used for SED derivation	SSA approach (mg/kg bw/d) *	Daily exposure F&R, 2017 (mg/kg bw/d)	Substance concentration (%)	Dermal absorption DAp (%)	SED (µg/kg/d)
SHOWER GEL	Ficheux et Roudot, 2017, gel douche					
Infants 0 - 0.5 yrs		*6.56*	**7.40**	0.02%	50.00%	0.74
Infants 0.5 - 1 yrs		*5.49*	**7.40**	0.02%	50.00%	0.74
Toddlers 1 - 3 yrs		*5.24*	**9.37**	0.02%	50.00%	0.94
HAND SOAP	Ficheux et Roudot, 2017, gel douche					
Infants 0 - 0.5 yrs		*6.90*	**7.40**	0.02%	50.00%	0.74
Infants 0.5 - 1 yrs		*5.78*	**7.40**	0.02%	50.00%	0.74
Toddlers 1 - 3 yrs		*5.52*	**9.37**	0.02%	50.00%	0.94
SHAMPOO	Ficheux et Roudot, 2017, shampoing					
Infants 0 - 0.5 yrs		*3.80*	**4.79**	0.02%	50.00%	0.48
Infants 0.5 - 1 yrs		*3.18*	**4.79**	0.02%	50.00%	0.48
Toddlers 1 - 3 yrs		*3.04*	**4.52**	0.02%	50.00%	0.45
HAIR CONDITIONER	Ficheux et Roudot, 2017, shampoing*					
Infants 0 - 0.5 yrs		*NA*	NA	NA	NA	NA
Infants 0.5 - 1 yrs		*NA*	NA	NA	NA	NA
Toddlers 1 - 3 yrs		*1.10*	**4.52**	0.02%	50.00%	0.45
BODY LOTION	Ficheux et Roudot, 2017, Crème Hydratante corps					
Infants 0 - 0.5 yrs		*270*	**839**	0.02%	50.00%	83.90
Infants 0.5 - 1 yrs		*226*	**839**	0.02%	50.00%	83.90
Toddlers 1 - 3 yrs		*216*	**981**	0.02%	50.00%	98.10
FACE CREAM	SSA Approach					
Infants 0 - 0.5 yrs		**53.2**	n.a.	0.02%	50.00%	5.32
Infants 0.5 - 1 yrs		**44.5**	n.a.	0.02%	50.00%	4.45
Toddlers 1 - 3 yrs		**42.5**	n.a.	0.02%	50.00%	4.25
HAND CREAM	SSA Approach					
Infants 0 - 0.5 yrs		**74.6**	n.a.	0.02%	50.00%	7.46
Infants 0.5 - 1 yrs		**62.4**	n.a.	0.02%	50.00%	6.24
Toddlers 1 - 3 yrs		**59.6**	n.a.	0.02%	50.00%	5.96
LIPSTICK	SSA Approach					
Infants 0 - 0.5 yrs		**1.97**	n.a.	0.02%	100.00%	0.39
Infants 0.5 - 1 yrs		**1.65**	n.a.	0.02%	100.00%	0.33

Toddlers 1 - 3 yrs		**1.57**	n.a.	0.02%	100.00%	0.31
FRAGRANCE PRODUCTS	Ficheux et Roudot, 2017, Eau de Toilette					
Infants 0 - 0.5 yrs		***9.67***	96.9	0.02%	50.00%	9.69
Infants 0.5 - 1 yrs		***8.09***	96.9	0.02%	50.00%	9.69
Toddlers 1 - 3 yrs		***7.72***	84.4	0.02%	50.00%	8.44
AGGREGATE DERMAL						
Infants 0 - 0.5 yrs						108.72
Infants 0.5 - 1 yrs						106.57
Toddlers 1 - 3 yrs						119.84

* for more details on the calculation, you can refer to the recent hexyl salicylate Opinion (SCCS/1668/24). The use amount of conditioner (if used at all) will be very similar to use amounts of shampoo. Therefore, as explained above, also for conditioner, the more reliable use amounts of shampoo derived by Ficheux and Roudot, 2017 were preferred over the data collected by self-administered questionnaires from Garcia-Hidalgo *et al.,* 2017.

