Scientific Committee on Consumer Safety

SCCS

OPINION on

salicylic acid

(CAS No. 69-72-7, EC No. 200-712-3)

The SCCS adopted this document
during plenary meeting on 6-7 June 2023

ACKNOWLEDGMENTS

SCCS members listed below are acknowledged for their valuable contribution to the finalisation of this Opinion.

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This Opinion has been subject to a commenting period of eight weeks after its initial publication (from 15 December 2022 until 17 February 2023). Comments received during this period were considered by the SCCS. For this Opinion, main changes occurred in the following sections: 3.3.1.2, 3.3.2.1, 3.3.2.2. SCCS comment, 3.3.2.3 SCCS comment, 3.5 (probabilistic scenario), discussion (under exposure assessment and safety evaluation) and conclusions accordingly.

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

1. ABSTRACT

The SCCS concludes the following:

1. In light of the data provided and taking under consideration the concerns related to potential endocrine disrupting properties of Salicylic acid,

   a) does the SCCS consider Salicylic acid safe when used as a preservative in cosmetic products up to a maximum concentration of 0.5%?

   Based on the safety assessment carried out in consideration of all available information, including the potential endocrine effects:

   - the SCCS is of the opinion that salicylic acid (CAS 69-72-7) is safe when used as preservative at a concentration of 0.5 % in cosmetic products, considering its current restrictions in place. The provided information shows that salicylic acid is an eye irritant with the potential to cause serious damage to the eye.

   - this Opinion is not applicable to any sprayable product (including mouth spray) that may lead to exposure of end-user's lungs by inhalation.

   b) does the SCCS consider Salicylic acid safe when used in cosmetic for purposes other than inhibiting the development of micro-organisms at a concentration up to:

   i. 3.0% for the cosmetic rinse-off hair products,

   ii. 2.0% for other products except body lotion, eye shadow, mascara, eyeliner, lipstick, non-spray deodorant, and

   iii. 0.5% for body lotion, eye shadow, mascara, eyeliner, lipstick, oral products and non-spray deodorant

   The SCCS assessment has shown that:

   The use of salicylic acid as a restricted ingredient for purposes other than inhibiting the development of micro-organisms is safe at a concentration:

   - up to 3.0 % for the cosmetic rinse-off hair products,
   - up to 2.0 % for other products, except body lotion, eye shadow, mascara, eyeliner, lipstick, non-spray deodorant, and
   - up to 0.5% for body lotion, eye shadow, mascara, eyeliner, lipstick, oral products and non-spray deodorant.

   This Opinion is not applicable to any sprayable product (including mouth spray) that may lead to exposure of end-user's lungs by inhalation.

2. Alternatively, what is according to the SCCS the maximum concentration considered safe for use of Salicylic acid in cosmetic products?

   /

3. Does the SCCS have any further scientific concerns with regard to the use of Salicylic acid in cosmetic products?

In the absence of exposure data of Salicylic acid in cosmetic products for children, safety concerns have been noted for the younger age groups (between 3-10 years).

Since the Cosmetic Regulation does not allow the use of salicylic acid in products for children under 3 years of age, this age category has not been considered in this Opinion.

The conclusions of this Opinion refer only to Salicylic Acid as a cosmetic ingredient and not to other salicylates or salicylic acid salts.

Keywords: SCCS, scientific opinion, salicylic acid, Regulation 1223/2009, CAS No. 69-72-7, EC No. 200-712-3

Opinion to be cited as: 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

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SCCS

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

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SCCS - Opinions (europa.eu)

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2. MANDATE FROM THE EUROPEAN COMMISSION

Background on substances with endocrine disrupting properties

On 7 November 2018, the Commission adopted the review[1] of Regulation (EC) No 1223/2009 on cosmetic products ('Cosmetics Regulation') regarding substances with endocrine disrupting (ED) properties. The review concluded that the Cosmetics Regulation provides the adequate tools to regulate the use of cosmetic substances that present a potential risk for human health, including when displaying ED properties.
The Cosmetics Regulation does not have explicit provisions on EDs. However, it provides a regulatory framework with a view to ensuring a high level of protection of human health. Environmental concerns that substances used in cosmetic products may raise are considered through the application of Regulation (EC) No 1907/2006 ('REACH Regulation').
In the review, the Commission commits to establishing a priority list of potential EDs not already covered by bans or restrictions in the Cosmetics Regulation for their subsequent safety assessment. A priority list of 28 potential EDs in cosmetics was consolidated in early 2019 based on input provided through a stakeholder consultation. The Commission carried out a public call for data in 2019[2] for 14 substances (Group A)[3] and a second call in 2021[4] for 10 substances (Group B)[5] in preparation of the safety assessment of these substances. Salicylic acid is one of the above-mentioned substances for which the call for data took place.

Background on Salicylic acid

Salicylic acid (CAS No. 69-72-7, EC No. 200-712-3) with the chemical name 'benzoic acid, 2-hydroxy' is used in cosmetic products with reported functions as a denaturant, hair and skin conditioning agent, exfoliant/keratolytic, anti-sebum agent, anti-dandruff/anti-seborrheic agent and a product preservative. Salicylic acid has been subject to a safety evaluation by SCCNFP in 2002[6] and SCCS in 2018[7]. In particular, the last SCCS assessment was performed in view the classification of Salicylic acid as a CMR2 (Repr.2) substance under the CLP Regulation and in accordance to the provisions laid out in Article 15 of the Cosmetics Regulation. It is currently regulated under Annex III (entry 98) and Annex V (entry 3), with specific maximum concentrations and conditions of use.

During the call for data, stakeholders submitted scientific evidence to demonstrate the safety of Salicylic acid in cosmetic products. The Commission requests the SCCS to carry out a safety assessment on Salicylic acid in view of the information provided, taking into account the maximum concentration and relevant provisions for different categories of cosmetic products listed in Annex III and V to the Cosmetics Regulation, as well as the intention of industry to use Salicylic acid in oral products as well.

[1] https://ec.europa.eu/transparency/regdoc/rep/1/2018/EN/COM-2018-739-F1-EN-MAIN-PART-1.PDF
[2] https://ec.europa.eu/growth/content/call-data-ingredients-potential-endocrine-disrupting-properties-used-cosmetic%20products_en
[3] Benzophenone-3, kojic acid, 4-methylbenzylidene camphor, propylparaben, triclosan, Homosalate, octocrylene, triclocarban, butylated hydroxytoluene (BHT), benzophenone, homosalate, benzyl salicylate, genistein and daidzein
[4] https://ec.europa.eu/growth/content/call-data-ingredients-potential-endocrine-disrupting-properties-used-cosmetic-products-0_en
[5] Butylparaben, Methylparaben, Ethylhexyl Methoxycinnamate (EHMC)/Octylmethoxycinnamate (OMC)/Octinoxate, Benzophenone-1 (BP-1), Benzophenone-2 (BP-2), Benzophenone-4 (BP-4), Benzophenone-5 (BP-5), BHA/Butylated hydroxyanisole/tert-butyl-4-hydroxyanisole, Triphenyl Phosphate and Salicylic Acid
[6] https://ec.europa.eu/health/ph_risk/committees/sccp/documents/out170_en.pdf
[7] https://ec.europa.eu/health/sites/default/files/scientific_committees/consumer_safety/docs/sccs_o_223.pdf

Terms of reference

(1) In light of the data provided and taking under consideration the concerns related to potential endocrine disrupting properties of Salicylic acid,

a) does the SCCS consider Salicylic acid safe when used as a preservative in cosmetic products up to a maximum concentration of 0.5%?

b) does the SCCS consider Salicylic acid safe when used in cosmetic for purposes other than inhibiting the development of micro-organisms at a concentration up to:

i. 3.0% for the cosmetic rinse-off hair products,
ii. 2.0% for other products except body lotion, eye shadow, mascara, eyeliner, lipstick, non-spray deodorant, and
iii. 0.5% for body lotion, eye shadow, mascara, eyeliner, lipstick, oral products and non-spray deodorant

(2) Alternatively, what is according to the SCCS the maximum concentration considered safe for use of Salicylic acid in cosmetic products?

(3) Does the SCCS have any further scientific concerns with regard to the use of Salicylic acid in cosmetic products?

3. OPINION

3.1 CHEMICAL AND PHYSICAL SPECIFICATIONS

3.1.1 Chemical identity

3.1.1.1 Primary name and/or INCI name

Salicylic acid

3.1.1.2 Chemical names

IUPAC: 2-hydroxybenzoic acid

3.1.1.3 Trade names and abbreviations

A. MeSH entry names:

1. 2 Hydroxybenzoic Acid
2. 2-Hydroxybenzoic Acid
3. Acid, 2-Hydroxybenzoic
4. Acid, o-Hydroxybenzoic
5. Acid, ortho-Hydroxybenzoic
6. Acid, Salicylic
7. o Hydroxybenzoic Acid
8. o-Hydroxybenzoic Acid
9. ortho Hydroxybenzoic Acid
10. ortho-Hydroxybenzoic Acid
11. Salicylic acid

B. Depository supplied synonyms can be found at the link provided below.

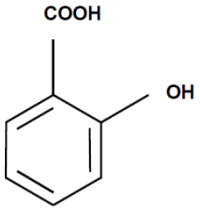
Ref: https://pubchem.ncbi.nlm.nih.gov/compound/338#section=Depositor-Supplied-Synonyms

3.1.1.4 CAS / EC number

CAS 69-72-7/ EC 200-712-3

Ref: Analytical Dossier; PubMed; ECHA, SigmaAldrich

3.1.1.5 Structural formula



3.1.1.6 Empirical formula

$C_7H_6O_3$

3.1.2 Physical form

Form: Crystalline powder Needles
Physical state: solid
Colour: white
Colourless

3.1.3 Molecular weight

138.12 g/mol

3.1.4 Purity, composition and substance codes

Purity: Salicylic acid is incorporated as an ultra-pure ingredient when used in cosmetics, and its typical purity level is 99.7-99.9%, with a minimum purity of 99% and maximum of 100%. Impurities could be phenol and sulphate, which are typically less than 0.02% and 0.04%, respectively.

