Scientific Committee on Consumer Safety

SCCS

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 -

The SCCS adopted this document
by written procedure on 26 July 2024

ACKNOWLEDGMENTS

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1. ABSTRACT

The SCCS concludes the following:

1. *In light of the data provided and taking under consideration the CMR Cat.2 classification (to be introduced in Annex VI to Reg. 1272/2008), does the SCCS consider Hexyl Salicylate safe for children below 3 years of age when used up to the maximum concentrations provided in the dossier?*

Based on the assessment of data provided and taking into consideration the concerns related to potential endocrine disrupting properties, the SCCS considers Hexyl Salicylate safe for children < 3 years old when used up to the maximum concentrations as provided below.

Product type	Maximum concentration (% w/w)
Shower gel, hand soap, shampoo, hair conditioner, body lotion, face cream, hand cream, lipstick/lip balm, fragrance products	0.1
Toothpaste	0.001

2. *Alternatively, what is according to the SCCS the maximum concentration of Hexyl Salicylate that is considered safe for children below 3 years of age?*

/

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

The results of the infant survey by Cosmetics Europe that have been available as draft to the SCCS show that a significant proportion of babies had "skin issues" and that children with damaged skin could be exposed to cosmetic products containing Salicylates. This raises concern to the SCCS as it is not known whether Salicylic Acid may be present in the products as an impurity or resulting from the breakdown of hexyl salicylate. Furthermore, Salicylic Acid is classified as a skin sensitiser Category 1 and Salicylic Acid is not permitted in cosmetic products used by children under the age of 3 years.

The amount of toothpaste ingested by children below 3 years old considered in this opinion for the calculation of the MoS has been adapted based on available data and now is much higher than the one used in previous opinions on Salicylates in cosmetic products used by children (eg. Methyl salicylates, SCCS/1654/23). This may raise concerns about their safety, in particular wwhere the MoS is close to 100.

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

Keywords: SCCS, scientific opinion, addendum, Hexyl Salicylate, CAS/EC No. 6259-76-3/228-408-6, children exposure, SCCS/1658/23, SCCS/1668/24, Regulation 1223/2009

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http://ec.europa.eu/health/scientific_committees/consumer_safety/index_en.htm

TABLE OF CONTENTS

2. MANDATE FROM THE EUROPEAN COMMISSION

Background

Hexyl Salicylate (CAS/EC No. 6259-76-3/228-408-6) is the INCI name of 'hexyl 2-hydroxybenzoate', an ingredient with sweet, floral, and fruity odour used in formulations of fragrances in multiple consumer goods including cosmetic, household cleaning products, detergents, and air care products.

Hexyl Salicylate is not listed in the Annexes to the Cosmetic Regulation (EC) No. 1223/2009 and its use is not otherwise restricted in cosmetic products.

The European Risk Assessment Committee (RAC) of ECHA issued in March 2022 an opinion[1] recommending a 'Toxic for Reproduction Category 2' (i.e., suspected of damaging the unborn child) and 'Skin sensitizer Category 1' classification for Hexyl Salicylate. These classifications were based on 'read across' from the structural analogue Methyl Salicylate and the metabolite Salicylic Acid and on the results of an LLNA assay, respectively.

Hexyl Salicylate is the ester of 1-hexanol and Salicylic Acid, with the latter being the main metabolite. Salicylic Acid has been subject to a safety evaluation by SCCNFP in 2002[2] and SCCS in 2018[3], while the SCCS has recently re-evaluating its safety in view of endocrine disrupting concerns[4]. In addition, the scientific committee has concluded on the safety of Methyl Salicylate in 2021[5].

Following the RAC opinion, it is expected that the European Commission will propose a classification for Hexyl Salicylate as a 'Toxic for Reproduction Category 2' and 'Skin sensitizer Category 1' (CLP Regulation Annex VI).

In December 2022, stakeholders submitted a dossier to support the safe use of Hexyl Salicylate according to Art. 15(1) Reg. 1223/2009 with specific concentration limits for various product types. The SCCS concluded in their Opinion SCCS/1658/23[6] that Hexyl Salicylate is safe when used up to the maximum concentrations as provided in Table 1 of that Opinion. However, the scientific committee noted that the Applicant did not provide any specific scenarios for children applying cosmetic products on their skin (dermal exposure), nor were the differences between age categories in some exposure parameters (body weight, amount of the products applied, body surface, etc) taken into consideration. The SCCS, nevertheless stress that in view of the high MoS for adults, far above 100, the MoS will also be above 100 for children between 3 to 10, considering also the products categories used by children of these ages.

In May 2024, industry submitted additional information to address the SCCS concerns relevant to children's exposure to Hexyl Salicylate, in particular for children below 3 years of age.

The Commission requests the SCCS to carry out a safety assessment on Hexyl Salicylate in view of the new information provided.

[1] https://echa.europa.eu/documents/10162/88845f59-c1f3-1302-2701-e684a9193ef7
[2] https://ec.europa.eu/health/ph_risk/committees/sccp/documents/out170_en.pdf
[3] SCCS (Scientific Committee on Consumer Safety), Opinion on salicylic acid (CAS 69-72-7) - Submission I, SCCS/1601/18, preliminary version of 10 September 2018, final version of 21 December 2018, CORRIGENDUM on 20-21 June 2019.
[4] SCCS (Scientific Committee on Consumer Safety), Opinion on salicylic acid (CAS No. 69-72-7, EC No. 200-712-3), preliminary version of 14 December 2022, final version of 6-7 June 2023, SCCS/1646/22.
[5] SCCS (Scientific Committee on Consumer Safety), Opinion on methyl salicylate (methyl 2-hydroxybenzoate), preliminary version of 24-25 June, final version of 26-27 October 2021, SCCS/1633/21. https://health.ec.europa.eu/publications/methyl-salicylate-methyl-2-hydroxybenzoate_en
[6] SCCS (Scientific Committee on Consumer Safety), Scientific Opinion on Hexyl Salicylate (CAS/EC No. 6259-76-3/228-408-6), preliminary version of 26 October 2023, final version of 28 February 2024, SCCS/1658/23

Terms of reference

1. *In light of the data provided and taking under consideration the CMR Cat.2 classification (to be introduced in Annex VI to Reg. 1272/2008), does the SCCS consider Hexyl Salicylate safe for children below 3 years of age when used up to the maximum concentrations provided in the dossier?*

2. *Alternatively, what is according to the SCCS the maximum concentration of Hexyl Salicylate that is considered safe for children below 3 years of age?*

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

3. ADDENDUM TO THE OPINION

All chapters with the exception of 3.4.2 (calculation of SEDs) have been taken over from the original opinion SCCS/1658/23.

3.1 CHEMICAL AND PHYSICAL SPECIFICATIONS

3.1.1 Chemical identity

3.1.1.1 Primary name and/or INCI name

Hexyl Salicylate

3.1.1.2 Chemical names

IUPAC, EC name: Hexyl Salicylate

Synonyms: hexyl 2-hydroxybenzoate; salicylic acid hexyl ester; benzoic acid, 2-hydroxy-,n-hexyl ester

3.1.1.3 Trade names and abbreviations

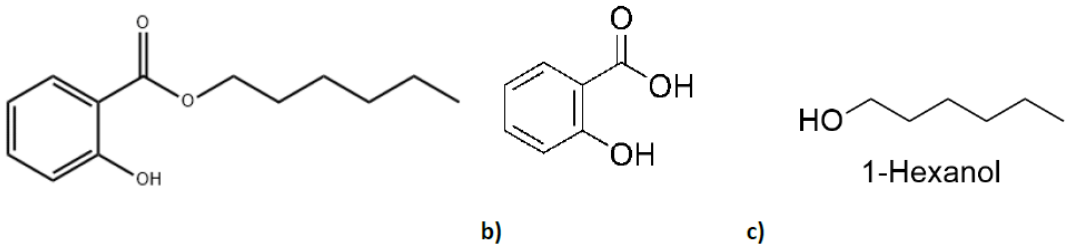
Benzoic acid, 2-hydroxy-, hexyl ester Hexyl Salicylate, Hexyl o-hydroxybenzoate, n-Hexyl Salicylate

3.1.1.4 CAS / EC number

CAS No: 6259-76-3
EC No: 228-408-6

3.1.1.5 Structural formula

The chemical structure of Hexyl Salicylate is shown in Figure 1a. Hexyl Salicylate is an ester of salicylic acid (Figure 1b) and 1-hexanol (Figure 1c).



a) b) c)

Figure 1 Chemical structure of a) hexyl salicylate (CAS 6259-76-3; EC number 228-408-6), b) salicylic acid (CAS 69-72-7; EC number 200-712-3) and c) 1-hexanol (CAS 111-27-3; EC number 203-852-3).

3.1.1.6 Empirical formula

$C_{13}H_{18}O_3$

3.1.2 Physical form

At 20°C colourless liquid.

3.1.3 Molecular weight

222.28 g/mol

3.1.4 Purity, composition and substance codes

> 99%

3.1.5 Impurities / accompanying contaminants

/

3.1.6 Solubility

2 mg/L in water at 23°C and pH 7
Registration Dossier - ECHA (europa.eu) consulted 6 September 2023

3.1.7 Partition coefficient (Log P_{ow})

5.5 at 30°C and pH 7 (OECD Test Guideline 117)

3.1.8 Additional physical and chemical specifications

Density: 1.038 at 20°C g/cm^3
Melting point: -4.15°C (equivalent to 269 ± 0.5 Kelvin at 101.325 kPa (OECD Test Guideline 102)
Boiling point: 297.84°C (equivalent to 571 ± 0.5 Kelvin at 100.62 kPa (OECD Test Guideline 103)
Vapour Pressure: 7.7 x 10^{-5} kPa at 23°C
Flash point: 151°C (EU Method A.9) at 101.1 kPa
pKa: 8.17±0.30 (Predicted)
https://www.chemicalbook.com/ProductChemicalPropertiesCB4430407_EN.htm
Consulted 6 September 2023

3.1.9 Homogeneity and Stability

According to the Applicant, compound is stable under recommended storage conditions.

SCCS comment
According to the Applicant, the information was taken from ECHA website (https://echa.europa.eu/fr/registration-dossier/-/registered-dossier/14766/3/1/6). The SCCS has corrected some points accordingly.

Information on the analytical methods used for the determination of purity and impurities of the test substance should be provided in accordance with the SCCS Notes of Guidance. Relevant data should be provided.

3.2 EXPOSURE ASSESSMENT & TOXICOKINETICS

3.2.1 Function and uses

Hexyl Salicylate (CAS 6259-76-3; EC No. 228-408-6) can be synthesised for use in a range of manufactured goods including cosmetic products, household cleaning products, detergents and air care products (Lapczynski *et al.* 2007).

3.2.1.1 Cosmetic uses

Hexyl Salicylate is used in the formulation of fragrances in cosmetics as it has a sweet, floral and fruity odour. Hexyl Salicylate is used globally in a wide range of cosmetics (Lapczynski *et al.*, 2007; CIR 2019).

The EU Cosmetics Regulation (Annex III) does not list Hexyl Salicylate as a restricted substance in cosmetics and personal care products.

EU companies in the Hexyl Salicylate Consortium surveyed the typical use concentrations of Hexyl Salicylate in cosmetic products in adults: the maximum use in fine fragrance products was up to 2%, with up to 0.5% in rinse off products and 0.3% in leave on products. A value of 0.001% is nominally applied for prospective use in oral care products, though no current use was reported by Consortium members. These % w/w use levels will be applied in the aggregate exposure assessment in this cosmetics safety evaluation.

For children, the Consortium intends to support different concentrations: due to the restriction of salicylic acid-containing cosmetic products for children below the age of 3 years a specific risk assessment is presented here for the use of 0.1% use of hexyl salicylate in cosmetic products for infants and children at the age of 0-3 years.

The exposure assessment is derived from data in 0-3 years old European infants and children from the recent Cosmetics Europe study in European Infants & Children (0–3 years old), Creme Report, 14th October 2022.

SCCS comment
The SCCS previously saw the data of the cited survey on infants' use of products and raised questions about it, asking for more details and explanations. These have not been received so far and, therefore, the SCCS considers the data from the study only as supporting evidence. The Applicant has submitted additional calculations based on body surface area as detailed below and as suggested in the Notes of Guidance.

The SCCS is of the opinion that the Applicant needs to explain whether the presence of Salicylic acid as an impurity or resulting from breakdown of Hexyl salicylate in the product will be taken into consideration. This is essential because Salicylic acid is not permitted in

products used by children below the age of 3 years (Annex III of Cosmetic Regulation EC/1223/2009).

3.2.1.2 Other uses

Hexyl Salicylate is also used as a fragrance ingredient in household cleaning products, detergents and air care products. A range of non-cosmetic consumer uses are included in the EU REACH dossier (https://echa.europa.eu/fr/registration-dossier/-/registered-dossier/14766/3/1/6).

3.2.2 Dermal / percutaneous absorption

3.2.2.1 *In vitro* animal skin absorption studies

No data available

3.2.2.2 *In vivo* animal skin absorption studies

No data available

3.2.2.3 *In vitro* human skin absorption studies

An OECD Test Guideline 428 study performed to GLP has been used to investigate absorption of Hexyl Salicylate *in vitro* using human skin as summarised in Table 1.