Face cream and hand creams have both been added in the aggregate exposure, because these may be used by consumers in Europe. However, for children 0-3 years Ficheux and Roudot, 2017 report only 8% users of face cream in that age category. Also, for hand cream only a small percentage of daily users is observed (Garcia-Hidalgo *et al*., 2017, Figure 8). It may therefore be argued that these product types could be neglected in the aggregate exposure assessment in view that body cream in the deterministic approach is assumed to be used daily.

However, in the absence of data for the whole European population the SCCS prefers for the time being to keep these products in the aggregate exposure, but instead of relying on the data for a small percentage of users in selected European countries, the SCCS considers it appropriate to use the value derived with the SA-approach from the European adult population.

Oral exposure

Toothpaste

This section has been revised compared to the previous Opinion SCCS/1633/21, as new data concerning the toothpaste use by children has been identified, as explained in the recent Opinion on hexyl salicylate (SCCS1668/24).

Intakes in Children up to 3 years:

Toothpaste use starts with the first erupted teeth and occurs with a high percentage of dentifrice ingestion. Considering data on toothpaste use published by Gomez-Berrada *et al*., 2018, Garcia-Hidalgo *et al.,* 2017 and Adé *et al*., 2024, the SCCS recommends the following amounts of toothpaste for calculating oral exposure of children: 1.92 g/day for babies (0-3 years). These represent the P95 values reported by Gomez-Berrada *et al.* 2018 for samples of N=96 children 2-6 years old which were assessed by weighing the toothpaste tubes before and after use, and thus considered to be the best data available to date. The data from Garcia-Hidalgo *et al.*, 2017, on a smaller sample assessed by means of a survey using pictures to illustrate the amounts, are similar and show that the findings are not specific for French children. In addition, a study by Adé *et al.*, 2024, on Swiss preschool children supports the use of higher amount values than the 0.25 g/application mentioned in the SCCS Notes of Guidance (SCCS/1647/22). However, no P95 values are available from this study.

Regarding bodyweight, the SCCS will use the more conservative median (P50) values from EFSA, 2012, which are 4.8, 8.7 kg and 11.6 kg for the 0-6 months, 6-12 months and 1-3 years age groups, respectively.

Table 4: Intake of Methyl Salicylate by children up to 3 years old using toothpaste

Age categories (years)	Amount used (g/day)	Retention Factor	Oral bioavailability (%)	Systemic exposure (mg)	Body weight (kg)	Relative daily exposure (mg/kg bw/d)	MeS content (%)	SED (mg/kg bw/d)
Infants up to 0.5 *	1.92	0.4	100	768	4.8	160.00	2.52	4.03
Infants (0.5-1)	1.92	0.4	100	768	8.7	88.28	2.52	2.22
Todlers (1-3)	1.92	0.4	100	768	11.6	66.21	2.52	1.67

(*) the use of toothpaste starts after the growth of the first teeth.

Exposure by inhalation

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

Aggregated exposure

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

An overview on the aggregated SEDs for Methyl Salicylate as an ingredient in cosmetic products is shown in Table 5.

Table 5. 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 up to 3 years.

Age categories		Dermal MeS in products (µg/kg bw/d)	ToothPaste (µg/kg bw/d)	Aggregated (µg/kg bw/d)
Infants	up to 0.5	109	4003	4112
Infants	0.5-1	107	2220	2327
Todlers	1-3	120	1670	1790

3.3 TOXICOLOGICAL EVALUATION

As this scientific advice only addresses exposure considerations the toxicological evaluation relies on the previous Opinion on Methyl salicylate.

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 CLP 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 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)

In this section to answer the mandate addressed to SCCS and in complement to Opinion *SCCS/1633/21 and SCCS/1654/23,* to assess the risk of Methyl Salicylate by systemic exposure, the MoS was calculated separately for children up to 0.5 year and between 0.5 to 1 and 1 to 3 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 6: MoS calculation for dermally applied products containing Methyl Salicylate in children up to 3 years old