Table 1. Physicochemical properties (purity) of salicylic acid

Property	**Salicylic Acid**
Purity	99.7-99.9%

Ref: https://echa.europa.eu/el/substance-information/-/substanceinfo/100.000.648
Novacyl Certificate of analysis

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

3.1.5 Impurities / accompanying contaminants

Taken from previous Opinion

Salicylic Acid, Batch B14E099PHA

Characteristic	Unit	Value	Lower Limit	Upper Limit
Chlorides	% wt	< 0.0100	-	0.0100
Melting Range (FP)	°C	160.3	158.0	161.0
Melting Range (IP)	°C	159.9	158.0	161.0
Identification	-	Pass	-	-
Heavy Metals (as Pb)	µg/g	< 20	-	20
Loss on Drying (KF)	% wt	0.066	-	0.500
Residue on Ignition	% wt	0.0140	-	0.0500
Sulphates	% wt	< 0.020	-	0.020
Assay	% wt	100.05	99.50	101.00
Related Compounds	% wt	0.0704	-	0.2000
Phenol	% wt	< 0.0010	-	0.0100
Other Impurities (sum)	% wt	< 0.0010	-	0.0500
4-Hydroxybenzoic Acid	% wt	0.0394	-	0.1000
4-Hydroxyisophthalic Acid	% wt	0.0310	-	0.0500
Sum of all Impurities	% wt	0.0704	-	0.2000

Ref: 24. 90916 SALICYLIC ACID%2c USP_COA

SCCS comment
Data on impurities of salicylic acid are provided only in the specification sheets. The analytical methods used for the determination of impurities in the test substance along with the results of these studies should be provided, according to the SCCS Notes of Guidance.

3.1.6 Solubility

In water: 2.24 mg/mL at 25 °C, 2 g/L at 20°C.
Readily soluble in acetone, oil of turpentine, alcohol, ether and benzene.
Solubility (weight percent): carbon tetrachloride 0.262 (25 °C); benzene 0.775 (25 °C); propanol 27.36 (21 °C); absolute ethanol 34.87 (21 °C); acetone 396 (23 °C)

Ref: ChemSpider (Royal Society of Chemistry); Lewis, 1993; Budavari 1989

3.1.7 Partition coefficient (Log Pow)

Octanol/water partition coefficient ($\log P_{o/w}$) = 2.25

Ref: Sheu et al, 1975; US EPA Chemistry Dashboard

3.1.8 Additional physical and chemical specifications

Table 2. Physicochemical properties of salicylic acid	
Property	**Values**
Molecular Formula	$C_7H_6O_3$
Molecular Weight (g/mol)	138.12
Physical Form	Solid at room temperature
Stability	Stable at room temperature
Boiling point (°C)	211 at 20mmHg; sublimes at 76°C[a]
Melting point (°C)	158-161[a]
pH of saturated aqueous solution	2.4 (saturated aqueous suspension)[b1], 2.4 (at 2 % m/v, aqueous suspension)[b2]
Vapour pressure	at 25°C: 0.000208 hPa[c]
pKa	2.9[d]
Density	1.44 g/cm^3 at 20 °C[e]
a. Lewis, 1993 b. 1. Budavari, 1989; 2. 24. 90916 SALICYLIC ACID%2c USP__MSDS c. ChemSpider (Royal Society of Chemistry) d. Kamal et al 2005. e. 24. 90916 SALICYLIC ACID%2c USP__MSDS NR = not reported, a published value could not be found.	

Where relevant:

- organoleptic properties (colour, odour, taste if relevant): /
- flash point: 157°C (salicylic acid)
- density: 1.443 g/cm^2 at 20°C (salicylic acid)
- viscosity: /
- refractive index: /
- UV/visible light absorption spectrum: UV max (4 mg percent in ethanol): 210, 234, 303 nm (molar extinction coefficient 8343, 5466, 3591).

Ref: Salicylic Acid Exposure FINAL 5 12 2017;
24. 90916 SALICYLIC ACID%2c USP__MSDS

3.1.9 Homogeneity and Stability

Stability: Salicylic acid gradually discolours in sunlight; when heated to decompose it emits acrid smoke and irritating fumes.

Ref: Budavari, S. (ed.). The Merck Index - Encyclopedia of Chemicals, Drugs and Biologicals. Rahway, NJ: Merck and Co., Inc., 1989., p. 1324; Lewis, R.J. Sr. (ed) Sax's Dangerous Properties of Industrial Materials. 11th Edition. Wiley-Interscience, Wiley & Sons, Inc. Hoboken, NJ. 2004., p. 3179

3.2 TOXICOKINETICS

The toxicology evaluation carried out in this Opinion is focused on the data available for salicylic acid.

3.2.1 Dermal / percutaneous absorption

According to the Applicant, comprehensive review of the available dermal penetration data was performed by the SCCS in the 2018 Opinion, and there has been no new dermal penetration data generated since that review. SCCS concluded that a dermal penetration value of 60% (higher than the usual SCCS default value of 50% used in the absence of data) should be used in this safety evaluation 'in view of the high variability in dermal penetration values' with vehicle and formulation (*e.g.* as observed in a study by Muhammad & Riviere, 2015). This value was also used by the Risk Assessment Committee (RAC) in their evaluation of salicylic acid as based on the observation of 59% skin penetration in an *in vivo* study in monkey (Bucks et al, 1990).

Studies related to the dermal/percutaneous absorption of salicylic acid have been assessed and commented upon by the SCCS in its previous Opinion (SCCS/1601/18) and the results are summarized below:
Salicylic acid is readily ionised and skin absorption is significantly affected by pH and other properties of the vehicle in which it is applied. In view of the high variability of dermal penetration values reported in the different studies, the SCCS estimated a dermal absorption rate of 60 % for salicylic acid. This value corresponds to the value of 60% absorption rate used by the Risk Assessment Committee (RAC) in March 2016.

Ref: Final Salicylic Acid Dossier, November 2021

SCCS comment
A dermal absorption rate of 60% for salicylic acid will be used for the calculation of internal dose and safety assessment.

3.2.2 Other studies on toxicokinetics

3.2.2.1 Non-dermal Absorption

Oral route
Salicylic acid is well absorbed across the GI tract and is rapidly distributed throughout the extracellular fluids and most tissues.

Ref: Goodman & Gilman, 2006

A comparison between rat and human oral kinetics is presented in Table 3.

Table 3. Data from a range of kinetics studies in rat and humans, comparing oral dose (in mg/kg/day) with reported C_{max} (µg/mL) values.

Substance	Species	Dose mg/kg	C_{max} (µg/mL) SA	T_{max}	$T_{1/2}$	AUC mg / L hr	Clearance	Source
Salicylic Acid	Rat	150	246.6 ±20.6	No data	No data	No data	No data	Tanaka et al 1973
Aspirin	Rat	150 mg/kg twice daily	238 ±20	No data	No data	No data	No data	Wilson *et al.*, 1977
Aspirin	Human	16	49					Kershaw et al 1987
Aspirin	Human	0.83	4.35					Bochner et al 1988
Aspirin	Human	1.35	5.28	0.71±0.25 (hr)	2.62± 0.46 (hr)	220.1		Davis et al 1997
Aspirin	Human	Single oral administration of 650 mg	56.4±14.2	1.03±0.39	2.23±0.27	319.8±105		Fung et al 2008
Aspirin	Human	8.3	22.85					Nagelschmitz et al 2014

*median values from a range of observed values.

SCCS comment
The SCCS notes that, at a minimum, comparing toxicokinetics between different species, requires T_{max} associated with C_{max}, as well as the values for half-life, AUC and clearance (ref: Miaskiewicz et al 1982). No robust data have been provided from either rat or human studies that could enable a comparison of the kinetic parameters for salicylic acid. Therefore, the SCCS is of the opinion that a factor of 4, accounting for inter-species toxicokinetic differences, is necessary.

Inhalation
Salicylic acid is neither volatile nor airborne and therefore, there are no studies on lung ADME. There are no spray or aerosol products containing salicylic acid in current use (Crème Global, 2017).

3.2.2.2 Distribution

Salicylic acid is a weak acid and after oral administration it is found in the unionised form in the stomach. Salicylic acid is well absorbed in humans from the gastrointestinal tract and rapidly distributed throughout the extracellular fluid and most tissues. High concentrations are found in the liver and the kidneys and 50 to 80 % of salicylic acid in plasma is bound to albumin and other proteins.

Placental absorption
Whole body autoradiography analysis of pregnant mice revealed that [^{14}C]-salicylic acid is able to pass through the placenta to reach the fetus (Tjalve *et al.* 1973; Koshakji & Schulert, 1973). Placental absorption of salicylic acid using a non-standardised *in vitro* model procedure has been studied by Shintaku *et al.* (2007) so as to devise a pharmacokinetic model of human placental absorption. *In vitro* human placental perfusion was carried out based on the method reported by Schneider *et al.* (1972). Salicylic acid at 8 µg/mL was dissolved into the maternal perfusate on the maternal side of the placenta. Maternal and 'fetal'-side effluents were sampled for 60 min. The study shows **the potential of salicylic acid to cross the placenta**.

SCCS comment
The SCCS has noted that the available evidence indicates that salicylic acid has the potential to cross the placenta.

Parenteral route
All available sub-cutaneous (SC) and intravenous (*i.v.)* ADME studies for salicylic acid are outlined in Table 4.

Table 4. Parenteral route studies on salicylic acid in animals and in humans.

Number/ species	**Dose**	**Application**	**Observations**	**Reference**
Salicylic acid				
Rat - Sprague Dawley	300 mg/kg	Sub-cutaneous injection to gravid rats terminated after 1h	4.06% of the injected dose was found in fetal tissue	Koshakji & Schulert, 1973
Male Fischer 344 Rat	5 or 50 mg/kg	3 and 25 months animals; *i.v.* in 4:1:1 solution Emulphor: ethanol:water	5 mg/kg: Plasma SA conc. 17-28 µg/ml $T_{1/2}$(3mth) 4.08h $T_{1/2}$(25mth) 21.3h 50 mg/kg: Plasma SA conc. 100-120 µg/ml $T_{1/2}$(3mth) 30.1h $T_{1/2}$(25mth) 21.9h	McMahon et al 1990
Dog	1g	*i.v.* in sodium bicarbonate	>90% recovered in urine over 30-36hr; 50% unchanged as salicylic acid; 25% glucuronates; 10% salicyluric acid; 4-5% gentisic acid	Alpen et al 1951
Human	Not reported	*i.v.*	89% recovered in urine after 4h	Feldmann & Maibach, 1970

Metabolism

Salicylic acid is the principal metabolite of acetylsalicylic acid (ASA, aspirin), which is a common analgesic medicine. A scheme of the major possible metabolites of salicylic acid, as identified in mammals, is presented in Figure 1.