Table 1: Summary of method details from an OECD Guideline 428 *in vitro* human skin absorption study for Hexyl Salicylate

Exposure concentration/vehicle	Application site details	Observations	Reference
0.1, 20 or 100% ^{14}C-hexyl salicylate (99.8% purity) in dipropylene glycol. The corresponding amounts as applied in 6.4 µL were: 10.2 ± 0.1; 2130 ± 15; 10745 ± 57 µg/cm^2, respectively.	Split-thickness (0.2-0.4mm) previously frozen human abdominal or breast skin membrane (n=8) from 4 female donors. Hexyl salicylate applied for 8 hours duration using automated flow-through cells maintained at 32°C. The experiment was terminated at 24 hours by washing the skin with 3% soap solution, the skin was tape stripped. Receptor fluid (physiological saline with 6% PEG 20) measurements were taken.	Overall recovery of hexyl salicylate in human skin was 93.5% ± 2.0%, 97.6% ± 0.9%, and 98.5% ± 1.9% for the 0.1%, 20%, and 100% solutions, respectively.	Maas *et al* 2016 (Triskelion report)

An *in vitro* human skin absorption study for Hexyl Salicylate (CAS 6259-76-3) was conducted following OECD TG 428 guidelines for 24 hours and according to the guidelines expected by the SCCS (2021), except that the dose was in contact with the skin surface for 8 hours (as might mimic worker exposures) and not 24 hours as requested for the general population. Skin membrane integrity was assured by performing a tritiated water test. The results from the OECD TG 428 study by Maas (2016) are summarised below in Table 2.

Table 2: Skin absorption results for Hexyl Salicylate as applied to human skin *in vitro*: Group A = 100% neat liquid; Group B = 20% and Group C = 0.1% in solvent dipropylene glycol. RF = receptor fluid.

Group	A	B	C
Number of replicates	8	8	8
75 % absorbed in RF in first half of study	No	No	No
Maximal flux (µg.cm^{-2}.h^{-1})	0.84 ± 0.12	0.83 ± 0.21	0.007 ± 0.001
	Recovery (% of dose, mean ± SD)		
Amount in RF	0.15 ± 0.02	0.64 ± 0.15	1.00 ± 0.16
Amount in receptor compartment wash	0.009 ± 0.001	0.072 ± 0.017	0.037 ± 0.018
Amount in (stripped) skin	0.38 ± 0.14	2.33 ± 1.32	1.30 ± 0.62
Amount in tape strips 1+2	0.12 ± 0.09	2.62 ± 1.76	0.12 ± 0.08
Amount in tape strips 3-last	0.12 ± 0.08	2.16 ± 1.11	0.24 ± 0.15
Amount in skin wash	97.6 ± 1.8	87.9 ± 4.3	90.0 ± 3.1
Total recovery	98.5 ± 1.9	97.6 ± 0.9	93.5 ± 2.0
Absorbed dose [1]	0.53 ± 0.14	3.04 ± 1.43	2.34 ± 0.69
Potentially absorbed dose [2]	0.65 ± 0.19	5.20 ± 2.41	2.58 ± 0.77

[1] The absorbed dose is defined as the amount in the receptor fluid, the receptor compartment wash and skin membrane, excluding tape strips.
[2] The potentially absorbed dose is defined as the amount in the receptor fluid, the receptor compartment wash, the skin and stratum corneum (except for the first 2 tape strips)

Illustrative data from the tape strips from Group B in this experiment are shown in Figure 2.

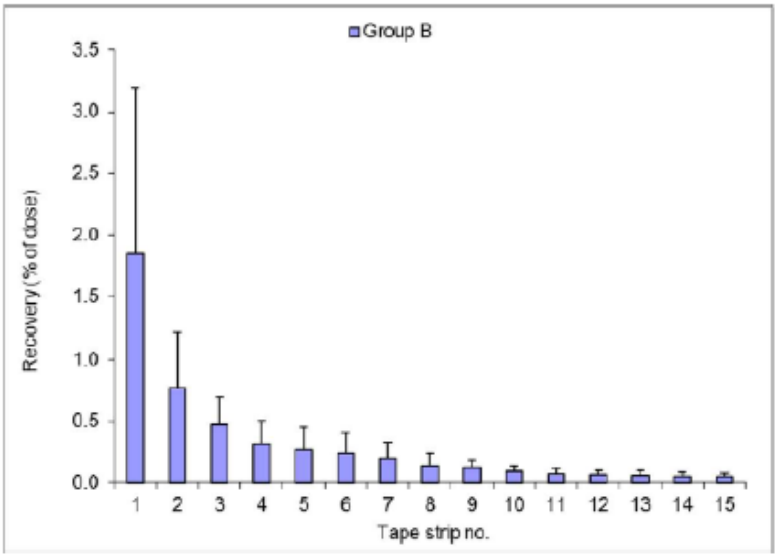


Figure 2: Distribution of [^{14}C]-Hexyl Salicylate in tape strips at 24 hours (Group B – 20% dose).

As can be seen in Table 2, the majority of the test material is rinsed from the skin surface and removed in the first few tape strips at 24 hours. Very low amounts penetrated into receptor fluid with the majority of the low-level absorbed dose remaining in the skin. The degree of total skin absorption is low for Hexyl Salicylate which is supported by its lipophilic nature.

The mean absorbed dose at 24 hours, as per SCCS Notes of Guidance (2021), which is measured as the compound-related radioactivity present in the receptor fluid + receptor compartment + epidermis + dermis, was 0.53 ± 0.14% (100% solution), 3.04 ± 1.43% (20 % solution) and 2.34 ± 0.69% (0.1% solution) of the applied dose, respectively.

To be conservative, taking the highest of these mean values for Group B, 3.04% plus 1 standard deviation of 1.43%, this leads to a total measured skin absorption value in this study of 4.47%.

Given that the dose was only on the skin for an 8-hour duration (to mimic worker exposure conditions), a correction factor of 3 has been applied to yield a value of 13.4% skin absorption to mimic the 24-hour use in a consumer safety assessment. This amount is based on measured radioactivity and it was hypothesised that this goes on to be absorbed mainly as salicylic acid following first pass skin metabolism by esterases; this was tested in the same study as described below.

3.2.2.4 *In vivo* human skin absorption

No data available.

3.2.3 Other studies on toxicokinetics

3.2.3.1 Dermal Metabolism data

From previous reviews on salicylates (CIR, 2019), it is known that n-alkyl salicylates are converted by skin esterases and systemically (liver) to salicylic acid as the main metabolite with the corresponding alcohol, in this case 1-hexanol. Various salicylates may be converted to salicylic acid at different kinetic rates and overall extent by the skin and systemically. The amount of systemic salicylic acid produced in the body is a function of both the dermal absorption of the salicylate across the *stratum corneum* and the extent of metabolic conversion of the absorbed substance by esterases. Not all salicylates may be substrates for the active site of the esterase enzymes. However, this can be tested *in vitro*.

In the same study by Maas (2016), dermal metabolism of Hexyl Salicylate was assessed using fresh human skin *in vitro*. Human breast skin was provided by female Donor 1 (n=3) and human abdomen skin by female Donor 2 (n=3). Upon arrival at the laboratory, subcutaneous fat was removed from the skin. Skin membranes were cut to a target thickness of 0.3-0.4 mm using a Dermatome (25 mm, Nouvag GmbH, Germany). The thickness of all skin membranes was measured with a digimatic micrometer (Mitutoyo Corporation, Japan). For logistic reasons, the skin discs were stored overnight, epidermal side up, on a gauze tissue slightly wetted with phosphate buffered saline (PBS) at 2-10°C until washing and start of exposure the following day. A two-compartment static diffusion cell system was used. 14C-Hexyl Salicylate was applied for 8 hours at 0.1% in dipropylene glycol. Approximately 15 µL of dose solution was applied to each 1.5 cm^2 skin sample, approximately 10 µl/cm^2. 24 hours later receptor fluid was collected as a single sample and skin samples were also stored at -18°C until processing and analysis. Radio high performance liquid chromatography (HPLC) was used to characterise and quantify Hexyl Salicylate and salicylic acid.

Analysis of the low level of radioactive substance that had penetrated into receptor fluid showed almost no parent compound (<1%). Salicylic acid was present at >94% in donor 1 and at >92% in donor 2. Analysis of the skin extracts showed some parent compound present, ranging from 5.73% to 10.70% in three replicates obtained from donor 1 and from 19.95% to 37.36% in three replicates isolated from donor 2. Salicylic acid was present at >86% in donor 1 and at >59.5% in donor 2. Hydrolysis of Hexyl Salicylate to salicylic acid was almost complete when applying a dose of 0.1% at 10 µl/cm^2 skin, therefore it will be assumed that at the low doses applied to the skin, 100% of the Hexyl Salicylate applied to human skin could be converted to salicylic acid *via* skin esterases within a period of 24 hours.

Dermal Systemic Availability - Conclusions from the Applicant:

The following generic statements regarding dermal absorption and metabolism are supported by the current body of data:

• There is good evidence that absorption of parent Hexyl Salicylate is low across human skin.

• A conservative skin absorption value of 13.4%, using a mean of (3.04% +1SD) x a correction factor of 3 to convert 8-hour worker exposure to 24-hour consumer exposure, will be taken forward from the OECD guideline 428 study (Maas 2016) for this safety evaluation. The plausibility of this skin absorption rate is supported by the good comparability with the skin absorption value for benzyl salicylate of 10.5% derived from an OECD Test Guideline 428 study, both compounds sharing similar LogP and MW.

• It is expected, also based on the evidence from methyl- and benzyl salicylate, that the majority of the substance measured by total radioactivity is in the form of salicylic acid.

• It is expected that subsequent phase 2 conjugation leads to effective clearance of salicylic acid (SCCS Opinion 2018).

SCCS comment
A value of 13.4% (3.04% + 1SD corrected for 24 hours, as described in 3.2.2.3) was calculated following a recent *in vitro* study using human skin that meets the basic criteria for skin absorption in SCCS Notes of Guidance (2021). This value will be used for the calculation of the MoS.

3.2.3.2 Oral ADME/kinetic data in animals or humans for salicylates

Salicylates are known to be well absorbed across the gut (Goodman & Gilman, 2006). There are no specific quantitative *in vivo* studies available on the ADME properties and kinetics of Hexyl Salicylate *via* the oral route in animals and humans, but oral absorption studies conducted on a similar analogue methyl salicylate indicate a rapid and nearly complete absorption following ingestion. As a result, for the assessment of potential effects of oral exposures to the salicylates from their use as cosmetic ingredients, an oral bioavailability of 100% is assumed (Belsito *et al.*, 2007). This is supported by the 2018 SCCS opinion on salicylic acid, where a 100% oral absorption was previously used (SCCS, 2018).

- Oral bioavailability

Davison *et al.* (1961) performed two studies in both rats and dogs for a similar substance, methyl salicylate.

Rat – 300 mg/kg bw (body weight) methyl salicylate in 2 % methylcellulose was administered by oral gavage as a single dose, to groups of 10 male Wistar rats (200-350g). Blood samples were taken at 20 and 60 min after administration. Plasma and brain tissues were analysed

for the presence of methyl salicylate and free salicylate. Methyl salicylate was completely hydrolysed within 20 min of a single oral dose. After 20 min, 217 and 8 mg/L free salicylate were found in the plasma and brain, respectively. After 60 min, these values were 278 and 42 mg/L, respectively. Methyl salicylate values were negligible.

Dogs – 300 mg/kg bw methyl salicylate was administered as a capsule in fasting male dogs weighing 12-15 kg. Blood was taken from the cephalic vein at 1 h and 4 h intervals, and the plasma was analysed. Hydrolysis was ~95% complete at both time points.

- Distribution

After absorption, salicylates and salicylic acid are distributed throughout most body tissues and most transcellular fluids, primarily by pH dependent passive processes. Salicylates are actively transported by a low-capacity, saturable system out of the cerebrospinal fluid (CSF) across the choroid plexus. Salicylates readily crosses the placental barrier. The plasma half-life for methyl salicylate is 2 to 3 h in low doses but may be as long as 15 to 30 h at high therapeutic doses or when there is intoxication (Gilman *et al.*, 1990) *e.g.* at high doses in animal toxicity studies. The *in vitro* protein binding of methyl salicylate is assumed to be around 86% based on a study in rats where the unbound fraction was found to be 14% (Dancik *et al.*, 2011). The plasma protein binding may be a major and important factor determining the extent of placental transfer and possibly also the teratogenicity of highly protein-bound drugs (Nau, 1986). The protein binding of acetyl salicylic acid is species dependent. In rats the protein binding is lower (30%) as compared to monkeys (~70%) and hence the placental transfer of free unbound salicylic acid is more from mother to fetus in rats as compared to monkeys.

- Excretion

Salicylates are excreted in the urine as free salicylic acid (10%), salicyluric 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 (Gilman, 1990).

3.2.3.3 Oral bioavailability of 1-hexanol metabolite

Upon hydrolysis of Hexyl Salicylate, salicylic acid and 1-hexanol are formed *in situ*. It is expected that the 1-hexanol will be absorbed rapidly across the gut and further metabolised in the liver by aldehyde and alcohol dehydrogenase enzymes to the corresponding hexanal and hexanoic acid metabolites. Endogenous Phase 2 metabolism in the body *via* the fatty acid pathway and tricarboxylic acid cycle will rapidly degrade 1-hexanol to carbon dioxide and its metabolites; excretion will be complete within 24 hours.

Conclusion on Oral ADME data from the Applicant:

Hexyl Salicylate, like methyl salicylate and benzyl salicylate, is expected to be rapidly and completely absorbed and metabolised, in both gut and liver tissue by first pass metabolism, to salicylic acid and 1-hexanol following oral exposure in both rat and humans. With rapid hydrolysis in the gut and liver, systemic exposure is primarily to salicylic acid and 1-hexanol, which do not accumulate in the body, and are rapidly excreted. This means that any point of departure from an oral toxicology study on either Hexyl Salicylate, salicylic acid or 1-hexanol can be regarded as a systemic point of departure (POD_{sys}).