Product type	Data source used for SED derivation	Applicant SSA approach (mg/kg bw/d)	Daily exposure F&R, 2017 (mg/kg bw/d)	substance concentration (%)	Dermal absorption DAp (%)	SED (µg/kg/d)	NOAEL (µg/kg/bw/d	MOS
SHOWER GEL	Ficheux et Roudot, 2017, gel douche							
Infants 0 - 0.5 yrs		*6,56*	7,40	0,02%	50,00%	0,74	75000	101351
Infants 0.5 - 1 yrs		*5,49*	7,40	0,02%	50,00%	0,74	75000	101351
Toddlers 1 - 3 yrs		*5,24*	9,37	0,02%	50,00%	0,94	75000	80043
HAND SOAP	Ficheux et Roudot, 2017, gel douche							
Infants 0 - 0.5 yrs		*6,90*	7,40	0,02%	50,00%	0,74	75000	101351
Infants 0.5 - 1 yrs		*5,78*	7,40	0,02%	50,00%	0,74	75000	101351
Toddlers 1 - 3 yrs		*5,52*	9,37	0,02%	50,00%	0,94	75000	80043
SHAMPOO	Ficheux et Roudot, 2017, shampoing							
Infants 0 - 0.5 yrs		*3,80*	4,79	0,02%	50,00%	0,48	75000	156576
Infants 0.5 - 1 yrs		*3,18*	4,79	0,02%	50,00%	0,48	75000	156576
Toddlers 1 - 3 yrs		*3,04*	4,52	0,02%	50,00%	0,45	75000	165929
HAIR CONDITIONER	Ficheux et Roudot, 2017, shampoing*							
Infants 0 - 0.5 yrs		*1,38*	NA	NA	NA	NA		NA
Infants 0.5 - 1 yrs		*1,15*	NA	NA	NA	NA	NA	NA
Toddlers 1 - 3 yrs		*1,11*	4,52	0,02%	50,00%	0,45	75000	165929
BODY LOTION	Ficheux et Roudot, 2017, Crème hydratante corps							
Infants 0 - 0.5 yrs		*270*	839	0,02%	50,00%	83,90	75000	894
Infants 0.5 - 1 yrs		*226*	839	0,02%	50,00%	83,90	75000	894
Toddlers 1 - 3 yrs		*216*	981	0,02%	50,00%	98,10	75000	765
FACE CREAM	Applicant with BW correction							
Infants 0 - 0.5 yrs		53,2	n.a.	0,02%	50,00%	5,32	75000	14106
Infants 0.5 - 1 yrs		44,5	n.a.	0,02%	50,00%	4,45	75000	16852
Toddlers 1 - 3 yrs		42,5	n.a.	0,02%	50,00%	4,25	75000	17655
HAND CREAM	Applicant with BW correction							
Infants 0 - 0.5 yrs		74,6	n.a.	0,02%	50,00%	7,46	75000	10058
Infants 0.5 - 1 yrs		62,4	n.a.	0,02%	50,00%	6,24	75000	12016
Toddlers 1 - 3 yrs		59,6	n.a.	0,02%	50,00%	5,96	75000	12588
LIPSTICK	Applicant with BW correction							
Infants 0 - 0.5 yrs		1,97	n.a.	0,02%	100,00%	0,39	75000	190355
Infants 0.5 - 1 yrs		1,65	n.a.	0,02%	100,00%	0,33	75000	227447
Toddlers 1 - 3 yrs		1,57	n.a.	0,02%	100,00%	0,31	75000	238919
FRAGRANCE PRODUCTS	Ficheux et Roudot, 2017, Eau de Toilette							
Infants 0 - 0.5 yrs		*9,67*	96,9	0,02%	50,00%	9,69	75000	7740
Infants 0.5 - 1 yrs		*8,09*	96,9	0,02%	50,00%	9,69	75000	7740
Toddlers 1 - 3 yrs		*7,72*	84,4	0,02%	50,00%	8,44	75000	8886
AGGREGATE DERMAL								
Infants 0 - 0.5 yrs						108,72	75000	690
Infants 0.5 - 1 yrs						106,57	75000	704
Toddlers 1 - 3 yrs						119,84	75000	626
*Garcia-Hidalgo et al, 2017 data suggest that use is comparable								

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

- Oral products

Table 7: MoS calculation for oral products (toothpaste) containing Methyl Salicylate in children between 0.5 and 6 years old

Product type	Age categories (years)	Relative daily exposure (mg/kg bw/d)	MeS content (%)	SED (mg/kg bw/d)	NOAEL (mg/kg bw/ d)	MoS
Toothpaste	Infants up to 0.5 *	160.00	2.52	4.03	75	18.60
	Infants (0.5-1)	88.28	2.52	2.22	75	33.71
	Todlers (1-3)	66.21	2.52	1.67	75	44.95

For systemic effects, considering exposure to Methyl Salicylate via toothpaste, the margin of safety is below 100. To have a MoS of 100 only *via* exposure to toothpaste, the concentration of Methyl Salicylate should not exceed 0.40% as shown in the table below.