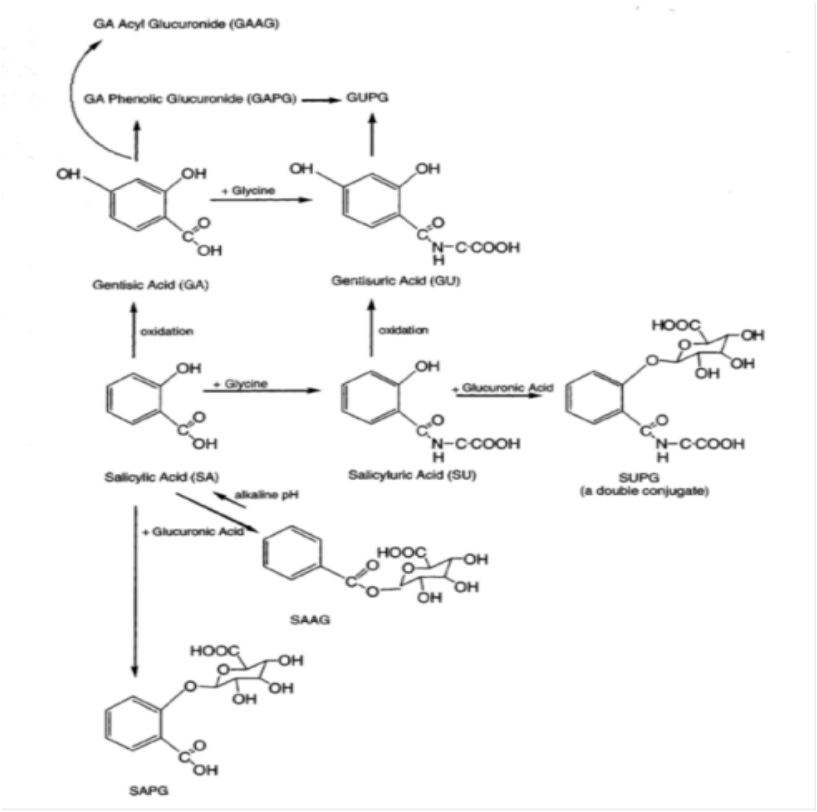


Figure 1. Scheme of the possible major metabolites of salicylic acid, Ref: CIR 2003 review

These metabolites have been detected and, in some cases, quantified in the ADME/PK studies described in this section. These metabolites are formed mainly as the result of hepatic microsomal cytochrome P450 enzymes and phase 2 glucuronosyl transferase (UGT) conjugation enzymes.
Studies reported by McMahon *et al.* (1990), performed on rats, demonstrated that salicylic acid can be metabolised to salicyluric acid, salicyl-glucuronic acid, oxidative metabolites (2,3-dihydroxybenzoic acid (gentisic acid) and 2,5-dihydroxybenzoic acid) and other glucuronides and glycine conjugates. All these metabolites, as well as unchanged salicylic acid, are eliminated almost entirely and rapidly via the urine.
Experiments in rats (McMahon *et al.*, 1990) showed that following single salicylic acid doses of 5 or 50 mg/kg bw, the compound is excreted in urine, predominantly as salicylic acid and salicyluric acid, and to a lesser extent oxidative metabolites (2,3- dihydroxybenzoic acid and 2,5 -dihydroxybenzoic acid), and other conjugated salicylic acid compounds (as salicyl ester glucuronide or salicyl ether glucuronide).
In humans the major metabolic pathway for elimination of salicylates is via conjugation. The principal metabolite in humans is salicyluric acid. A minor oxidative pathway leads to the production of 2,5-dihydroxybenzoic acid (gentisic acid, 25DHBA) and 2,3-dihydroxybenzoic acid.

SCCS comment
Based on the studies provided by the Applicant, the SCCS is of the opinion that metabolism of salicylic acid in rats and humans follows a similar route. It is metabolised mainly to salicyluric acid, and conjugated salicylic acid compounds, with a small proportion of oxidative metabolites.

3.2.2.4 Excretion

McMahon *et al.* (1990) showed that oral salicylic acid is excreted almost exclusively in the urine in rats. Less than 1 % was found in bile (as unmetabolised salicylic acid), as exhaled carbon dioxide or in feces. This study reported a shift in urinary excretion at high concentrations, towards a higher proportion of oxidative metabolites in older rats. Salicylic acid is excreted by renal excretion as an unchanged chemical entity (10 %) or after conjugation with glycine (salicyluric acid 75 %), with glucuronic acid (salicyl acyl and phenolic glucuronides 5 %) and/or after hydroxylation (gentisic acid < 1 %) (Goodman & Gilman 2006). Excretion is almost complete in rats within 24 hours, irrespective of the route of administration. Similarly, in humans, excretion is almost all in urine, and almost complete within 24 hours after all routes of exposure.

SCCS comment
The SCCS has noted that salicylic acid has been reported to be almost completely excreted via urine both in rat and humans.

3.3 EXPOSURE ASSESSMENT

3.3.1 Function and uses

3.3.1.1 Cosmetic product uses as per Cosmetic Products Regulation EC 1223/2009

Salicylic acid is used in cosmetic products as a denaturant, a hair and skin conditioning agent, an exfoliant, an anti-acne cleansing agent, an anti-dandruff agent and a product preservative. The use of salicylic acid in cosmetics is regulated in Cosmetic Products Regulation EC 1223/2009 of the European Union. It is a restricted substance listed in Annex III (entry 98) and is an allowed preservative in Annex V (entry 3), with the maximum concentrations and restriction comments as below:

Table 5. Restricted Substances: Annex III, Regulation 1223/2009/EC on Cosmetic Products, entry 98

98	Benzoic acid, 2-hydroxy-	SALICYLIC ACID	69-72-7	200-712-3	(a) Rinse-off hair products (b) Other products except body lotion, eye shadow, mascara, eyeliner, lipstick, roll-on deodorant (c) Body lotion, eye shadow, mascara, eyeliner, lipstick, roll-on deodorant	(a) 3.0% (b) 2.0% (c) 0.5%	(a) (b) (c) Not to be used in preparations for children under 3 years of age. Not to be used in applications that may lead to exposure of the end-user's lungs by inhalation. Not to be used in oral products. For purposes other than inhibiting the development of micro-organisms in the product. This purpose has to be apparent from the presentation of the product. These levels are inclusive of any use of salicylic acid.	(a) (b) (c) Not to be used for children under 3 years of age* * Solely for products which might be used for children under 3 years of age.	31/05/2021

Table 6. Allowed Preservatives: Annex V, Regulation 1223/2009/EC on Cosmetic Products – extract of entry 3*

3	Salicylic acid and its salts	SALICYLIC ACID, CALCIUM SALICYLATE, MAGNESIUM SALICYLATE, MEA-SALICYLATE, SODIUM SALICYLATE, POTASSIUM SALICYLATE, TEA-SALICYLATE	69-72-7[1]/ 824-35-1[2]/ 18917-89-0[3]/ 59866-70-5[4]/ 54-21-7[5]/ 578-36-9[6]/ 2174-16-5[7]	200-712-3[1]/ 212-525-4[2]/ 242-669-3[3]/ 261-963-2[4]/ 200-198-0[5]/ 209-421-6[6]/ 218-531-3[7]		Salicylic acid: 0,5 % (acid) Salicylic acid salts: 0,5 % (acid)	Salicylic acid: Not to be used in products for children under 3 years of age. Not to be used in oral products. Not to be used in applications that may lead to exposure of the end-user's lungs by inhalation. Salicylic acid	Salicylic acid: Not to be used for children under 3 years of age** **Solely for products which might be used for children under 3 years of age. Salicylic acid salts: Not to be used for children under 3 years of	27/07/2020

*Annex V, entry 3 is referred to salicylic acid and its salts, in this mandate only Salicylic acid is assessed.

Ref: Updated Dossier on the Human Safety Evaluation of Salicylic Acid in Cosmetic Products, 2021

The proposed concentration in Annex III includes the 0.5% as preservative from Annex V (for the specific product types that are further restricted under Annex III).

3.3.1.2 Cosmetic product uses as per Cosmetics Europe 2017 Survey

According to the CE survey 2017 (presenting use data from 2016), the salts of salicylic acid are used as preservatives in all cosmetic products except toothpaste or mouthwash products (see Table 7). The respective occurrence data were not used in the assessments described in this report but are provided here for reference.

Salicylic acid according to the survey is not used in eye liner and mascara. Oral care products are included in this updated opinion up to a potential maximum concentration of 0.5%.

Table 7 shows the proportion of product, calculated as percentage of total tonnage, in which salicylic acid is present. The occurrence by tonnage is defined as the percentage of total tonnage that contains salicylic acid at any concentration above 1ppm. Liquid make-up foundation and mascara contain the highest amounts of salicylic acid by percentage of total tonnage.
Note that there was no reported use of salicylic acid for product types (year 2016): eye pencil, mascara, mouthwash, and toothpaste. However, a representative concentration of 0.5% salicylic acid in eye pencil and mascara.

Table 7: Percent of total product category (% by tonnage) salicylic acid

Category	Total Formulations	Formulations with Salicylic Acid	Occurrence (%)
Body Lotion	3200	61	1.906
Deodorant Roll On	1374	16	1.164
Eye makeup	6140	4	0.065
Eyeliner	1599	0	0.000
Face Moisturizer	5218	432	8.279
Hair styling	2311	20	0.865
Hand Cream	641	8	1.248
Lipstick	9751	4	0.041
Liquid hand soap	409	33	8.068
Liquid make up foundation	8336	194	2.327
Make up remover	1454	163	11.210
Mascara	906	0	0.000
Mouthwash	68	0	0.000
Rinse off conditioner	2071	39	1.883

Shampoo	2692	575	21.360
Shower gel	2985	386	12.931
Toothpaste	517	0	0.000

Ref: Updated Dossier on the Human Safety Evaluation of Salicylic Acid in Cosmetic Products, 2021

SCCS comment
The SCCS has noted that no data have been provided in the submitted dossier to support the use of salicylic acid in sprayable products.

3.3.1.3 Other uses than cosmetics

Salicylic acid is used (at 15-40%) as a spot-treatment medication to treat warts and callouses because of its keratoplastic properties, and it is also used clinically as a skin peeling agent.