SCCS comment
Based on the available data indicating rapid and complete absorption, the SCCS considers that an absorption value by oral route of 100% can be used in the risk assessment.

This value is also supported by another study performed with Methyl Salicylate (Yamagata *et al.,* 1976). This study is summarised in the Harmonised Classification and Labelling Report on Methyl Salicylate. See CLH report template (europa.eu)

3.2.3.4 Inhalation and absorption through the lung

There are no data on the extent of Hexyl Salicylate absorption in the lung. Based on the high log Po/w and low water solubility it is expected that Hexyl Salicylate will be poorly absorbed by the inhalation route. An assumption of 100% absorption is therefore very conservative.

3.2.4 Calculation of SED/LED

In the original submission, the Applicant presented an exposure assessment for children with the following information:
Due to the restriction of salicylic acid-containing cosmetic products for children below the age of 3 years a specific risk assessment is presented here for the use of 0.1% use of hexyl salicylate in cosmetic products for infants and children at the age of 0-3 years. The exposure assessment is derived from data in 0-3 years old European infants and children from the recent Cosmetics Europe study in European Infants & Children (0–3 years old), Creme Report, 14th October 2022. Based on this, the following Margin of Safety for the aggregate exposure to all products (including toothpaste) for the age group 0-3 years is calculated:

Table 3: Calculated **SED for the aggregate exposure** to all products (including toothpaste) for the age group 0-3 years (from submission 2024/01/30, updated with a new footnote (**))

Cosmetic product	Estimated exposure to product (P95) (mg/kg bw/day)	Maximum use concentration (%)**	SED (P95) (mg/kg/day) 13.4% dermal penetration	NOAEL (mg/kg/day)	MOS
All products as outlined below*	1200	0.1	0.161	75	466

* Baby oil, baby ointment/nappy cream/liniment, baby wind and weather cream/cold cream, baby wipes, bath product (added to bath water), body cream, conditioner, eau de toilette/parfum, face cream/lotion, facial cleansing wipes, hand cream, hand sanitiser, liquid hand wash product/liquid soap, shampoo, shower gel/body wash, sunscreen, toothpaste.
**Despite the listed maximum use concentration of 0.1% in this table, for toothpaste the defended max use concentration is 0.001%.

In a new submission, the Applicant presents a deterministic assessment, which according to the Applicant follows the SCCS approach for children under 3 years of age (see Table 4). In a survey the Applicant found that hexylsalicylate is also used in children hydroalcoholic fragrance and lip balm. Therefore, the Applicant has also included these products in the assessment although they are currently not covered in the SCCS Notes of Guidance.

1 **Table 4: SED for children under 3 years per product type**
2

Product type	Mean bodyweight (kg) EFSA (2012)	Body surface** (cm^2)	Daily exposure (g/d	Relative daily exposure (mg/kg bw/d) *	substance conc. (%)	Dermal absorption DAp (%)	SED (µg/kg/d)	SED Salicylic acid equivalent (µg/kg/d)
SHOWER GEL								
Adults	60	17500	0.19	2.79	0.50%	13.40%	1.87	1.16
Infants 0.5 - 1 yrs	8.8	4400	0.05	5.43	0.10%	13.40%	0.73	0.45
Toddlers 1 - 3 yrs	11.9	5600	0.06	5.11	0.10%	13.40%	0.68	0.43
HAND SOAP								
Adults	60	860	0.2	3.33	0.50%	13.40%	2.23	1.39
Infants 0 - 0.5 yrs	4.8	143	0.03	6.9	0.10%	13.40%	0.93	0.58
Infants 0.5 - 1 yrs	8.8	216	0.05	5.71	0.10%	13.40%	0.77	0.48
Toddlers 1 - 3 yrs	11.9	275	0.06	5.38	0.10%	13.40%	0.72	0.45
SHAMPOO								
Adults	60	1440	0.11	1.51	0.50%	13.40%	1.01	0.63
Infants 0 - 0.5 yrs	4.8	239	0.02	3.8	0.10%	13.40%	0.51	0.32
Infants 0.5 - 1 yrs	8.8	362	0.03	3.14	0.10%	13.40%	0.42	0.26
Toddlers 1 - 3 yrs	11.9	461	0.04	2.96	0.10%	13.40%	0.4	0.25
HAIR CONDITIONER								
Adults	60	1440	0.04	0.67	0.50%	13.40%	0.45	0.28
Infants 0 - 0.5 yrs	4.8	239	0.01	1.38	0.10%	13.40%	0.19	0.12
Infants 0.5 - 1 yrs	8.8	362	0.01	1.14	0.10%	13.40%	0.15	0.1
Toddlers 1 - 3 yrs	11.9	461	0.01	1.08	0.10%	13.40%	0.14	0.09

BODY LOTION								
Adults	60	15670	7.82	123.2	0.30%	13.40%	49.5	30.8
Infants 0 - 0.5 yrs	4.8	2597	1.3	269.98	0.10%	13.40%	36.2	22.5
Infants 0.5 - 1 yrs	8.8	3940	1.97	223.43	0.10%	13.40%	29.9	18.6
Toddlers 1 - 3 yrs	11.9	5014	2.5	210.29	0.10%	13.40%	28.2	17.5
FACE CREAM								
Adults	60	565	1.54	24.14	0.30%	13.40%	9.7	6.03
Infants 0 - 0.5 yrs	4.8	94	0.26	53.17	0.10%	13.40%	7.12	4.43
Infants 0.5 - 1 yrs	8.8	142	0.39	44	0.10%	13.40%	5.9	3.67
Toddlers 1 - 3 yrs	11.9	181	0.49	41.41	0.10%	13.40%	5.55	3.45
HAND CREAM								
Adults	60	860	2.16	32.7	0.30%	13.40%	13.15	8.17
Infants 0 - 0.5 yrs	4.8	143	0.36	74.57	0.10%	13.40%	9.99	6.21
Infants 0.5 - 1 yrs	8.8	216	0.54	61.71	0.10%	13.40%	8.27	5.14
Toddlers 1 - 3 yrs	11.9	275	0.69	58.08	0.10%	13.40%	7.78	4.84
LIPSTICK								
Adults	60	4.8	0.057	0.9	0.30%	100%	2.7	1.68
Infants 0 - 0.5 yrs	4.8	0.8	0.01	1.97	0.10%	100%	1.97	1.22
Infants 0.5 - 1 yrs	8.8	1.21	0.01	1.63	0.10%	100%	1.63	1.01
Toddlers 1 - 3 yrs	11.9	1.54	0.02	1.53	0.10%	100%	1.53	0.95
FRAGRANCE PRODUCTS								
Adults	60	200	0.28	4.67	2.00%	13.40%	12.51	7.77
Infants 0 - 0.5 yrs	4.8	33.14	0.05	9.67	0.10%	13.40%	1.3	0.81

Infants 0.5 - 1 yrs	8.8	50.29	0.07	8	0.10%	13.40%	1.07	0.67
Toddlers 1 - 3 yrs	11.9	64	0.09	7.53	0.10%	13.40%	1.01	0.63
TOOTHPASTE								
Adults	60		0.14	2.16	0.001%	100%	0.02	0.01
Infants 0 - 0.5 yrs	4.8		0.1	20.83	0.001%	100%	0.21	0.13
Infants 0.5 - 1 yrs	8.8		0.1	11.36	0.001%	100%	0.11	0.07
Toddlers 1 - 3 yrs	11.9		0.2	16.81	0.001%	100%	0.17	0.1

*For adult: data Table 3A from the SCCS NoG 12th, that is, not calculated with the default value of 60 kg, except for fragrance products from Ficheux 2017.

**Surface of children are retrieved from the Sharkey *et al.*, 2001.

SCCS comment

The report on children's use of cosmetics mentioned above has not been made available to SCCS in a finalised form and is not publicly available. The presented probabilistic calculations (Table 3) based on this data will therefore only be used as supporting evidence.

The Applicant uses the product categories suggested for children's aggregate exposure from the Notes of Guidance SCCS/1647/22 and additional product categories known to be used by children < 3 years. Since lipstick will seldomly be used by children <3 years old, the SCCS assumes that the product category "lipstick" was used as a surrogate for "lip balm". The selection of product categories is accepted by the SCCS in this Opinion. Once the survey by Cosmetics Europe becomes publicly available, the SCCS will consider whether the SCCS Notes of Guidance need to be updated for other product categories for children.

The exposure calculations for children lack an explanation on how the exposure estimates for children were derived. The Applicant refers to an "SCCS approach", but the SCCS would like to point out that the suggestion in Appendix A7.2.1 is just one possibility for calculating children's exposure in the current absence of better data, and is not an "SCCS approach". Recalculation by SCCS showed that the Applicant has used a correction factor for surface area to derive the exposure estimates. This implies that no children-specific use amounts have been taken into account, but it was assumed that the same amount per surface area would be used for children and adults. The resulting SED was then transformed into an SED as salicylic acid equivalent by applying a factor of 138.12/222.28 (derived from the molecular weight relation between SA and Hexylsalicylate). A 2017 study in Swiss children by Garcia-Hidalgo *et al.* shows that for toddlers 0-5 years old, the derived data for use amounts covers approximately the P95. The approach is therefore accepted.

No information was given on how the SED for toothpaste was derived. Considering data on toothpaste use by Gomez-Berrada *et al.*, 2018, Garcia-Hidalgo *et al.*, 2017 and Adé *et al.*, 2024, the SCCS uses for babies (0-3 years old) the P95 from Gomez-Berrada *et al.*, 2018, for children 2-6 years (1.18 g/application) to derive a daily amount of 2.4 mg/day (Frequency: 2 times per day). The data from Gomez-Berrada *et al.*, 2018, were assessed for a sample of N=96 children 2-6 years old 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 and assessed by means of a survey using pictures for 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.

The SCCS has recalculated the oral exposure to Hexyl Salicylate in toothpaste based on an amount of 2.4 g/day, retention factor 0.4 (SCCS/1647/22) and bodyweight according to EFSA (see Table 5). These values are aggregated with the exposure to dermal products from Table 4 (see Table 6).

Table 5: Oral exposure to toothpaste for children 0-3 years old

TOOTHPASTE							
	Body weight (kg)	retention factor	daily amount (g/d)	**calculated relative daily exposure (mg/kg bw/d)**	conc HexS (%)	**SED (µg/kg/d)**	**SED Salicylic acid equivalent (µg/kg/d)**
Infants 0 - 0.5 yrs	4.8	0.4	2.4	200	0.001%	2.00	1.25
Infants 0.5 - 1 yrs	8.8	0.4	2.4	109	0.001%	1.09	0.68
Toddlers 1 - 3 yrs	11.9	0.4	2.4	80.7	0.001%	0.81	0.51

Table 6: Aggregate exposure (oral exposure only from toothpaste)

	bodyweight (kg)	dermal SED (µg/kg bw /d)	Oral SED (µg/kg bw /d)	Agg. SED (µg/kg bw /d)	Agg. SED SA eq. (µg/kg bw /d)
Infants 0 - 0.5 yrs	4.8	58.4	2.00	60.4	37.9
Infants 0.5 - 1 yrs	8.8	49.0	1.09	50.0	31.4
Toddlers 1 - 3 yrs	11.9	46.2	0.81	47.0	29.5

3.3 TOXICOLOGICAL EVALUATION

3.3.1. Irritation and corrosivity

3.3.1.1 Skin irritation

- Animal data

A summary of the available skin irritation data in animal models is provided in Table 7 below.

Table 7: Skin irritation studies in animals for Hexyl Salicylate

Method	Dose (%)	Species	Results	References
Preliminary intradermal irritation screen (for modified Draize test)	0.1% (ICC)	Guinea pigs	Slight but perceptible irritation ICC = 0.1% ACC = 5%	Sharp (1978)
Preliminary topical irritation screen (for modified Draize test)	5% (ACC)	Guinea pigs	No irritation was observed	Sharp (1978)
Preliminary topical irritation screen (for maximization test)	10%, 20%, 50% 25% 50%	Guinea pigs	No irritation at 10% Slight erythema at 25% and 50%	RIFM (1981)
Preliminary intradermal irritation screen (for maximization test)	0.1%, 0.25%, 0.5%, 1.0%, 2.0% in DOBS/saline	Guinea pigs	Very slight erythema observed at 0.1% Slight erythema and edema observed at 0.25-2%	RIFM (1981)
Irritation evaluated as part of a photoallergy study	1-50% in 3:1 DEP/EtOH 100%	Guinea pigs	No irritation	RIFM (2003)
Irritation evaluated as part of phototoxicity study	100%	Miniature swine	No irritation	RIFM (1975b)
Primary irritation test	10%, 15%, 50% in DEP, 100%	Rabbits	Irritation observed at 50% and 100%	RIFM (1984); RIFM (1985); RIFM (1986a); RIFM (1986b)
Irritation evaluated as part of acute toxicity study	100%	Rabbits	Irritation observed	RIFM (1975a)
Irritation evaluated as part of phototoxicity study	100%	Mice	No irritation	RIFM (1975b)

Moderate skin irritation was reported in an OECD Guideline 404 study available in the ECHA registration dossier (RIFM, 1986). In this study, female rabbits were exposed to 50% and 100% Hexyl Salicylate in DEP for 4 hours under semi-occlusive conditions. At 50% Hexyl Salicylate, the mean erythema and oedema scores were respectively 2.0 and 1.4. The observed effects were fully reversible within 7 days. For the undiluted substance, the mean scores for erythema and oedema over the 24–72-hour period were respectively 2.0 and 2.16. In this case, it was reported that one rabbit showed remaining erythema and oedema after 7 days. Nevertheless, these effects concerned only one animal and no information was available for 14 days, which is the normal observation period recommended by OECD Guideline 404.