Table 8: MoS calculation for oral products (toothpaste) containing Methyl Salicylate at 0.4% in children between 0.5 and 6 years old

Product type	Age categories (years)	Relative daily exposure (mg/kg bw/d)	MeS content (%)	SED (mg/kg bw/d)	NOAEL (mg/kg bw/ d)	MoS
Toothpaste	Infants up to 0.5 *	160.00	0.4	0.64	75	117.19
	Infants (0.5-1)	88.28	0.4	0.35	75	212.40
	Todlers (1-3)	66.21	0.4	0.26	75	283.20

- Aggregated exposure

Table 9: MoS calculation for dermally applied and oral products (toothpaste) containing Methyl Salicylate in children below 3 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	up to 0.5	109	640	749	75000	100
Infants	0.5-1	107	350	457	75000	164
Todlers	1-3	120	260	380	75000	197

For systemic effects, considering the aggregated exposure to Methyl Salicylate, the margin of safety is below 100. To have a MoS of 100 only *via* exposure to toothpaste and other dermally applied products, the concentration of Methyl Salicylate should not exceed 0.4% in the toothpaste and 0.02% in the other products.

3.5 DISCUSSION

In view of the higher amount of toothpaste ingested by children below 3 years old considered in the last addendum on hexyl salicylate, in this scientific advice, the SCCS has re-assessed the safety of Methyl Salicylate in cosmetic products intended for children below 3 years old. Only the amount of cosmetic products intended to be used for children below 3 years has been updated comparing to the previous opinion on methyl salicylate. The dermal absorption as well as the Point of Departure considered for the MoS calculation have not been changed.

The SCCS has recalculated the aggregate dermal exposure by relying on children-specific data when available, and when it was not available, used the Skin Surface Area (SSA) approach as explained also in the recent hexyl salicylate Opinion (SCCS/1668/24). Concerning toothpaste, the SCCS considered an amount of 1.92 g/day for the purposes of its assessment.

Regarding bodyweight, the SCCS has used the more conservative median (P50) values from EFSA, 2012, which are 8.7 kg and 11.6 kg for the 0-6 months, 6-12 months and 1-3 years age groups, respectively.

The MoS was then calculated separately for children up to 0.5 year, and between 0.5 to 1 and 1 to 3 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).

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

For systemic effects, considering exposure to Methyl Salicylate *via* toothpastes, the margin of safety is below 100. To have a MoS of 100 only *via* exposure to toothpaste, the concentration of Methyl Salicylate should not exceed 0.4%

For systemic effects, considering the aggregated exposure to methyl salicylate, the margin of safety is below 100. To have a MoS of 100 only *via* exposure to toothpaste and other dermally applied products, the concentration of Methyl Salicylate should not exceed 0.4% in the toothpaste and 0.02% in the other products.

4. CONCLUSION

1. *Taking under consideration the conclusions of SCCS/1658/23 and the aggregate exposure, the SCCS is requested to re-assess the maximum concentration of Methyl Salicylate that is considered safe when used in products intended for children of age 0-3.*

   The SCCS is of the view that, to be considered safe, the concentration of Methyl Salicylate should not exceed 0.4% in toothpaste and 0.02% in other products when used in products intended for children of age 0-3 years.

2. *Does the SCCS have any further scientific concerns with regard to the use of Methyl Salicylate in cosmetic products and children's exposure?*

   The SCCS mandates do not address environmental aspects. Therefore, this assessment did not cover the safety of Methyl Salicylate for the environment.

5. MINORITY OPINION

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6. REFERENCES

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- SCCS (2022) opinion on methyl salicylate
- SCCS (2024) Addendum to the Scientific Opinion on Hexyl Salicylate SCCS/1658/23 – children exposure 0-3 y.o. (SCCS/1668/24)

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