Ref: Arif, 2015

Salicylic acid is used as a preservative in food, as a chemical raw material for the synthesis of dyes and aspirin, and as an antiseptic and antifungal agent by topical application in veterinary medicine. Aspirin is metabolised to salicylic acid in the human body.

Taken from Biocide opinion/ ECHA:

- The active substance is used in product-type 2 (PT2), ready-to-use product for disinfection of dishwashing sponges between dishwashing sessions (and therefore prevention of spread of micro-organisms onto other kitchen utensils and surfaces) by non-professional users. Disinfection of sponges is considered as a PT2 use since the sponge itself will not come into contact with food. For the risk assessment the possible exposure via food is taken into account.
- The active substance is used in product-type 3 (PT3), ready-to-use product to disinfect teats of dairy cows in a pre- and/or post-milking application as a dip or spray. The product is intended for agricultural usage by farmers.
- The active substance is used in product-type 4 (PT4) by professional users as a disinfectant for surfaces in the (soft) drinks industry, including breweries, where drinks are prepared, processed and stored.

3.3.2 Calculation of SED/LED

According to the Applicant, salicylic acid is currently not contained in oral care products on the European market, and the application is intended to provide the basis for the future use of salicylic acid in oral care products at a maximum concentration of 0.5%.

The Applicant presented several aggregate exposure calculations based on different exposure scenarios. All of these assume 100% occurrence of salicylic acid in all product categories.

3.3.2.1 Deterministic aggregate exposure assessment: Scenario 1

Scenario 1 comprises two different deterministic calculations: Scenario 1A (Table 8) is deterministic and based on the SCCS Notes of Guidance recommendations. Scenario 1B is a deterministic consumer aggregate exposure assessment using P95 use data from a

Cosmetics Europe % use survey data from use in the year 2016 (Cosmetics Europe 2017 report).

Table 8: Maximum use levels of salicylic acid and associated worst case **deterministic aggregate assessment** calculated **by the Applicant** for 17 cosmetic products based on NoG (100% occurrence and daily use)

Product	Calculated relative daily exposure to product[1] (mg/kg bw/day)	Maximum allowable % use levels	Total dermal exposure to salicylic acid with maximum allowable % levels (mg/kg bw/day)	Calculated SED[2] for salicylic acid (mg/kg bw/day)	MoS (Calculated by the SCCS)
Shower gel	2.79	2	0.0553	0.03348	2240
Hand wash	3.33	2	0.0666	0.03996	1877
Shampoo	1.51	3	0.0453	0.02718	2759
Hair conditioner	0.67	3	0.0201	0.01206	6219
Hair Styling	5.74	2	0.1148	0.06888	1089
Body lotion	123.20	**0.5**	0.616	0.3696	203
Face cream	24.14	2	0.4328	0.28968	259
Hand cream	32.70	2	0.654	0.3924	191
Liquid foundation	7.90	2	0.153	0.0948	791
Lipstick/salve[3]	0.90	**0.5**	0.0045	0.0027	27778
Make-up remover	8.33	2	0.1666	0.09996	750
Eye shadow	0.33	**0.5**	0.00165	0.00099	75758
Mascara	0.42	**0.5**	0.0021	0.00126	59524
Eyeliner	0.08	**0.5**	0.0004	0.00024	312500
Non-spray Deodorant	22.08	0.5	0.1104	0.06624	1132
Toothpaste[3]	2.16	**0.5**	0.0108	0.00648	11574
Mouthwash[3]	32.54	**0.5**	0.1627	0.0976	768
Aggregate			**2.67**	**1.67**	**45**

1. According to values as derived in Tables 3A and 3B in the SCCS notes of guidance (11th revision) (2021). These are common values for all product types, as set by the SCCS in this model.
2. Total dermal external exposure x 60% dermal penetration (SCCS 2017)
3. No dermal penetration applied to lipstick, toothpaste and mouthwash; SCCS default 100% absorption used.

The MoS in Table 8 is calculated based on a NOAEL of 75 mg/kg bw/d and it is below the safe level of 100.
In accordance with a tiered approach, a probabilistic exposure assessment (see chapter 3.3.2.2) was presented by the Applicant.**3.3.2.2 Probabilistic aggregate exposure assessment: Scenario 2.**

Scenario 2 comprises different probabilistic calculations: Scenario 2A uses maximum salicylic acid concentrations in all product categories, whereas Scenario 2B is based on concentration distributions based on a survey among the cosmetics industry.
Initially, the Applicant had performed aggregate exposure assessments for a population including children and adults (11-94) (Scenario 2A-Annex A-I and Scenario 2B, Annex A-II). After the commentary period, based on the SCCS comment on the assessed population for the probabilistic scenarios mentioned above, the Applicant presented separate Scenario 2A assessments for adults 18-94 (Table 12) and adolescents 11-17 years old (Annex A-III).

According to the Applicant, the parameter and scenario information encompass study population (a), use amounts (b), retention factors and uptake fraction (c), which are used to calculate the probabilistic aggregate exposure (d).

a) study population

The probabilistic scenarios are calculated with the CRÈME model (Comiskey *et al.*, 2015, 2017) by using the total and the exposed population, respectively. For the assessment, habits and practices data of European subjects of age 11 -94 years old (30,756 subjects) from the Kantar database (http://www.kantarworldpanel.com/global) were considered. Usage events logged in the diary describe the day and time of a usage event, the product category used and the site(s) of application. Every participant listed product use by the hour in the habits and practice database for 7 consecutive days. If multiple products were used at the same time, these were listed as separate records. This provides detailed daily product co-use information.

According to the Applicant, subject bodyweights and heights are essential pieces of information for the exposure algorithm. These are used to calculate relative exposure, *i.e.*, per unit bodyweight or per unit surface area of skin. As the Kantar habits and practices survey data does not record subjects' bodyweight and height, these data had to be supplied from elsewhere.
No dataset of European body measurements (bodyweight and height) for the European population that is both comprehensive and paired was available. So, a data-based simulation method was developed to assign measurements to European subjects stratified by gender and age. The method modelled height and weight as a bivariate distribution, based on national mean height and weight data, stratified by gender and age (see Table 9 for sources of those data).
Variance and covariance parameters describe how variables vary, singly and together. With the assumption that covariance between height and log weight is independent of country, covariance matrices were derived from over 20,000 paired measurements obtained the National Health and Nutrition Examination Survey (NHANES) data. NHANES is a program of studies designed to assess the health and nutritional status of United States citizens, from which detailed body measurement data for the US population can be extracted.

These NHANES covariances were combined with the national mean heights and weights for each European country to form distributions that were used to generate paired height and weight values that were stochastically assigned to European subjects.

Table 9: Sources for national mean body weight and height data

Country	Age Group	Source
Spain	19 – 24	Carrascosa Lezcano *et al.* (2008)
Spain	11 – 23	López-Siguero *et al.* (2008)
Italy	11 – 95+	ExpoFacts[1]
Germany	11 – 59	Bergmann and Mensink, (1999)
Great Britain	16 – 85+	HSE[2]
France	11 – 71+	INCA2[3]
Poland	14 - 18	Klimek-Piotrowska *et al.* (2015)

[1] http://expofacts.jrc.ec.europa.eu/index.php?category=database&source=db_a&
[2] http://content.digital.nhs.uk/healthsurveyengland
[3] https://www.data.gouv.fr/_uploads/resources/Table_indiv.csv

b) use amounts

According to the Applicant, the amount of product applied in a usage event is a crucial component in the exposure model. Amount per use data for each product was collected from studies on consumers in the USA and UK and described in recent publications. Amount data for the Creme Care and Cosmetics model was derived from these sources. Table 10 lists the product categories and supplies the relevant reference.
From these data sources, probability distribution expressions were derived. Amount distributions describe the variability and range of amounts of each product consumed by the subjects, according to age, gender, and country.

Table 10: Sources of amounts per use data Creme Care and Cosmetics model products

Product	Source
Body lotion Face moisturizer Lipstick	(Hall *et al.*, 2007)
Toothpaste	(Hall *et al.*, 2007)
Deodorant non-spray Shampoo	(Hall *et al.*, 2007)
Eye shadow Eyeliner Mascara Make-up remover	(Biesterbos *et al.* 2013b)
Hair spray	(Loretz *et al.*, 2006)
Hair styling Hand cream Mouthwash	(Hall *et al.*, 2011)
Liquid hand soap	(Larsen & Andersen, 2006)
Liquid make-up foundation Shower gel	(Hall *et al.*, 2011)
Rinse-off conditioner	(Loretz *et al.*, 2008)

c) retention factors and uptake rate

Retention factors used in all assessments of exposure are detailed in Table 11. Dermal retention factors represent the percentage (fraction) of product that remains on the skin after application. Dermal Retention factors were provided by Cosmetics Europe and derived from SCCS Notes of Guidance (European Commission, 2021).
Ingestion and inhalation retention were disregarded in this analysis.
Dermal absorption is the percentage of product that penetrates the skin. A value of 60% was applied to all products, excluding Oral Care products (toothpaste and mouthwash, via oral exposure) and Lipstick, which were considered at 100% dermal penetration in both scenarios. See Table 11 for a list of the retention and absorption factors used in this study.

Table 11: Retention and dermal absorption factors used in exposure assessments.

Creme Product Type	Dermal penetration (%)	Dermal Retention Factor (%)
Shower gel	60	1
Liquid hand soap	60	1
Shampoo	60	1
Rinse-off conditioner	60	1
Hair styling	60	10
Body lotion (mass market, prestige, other)	60	100
Face moisturizer	60	100
Hand cream	60	100
Liquid make-up foundation	60	100
Deodorant roll-on	60	100
Lipstick	100	100
Toothpaste	100	5
Mouthwash*	100	10
Make-up remover	60	10
Eye shadow	60	100
Mascara	60	100
Eye pencil	60	100

* 100% oral/mucosal absorption is applied here as a worst-case assumption; retention factors have already been factored into the Eproduct calculation in Table 5 of the SCCS 2021 Notes of Guidance, and it is assumed all of the retained Salicylic Acid can enter the systemic circulation via dermal and oral routes

d) Resulting single and aggregate exposure values

The Scenario 2A aggregate exposure estimates for the exposed population are presented in Table 12.

Table 12. Probabilistic P95 of the systemic exposure doses for salicylic acid calculated **by the Applicant** with the Crème RIFM model for the **adult** exposed population by using allowed maximum concentrations for all products and 100% occurrence (Scenario 2A).