Overall, the results of the study could not trigger a classification for skin irritation according to the CLP criteria.

Pivotal animal irritation study: Mild to moderate irritation can occur, but Hexyl Salicylate is not a classifiable irritant.

- Human data

A range of skin irritation tests in humans are presented in Table 8.

Table 8: Skin irritation studies with Hexyl Salicylate in humans

Method	Dose (%)	Vehicle	Results	References
HRIPT (induction phase)	30	3:1 DEP:EtOH	3/103	RIFM (2004a)
Maximization pre-test	3	Petrolatum	No irritation	RIFM (1975b)
Primary irritation	100	N/A	No irritation	Basketter *et al* (2004)
Irritation evaluated as a part of phototoxicity study	0.3, 3, 30	3:1 DEP:EtOH	No irritation	RIFM (2004b)

In a 24-h patch test involving 56 subjects, Hexyl Salicylate was evaluated for skin irritation potential at concentrations of 0.3%, 3%, or 30% in 3:1 diethyl phthalate: ethanol. Results indicated Hexyl Salicylate was not an irritant of concern.

Skin Irritation & Corrosivity Conclusion from the Applicant:

Overall, Hexyl Salicylate shows some irritant reactions in animal models at concentrations of 25% and above and very low skin reactions in one human study at 30%, but it is not considered to be an irritant of concern at the concentrations used in cosmetic products.

3.3.1.2 Mucous membrane irritation / eye irritation

- *In vitro* data

No data

- *In vivo* data

An *in vivo* rabbit eye irritation study is reported in the ECHA REACH dossier (Schreiter U, 2000; https://echa.europa.eu/fr/registration-dossier/-/registered-dossier/14766/7/4/3), which is an OECD Guideline 405/EU Method B.5 GLP compliant study. Hexyl Salicylate was applied undiluted to the eyes of 4 female SPF albino rabbits in a volume of 0.1ml. Slight to well-defined signs of irritation were observed in the treated eyes at the 1, 24 and 48 hour examination time-points. However, all effects were fully reversible and no signs of irritation were observed after 72 hours. Under the conditions of this study, Hexyl Salicylate does not induce irritation of the eyes following its application. Based on these results, it does not need to be classified according to Regulation EC No. 1272/2008.

Eye Irritation Conclusion from the Applicant:

Undiluted Hexyl Salicylate is not an eye irritant *in vivo* and there is no risk of eye damage at the maximum concentrations of Hexyl Salicylate used in cosmetic products.

3.3.2 Skin sensitisation

From the Applicant:
Data for assessing the skin sensitisation endpoint are available for Hexyl Salicylate from new approach method (NAM) assays, animal models (LLNA and GPMT assays) and human studies.

For the purposes of cosmetics safety evaluation, in this dossier we present the body of evidence for evaluation in the context of risk assessment (see Table 9).

Table 9: A summary of skin sensitisation data available for Hexyl Salicylate: negative = non-sensitising.

Assay type	Methods & Observations	Outcome	Reference
OECD Toolbox v4.2 In silico predictions	No alerts found for hexyl salicylate (parent, autoxidation/metabolism)	Negative	Personal communications with RIFM
In chemico Direct Peptide Reactivity Assay (DPRA)	Hexyl salicylate analysed in triplicate, following a protocol equivalent to OECD TG 442C: 1.96%, 2.83%, and 0% depletion.	Negative	RIFM (2014)
In chemico Direct Peptide Reactivity Assay (DPRA)	Hexyl salicylate analysed in duplicate, following a protocol equivalent to OECD TG 442C: 3.9% and 1.1% depletion.	Negative – key event 1	Urbisch *et al* (2015)
In vitro KeratinoSens cell-based assay	Hexyl salicylate analysed in triplicate, following a protocol equivalent to OECD TG 442D. ARE-dependent luciferase gene activity >1.67-fold compared to the solvent control (cf. cell viability was <70%) A mean Imax (maximal induction factor of luciferase activity compared to solvent control) value of 2.64 was reported, while the EC 1.5 and mean IC50 were 28.67 µM and 58.29 µM, respectively	Negative – key event 2	RIFM (2015)
In vitro KeratinoSens cell-based assay	Hexyl salicylate analysed in triplicate, following a protocol equivalent to OECD TG 442D.	Negative – key event 2	Urbisch *et al*. (2015)

	Nrf2 gene expression was not induced when tested up to 4 mM		
In vitro h-CLAT cell-based assay	Hexyl salicylate stimulated CD54 2-fold with an EC200 of 52.73 µg/mL but did not result in stimulation of CD86 1.5-fold at the highest tested concentration of 177.20 µg/mL. Cell viability not reported.	Low level response – key event 3 Equivocal	Urbisch *et al*. 2015
In vitro U-SENS cell-based assay	Hexyl salicylate was found to induce CD86 expression 1.5-fold at 27 µg/mL.	Low level response - key event 3 Equivocal	Piroird *et al*. 2015
Murine local lymph node assay (LLNA)	5 treated groups of 4 animals received hexyl salicylate at 1%, 2.5%, 5%, 10%, or 25% w/v in 1:3 ethanol:diethyl phthalate. Negative control group of n=4 animals vehicle only. 25% α-hexylcinnamald-ehyde (HCA), a sensitiser, in 4:1 acetone:olive oil. SIs of 1.9, 3.6, 5.6, 10.8, and 10.8 were observed with 0.05%, 0.25%, 0.5%, 1%, and 2.5% w/v hexyl salicylate in 1:3 ethanol:diethyl phthalate, respectively. The EC3 value was calculated to be 0.18% (45 µg/cm$_2$).	Positive	Betts, 2006
Guinea-pig maximisation test (GPMT)	10 test and 8 control albino guinea pigs (Dunkin Hartley strain). Dose range finding: 0.1%, 0.25%, 0.5%, 1%, and 2% hexyl salicylate in 0.01% Dobs/saline (intradermal injections). 10%, 25%, and 50% hexyl salicylate in acetone was used for topical application. The concentration suitable for intradermal injection was found to be 1% in 0.01% Dobs/saline, while 40% and 10% hexyl salicylate in acetone were chosen for topical induction and challenge.	Negative	RIFM (Quest) 1981
Guinea-pig modified Draize test	n=10 inbred Hartley albino guinea pigs. Four intradermal injections were administered with 0.1 ml of hexyl salicylate at 2.5 times the ICC (Injection Challenge Concentration = 0.1%) at four sites overlying the two auxillary and the two inguinal lymph nodes. 14 days challenge with intradermal injection in one flank and a topical application in the other flank using 0.1 ml hexyl salicylate at 0.1% (ICC) and 5% (ACC), respectively. A second challenge was conducted 7 days later. Sensitisation reactions were observed after the second challenge.	Positive	Sharp 1978

1

Guinea-pig photoallergy test	Groups of n=5 Crl:IAF(HA)-hrBR outbred albino hairless guinea pigs. Topical induction: 0.3 ml dose of 100% hexyl salicylate applied on days 3,5,8,10,12 of induction phase. Day 22, topical challeng: 50% hexyl salicylate in 3:1 diethyl phthalate (DEP):ethanol and 100% hexyl salicylate. Test sites were observed at 1, 4 hours, and days 1,2 and 3. No sensitisation was observed.	Negative	RIFM (2003)
Human Maximisation Test	Patch sites pre-treated with 5% SLS in water. 3% (2070 µg/cm2) hexyl salicylate applied in petrolatum, under occlusion on the volar forearm n=22 subjects, 5 alternate day 48 hour periods. 10-14 days rest period. Challenge with 3% (2070 µg/cm2) hexyl salicylate.	Negative	RIFM (Epstein) 1975
Human Diagnostic patch test multicentre study	5% Hexyl Salicylate in petrolatum. No reactions were observed in 218 fragrance sensitive patients with proven contact dermatitis.	Negative	Larsen *et al* 2002
Human Repeat Insult Patch Test (HRIPT)	n = 103 males and females. 25-mm Hill Top Chamber System® was used occlusively. 0.3 mL of 30% or 35,433 µg/cm² hexyl salicylate in 3:1 diethyl phthalate:ethanol was applied to each patch on the left side of the back for 24 hours; Mon, Wed, Fri schedule. 9 patches over 3 weeks in total. 2 week rest then challenge with 0.3 mL of 30% hexyl salicylate. No reactions were observed.	Negative A No Expected Sensitisation Induction Level (NESIL) was derived as 35,400 µg/cm²	RIFM (Harrison) 2004

In silico, mechanistic and *in vitro* skin sensitisation (new approach method, NAM) data

From the chemical structure of Hexyl Salicylate, it does not contain any electrophilic protein reactive groups and mechanistically, from its parent structure, as predicted in the OECD Toolbox v4.2, it is not expected to be a skin sensitiser.

As per the skin sensitisation adverse outcome pathway (OECD, 2014), the *in vitro* direct peptide reactivity assay (DPRA), Keratinosens and the h-CLAT/U-Sens tests represent key events 1, 2 and 3, respectively. The results were evaluated following the OECD Guideline No. 497: Defined Approaches on Skin Sensitisation (OECD, 2021). Based on the two out of three 'Defined Approach', Hexyl Salicylate is predicted *in vitro* to be a non-sensitiser (see Table 13).

Animal skin sensitisation study data

Local Lymph Node Assay: An OECD Guideline 429 murine (n=4 female CBA mice) LLNA was performed on Hexyl Salicylate (using the vehicle 1:3 ethanol: diethylphthalate) to GLP (Betts, 2006). A very low EC3 (0.18%; EC3 = effective concentration that induces a 3-fold increase in local lymph node proliferative activity) was reported, indicating Hexyl Salicylate to be a classifiable sensitiser in this assay. This is a surprising result for Hexyl Salicylate that requires mechanistic interrogation. It is unlikely that an impurity has caused this strong reaction, as Hexyl Salicylate had an analytical purity of 98.5%. The detailed results of this

LLNA show that the increase in stimulation index is not always dose-dependent which may indicate that an additional mechanism may be involved. It is known (Maas 2016) that a metabolite (1-hexanol) can be formed *in situ* in the skin *via* the action of esterases, and the alcohol could go on to be oxidised further to 1-hexanal quite rapidly by skin alcohol dehydrogenase enzymes. If the test substance was applied to the mouse ear and 1-hexanal was formed but not effectively cleared, 1-hexanal could be the sensitising metabolite in this assay. Another explanation proposed was that irritation, being a confounding factor in the LLNA, may have led to false positive responses (Kolle *et al.*, 2019). However, overall, there is no apparent chemical or biological reason for the positive response.

Guinea-pig Maximisation Test: A Magnusson-Kligman Guinea-Pig Maximisation Test (GPMT) according to OECD Guideline 406 was performed using a group of 10 albino Dunkin Hartley guinea pigs weighing 440-554g. Induction consisted of intradermal injection followed one week later by a 48h occluded patch. The six intradermal injections were made to a 2.4 cm clipped, shaved area in the dorsal shoulder region. There were two 0.1 ml injections of 1% Hexyl Salicylate in 0.01% DOBS/saline, two 0.1 ml injections of 1% Hexyl Salicylate in 50% Complete Freund's Adjuvant, and two 0.1 ml injections of 50% Complete Freund's Adjuvant. Seven days later, the site was clipped and shaved, and induction was supplemented topically with a 48h occluded patch with 40% Hexyl Salicylate in acetone over the shoulder injection sites. Thirteen to fourteen days after application of the shoulder patch, the guinea pigs were challenged on the clipped and shaved flank using an 8 mm diameter filter paper patch saturated with 10% Hexyl Salicylate in acetone which was applied for 24 h under occlusion. Reactions were assessed at 24 and 48 h after patch removal. Three additional challenge applications with 10% Hexyl Salicylate in acetone were made at weekly intervals on the contralateral flanks. No sensitisation reactions were observed under the conditions of this study (RIFM, 1981).

Guinea-pig modified Draize test: Hexyl Salicylate was tested in guinea pigs using a modified Draize sensitisation study procedure in n=10 inbred Hartley albino guinea pigs initially weighing approximately 350 g each. Four intradermal injections were administered with 0.1 ml of Hexyl Salicylate at 2.5 times the ICC (Injection Challenge Concentration = 0.1%) at four sites overlying the two axillary and the two inguinal lymph nodes. Fourteen days later the animals were challenged with an intradermal injection in one flank and a topical application in the other flank using 0.1 ml Hexyl Salicylate at 0.1% (ICC) and 5% (ACC), respectively. A second challenge was conducted 7 days later. Sensitisation reactions were observed after the second challenge (Sharp, 1978).

Sensitisation was also assessed during a photoallergy test using groups of five Crl:IAF(HA)-hrBR outbred albino hairless guinea pigs. Topical induction was performed using a 0.3 ml dose of 100% Hexyl Salicylate. Doses were applied on days 3, 5, 8, 10 and 12 of the induction phase. On day 22, topical challenge was performed with 50% Hexyl Salicylate in 3:1 diethyl phthalate (DEP): ethanol and 100% Hexyl Salicylate. Test sites were observed at 1 and 4 hours, and days 1, 2 and 3. No sensitisation was observed (RIFM, 2003).

Human data

Diagnostic patch test studies: In a multicenter study, 218 fragrance sensitive patients with proven contact dermatitis were patch tested with various fragrance materials according to internationally accepted criteria. No reactions were observed with 5% Hexyl Salicylate in petrolatum (Larsen *et al.*, 2002).