Aggregation	Concentration (w/w %)	P95 Exposure (µg/kg bw/day)	95% Confidence Interval
Body Lotion Mass	0.5	329.1360	(310.1776, 353.4964)
Body Lotion Other	0.5	372.0568	(304.5213, 390.5516)
Body Lotion Prestige	0.5	344.1675	(292.2409, 366.8085)
Deodorant Roll On	0.5	42.9007	(42.081, 43.7355)
Eyeliner	0.5	0.0271	(0.0268, 0.0277)
Eye Shadow	0.5	0.2534	(0.2496, 0.2571)
Face Moisturizer	2.0	240.1286	(231.619, 245.2467)
Hair Styling	2.0	77.1875	(76.3749, 81.3535)
Hand Cream	2.0	520.6520	(488.9647, 541.16)
Lipstick	0.5	1.5378	(1.4716, 1.6238)
Liquid Hand Soap	2.0	8.4176	(8.2037, 8.6035)
Liquid Make up Foundation	2.0	108.9766	(105.7753, 112.239)
Makeup Remover Cream Wipe Off	2.0	81.3042	(79.2389, 87.013)
Mascara	0.5	1.1069	(1.0907, 1.115)
Mouthwash	0.5	229.7310	(224.4147, 233.6174)
Rinse off Conditioner	3.0	33.5542	(32.6411, 34.5961)
Shampoo	3.0	28.4066	(28.2378, 28.9938)
Shower gel	2.0	42.5775	(41.7617, 43.0859)
Toothpaste	0.5	11.1554	(11.091,

			11.2)
All products (Aggregate Exposure)		**448.0738**	**(436.8132, 453.3289)**

*Oral care is included here in relation to potential prospective use (up to 0.5%).

Hence, the SEDs calculated for the deterministic Scenario 1A and the probabilistic Scenario 2A exposure calculation, are **1.67 mg/kg bw/day and 0.45 mg/kg bw/day,** respectively.

SCCS comment
The SCCS considers the probabilistic assessments using 100% occurrence and maximum use levels of a substance in each product category as adequately conservative for risk assessment. In view of this, the SCCS uses the aggregate exposure of 0.45 mg/kg bw/day from Scenario 2A (Table 12) in MoS calculations.
According to information by the Applicant, salicylic acid is not used in mouth spray. This product is therefore not included in the assessment.

3.3.2.3 Calculation of SED following oral ingestion in children

According to the Applicant, the use of oral care products inevitably leads to the retention and subsequent unintentional ingestion of a fraction of the product used. Adult use is taken into account using 100% absorption in the overall aggregated exposure assessment. In general, children are expected to ingest more toothpaste and mouthwash than adults, therefore a separate safety evaluation is done here.

Bodyweight values for European children in the assessment
EFSA (2012b) provides default values for use in risk assessment where there is no specific measured data. In this risk assessment of oral ingestion below, firstly intake values based on typical usage are calculated for 1-6 years and 7-18 years. The body weight data as per the EFSA values (Table 13), is then used to perform risk assessments for 3-10, 10-14, and 14-18 years categories for European consumers.

Table 13. Body weight (kg) statistics for infants, children, and adolescents in all surveys of the EFSA (Comprehensive database (EFSA 2012b)).

Age (years)	Gender	N	Mean	StdDev	Median	P5	P95
Infants [0-3 months[	♀+♂	205	4.8	1.4	4.8	3.2	6.4
Infants [3-6 months[	♀+♂	231	6.7	1.0	6.7	5.1	8.5
Infants [6-12 months[	♀+♂	441	8.8	1.2	8.7	7.0	11.0
Toddlers [1-3 years[	♀+♂	1679	11.9	2.2	11.6	8.7	15.9
Other children [3-10 years[	♀+♂	8902	23.1	7.1	21.7	14.0	37.0
Adolescents [10-14 years[	♀+♂	3222	43.4	10.6	42.0	29.4	62.0
Adolescents [14-18 years[	♀+♂	3996	61.3	11.9	60.0	45.0	83.0

Intakes for 1-6 years of age: toothpaste
According to the Applicant, the use of toothpaste starts with first erupted teeth and occurs with a high percentage of dentifrice ingestion. Therefore, the amount of toothpaste to be used by children age 6 and under, as implemented for fluoride toothpastes, is generally set at a pea size amount. The SCCNFP (2003) defined this as 0.25 grams when assessing the safety of fluoridated oral care products for children. Furthermore, a retention factor of 40% for children 7 months-8 years of age was explicitly stated to be "already an overestimate" when these exposure calculations were revisited (SCCP 2005). Therefore, it was

appropriately conservative to assume that children of this age use a pea-sized amount (0.25 g) of toothpaste twice a day with a retention factor (RF) of 40% (SCCP, 2005). Oral retention factors are needed to consider that only a fraction of the orally applied products will be ingested. An industry-wide usage survey was conducted, and at the present time salicylic acid is not used in toothpaste, but to support innovation a calculation is performed as if 0.5% salicylic acid were used. Some children's toothpastes are not as strong in flavour as adult toothpastes and lower % levels of salicylic acid would be used in principle due to its bitter taste. However, this is modelling the worst case if a high-dose adult toothpaste were to be used by children of different ages.

Table 14. Intake levels calculation of 1-6 year of age in toothpaste

1-6 years of age: Toothpaste			
Max Salicylic acid Concentration	IC	0.5	%
Amount used	A	0.25	g/use
Frequency	FQ	2	uses/day
Retention Factor	RF	40	%
Conversion Factor	CF	1000	mg/g
Systemic Exposure (mg/person/day) =		(IC)(A)(FQ)(RF)(CF)	
Systemic Exposure (mg/person/day) =		0.5/100 (0.25 g/use) (2 uses/day) (40)/100 (1000 mg/g)	
Intake (mg/person/day) =		**1**	

Intakes 7-18 years of age: toothpaste
For this age group, ingestion of toothpaste is lower primarily because children of this age can spit it out after use. Using the SCCP (2005) and SCCS (2018) guidance document for oral care products, it is assumed that 2.75 g of toothpaste is used per day for adolescents and adults, with a RF of 5 %. An industry-wide usage survey was conducted, and it was determined that currently marketed toothpaste contains up to 0.5% Salicylic acid.

The following intake levels can therefore be calculated:

Table 15: Intake levels calculation of 7-18 year of age in toothpaste

7-18 years of age: Toothpaste			
Max Salicylic acid Concentration	IC	0.5	%
Amount used	A	2.75	g/day
Retention Factor	RF	5	%
Conversion Factor	CF	1000	mg/g
Systemic Exposure (mg/person/day) =		(IC)(A)(RF)(CF)	
Systemic Exposure (mg/person/day) =		0.5/100 (2.75 g/day) (5)/100 (1000 mg/g)	
Intake (mg/person/day) =		**0.69**	

Intake from Mouthwash 6-18 years
The use of mouthwash can start at age 6 (it is generally recommended that children under 6 should not use mouthwash) (www.ada.org; Zuanon, 2005). The usage volume for adults of 21.62 mL/day and retention factor of 10 % from SCCS's 2021 Notes of Guidance is used.

This is appropriate, considering published literature on the ingestion of mouthwash by six-year-old children, with a reported 8 % retention (Zuanon, 2005). An industry-wide usage survey was conducted, and at the present time salicylic acid is not used in mouthwash, but to support innovation, a calculation is performed as if 0.5 % salicylic acid were used, and assuming roughly 1 mL mouthwash is equivalent to 1 g.

Table 16 Intake levels calculation of 6-18 year of age in mouthwash

6 years of age to 18: Mouthwash			
Max Salicylic acid Concentration	IC	0.5	%
Amount used	A	21.62	g/day
Retention Factor	RF	10	%
Conversion Factor	CF	1000	mg/g
Systemic Exposure (mg/person/day) =		(IC)(A)(RF)(CF)	
Systemic Exposure (mg/person/day) =		0.5/100 (21.62 g/day) (10)/100 (1000 mg/g)	
Intake (mg/person/day) =		**10.81**	

SCCS comment
The SCCS agrees that the amount of toothpaste used by children aged 6 years and under is generally 0.25 grams. Since children up to 6 years of age can be expected to ingest more toothpaste than adults, a retention factor of 0.4 for children aged 3-6 years, and 0.1 for children aged 6-10 years is appropriate for SED calculations.

The Applicant did not provide any specific scenarios for children applying cosmetic products on their skin (dermal exposure), taking also under consideration the differences between age categories in some exposure parameters (body weight, amount of the products applied, body's surfaces, etc). As the concern for this Opinion is on ED, which may lead to some specific effects in vulnerable populations such as children, specific exposure calculations for children (between 3 to 10 years old) are needed.

3.4 TOXICOLOGICAL EVALUATION

The data related to toxicological evaluation were assessed and commented upon by the SCCS in the previous Opinion (SCCS/1601/18). Only SCCS' comments and main conclusions are included in this section.

3.4.1. Irritation and corrosivity

/

SCCS general comment
In SCCNFP/0522/01, mostly product-based information was evaluated for skin and eye irritation. However, risk assessment of cosmetic ingredients within the remit of the SCCS is based on the assessment of the ingredient and not of cosmetic formulations. Test results based on cosmetic formulations have therefore not been taken into consideration in this Opinion.

3.4.1.1 **Skin irritation**

/

SCCS comment from previous Opinion
Based on previous animal skin irritation studies using alcoholic solutions of salicylic acid, the SCCNFP had considered in its Opinion (SCCNFP/0522/01 of 2002) that salicylic acid is mild to non-irritating to skin. Based on the TLK 2008 study, the SCCS had concluded in its Opinion (SCCS/1601/18) that neat salicylic acid is not irritating to skin.

3.4.1.2 **Mucous membrane irritation / eye irritation**

/

SCCS conclusion on eye irritation from previous Opinion
Based on all available data concerning ingredients, SCCS considered in its Opinion (SCCS/1601/18) that salicylic acid can cause serious damage to the eye. Salicylic acid is classified as Eye Dam. 1 (H318 Causes serious eye damage) and was included in annex VI of CLP (Regulation 2018/1480).