Human Maximisation Test (HMT): A human maximisation test according to the method of Magnusson and Kligman (1969) was carried out with 3% Hexyl Salicylate in petrolatum on 22 adult volunteers. Application was under occlusion to the same site on the volar forearms or backs for five alternate-day 48-h periods. Patch test sites were pre-treated for 24 h with 5% aqueous sodium lauryl sulphate under occlusion. Following a 10-day rest period, a

challenge patch was applied to a fresh site for 48 h under occlusion. The challenge sites were pre-treated for 30 min with 2% aqueous SLS under occlusion on the left side of the back whereas Hexyl Salicylate was applied without SLS on the right side. Reactions to challenge were read at patch removal and 24 h after patch removal. No reactions were produced (RIFM (Epstein), 1975).
Human Repeat Insult Patch Test (HRIPT): A repeated insult patch test was conducted in 103 subjects (29 males and 74 females) to provide confirmatory evidence that Hexyl Salicylate is not a skin sensitiser in humans. During the induction phase a 0.3 ml aliquot of 30% Hexyl Salicylate in 3:1 DEP:EtOH was applied to Webril/adhesive patches (25 mm Hilltop_ Chamber System) on the left side of the back of each subject. This represented a dose of 35,433 µg/cm2. Patches remained in place and were kept dry for approximately 24 h and then removed. A series of nine induction applications were completed over a period of three weeks. A rest period of approximately 2 weeks followed the last induction. At the challenge phase, patches were applied as in the induction phase and kept in place for 24 h, after which time they were removed and the challenge sites were scored. The test sites were also scored at 48, 72 and 96 h post-patching. No sensitisation reactions were observed (RIFM (Harrison), 2004). **The HRIPT NOEL was therefore 35,433 µg/cm^2**.

Hexyl Salicylate has been classified **as a Category 4 substance** (infrequent cause of contact allergy in relation to level of exposure) with regard to its human skin sensitisation potential (Basketter *et al.*, 2014). This classification by authors of the study is based on an analysis of human data adapted from a number of published references. Substances in Category 4 are rarely important clinical allergens, because they require considerable/prolonged exposure to higher dose levels to produce sensitisation, which even then is unlikely to exceed 0.01% of the exposed population.

Conclusion from the Applicant:

The skin sensitisation potential of Hexyl Salicylate has been investigated extensively. All studies in humans, which carry the greatest weight, have been consistently negative indicating that Hexyl Salicylate is a rare sensitiser in humans, if any. NAM *in silico* and *in vitro* data also support this conclusion. Two rodent assays show anomalous results for Hexyl Salicylate, indicating that rodent ADME or mechanisms of action may be different to humans.

Taken from the RAC opinion

Conclusion:

With EC3 values =< 2% in the LLNA, Hexyl Salicylate fulfils criteria for classification Skin Sens. 1A according to the CLP guidance. Regarding human data, the HRIPT cannot be used for the purpose of classification due to its low reliability. Nevertheless, the maximisation assay and both diagnostic studies were negative and were considered reliable.

There are several possible reasons for the absence of sensitising reactions in these studies:

- The patch test for Hexyl Salicylate is not marketed. In fact, 46 fragrances are marketed by Chemotechnique for patch testing, but Hexyl Salicylate is not part of the list. Hexyl Salicylate was therefore only tested for prospecting purposes. This could explain why only 2 diagnostic studies with different concentrations of this substance have been published.
- Hexyl Salicylate is not included in the list of 26 sensitising fragrances for humans that require labelling. Therefore, it would be difficult to determine whether Hexyl Salicylate is responsible for contact dermatitis following exposure to a fragrance.
- Although this substance is widely used in perfumes, the concentrations used are low. In leave-on products for face and body, the concentrations are between 0.02 and 0.03 % and between 0.08 and 0.12 %, respectively. The highest concentrations are used in rinse-

off products, reaching 0.52 % in soaps and cleansers (Cosmetic Ingredient Review on salicylic acid and salicylates (2018)). These concentrations are below the concentration limits recommended by the International Fragrance Association (IFRA).

Therefore, the absence of sensitising reactions observed in humans could be due to primary prevention related to these concentration limits, more than the absence of sensitising properties.
Due to the significant discrepancies between positive animal data and negative human studies, sub-categorisation does not seem appropriate according to the CLP-guidance.
With the positive results of the LLNA of good quality, Category 1A would be justified. However, since data are not sufficient for sub-categorisation, RAC agrees with the DS that Hexyl Salicylate should be classified Skin Sens. 1 – H317.

SCCS comment
The SCCS agrees with the Applicant and the RAC opinion that the available human, animal and NAM data are contradictory. In a well-conducted LLNA, Hexyl Salicylate was positive at a relatively low concentration, whereas the GPMT was negative. *In silico* data showed no protein binding alerts, which was confirmed in the DPRA. In addition, the Keratinosens was negative, whereas the h-CLAT and U-SENS were positive. If for example the 2o3 DA (two out of three defined approach) was performed, according to OECD Guideline 497, Hexyl Salicylate would have been considered as a non-sensitiser. Human evidence is limited, but the data available is all negative. This was already recognised in an earlier SCCS Opinion on fragrance allergens (SCCS/1459/11) and no new evidence indicating that Hexyl Salicylate is a relevant skin sensitiser in humans has emerged in literature.

Despite these considerations, the SCCS notes that Hexyl Salicylate is classified as a skin sensitiser and the draft results of the infant survey by Cosmetics Europe that have been available to the SCCS show that a significant proportion of babies had "skin issues". As such, the children with damaged skin could be exposed to cosmetic products containing Salicylates, and potentially Salicylic Acid. This raises additional concern to the SCCS. This is an important consideration for comprehensive risk assessment because Salicylic Acid is not permitted in cosmetic products used by children under the age of 3 years (Annex III of Cosmetic Regulation EC/1223/2009) + (ref. not published).

3.3.3 Acute toxicity

3.3.3.1 Acute oral toxicity

There is one study in animals (RIFM 1975; Lapczynski *et al.,* 2007) covering the acute oral toxicity of Hexyl Salicylate as summarised in Table 10.

Table 10: Acute oral toxicity studies for Hexyl Salicylate

Reference	Species	Dosing (g/kg)	Oral LD_{50} (mg/kg)	Observed effects
RIFM 1975	Rats	Single oral dose N=10 animals per group	>5000	1/10 deaths at the top dose on Day 4. Urinary incontinence observed at 24h.

The animals in this study were observed daily for a period of 14 days for any signs of systemic toxicity.

3.3.3.2 Acute dermal toxicity

There is one study in animals (RIFM 1975; Lapczynski *et al.,* 2007) covering the acute dermal toxicity of Hexyl Salicylate as summarised in Table 11.

Table 11: Acute dermal toxicity study for Hexyl Salicylate

Reference	Species	Dosing	Dermal LD_{50} (mg/kg bw)	Observed effects
RIFM 1975	Rabbit	Single dermal dose. Neat hexyl salicylate N=10 animals per group	>5000	0/10 deaths. No clinical signs of toxicity.

The animals in this study were observed daily for a period of 14 days for any signs of systemic toxicity.

3.3.3.3 Acute inhalation toxicity

There are no acute inhalation toxicity data available in animals for Hexyl Salicylate. The use of Hexyl Salicylate in consumer products for decades has revealed no adverse effects in the lung. Hexyl Salicylate is not irritating to the skin and eye at the concentrations used in cosmetic products and therefore, is not expected to be irritating or toxic to respiratory tract and lung at the concentrations used in cosmetic products.

3.3.3.4 Acute subcutaneous toxicity

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3.3.3.5 Acute intraperitoneal toxicity

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Acute Toxicity Conclusion from the Applicant:

Hexyl Salicylate is not acutely toxic *via* any route of exposure.

3.3.4 Repeated dose toxicity

No repeat dose toxicity data are available on Hexyl Salicylate. Given that Hexyl Salicylate itself is not regarded as the main toxicant, but rather salicylic acid as the chief hydrolysis product, for the purposes of performing a cosmetics safety assessment, this section discusses the available repeat dose toxicity data and conclusions for the primary Hexyl Salicylate metabolites salicylic acid and 1-hexanol (Belsito *et al.*, 2007). All data for salicylic acid were recently reviewed by the SCCS in its recent opinion (SCCS, 2018).

SCCS comment
As the SCCS recently published a new Opinion on salicylic acid, data on this metabolite are not reported in this Opinion. Only data provided by the Applicant on 1-Hexanol are reported in this Opinion.

3.3.4.1 Repeated dose sub-acute and sub-chronic oral / dermal / inhalation toxicity

1-Hexanol

- Oral route

As summarised in the ECHA REACH dossier for 1-hexanol, a 13-week dietary study in rats using hexan-1-ol reported a No Observed Adverse Effect Level (NOAEL) of 1127 mg/kg (study reported as by Scientific Associates Inc., 1966). No adverse effects were noted at any of the dose levels administered during the study. The results of this key study are supported by the reliable (Klimisch score 2) 3-week feeding study in rats which reported a NOAEL of approximately 1000 mg/kg bw/day (Moody and Reddy, 1978, 1982). In addition, a 13-week study in dogs reported a NOAEL for 370 mg/kg bw/day for male dogs and 435 mg/kg bw/day for female dogs (study reported as by Scientific Associates, 1966). Although this study had some methodology discrepancies, it is still considered to be reliable (Klimisch score 2).

- Dermal route

No data reported on 1-hexanol

- Inhalation

There are no data for Hexyl Salicylate that were generated before March 2013. Reference to the similar ingredient methyl salicylate is provided below.

Methyl salicylate

Gage (1970) reported a study on methyl salicylate in rats (n=4; average weight 200g) where 20 x 7 h exposures were administered at 120ppm in a saturated atmosphere of 700 mg/m^3. The atmospheres were dynamic and passed through the exposure chamber. Haematological parameters were measured and the following organs were taken for microscopical examination after fixation in formol-corrosive: lungs, liver, kidneys, spleen, and adrenals; and occasionally heart, jejunum, ileum, and thymus. No toxicity was reported and all organs appeared normal at necropsy. This provides evidence for a NOEC for methyl salicylate of 700 mg/m^3.

3.3.4.3 Chronic (> 12 months) toxicity

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Conclusions from the Applicant on repeat dose toxicity studies:

As there are no pre-2013 repeat dose data on Hexyl Salicylate, evidence that can be used to perform a cosmetics safety assessment has long been provided from data on its main metabolites, salicylic acid and 1-hexanol, to which the body may be systemically exposed.

No significant concerns are presented for salicylic acid in terms of repeat dose endpoints as summarised by the SCCS conclusion below. Similarly, there are no safety concerns regarding the generation of a 1-hexanol metabolite.

SCCS comment
SCCS noted that there are no repeated dose toxicity studies available on Hexyl Salicylate and will therefore rely on its main metabolite, salicylic acid, for the safety assessment.

During the consultation, SCCS was informed that, in the context of REACH Regulation, a decision on testing proposals (TPE) is ongoing for Hexyl Salicylate. The deadline for submission is 23 February 2026.

A. Information required from the registrants subject to Annex IX of Reach:

- Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) by oral route, in rats with an additional reproductive toxicity cohort of females included to cover the endpoints of a reproduction/developmental screening test (according to OECD TG 421)

This Opinion may therefore require updating when this study becomes available, and depending on the study results.

Ref. https://echa.europa.eu/documents/10162/7dd23fc0-a3e3-910b-55f3-4c17bc72030c

3.3.5 Reproductive toxicity

No reproductive/developmental toxicity data are available on Hexyl Salicylate. The proposal for classification is based upon read across to salicylic acid and methyl salicylate data, and the assumption that Hexyl Salicylate is metabolised to the same common metabolite, salicylic acid.

Given that Hexyl Salicylate itself is not regarded as the main toxicant, but rather salicylic acid as the chief hydrolysis product, for the purposes of performing a cosmetics safety assessment, this section also discusses the available reproductive/developmental toxicity data and conclusions for the primary metabolite salicylic acid and 1-hexanol to which the body may be principally exposed.

SCCS comment
As the SCCS recently published a new Opinion on Salicylic Acid, data on this metabolite are not reported in this Opinion. Only data provided by the Applicant on other analogues are reported in this Opinion.

3.3.5.1 Reproductive and Developmental – oral

As the main premise for the safety evaluation (given there are no repeat dose toxicology data for Hexyl Salicylate) is a confident analogue read-across using data on the metabolite salicylic acid, it is not necessary to rely on safety data for other structural analogues in this dossier.

However, for awareness and completeness, there is evidence concerning other simple alkyl salicylates that substantiates the outcome from the safety evaluation performed in this dossier and can lend added confidence to the findings.

Cyclohexyl Salicylate

An OECD Guideline 415 one-generation reproduction toxicity study was performed to GLP in Wistar rats treated orally with Hexyl Salicylate (Schmidt, 1995). Dose levels were 60, 180 and 540 mg/kg bw/day in corn oil. Some general toxicity effects were seen in the F0 generation at the top dose, and a NOAEL could be determined at 180 mg/kg bw/day; this dose had no effects on reproduction. In males a NOAEL was defined as 540 mg/kg bw/day.

With the F1-generation, a NOAEL of 180 mg/kg bw/day as effects on litter responses, survival, growth and behaviour were seen at the top dose.

An embryotoxicity study (including teratogenicity) was performed to GLP (Pitterman, 1996). Dose levels were 0, 40, 120 and 360 mg/kg bw/day, dosed daily in arachidis oil from day 6 to 15 of gestation. A standard dose volume of 5ml/kg bw was used. Each group was n=24 female rats. There were no effects of treatment seen in dams and there were no embryotoxic or teratogenic effects seen up to 360 mg/kg/day.

SCCS comments
Full reports of these 2 studies on Cyclohexyl Salicylate have not been provided to the SCCS and only limited information is available on the ECHA website.