3.5.2 Skin sensitisation

/

SCCNFP/0522/01/2002 comments
According to the modified Buehler test protocol using the guinea pig, salicylic acid was not considered as a sensitising agent. However, no data were provided about the experimental potential risk under maximising conditions or to the confirmation of absence of risk to humans.
The results of human repeated insult patch tests conducted with formulation up to 2% salicylic acid confirm that topical application does not cause skin sensitisation. Salicylic acid is not known as a sensitiser.

SCCS/1601/18 comments
The sensitising potential of salicylic acid has been studied in three different LLNA studies. Salicylic acid was positive in one LLNA at a concentration of 20% and negative in the other two LLNA studies. It is well known that strong irritants like salicylic acid can give a false-positive response in the LLNA, explaining the results observed by Gerberick *et al.* (1992). Together with the evidence from the Buehler test provided in Submission I (SCCNFP/0522/01, 2002), it can be concluded that salicylic acid has no skin sensitising potential.

3.5.3 Acute toxicity

3.5.3.1 **Acute oral toxicity**

/

SCCS comment from previous Opinion
Salicylic acid is (Regulation 2018/1480) included in annex VI of CLP and as regards acute oral toxicity, it is classified as Acute Toxicity Category 4, H302 (Harmful if swallowed). Even

though all the studies and publications submitted have certain shortcomings, the available data support this classification.

3.5.3.2 **Acute dermal toxicity**

/

SCCS comment from previous Opinion
Based on the results of an animal study covering the acute dermal toxicity of salicylic acid, the SCCS considers salicylic acid as a low dermal acute toxicant.

3.5.3.3 **Acute inhalation toxicity**

The Applicant's dossier has not indicated the intention to use salicylic acid in spray or aerosol cosmetics.

SCCS comment
No data have been provided on acute toxicity of salicylic acid by inhalation. The SCCS has noted that salicylic acid is not intended for use in spray or aerosol cosmetics, and therefore the safety of such uses has not been assessed in this Opinion.

3.5.4 Repeated dose toxicity

No OECD guideline repeat dose 28-day or 90-day sub-chronic study data are available on salicylic acid via the oral or inhalation routes.

3.5.4.1 Repeated dose (28 days) oral / dermal / inhalation toxicity

Repeated dose dermal toxicity

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Repeated dose inhalation toxicity
Salicylic acid is not used in spray or aerosol cosmetics. This was verified by Crème Global (2017).

3.5.4.2 Sub-chronic (90 days) oral / dermal / inhalation toxicity

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3.5.4.3 Chronic (> 12 months) toxicity

No chronic data have been submitted.

SCCS overall conclusion of repeated dose toxicity
The SCCS considers that the assessment from SCCNFP (2002) and SCCS (2018) concerning the toxicity of salicylic acid after repeated exposure remains valid. In particular that:

- No systemic toxicity was noted from sub-chronic dermal toxicity studies conducted in rabbit at the highest dosage of 120 mg/kg bw/day salicylic acid formulations; dermal irritation was the main recorded observation.
- In humans, toxic effects have been reported after topical application of salicylic acid to extensive areas of the body with diseased skin. Children are more sensitive than adults to

develop salicylism, and the topical application of salicylic acid may thus involve a risk of toxicity in children. Reye's syndrome in children has been associated with the use of acetylsalicylic acid during a viral illness.
- No robust data have been provided to enable proper assessment of the repeated dose toxicity by inhalation. However, since the use salicylic acid is not intended in spray/aerosol products, this Opinion has not assessed inhalation toxicity of salicylic acid.

3.5.5 Reproductive toxicity

There is no standard guideline two-generation reproductive toxicity study available for salicylic acid by any route. As per the SCCNFP 2002 Opinion, the REACH dossier for salicylic acid and the RAC 2016 Opinion, evidence on fertility and reproductive parameters following oral exposure to sodium salicylate or acetylsalicylic acid (aspirin) are used to support the conclusion that salicylic acid does not have significant effects on fertility. This is on the basis that sodium salicylate and aspirin ingested orally are readily converted to systemic salicylic acid, and so in essence the reproductive organs are actually exposed to salicylic acid following intake.

A detailed analysis of reproduction in humans exposed to aspirin was conducted by Novacyl, including review of a new epidemiology literature analysis by an external expert. In 2013, a CLH dossier was provided by industry with an update including this new data analysis of human exposures and the lack of reproductive effects for the fertility endpoints observed following widespread exposures to aspirin.

Taken from RAC (March 2016)

The assessment of salicylic acid is based on read-across data from studies on methyl salicylate (MeS) and acetylsalicylic acid (ASA). The studies used in the assessment are summarised in the Table below.

Table 17. Summary of fertility studies

Summary of the fertility studies taken into assessment

Study design, test material, species	***Doses***	***Conclusions***
3-generation study (Collins *et al.*, 1971), MeS, male and female Osborne-Mendel rats	500, 1500, 3000 and 5000 ppm (equivalent to 22.5, 67.5, 135, 225 mg/kg bw/d as salicylic acid) in the diet	No statistically significant decrease in fertility index was reported at any dose for any generation.
2-generation study (Abbott & Harrisson, 1978), MeS, male and female Wistar rats	2500 and 5000 ppm (equivalent to 113 and 225 mg/kg bw/d as salicylic acid) in the diet	Non-significant decrease in mating performance for the first generation.
2-generation study (Abbott & Harrisson, 1978), MeS, male and female mice	2500 and 5000 ppm (equivalent to 324 and 648 mg/kg bw/d as salicylic acid) in the diet	No adverse effects were reported on any reproductive parameter.
2-generation study,(NTP, 1984a) continuous breeding protocol , MeS, CD-1 mice	25, 50 and 100 mg/kg bw/d (22.5, 45 and 90 mg/kg bw/d as salicylic acid) by gavage	No effects on fertility were reported.
1-generation study (NTP, 1984b), continuous breeding protocol , MeS, CD-1 mice	100, 250 and 500 mg/kg bw/d (90, 225 and 450 mg/kg bw/d as salicylic acid)	No effect on fertility index.
Fertility test, (Schardein *et al.*, 1969), ASA , male and female rats	A single dose level of 0.4% in the diet (210 mg/kg bw ASA, equivalent to 161 mg/kg bw as salicylic acid)	ASA did not significantly affect male or female fertility. This dose caused moderate bw depression in males and severe bw depression in females.

Note: all the studies in the table above have a Klimisch reliability score of 2

None of these studies have been done with salicylic acid but with methyl salicylate or acetylsalicylic acid. These studies also showed a number of deficiencies in relation to current test guidelines in terms of parameters studied, but the results were consistent. No statistically significant effect on fertility was reported in any study. In addition, 2-year chronic toxicity studies in rats and dogs (Webb, 1963) showed no abnormalities in sexual organs (testes/prostate or ovaries/uterus). The adverse effects on reduced viability of offspring reported primarily in rats represent developmental toxicity rather than a reduction in fertility in either males or females.

3.5.5.1 Fertility and reproductive toxicity

***In vivo* assays**

Information taken from Hass *et al.* (2018)

Davis *et al.* (1996)

This study investigates the effect on maternal reproduction in rats after oral exposure to salicylic acid and looks at the structure-toxicity relationship between acetylsalicylic acid and salicylic acid with respect to the effects measured in the maternal reproduction parameters.
Sprague-Dawley virgin female rats (n=105) at the age of 63 days were mated and the presence of a copulating plug marked gestation day 0. Randomly assigned animals were divided into dose groups receiving sodium salicylate at 0 mg/kg/day, 20 mg/kg bw/day, 80 mg/kg bw/day, and 200 mg/kg/day. A single group received a dose of acetylsalicylic acid at 260 mg/kg bw/day. All groups were exposed by oral gavage on day 15-21 during gestation and administration of the compound was conducted twice a day (one half morning / one half 6-8 h after). Parameters recorded from the dams were: body weight (measured on day: 0,

6 and 15-21), duration of gestation, labor time (time between the first and last born) and gross examination of uterus and ovaries (post-mortem). Registrations from pups included examination for external abnormalities, number of viable/non-viable, sex determination and weight. The results of the study showed that the groups exposed to 200 mg salicylic acid/kg bw/day and 260 mg acetylsalicylic acid /kg/day had a delay in the onset of labor, an increase in labor time and a significantly increase in maternal perinatal mortality. Regarding the treatment-associated fetotoxicity only the group exposed to Acetyl salicylic acid at 260 mg/kg bw/day showed a significant increase in stillborn pups and peripartum death. Additionally, both compounds were well-tolerated in all treatment groups. No substantial potency difference between the salicylate congeners, acetyl salicylic acid and salicylic acid could be established only the differences in toxicity profile were evident.
Study quality and assessment: Although the study is well-described, information about CAS n° and purity are missing regarding sodium salicylate and acetylsalicylic acid. Overall the quality of the study is assessed to be high and from the result found it provides a moderate evidence of adverse effect on maternal reproduction and fetotoxicity including prolongation of labour and gestation after sodium salicylate exposure
Collins *et al.* (1971): The aim of this study was to investigate the effect of methyl salicylate on rat reproduction. The study included a main part and a supplemental study but due to a mixed-compound exposure in the supplemental study, the result was found to be non-relevant and only the main part will be included in this summary. Osborne-Mendel rats were divided in groups of 20 pair (litter mated) and fed methyl salicylate through the diet for 100 days prior to mating at the levels of 0, 500, 1500, 3000 and 5000 ppm. Two litters, F1a and F1b were produced by F0 and on day 4 all litters were reduced to include maximum 10 pups per litter. At weaning F1b were pair-housed and mated (20 pairs per group). Same procedure was followed for the following generations. Parameters investigated were fertility index (number of litters cast/number of females exposed to mating), Litter size, number of live born, viability index (number of live-born/total number born), surviving from day 0-4, survival index (number alive at day 4/number born alive), number of progenies weaned at day 21, weight of weanlings and abnormalities by external examination. Autopsy and histopathological examination (liver and kidney) was only performed on the weanlings from the third generation. The results from the study revealed significant findings at dose levels of 3000 and 5000 ppm regarding a decrease in the average litter size, number of live-born progeny, number of survivors to day 4 and number of survivors to day 21. The decrease in number of live-born appeared to be dose-related. At the lower dose levels only, a non-significant decrease was observed. This paper is included in the REACH registration dossier for salicylic acid on toxicity to reproduction. Study quality and assessment: The study has a number of shortcomings. For example, the details on diet preparations, the description of the 3-generation study and the reason for the choice of concentrations refers to earlier studies and is only roughly described in the text. No report of CAS number and purity of the substance used could be found. Overall the study is assessed to be of medium quality and it provides moderate evidence for reproductive adverse effect after exposure to methyl salicylate during pregnancy.
Also, this study investigated the effect of methyl salicylate, which is metabolized in salicylic acid. It is then difficult to consider only the effect of this one specific metabolite, although it may be the main one.

Comments of Hass *et al.* (2018)- REACH registration dossier: Following studies and reviews from "Toxicity to reproduction" in the REACH registration dossier has already been included here (Collins *et al.*1971 and Chapin and Sloane 1997) and summaries of their data can be found under the section for *in vivo* studies or reviews. Based on information available in the REACH registration Dossier a short summary of all the additional studies has been added below.
The studies did not add significant value or new information to the ED MoA or endocrine-related adverse effects on salicylic acid. In general, the studies show a dose-related decrease in the average litter size and pup weight, effects on offspring viability and some studies investigated the effect on male/female reproduction but without any significant findings. The quality of the unavailable studies cannot be assessed based on summaries

available on REACH registration dossier. They all report to have a minimum of 20 animals/ dose group and a few is performed under GLP and follow a guideline. In the experiments that observe some changes, half of them report that the findings were significant so in general the studies are assessed to provide moderate evidence for adverse effect on reproduction.

Other studies:

Information taken from Hass *et al.* (2018)

Schardein et al (1969) presented a study with focus on male/female fertility (rats), the teratogenic potential (rats and rabbits) and the effect of treatment in the perinatal and postnatal period (rats). It should be noted that treated animals in all groups showed moderate to severe reduction of weight gain. Skeletal malformations, reduced litter size and reduced viability of the pups were noted and for the dams treated with aspirin in large doses a (> 210 mg/kg) all pregnancies resulted in resorption of all fetuses.
Cappon *et al.* (2003) conducted a study with focus on comparing the developmental toxicity of Aspirin (acetyl salicylic acid) in rabbits when it was administrated throughout organogenesis or during sensitive windows of development. A repeated dose study was conducted on GD 7-19 with doses of 125, 250 and 350 mg/kg and a single dose study was conducted on day 9, 10 or 11 with dose levels of 500, 750 or 1000 mg/kg. On GD 29 caesarean sections were performed and an examination of foetuses was done with focus on external, visceral and skeletal development but the results from the study showed no malformations associated with the exposure to Aspirin.
Erikson (1970) investigated the role of dosage and the frequency of administrating on the prenatal effect in rats produced by salicylate. Late pregnancy effect in the foetuses included superficial liver and gastric haemorrhage and vessel abnormalities and increased death.

SCCS comment
Most of the available studies have been performed on aspirin (acetyl salicylic acid), which is mainly metabolised to salicylic acid, along with other metabolites. Since some of the metabolites may confound the effects reported in these studies, it is difficult to ascertain whether or not the effects are due to salicylic acid alone. Further studies specifically using salicylic acid are needed in this regard. Based on the currently available data, the SCCS considers that salicylic acid should not be regarded as a reproductive toxicant for the fertility endpoints.

3.5.5.2 Developmental Toxicity

In March 2016, the Committee for Risk Assessment of the European Chemical Agency proposed to classify salicylic acid as a category 2 reproductive toxicant (ECHA, 2016). The classification is based on adverse developmental effects in two animal species (rat and monkey). All developmental studies on salicylic acid have been performed in rats and are summarised in Table 18.

Table 18. Reproductive and developmental animal studies with salicylic acid

Species	Test article	Route of exposure	Dosage	Results	Reference
Wistar Rat 20 per group	Salicylic acid	Oral, days 8-14 of gestation	0.06, 0.1, 0.2 & 0.4 % in diet (50 to 200 mg/kg/ day)	Maternal mortality 0%. **0.4 %:** body weight loss, toxic symptoms, 71% neonatal mortality and growth retardation in foetuses. **0.2 %:** growth retardation, skeletal abnormalities. **0.1 %** and **0.06 %** no significant adverse effects. **NOAEL** approx. **75 mg/kg/day**	Tanaka et al 1973a*
Wistar Rat 20 per group	Salicylic acid	Oral, days 8-14 of gestation	75, 150 or 300 mg/kg once daily	**300 mg/kg/day**: 3 dams died; 100% fetal mortality. **150 mg/kg/day**: 26 % fetal mortality, reproductive effects. **NOAEL 75 mg/kg/day**	Tanaka et al 1973b*
Sprague Dawley Rat n = 10	Salicylic acid	Oral, 10 mg/kg twice daily, days 20 &21 of gestation	20 mg/kg/day	Increase in time of onset of parturition; duration of parturition increased in one animal; increased bleeding at parturition in 4 animals. No fetal deaths.	Waltman *et al.*, 1973
Sprague Dawley Rat n = 17	Salicylic acid	Sub-cutaneous dose on day 9 of gestation	380 mg/kg/day	Marked maternal weight loss; decreased fetal weight; 46.6% resorption rate, 5.3% fetal malformations.	Koshakji & Schulert, 1973

*From this review, Tanaka et al 1973a is the pivotal study yielding the lowest NOAEL for the risk assessment.

Following review of the available toxicology data, the pivotal study (for deriving the point of departure (POD) as a toxicological benchmark for the safety evaluation of salicylic acid) remains the same in this dossier as was concluded by the SCCNFP in 2002, namely the developmental toxicity study on salicylic acid by Tanaka *et al.*, 1973a. The POD is expressed as a no observed adverse effect level (NOAEL) of 75 mg/kg bw/day relating to the most sensitive toxic endpoint *i.e.* teratogenicity in the rat as the most sensitive species.

Tanaka *et al.*, 1973a (Former opinion and new applicant's dossier)

Guideline/method: Equivalent to OECD Guideline 414 (Prenatal Developmental Toxicity Study)
Species/strain: Rat/Wistar
Group size: 20 females per dose
Test substance: Test substance: salicylic acid; 0.5% in CMC (carboxymethyl cellulose); No other data
Batch:
Dose levels: 0.06%, 0.1%, 0.2% and 0.4% in the diet (50.7 ± 0.6, 77.4 ± 1.0, 165 ± 2.1, 205.9 ± 18.9 mg/kg bw/d, respectively)
Positive control: /
Route: Oral dietary administrations
Exposure period: Exposure was limited to the period of organogenesis (GD 8-14 only)
Exposure frequency: Daily
GLP: No
Study period: /

On day 20 of gestation, 15 of the 20 animals were sacrificed and 5 were allowed to deliver their offspring. The offspring were weaned on day 21 and their weight and growth recorded

every 3 days. After 56 days, the offspring were sacrificed, and any visceral or skeletal abnormalities were recorded.

Results

In the 0.4% dose group (205 mg/kg bw/day):
- a marked body weight loss was observed in dams at the beginning of salicylic acid administration, but a gradual increase in body weight was then observed after 11 days. This decrease in body weight was assumed to be due to a decrease in food intake, but no deaths were observed.
- uterine and placental weights were significantly lower than controls, but there were no marked differences in the number of corpora lutea or in the rate of nidation in all groups. There was 71.2% neonatal mortality in this group. One dam gave birth to six offspring, and all died within a day.
- litter size and body weight and length as well as tail length were statistically significantly decreased. Effects observed at 56 days in offspring were 29.6% external anomalies, 13.6% internal organ anomalies and 46.8% skeletal anomalies.
- maternal effects expressed as temporary body weight loss with toxic symptoms (salivation, piloerection) and the following fetal effects: high fetal mortality (no live fetuses in 9/15 dams examined), high frequency of complex anomalies (cranioschisis, myeloschisis, pes varus, oligodactyly etc.) and dose-related fetal growth retardation.

In the 0.2% dose group (165 mg/kg bw/d):
- fetal effects (fetal anomalies and growth retardation) were seen in the absence of maternal effects. This dose resulted in a maternal serum concentration of about 116 microgram/mL.
- the body weight and length and the tail length were statistically significantly decreased. Effects observed at 56 days in offspring were 3.8% external anomalies, no internal organ anomalies and 14.6% skeletal anomalies.

In the 0.1 and 0.06% dose (approximately 75 and 50 mg/kg bw/day, respectively) groups:
- the two lower doses caused neither maternal nor fetal effects.

In conclusion, this academic non-GLP compliant study illustrates the potential of salicylic acid to induce embryofetal toxicity at dose levels equal to or higher than 0.2% and malformations at the maternally toxic dose level of 0.4% following dietary administration in Wistar rats between days 8 and 14 of gestation.

The no observed adverse effect levels (NOAELs) were defined at 0.2% (165 mg/kg bw/day) for maternal toxicity and 0.1% (75 mg/kg bw/day) for developmental toxicity.

Tanaka *et al.*, 1973b (former opinion)

Guideline/method:	Equivalent to OECD Guideline 414 (Prenatal Developmental Toxicity Study)
Species/strain:	Rat/Wistar
Group size:	20 females per dose
Test substance:	Test substance: salicylic acid; 0.5% in CMC (carboxymethyl cellulose); No other data
Batch:	
Dose levels:	75, 150 and 300 mg/kg in a 0.5% solution of sodium carboxymethylcellulose
Positive control:	/
Route:	Oral gavage
Exposure period:	Exposure was limited to the period of organogenesis (GD 8-14 only)

Exposure frequency: Daily
GLP: No
Study period: /

Results
In the 300 mg/kg group of salicylic acid, the body weight gains were inhibited with toxic symptoms such as salivation and piloerection, and some animals died within a few days after the beginning of the administration and high fetal mortality prevailed. Decreased uterine weight was observed in animals of the 150 and 300 mg/kg dose groups as compared to controls; these groups had 25.7% and 100% fetal mortality, respectively.

Litter size and neonatal body weight, body length, and tail length were significantly decreased in the 150 mg/kg dose group.

The incidences of external, internal, and skeletal anomalies in offspring autopsied at the 56th day were 1.8%, 0%, and 2.5%, respectively, for the 75 mg/kg group and 27.8%, 12.7%, and 65.7%, respectively; for the 150 mg/kg group. The offspring from animals of 150 mg/kg salicylic acid group had decreased body length and tail length compared to controls.
The thyroid weight of male offspring from the 75 mg/kg group was significantly decreased compared to controls. The incidences of external organ, internal organ, and skeletal anomalies in offspring were 0%, 5.0% and 0% respectively, for the 75 mg/kg group and 13.7%, 17.2% and 79.2% respectively, for the 150 mg/kg group.