Methyl Salicylate

An SCCS Opinion was published for methyl salicylate in 2021 (SCCS, 2021). The pivotal study that can be used to derive a point of departure (POD) for reproductive and development toxicity is that from a 3-generation study by Collins *et al.* (1971), where the derived POD is 75 mg/kg bw/day. This provides further assurance that the POD derived from salicylic acid data is relevant to use in this safety evaluation.

3.3.5.2 Reproductive and Developmental – dermal

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Conclusions from the Applicant on reproduction and developmental toxicology studies:

Salicylates do not affect fertility or reproduction. As there are no specific reproductive and developmental data on Hexyl Salicylate from before March 2013, evidence is provided for cosmetics safety assessment from data on its main metabolites, salicylic acid and 1-hexanol, to which the body may be principally exposed. Since 1-hexanol is not classified for reproductive toxicity, the focus is on the more relevant metabolite salicylic acid data.

SCCS comments
The SCCS agrees that salicylic acid is a developmental toxicant. Harmonised classification of Salicylic Acid was recently published in Regulation 2018/1480 and is classified as Repr. 2 (H361d Suspected of damaging the unborn child). For MoS calculation, SCCS uses the developmental NOAEL of 0.1% (75 mg/kg bw/day) derived from Tanaka *et al.* (1973a). The developmental effects observed in this study are the most sensitive effects after repeated exposure to salicylic acid. This is also in agreement with the previous SCCNFP Opinion (2002) and is also supported by Tanaka *et al.* (1973b).

In addition, due to the evidence for high (100%) oral bioavailability in humans, the oral NOAEL of 75 mg/kg bw/day is defined as systemic NOAEL ($NOAEL_{sys}$) by SCCS for salicylic acid.

This POD for Salicylic Acid can act as a conservative surrogate POD for Hexyl Salicylate. On a molar basis, 1 mole of Hexyl Salicylate is converted to 1 mole of Salicylic Acid. An assumption is made that 100% of Hexyl Salicylate is metabolised to Salicylic Acid and 1-hexanol, and salicylic acid is the driver of any observed Hexyl Salicylate toxicity. The salicylic acid $NOAEL_{sys}$ = 75 mg/kg bw/day. A salicylic acid equivalent SED was calculated (see Table 6) and compared with this POD.

During the consultation, the SCCS was informed that, in the context of REACH Regulation, a decision on testing proposals (TPE) is ongoing for Hexyl Salicylate. The deadline for submission is 23 February 2026.

A. Information required from the registrants subject to Annex IX of Reach:
- Prenatal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) by oral route, in one species (rat or rabbit)

B. Information required from the registrants subject to Annex X of Reach:
• Prenatal developmental toxicity study (Annex X, Section 8.7.2.; test method: EU B.31./OECD TG 414) by oral route, in a second species (rat/rabbit)

This Opinion may therefore require updating when these studies become available, depending on the study results obtained.

Ref.
https://echa.europa.eu/fr/registration-dossier/-/registered-dossier/14203/7/9/3
https://echa.europa.eu/documents/10162/7dd23fc0-a3e3-910b-55f3-4c17bc72030c

3.3.6 Endocrine disrupting effects

Hexyl Salicylate has not been identified by the European Commission as a suspected endocrine disruptor. However, its major metabolite is salicylic acid, which is on the Commission List of suspected endocrine disruptors. There is no convincing evidence that reproductive and developmental effects are caused by an endocrine mechanism of action: the rationale for reaching this conclusion is provided below. SCCS has recently adopted an Opinion on Salicylic acid (SCCS/1646/22, June 2023).

In December 2017, the Danish Centre on Endocrine Disrupters published a report (Hass *et al.,* 2018) in which it was evaluated that salicylic acid meets the WHO definition of an endocrine disruptor (ED) from 2002. It was concluded that there was moderate evidence of with an anti-androgenic mode of action which seemed plausibly linked to adverse effects as inhibition of androgen response to hCG (Human chorionic gonadotrophin) stimulation in humans and decreased testicular weight, decreased activity of testicular enzymes and impairment of spermatogenesis in rats. It is the view of the SCCS that although the toxicology evidence suggests salicylic acid is a developmental toxicant (observations are on skeletal abnormalities), there is no definitive evidence that salicylic acid causes adverse health effects in an intact organism directly as a result of an endocrine mechanism. Nor is an anti-androgenic mode of action hypothetically linked to skeletal abnormalities. This connection between mode/mechanism of action and observed adverse effect is a basic requirement for substances falling within the Commission's ED criteria and the ECHA/EFSA Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009 and based upon the WHO IPCS 2002 Definition.

Level 1 and 2 evidence is available for evaluating salicylic acid within the OECD Endocrine Disruption Framework. Salicylic acid has been tested in the US EPA Endocrine Screening Program in a range of *in vitro* assays (Level 2) and there was no evidence of an endocrine activity in the assays tested.

There are no *in vivo* assays with salicylic acid that explicitly investigated a potential endocrine mode of action. However, as mentioned above, there is no evidence from the available data of an adverse effect of salicylic acid as a result of an endocrine mechanism, *e.g.*, there is no adverse effect on fertility.

The evidence given the greatest weight in the Danish review for salicylic acid in drawing their conclusions is from Level 4 data on read-across analogue aspirin (acetylsalicylic acid, ASA) and are of questionable quality with limitations in the data as discussed below. There are no level 5 studies.

Level 1 data: Existing Data and Non-Test Information

Chemical structure and physicochemical properties *e.g*. as per Table 1.

Level 2 data: *In vitro* assays providing data about selected endocrine

Mechanism(s)/pathways(s) (Mammalian and non-mammalian methods)
Salicylic acid has been tested (purity >90%) in the Endocrine Disruptor Screening Program (EDSP) within the US EPA Tox21 programme.
https://comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID7026368#invitrodb-bioassays-toxcast-data
There was no activity seen in 18 oestrogen receptor assays, there was no activity in 9 thyroid receptor assays, and it was not steroidogenic in 2 assays. Of the 15 androgen receptor assays, only one was registered as positive above a cut-off value but this was a marginal and inconclusive observation. There was no evidence that salicylic acid was endocrine active in these systems.
Similarly, no *in vitro* assays were positive in the EDSP for the structurally related substance acetylsalicylic acid (aspirin).

Level 3 data: *In vivo* assays providing data about selected endocrine

mechanism(s)/pathway(s)
No data

Level 4 studies (on a read-across analogue aspirin):

Study 1

In a developmental toxicity study (Gupta *et al.*, 2003), 7 pregnant rats were given ASA by oral (gavage) administration between days 6 to 17 after mating. At the highest dose (250 mg/kg bw/day) 2 fetuses from 2 litters were observed to have hypoplastic testes. There were no hypoplastic testes in the control group. There were no other findings in that study suggestive of an anti-androgenic mode of action (*e.g.* cryptorchidism or hypospadias). The testes findings were accompanied by severe maternal and fetal toxicity at the same dose, which strongly suggests an absence of a specific endocrine mode of action but rather an adverse secondary impact by general toxicity.

Study 2

In another *in vivo* rat study (Kristensen *et al.,* 2011) females were treated with ASA at doses of 150, 200 or 250 mg/kg bw/day between gestation days 13-21. In Hass *et al.* (2018), it was noted that reduced anogenital distance in male rats (a marker of impaired androgen signalling) was seen. The SCCS notes that when corrected for bodyweight, no effect on anogenital distance was apparent. This is significant because proper evaluation of changes in this parameter requires correction for bodyweight. That study also showed reduced *in vivo* production of testicular testosterone in all dose groups, with significance in the mid dose group. There was however no dose-response for this effect and in view of the SCCS, it is unlikely to be related to treatment. It is interesting to note that these data are not presented in the main article but embedded in the supplementary materials. In that same study, questionnaires were given to Danish and Finnish women to report on their analgesic use during pregnancy. The authors discovered that in the Danish cohort, an association was found

between cryptorchidism and use of analgesics. The association was not found in the Finnish cohort. The numbers of pregnancies evaluated were small, and several factors were not taken into account, such as the familial occurrence of undescended testes and the association of this finding with multiple gestation. In general, human data from observational epidemiological studies based on questionnaires are susceptible to recall bias since self-reporting information may be incomplete or inaccurate (as the authors mentioned themselves). The critical factor is the lack of robust exposure data which is needed to strengthen the assumed association between cryptorchidism and use of analgesics. Another confounding factor with respect to this study may be that humans are generally exposed to measurable levels of salicylic acid *via* dietary sources such as fruits and vegetables; one study even found that vegetarians not taking aspirin had urinary levels of salicylic acid higher than the non-vegetarians (Lawrence *et al.*, 2003).

Study 3

The suggested link between ASA and effects on spermatogenesis comes from a study published in 1980, in which groups of 6 young (21-24 days of age) or adult (age not specified) rats received 50 mg ASA/kg bw/day for 30 days (Didolkar *et al.*, 1980). After treatment, testes were weighed and subjected to analysis of the activity of certain enzymes and histopathology. These assessments suggested a significant decrease in testicular weight in the younger (but not in the older) animals, and reduced activity of testicular sorbitol dehydrogenase and hyaluronidase. Fewer spermatids were also observed in the treated groups. The results of this study need to be viewed with caution, since it was a low-powered study (6 animals/group) and not thoroughly documented. If these effects were real, they do not necessarily indicate an endocrine mode of action. Given the many other *in vivo* studies available on ASA and methyl salicylate as summarised in the draft SCCS opinion on SA, none shows any clear adverse effects relevant to an anti-androgenic mode of action (neither in terms of development nor fertility), so it seems unlikely that SA is anti-androgenic *in vivo*.

The overall conclusion is therefore that there is insufficient data to show that SA causes adverse effects arising from an ED mode of action. .

The appendices of Hass *et al.* (2018) also discuss the ability of SA to displace thyroid hormones from plasma proteins. The report concludes that 'no studies investigated endpoints relevant for evaluation of adverse effects related to thyroid disruption were found'. It should however be noted that the SCCS Opinion quotes historical carcinogenicity studies on ASA performed in rats and mice, both of which were negative.

Conclusion from the Applicant:

On the basis of evidence available to date, there is no definitive data to show that salicylic acid (and hence Hexyl Salicylate) causes adverse effects in an intact organism arising from an endocrine mode of action.

SCCS comment

For the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009, and based upon the WHO IPCS 2002 Definition, a connection between mode/mechanism of action and observed adverse effect is a basic requirement for substances falling within the Commission's ED criteria and the ECHA/EFSA Guidance. There is no evidence from the available *in vivo* data of an adverse effect of Hexyl Salicylate and salicylic acid resulting from an endocrine mechanism, *e.g.,* there is no adverse effect on fertility. The available evidence is therefore not strong enough to conclude on an endocrine effect linking a mode of action with an adverse outcome. *In vitro* data did not show any estrogenic, or any androgenic, thyroid or steroidogenic properties of Hexyl Salicylate and salicylic acid.

3.3.7 Mutagenicity / genotoxicity

The *in vitro* mutagenicity and genotoxicity studies that have been performed for Hexyl Salicylate are summarised below.

3.3.7.1 Mutagenicity / genotoxicity *in vitro*

Bacterial gene mutation assay (Ames test)

Guideline:	OECD 471, EU B.13/14
Species/strain:	*S. typhimurium*, TA98, TA100, TA102, TA1535, TA1537;
Replicates:	Triplicates in two independent tests
Test substance:	Hexyl Salicylate
Batch:	50554361
Purity:	data not provided
Solvent:	dimethyl sulfoxide (DMSO; 50 µl/plate)
Positive controls:	Sodium azide, 2-nitrofluorene, 9-aminoacridine, mytomycin C, and 2-aminoanthracene
Metabolic activation:	S9 liver fraction from Aroclor 1254 pretreated male rats
Concentrations:	experiment I: 50, 150, 500, 1500, 5000 µg/plate without S9-mix 50, 150, 500, 1500, 5000 µg/plate with S9-mix experiment II: 15 (for TA102 and TA 1537), 50, 150, 500, 1500, 5000 µg/plate without S9-mix 5 and 15 (for TA102 and TA 1537), 50, 150, 500, 1500, 5000 µg/plate with S9-mix
Treatment:	experiment I: direct plate incorporation method with 48-72 h incubation without and with S9-mix experiment II: direct plate incorporation method with 48 – 72 h incubation without S9-mix
GLP:	in compliance
Study period:	30.5.2000

The mutagenicity of the substance Hexyl Salicylate was studied with five mutant strains of Salmonella typhimurium (TA1535, TA1537, TA98, TA100, and TA102). The investigations were carried using the standard plate incorporation assay with and without liver homogenate (S9) from Aroclor 1254 pre-treated male rats as metabolic activation system.

Hexyl Salicylate was dissolved in DMSO and tested in concentrations of 5 to 5000 µg per plate in the presence and 15 to 5000 µg per plate in the absence of S9. In the presence of S9-mix Hexyl Salicylate was bacteriotoxic towards the strain TA1537 at 500µg/plate, towards the strains TA100 and TA102 at 1504 µg/plate and towards the strains TA98 and TA1535 at 5000 µg/plate. In the absence of S9-mix Hexyl Salicylate was bacteriotoxic towards the strain TA1537 at 500 µg/plate and towards the strains TA98, TA100, and TA102 at 500 µg/plate. Precipitation of the test compound at the plates was observed at 1500 and 5000 µg/plate. Sodium azide, 2-nitrofluorene, 9-aminoacridine, mytomycin C, and 2-aminoanthracene served as positive controls to confirm the reversion properties and the specificity of the bacterial strains as well as the efficacy of the metabolising system.
In the concentration range investigated, Hexyl Salicylate did not induce a significant increase in the mutation frequency of the tester strains in the presence or absence of a metabolic activation system.

In conclusion, these results indicate that Hexyl Salicylate under the experimental conditions described, was not mutagenic to Salmonella typhimurium strains TA1535, TA1537, TA98, TA100, and TA102 in the presence and absence of a metabolizing system.

King MT, 28 February 2000 Study (AM02000N)

SCCS comment
Data on the purity of test item have not been provided. Hexyl Salicylate was dissolved in DMSO, but no description of the test solution preparation was given. Precipitation of the test substance on the plates was observed at 1500 and 5000 µg/plate. The SCCS noted that Hexyl Salicylate was bacteriotoxic in the presence and absence of S9-mix towards several strains at concentrations 500 or 1500 µg/plate and above.

***In vitro* micronucleus assay**:

Guideline:	OECD 487 (2016)
Test system:	Isolated human lymphocytes
Replicates:	duplicates
Test substance:	Hexyl Salicylate
Batch (Purity):	80854 (99.6%)
Solvent:	dimethyl sulphoxide (DMSO)
Metabolic activation:	Phenobarbital-5,6 Benzoflavone-induced rat liver (S9 mix),
Concentrations and treatment:	
	3h without S9: 43.90, 65.84, 98.77 µg/mL
	3h + S9-mix: 98.77, 148.1, 222.2 µg/mL
	24h without S9-mix: 29.26, 43.90, 65.84 µg/mL
After treatment exposure:	Cytochalasin B (cytoB) 6 µM (after 3h exposure cyoB 21h, in 24h exposure added simultaneously with test item)
Positive controls:	-S9: Mitomycin C (MMC): 50 ng/mL (3 h), 30 ng/mL (24 h)
	Colchicine: 7.5 ng/mL (24 h)
	+S9: Cyclophosphamide (CP) 4 /mL (3h)
Negative control:	Vehicle
Statistics:	Pair-wise statistical analysis employing a one-sided Fisher's Exact test, Cochran-Armitage trend
GLP:	in compliance
Study period:	November 3, 2022

Hexyl Salicylate was tested for its potential to induce micronucleus formation in the *in vitro* micronucleus test. Lymphocytes isolated from fresh whole human blood were used in the study. In all treatments, the solvent used for the test item was dimethyl sulphoxide (DMSO). Based on findings in the preliminary assessment of solubility, the test item was prepared in DMSO at 50.00 mg/mL. The test item was then prepared in a dilution series, typically with a 1.5-fold dilution factor. Cells were cytokinesis blocked using cytochalasin B (cytoB). To enable calculation of the Cytokinesis Block Proliferation Index (CBPI), in order to determine cytotoxicity, at least 500 cells from appropriate cultures were scored. For the selected concentrations, the micronucleus frequency was determined in 2000 binucleated cells per concentration. The final concentration ranges analysed for micronuclei were: 3h +S9 treatment schedule 98.77 to 222.2 µg/mL 3h -S9 treatment schedule 43.90 to 98.77 µg/mL continuous treatment schedule (24h -S9) 29.26 to 65.84 µg/mL

The recommended maximum level of cytotoxicity (55 ± 5%) was achieved in all treatment schedules. At the highest concentration selected for analysis, the following levels of cytotoxicity were observed: 3h +S9 treatment schedule 57.65% at 222.2 µg/mL 3h -S9 treatment schedule 51.43% at 98.77 µg/mL continuous treatment schedule (24h -S9) 54.08% at 65.84 µg/mL. Upon addition of test item to the culture medium, a precipitate of the test item was observed at a concentration of 222.2 µg/mL and above in all treatment schedules. At the end of the treatment period, precipitate was observed at a concentration of 333.3 µg/mL and above in the 3h -S9 and continuous treatment schedules, and at a concentration of 500.0 µg/mL in the 3h +S9 treatment schedule. The observations of precipitate did not affect the selection of dose levels for evaluation of micronucleus frequency.

For all treatment schedules, data for background micronucleus induction in the solvent controls were consistent with the test facility's historical control databases (based on 95% Poisson confidence limits) for human lymphocyte cells.

The number of micronuclei analysed from 2000 binucleated cells for each selected test item dose was compared with that from the concurrent solvent control.

The concurrent positive controls produced statistically significant increases in micronuclei compared with the concurrent negative controls. No statistically significant increases in micronucleus formation in the test item-treated cultures were observed as a result of any of the treatment schedules.

There were no concentration-related increases when evaluated with Cochran-Armitage trend tests. All criteria for a negative result were met after expert evaluation of the data.

It was concluded that Hexyl Salicylate did not induce the formation of micronuclei (MN) in human lymphocytes in the presence or absence of S9, under the test conditions used. The criteria for a negative response, as defined in OECD 487 and in the Study Plan, were met.

SCCS comment
A precipitate was noted at final concentrations of 250.0, 500.0, 1000 and 2000 µg/mL. The SCCS agrees with conclusion of the study that Hexyl Salicylate did not induce the formation of micronuclei in human lymphocytes in the presence or absence of S9, under the test conditions used.

3.3.7.2 Mutagenicity / genotoxicity *in vivo*

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Mutagenicity and Genotoxicity overall conclusion from the Applicant:

Hexyl Salicylate is not genotoxic or mutagenic in the OECD guideline *in vitro* assays performed. The mutagenicity and genotoxicity data for salicylic acid were recently reviewed by the SCCS (SCCS, 2018) and 1-hexanol is also not genotoxic or mutagenic (CIR, 2017). There are no concerns in relation to these endpoints for Hexyl Salicylate.

Overall SCCS comment
SCCS agrees that Hexyl Salicylate was not genotoxic or mutagenic in the *in vitro* assays performed.

During the consultation, SCCS has been informed that in the context of REACH Regulation, a decision on compliance check (CCH) is ongoing for Hexyl Salicylate. The deadline for submissions is 22 April 2025.

A. Information required from all the registrants subject to Annex VIII of Reach
- *In vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490).

The evaluation of mutagenicity may be need to be updated when this study becomes available.

3.3.8 Carcinogenicity

There are no carcinogenicity studies for Hexyl Salicylate. However, given that there are no genotoxicity/ mutagenicity concerns from *in vitro* assays with or without S9, and it is also highly unlikely that the main metabolites salicylic acid and 1-hexanol may act as carcinogens, then there are no known concerns to address for Hexyl Salicylate.

Conclusion from the Applicant:

Hexyl Salicylate is not expected to be a carcinogen in animals.

SCCS comment
After analysis of the available data, the SCCS considers that Hexyl Salicylate is not likely to be a carcinogen.

3.3.9 Photo-induced toxicity

The photoirritation/photoallergenicity endpoints were evaluated based on data and ultraviolet/visible (UV/Vis) spectra, *in vitro* data and *in vivo* data as described below.

UV Spectra Analysis (RIFM (Sears), 2014):

The available UV/Vis spectra (OECD TG 101) for Hexyl Salicylate indicate significant absorbance between 290–700 nm, with peak absorbance at 305 nm and returning to baseline by 330 nm. The molar absorption coefficient for wavelengths between 290–700 nm is above the benchmark of concern (1000 L · mol-1 · cm-1) for photoirritating effects.

***In vitro* 3T3 cells (RIFM (Harbell), 2002):**

Hexyl Salicylate was tested in the 3T3 Neutral Red Uptake (NRU) Photoirritation Assay. Duplicate 96-well monolayers of 3T3 fibroblast were exposed to dilutions of test material (up to 100 µg/mL); 1 plate was exposed to 5 J/cm2 UVA irradiation (photoirritation), and the other was not exposed to UV irradiation (cytotoxicity). The treatment medium was then replaced by a culture medium, and, at approximately 24 hours after treatment, the number of viable cells was determined by NRU. The number of viable cells present for each concentration of test material was compared to that of untreated controls, and the percent inhibition of growth was calculated. The IC50 concentration (i.e., the concentration producing 50% inhibition of growth) was calculated and expressed as µg/mL for both the photoirritation and cytotoxicity plates. A photoirritancy factor was then calculated by comparing the IC50 value obtained with and without UVA exposure. The results indicate that Hexyl Salicylate does not have a photoirritating potential. No photoirritating responses were observed.

Mouse study (RIFM (Urbach), 1975):

Undiluted Hexyl Salicylate (20 µl) was applied to a 2cm2 area of the back in n=6 Skh:hairless-1 mutant mice exposed to light from a long arc xenon lamp and fluorescent blacklight lamps. Six mice were used as a positive control group using 8-methoxypsoralen (8-MOP) in methanol (0.01% w/v). Treated animals were exposed to a 6-kW long arc xenon lamp (distances = 1 meter, intensity = 0.1667 W/m2) for 40 minutes and 4 fluorescent F40BL-type blacklight lamps with exposure for 1 hour with an intensity of 3 W/m2. The irradiation area was defined by a 1 cm diameter hole punched in an aluminium foil adhesive tape, and the tape masked the skin surrounding the exposure area. Reactions were assessed at 4, 24, 48, 72, and 96 hours. Phototoxic reactions were observed at the irradiated positive control sites. No reactions

were observed at either the irradiated or non-irradiated test material treated sites. Hexyl Salicylate was not phototoxic.

Miniature pig study (RIFM (Urbach), 1975):

Phototoxicity was also not observed in two miniature swine tested with undiluted Hexyl Salicylate (20 µl), according to the same procedure as for mouse test described above.

Guinea-pig (RIFM (Learn), 2003):

Photoirritation of Hexyl Salicylate was evaluated in two groups of n=5 Crl:IAF (HA)-hrBR outbred albino hairless guinea pigs. A 0.3-mL aliquot of Hexyl Salicylate at 0%, 5%, 10%, 50%, and 100% in 3:1 diethylphtalate (DEP):EtOH was topically administered using Hilltop chamber patches (25-mm diameter) to the dorsal skin along the midline of each guinea pig and occluded with a dental dam. Two hours later, the patches were removed, and the application sites were gently wiped with disposable paper towels moistened with deionized water. The animals were exposed to UV radiation using a 6.5-kW long arc xenon water-cooled lamp with a filter used to attenuate mid-range ultraviolet radiation (UVB). A dose of about 2.25 instrumental MED was delivered for each exposure session (approximately 2.25 hours). MED refers to a UVR dose adequate to elicit a barely perceptible response in human skin. Clinical observations were made immediately, 1 and 4 hours, and 1, 2, and 3 days after test material administration and UV exposure. Hexyl Salicylate did not cause skin changes indicative of photoirritation.

Guinea-pig (RIFM (Learn) 2003):

Photoallergy was not observed in two groups of n=5 Crl:IAF (HA)-hrBR outbred albino hairless guinea pigs exposed to Hexyl Salicylate (50% and 100%). A nuchal area of skin, approximately 2.5 cm^2, was defined by intradermal injections (0.1 mL/corner) with a formulation of sterile water and Freund's complete adjuvant (1:1 v/v) in each animal. This skin area was then tape stripped 5 times. A 0.3-mL aliquot of Hexyl Salicylate in 3:1 DEP:EtOH was applied to Hilltop® chamber patches (25-mm diameter) and then applied to the nuchal area and occluded with a dental dam. After 2 hours, the patches were removed, and the application sites were gently wiped with disposable paper towels moistened with reverse osmosis membrane processed deionized water. The nuchal area of animals was exposed to UVR for approximately 2.25 hours. The UVR source was a 6.5kw long arc xenon water-cooled lamp with a filter used to attenuate mid-range ultraviolet radiation (UVB). Exposures were monitored by a customised detector that records both intensity and UVR dose. A dose of about 2.25 instrumental MED was delivered for each exposure session. Procedures were repeated once daily on days 3, 5, 8, 10, and 12 of the induction phase. On day 22, using the induction procedure, Hexyl Salicylate at 50% and 100% was topically applied to each animal. Animals were exposed to UVR for 2.25 hours, 2 hours after patch application. The sites were scored 1 and 4 hours after dosage administration and/or UVR exposure. Minimal flaking was observed. Based on the results from the study, Hexyl Salicylate was not considered a photoallergen.

3.3.10 Human data

Human studies (RIFM (Potrebka), 2004):

Photoirritation potential was studied in 56 subjects (41 females and 15 males) who were patch tested with Hexyl Salicylate (0.3%, 3%, and 30% in 3:1 DEP:ethanol), followed by irradiation of sites with UVA and UVB. The test materials or controls were applied to 25-mm Hilltop® Chambers, which were applied to the back of each subject. Each subject received duplicate patches of the 3 concentrations of test material, and of 3 controls (vehicle alone, saline, and a blank (no test material patch)) which were placed on both sides of the spine. Patches

remained in place for 24 hours. After 24 hours, the patches on the left paraspinal region were removed, and the skin sites were irradiated with 16 Joules/cm2 of UVA irradiation for 10 minutes. Then the sites were irradiated with 0.75 Minimal Erythema Doses (MED) UVB. A 150-Watt Berger Solar Ultraviolet Simulator was used as the ultraviolet radiation source in the study. Patches were removed from the non-irradiated test sites on the right paraspinal region after the UVA/UVB dosing was complete. The non-irradiated sites were used as controls to assess the irritation potential of the test material. Reactions were assessed at 1, 24, 48, and 72 hours following UVA and UVB irradiation. No reactions were observed.

Conclusion from the Applicant on Photo-induced toxicity:

Based on the available *in vitro*, *in vivo* and human data, Hexyl Salicylate is not phototoxic or photoallergenic.

3.3.11 Special investigations

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3.4 SAFETY EVALUATION (including calculation of the MoS)

There are no repeat dose toxicity data for Hexyl Salicylate to use in a cosmetic safety assessment. However, given that Hexyl Salicylate itself is not regarded as the main toxicant, but rather salicylic acid as the chief hydrolysis product via all routes of exposure, it is possible to perform a cosmetic safety evaluation for Hexyl Salicylate using the study by Tanaka *et al.* 1973 (from the reproductive/developmental data shown in section 3.4.5) for its principal primary metabolite, Salicylic Acid.

Salicylic Acid was reviewed recently by the SCCS in its Opinion from December 2023. The POD for Salicylic Acid (SA) was selected as a no observed adverse effect level (NOAEL) of 75 mg/kg/day based upon the most sensitive observations in orally dosed rats, of teratogenic effects, in the Tanaka *et al.* 1973 study.

A value for skin penetration of 13.4% (mean (3.04 +1SD) x a correction factor of 3) has been used in all calculations of systemic exposure dose for dermally applied products (see section 3.2.2).

Based on the exposure information in section 3.2, the Margins of Safety for children's exposure to Hexyl Salicylate in cosmetic products used by children are shown in Table 12 below.

Table 12: MoS for children under 3 years for aggregate exposure at all age groups

	mean bodyweight (kg) (EFSA 2012)	**SED (µg/kg/d)**	**SED SA equivalent (µg/kg/d)**	**MoS for SA equivalents** (NOAEL = 75000 µg/kg/d)
Infants 0 - 0.5 yrs	4.8	60.4	37.9	1979
Infants 0.5 - 1 yrs	8.8	50.0	31.4	2390
Toddlers 1 - 3 yrs	11.9	47.0	29.5	2545

SA: salicylic acid

In light of the high value of the MoS, the SCCS considers that Hexyl Salicylate is safe for children below 3 years, if used only in the products included in the aggregate exposure assessment at the presented maximum concentrations.

3.5 DISCUSSION

Hexyl Salicylate (CAS/EC No. 6259-76-3/228-408-6) is the INCI name of 'hexyl 2-hydroxybenzoate', an ingredient with sweet, floral, and fruity odour used in formulations of fragrances in multiple consumer goods including cosmetic, household cleaning products, detergents, and air care products.

Hexyl Salicylate is not listed in the Annexes to the Cosmetic Regulation (EC) No. 1223/2009 and its use is not otherwise restricted in cosmetic products.

Physicochemical properties

Information on the analytical methods used for the determination of purity and impurities of the test substance and their results should be provided in accordance with the SCCS Notes of Guidance.

Exposure

Dermal/percutaneous absorption

A value of 13.4 % (3.04% + 1SD corrected for 24 hours) was calculated following a recent *in vitro* study using human skin that meets the basic criteria for skin absorption in SCCS Notes of Guidance (2021). This value will be used for the calculation of the MoS.

Toxicokinetics

Hexyl Salicylate, like Methyl Salicylate and Benzyl Salicylate, is expected to be rapidly and completely absorbed and metabolised, in both gut and liver tissue by first-pass metabolism, to salicylic acid and 1-hexanol following oral exposure in both rat and humans. With rapid hydrolysis in the gut and liver, systemic exposure is primarily to Salicylic Acid and 1-hexanol, which do not accumulate in the body, and are rapidly excreted.

Systemic Exposure

The report on children's use of cosmetics mentioned above has not been made available to SCCS in a finalised form and is not publicly available. The presented probabilistic calculations (Table 3) based on this data will therefore only be used as supporting evidence.

The Applicant uses the product categories suggested for children aggregate exposure from the Notes of guidance SCCS/1647/22, and additional product categories known to be used by children < 3 years. Since lipstick will seldomly be used by children<3 years old, the SCCS assumes that the product category "lipstick" was used as a surrogate for "lipbalm". The selection of product categories is accepted by the SCCS in this Opinion. Once the survey of Cosmetics Europe will be publicly available, the SCCS will consider whether the SCCS Notes of Guidance need to be updated for other product categories for children.

The exposure calculations for children lack an explanation on how the children exposure estimates were derived. The Applicant refers to an "SCCS approach", but the SCCS would like to point out that the suggestion in Appendix A7.2.1 is just one possibility for calculating children exposure in the current absence of better data, and not an "SCCS approach". Recalculation by SCCS showed that the Applicant has used a correction factor for surface area to derive the exposure estimates. This implies that no children specific use amounts have been taken into account, but it was assumed that the same amount per surface area would be used for children and adults. The resulting SED was then transformed into an SED as Salicylic Acid equivalent by applying a factor of 138.12/222.28 (derived from molecular weight relation between Salicylic Acid and Hexylsalicylate). A study in Swiss children by Garcia-Hidalgo *et al.*, 2017 shows that for toddlers 0-5 years old the derived data for use amounts covers approximately the P95. The approach is therefore accepted.

No information was given on how the SED for toothpaste was derived. Considering data on toothpaste use by Gomez-Berrada *et al.*., 2018, Garcia-Hidalgo *et al*., 2017 and Adé *et al*., 2024, the SCCS uses for babies (0-3 years old) the P95 from Gomez-Berrada *et al*., 2018 for children 2-6 years (1.18 g/application) to derive a daily amount of 2.4 mg/day (Frequency: 2 times per day). The data from Gomez-Berrada were assessed for a sample of N=96 children 2-6 years old 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 and assessed by means of a survey using pictures for amounts are similar and show that the findings are not specific for French children. Also, 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), which were based on SCCNFP/0653/03 (recommendation for parents for toothpaste use). However, no P95 values are available from this study.
The SCCS has recalculated the oral exposure to Hexyl Salicylate in toothpaste based on an amount of 2.4 g/day, retention factor 0.4 (SCCS/1647/22) and bodyweight according to EFSA. These values are aggregated with the exposure to dermal products.

Toxicological Evaluation

Irritation and corrosivity

Hexyl Salicylate shows some irritant reactions in animal models at concentrations of 25% and above and very low skin reactions in one human study at 30%, but it is not considered to be an irritant of concern at the concentrations used in cosmetic products.

Undiluted Hexyl Salicylate is not an eye irritant *in vivo* and there is no risk of eye irritation at the maximum concentrations of Hexyl Salicylate used in cosmetic products.

Skin sensitisation

Available human, animal and NAM data on Hexyl Salicylate are contradictory. In a well-conducted LLNA, Hexyl Salicylate was positive at a relatively low concentration, whereas the GPMT was negative. *In silico* data showed no protein binding alerts, which was confirmed in the DPRA. In addition, the Keratinosens was negative, whereas the h-CLAT and U-SENS were positive. If, for example, the 2o3 DA (two out of three defined approach) was performed according to OECD Guideline 497, Hexyl Salicylate would have been considered as a non-sensitiser. Human evidence is limited, but the data available is all negative. This was already observed in an earlier SCCS Opinion on fragrance allergens (SCCS/1459/11) and no new evidence indicating that Hexyl Salicylate is a relevant skin sensitiser in humans has emerged in literature.

Taking all the evidence together, the SCCS concludes that although Hexyl Salicylate is classified as a skin sensitiser, based on clinical evidence, the risk of skin sensitisation in humans from the use in cosmetic products can be considered negligible.

However, it is not known whether Salicylic acid may be present in the products as an impurity or resulting from the breakdown of hexyl salicylate. Salicylic acid is classified as a skin sensitiser Category 1. The results of the infant survey by Cosmetics Europe that have been available as draft to the SCCS show that a significant proportion of babies had "skin issues" and that children with damaged skin could be exposed to cosmetic products containing Salicylates. This is an important consideration for comprehensive risk assessment because Salicylic Acid is not permitted in cosmetic products used by children under the age of 3 years (Annex III of Cosmetic Regulation EC/1223/2009) + (ref. not published).

Acute toxicity

Hexyl Salicylate is not acutely toxic *via* any route of exposure.

Repeated dose toxicity

No repeat dose toxicity data are available on Hexyl Salicylate. Given that Hexyl Salicylate itself is not regarded as the main toxicant, but rather its chief hydrolysis product, salicylic acid, the available repeat dose toxicity data and conclusions for the primary Hexyl Salicylate metabolites salicylic acid and 1-hexanol were reviewed for the purposes of performing a cosmetics safety assessment. All data for salicylic acid were also recently reviewed by the SCCS in its recent Opinion (SCCS, 2018).

Reproductive toxicity

No reproductive/developmental toxicity data are available on Hexyl Salicylate. The proposal for classification is based upon read across to salicylic acid and methyl salicylate data, and the assumption that Hexyl Salicylate is metabolised to the same common metabolite, salicylic acid.

Given that Hexyl Salicylate itself is not regarded as the main toxicant, but rather salicylic acid as the chief hydrolysis product, available reproductive/developmental toxicity data and conclusions for the primary metabolite salicylic acid and 1-hexanol to which the body may be principally exposed were reviewed for the purposes of performing a cosmetics safety assessment.

SCCS considers that salicylic acid is a developmental toxicant. Harmonised classification of salicylic acid was recently published in Regulation 2018/1480 and is classified as Repr. 2 (H361d Suspected of damaging the unborn child). For MoS calculation, SCCS uses the developmental NOAEL of 0.1% (75 mg/kg bw/day) derived from Tanaka *et al.* (1973a).

In addition, due to the evidence for high (100%) oral bioavailability in humans, the oral NOAEL of 75 mg/kg bw/day is defined as systemic NOAEL (NOAELsys) by SCCS for salicylic acid.

This POD for salicylic acid can act as a conservative surrogate POD for Hexyl Salicylate. On a molar basis, 1 mole of Hexyl Salicylate is converted to 1 mole of salicylic acid. An assumption is made that 100% of Hexyl Salicylate is metabolised to salicylic acid and 1-hexanol, and salicylic acid is the driver of any observed Hexyl Salicylate toxicity. The salicylic acid NOAELsys = 75 mg/kg bw/day. A salicylic acid equivalent SED can be calculated and compared with this POD.

Mutagenicity / genotoxicity

SCCS concludes that Hexyl Salicylate was not genotoxic or mutagenic *in the vitro* assays performed.

Carcinogenicity

After analysis of the available data, the SCCS considers that Hexyl Salicylate is not likely to be a carcinogen.

Photo-induced toxicity

Based on the available *in vitro*, *in vivo* and human data, Hexyl Salicylate is not phototoxic or photoallergenic.

Special investigation: endocrine disrupting effects

For the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009 and based upon the WHO IPCS 2002 Definition, a connection between mode/mechanism of action and observed adverse effect must be demonstrated for substances falling within the Commission's ED criteria and the ECHA/EFSA Guidance. There is no evidence from the available *in vivo* data of an adverse effect of Hexyl Salicylate and salicylic acid as a result of an endocrine mechanism, *e.g.,* there is no adverse effect on fertility. The available evidence is not strong enough to conclude on an endocrine effect linking a mode of action with an adverse outcome. *In vitro* data did not show any estrogenic effects, nor any androgenic, thyroid or steroidogenic properties of Hexyl Salicylate and salicylic acid.

4. CONCLUSION

1. *In light of the data provided and taking under consideration the CMR Cat.2 classification (to be introduced in Annex VI to Reg. 1272/2008), does the SCCS consider Hexyl Salicylate safe for children below 3 years of age when used up to the maximum concentrations provided in the dossier?*

Based on the assessment of data provided and taking into consideration the concerns related to potential endocrine disrupting properties, the SCCS considers Hexyl Salicylate safe for children < 3 years old when used up to the maximum concentrations as provided below.

Product type	**Maximum concentration (% w/w)**
Shower gel, hand soap, shampoo, hair conditioner, body lotion, face cream, hand cream, lipstick/lip balm, fragrance products	0.1
Toothpaste	0.001

2. *Alternatively, what is according to the SCCS the maximum concentration of Hexyl Salicylate that is considered safe for children below 3 years of age?*

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

The results of the infant survey by Cosmetics Europe that have been available as draft to the SCCS show that a significant proportion of babies had "skin issues" and that children with damaged skin could be exposed to cosmetic products containing Salicylates. This raises concern to the SCCS as it is not known whether Salicylic Acid may be present in the products as an impurity or resulting from the breakdown of hexyl salicylate. Furthermore, Salicylic Acid is classified as a skin sensitiser Category 1 and Salicylic Acid is not permitted in cosmetic products used by children under the age of 3 years.

The amount of toothpaste ingested by children below 3 years old considered in this opinion for the calculation of the MoS has been adapted based on available data and now is much higher than the one used in previous opinions on Salicylates in cosmetic products used by children (eg. Methyl salicylates, SCCS/1654/23). This may raise concerns about their safety, in particular wwhere the MoS is close to 100.

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

5. MINORITY OPINION

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7. Appendix 1 Literature & Data Search for toxicology evidence on Hexyl Salicylate

It is assumed in the preparation of this dossier that, in addition to available industry studies, the following authoritative public reviews on Hexyl Salicylate can be drawn upon for necessary safety information for the dossier.

- Cosmetics Ingredient Review (CIR) 2018-2019 (Final June 2019 report) https://www.cir-safety.org/sites/default/files/salicy042019FAR.pdf
- EU REACH substance dossier for Hexyl Salicylate https://echa.europa.eu/fr/registration-dossier/-/registered-dossier/14766/7/1
- European Chemicals Agency RAC CLH Opinion (CLP)(ECHA) 2022 https://echa.europa.eu/fr/registry-of-clh-intentions-until-outcome/-/dislist/details/0b0236e18471782f
- RIFM Fragrance Material Review (Lapczynski *et al.* 2007; Belsito *et al.* 2007)
- SCCNFP/0017/98 Final report 1999 Fragrance Allergy https://ec.europa.eu/health/ph_risk/committees/sccp/documents/out98_en.pdf
- SCCS 2011 report Fragrance allergen's opinion SCCS/1459/11 https://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_073.pdf

8. 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.

9. LIST OF ABBREVIATIONS

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.