Under the conditions of the present experiment, salicylic acid administered by gavage is embryotoxic in the rats and induces malformations at maternally toxic doses. The teratogenic effect of salicylic acid may be considered as possibly due to direct action of the agent on the foetus, since a relative distribution of the agent was found in the foetus through the placental barrier.

The NOAEL (maternal): 150 mg/kg bw/day and the NOAEL (development): 75 mg/kg bw/day were identified.

Taken from RAC (March 2016, former Opinion)

The results of the studies demonstrated that salicylic acid has an embryo-/fetotoxic effect in rats with dose-dependent growth delays, foetal death and malformations. Early developmental effects were clearly seen in the absence of maternal effects. The teratogenicity of salicylic acid may be attributable to a direct action of the compound. This finding is further supported by the mechanistic study of Greenaway (1982) in which teratogenicity of salicylate in rat embryos was shown independent of maternal factors after exposure *in vitro*.
However, although there was a general resemblance in terms of skeletal and internal organ abnormalities observed, the pattern of malformations following exposures to salicylic acid and acetylsalicylic acid is slightly different, as described in the studies of Tanaka and Gupta. One explanation could be the differences in the experimental protocol, such as the moment of exposure during organogenesis. However, differences in effects following exposure to salicylic acid and acetylsalicylic acid were shown in *in vitro* cultured rat embryos (Yokoyama, 1984): the anomalies induced by acetylsalicylic acid were systemic (*e.g.* crown-rump length significantly reduced) while those induced by salicylic acid were more localised (*e.g*. facial anomalies).
The study **in monkeys** also showed teratogenic properties with acetylsalicylic acid but with lower magnitude.
By contrast, the effects **in rabbits** were limited to slight growth retardation and were present only at doses much higher than in the rats and monkeys. No skeletal malformations were reported and at the highest dose only one kit of a dam had hydrocephaly.

Overall, salicylic acid was shown to have teratogenic properties but with species differences in potency: strong in rats and lower in monkeys. In contrast, the teratogenic potential in rabbits was practically non-existent. The data from humans are considered inconclusive.
In conclusion, taking into account the available data, including pharmacokinetics, *in vitro* tests with acetylsalicylic acid and salicylic acid, developmental studies in animals (positive findings in rat and monkey studies and a negative rabbit study), human epidemiology and medical experience, the RAC considered classification of salicylic acid as Repr. 2; H361d (Suspected of damaging the unborn child) to be justified.

SCCS comments
The SCCS maintains its previous opinion (SCCS/1601/18) and agrees with RAC that salicylic acid is a developmental toxicant. Harmonised classification of salicylic acid has recently been published in Regulation 2018/1480, where it has been classified as Repr. 2 (H361d Suspected of damaging the unborn child).

For MoS calculations, the SCCS will use the developmental toxicity NOAEL of 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 supported by Tanaka *et al.* (1973b).

3.5.6 Mutagenicity / genotoxicity

A range of studies have been performed to assess the mutagenic/genotoxic potential of salicylic acid. These studies were assessed and commented upon by the SCCS in the previous Opinion (SCCS/1601/18). Only SCCS' comments and main conclusions from SCCS/1601/18 are included in this section.

3.5.6.1 Mutagenicity / genotoxicity *in vitro*

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3.5.6.2 Mutagenicity / genotoxicity *in vivo*

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SCCS comment from previous Opinion (SCCS/1601/18)

- The results of the gene mutation assays using bacteria have indicated no mutagenic effect of salicylic acid in the absence or presence of S9 mix in all bacterial strains tested. The SCCS has noted that the provided information does not make it clear whether the study was performed under GLP standard. Furthermore, it is not clear who performed the study, when it was performed, what concentrations of the positive control substances were used, and what were the historical values of revertants number for control and positive substances.
- In the *in vitro* gene mutation study in mammalian cells, a significant trend ($p=0.001$) was observed in the first culture of the second experiment, and mutation frequency for the two highest concentrations was outside the historical control range. The RSG at the highest concentration of 1400 µg/mL was below 10% meaning a strong cytotoxic effect. Considering this, and also the fact that this effect was not repeated in the second culture (although significance level was at $p=0.052$), the significant trend can be regarded as not biologically meaningful. Hence, overall, the study indicates no mutagenic effect of salicylic acid in the mouse lymphoma assay.
- Only one study on chromosomal aberrations *in vitro* with salicylic acid is available in the open literature, which was also submitted by the Applicant. In this study (Stich

et al., 1981), Chinese Hamster Ovary cells were exposed to salicylic acid for 3 hours, with and without S9-mix. The result of the study was negative. However, the SCCS emphasises that the study is not GLP-compliant and is of limited value for use in safety assessment since apparently only one concentration of salicylic acid was tested (25 mg/mL) in the main experiment, and no result with a positive control without S9-mix was provided. Moreover, for each sample 200 metaphase plates were analysed for chromosome aberrations, which contrasts with the current recommendation of scoring at least 300 well-spread metaphases per concentration and control to conclude a test chemical as clearly negative (OECD TG 473 adopted 29 July 2016). In the second study, *i.e.* Ishidate *et al.* (1983) on chromosomal aberration test *in vitro,* Chinese hamster fibroblast cells were exposed to 1 and 1.25 mg/mL salicylic acid for 48h. The result was regarded as positive by the Applicant. However, the original publication was not provided for verification in the submission II.

- The SCCS considers the result of the submitted *in vivo* study (Giri *et al.*, 1996) on chromosomal aberrations and sister chromatid exchanges of salicylic acid as negative.

Overall SCCS comments on mutagenicity from previous Opinion (SCCS/1601/18)
The SCCS comments are based on available, *i.e.* currently and previously submitted data on mutagenicity testing of salicylic acid. The genotoxicity of salicylic acid was investigated with valid genotoxicity tests for *in vitro* gene mutations, in both bacterial (Ministry of Labour/Japan, 2000) and mammalian test system (RCC, 2008b). Although no valid *in vitro* test results on chromosomal aberrations were provided, the *in vivo* chromosomal aberration and sister chromatid exchange tests in mice showed no mutagenic activity of salicylic acid (Giri *et al.*, 1996).
Based on the results provided, the SCCS is of the opinion that salicylic acid can be considered to pose no genotoxic hazard.

3.5.7 Carcinogenicity

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Overall SCCS comment on carcinogenicity from previous Opinion (SCCS/1601/18)
On the basis of the evidence available on negative results of genotoxicity, and some evidence on the absence of carcinogenicity, the SCCS considers salicylic acid as unlikely to be a carcinogen.

3.5.8 Photo-induced toxicity

3.5.8.1 Phototoxicity / photo-irritation and photosensitisation

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SCCS comment from previous Opinion
Although safety assessment within the SCCS remit is based on assessment of the ingredients and not formulations, test results of phototoxicity studies that have been used in commercial (probably cosmetic) formulations have also been reviewed by the SCCS. The SCCS agrees that, based on the submitted studies (on humans and mice), salicylic acid does not have photo-irritant, photosensitising, or photocarcinogenic properties.

3.5.8.2 Photomutagenicity / photoclastogenicity

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3.5.9 Human data

3.5.10 Special investigations

Endocrine activity

1) **Non-test information, *in silico*, read across, *in chemico***

Information taken from Hass *et al.* 2018
Davis *et al.* (1996): This study has a two-fold purpose. One part investigates the effect on maternal reproduction in rats after oral exposure to sodium salicylate and is detailed in the following section. The other part looks at the structure-toxicity relationship between acetylsalicylic acid (ASA) and salicylic acid (SA) with respect to the effects measured in the first part of the study. No substantial potency difference between the salicylate congeners, ASA and SA could be established.

2) ***In vitro*** **and other assays**

Information taken from Hass *et al.* 2018
As previously mentioned, very few studies have been performed on Salicylic Acid itself. Some endocrine properties have been reported on SA congeners:

Mazaud-Guittot *et al.* (2013) provided strong evidence for an endocrine disrupting (ED) mode of action (MoA) from aspirin exposure.

Albert *et al.* (2013) provided moderate evidence for ED MoA by direct exposure to aspirin in NCI-H295R cell line.

Abend *et al.* (1991), although the study was assessed to be of medium quality, did not provide any evidence for an ED MoA on the activity of type II 5'-Deiodase after exposure to sodium salicylate to examine the feedback mechanism from T3 / T4 on TSH by looking at the role of this enzyme.

Larsen, P.R. (1972) conducted a study to clarify the effect of SA on the protein binding of the two thyroid hormones (T3 / T4) in human serum. The investigation was made up from several smaller studies using sodium salicylate added in increasing amounts to pooled human serum. The study quality is assessed to be medium (No report of CAS no. neither purity of the substance but the evidence for a thyroid disrupting MoA of SA *in vitro* is strong.

Hansen and Mogensen (1964) investigated the effect of sodium salicylate on the uptake of [^{131}I]- 1-triiodothyronine by human erythrocytes. The study provides no evidence for a thyroid disrupting MoA of sodium salicylate through binding of T3 to erythrocytes *in vitro*.

Wolff *et al.* (1961): The aim of the study was to investigate T4 displacement from serum proteins in human serum after addition of natrium salicylate. Overall, the study is assessed to be of high quality and provides strong evidence for a thyroid disrupting MoA of natrium salicylate.

From the Updated Dossier on the Human Safety Evaluation of Salicylic Acid in Cosmetic Products submitted by the applicant (Nov 2021)

Salicylic acid (purity >90%) has been tested in the Endocrine Disruptor Screening Program (EDSP) within the US EPA Tox21 program.
https://comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID7026368#invitrodb-bioassaystoxcast-data
There was no activity reported in 18 estrogen 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 activity that salicylic acid was endocrine active in these systems.

3) In vivo and ex-vivo assays

Information taken from Hass *et al.* 2018
Kristensen *et al.* (2012): This study aimed at investigating effects of mild analgesics (paracetamol, indomethacin and aspirin) on *ex vivo* rat foetal testis development. The study is well described and thorough, although there is no report on the CAS number and purity of the substance used. The study is rated as high quality and provides strong evidence for an anti-androgenic MoA of ED after exposure to aspirin.

Kristensen *et al.* (2011): The *in vivo* part of the study is described here, focusing on intrauterine exposure to mild analgesics as a risk factor for development of male reproductive disorders in rats. Pregnant rat dams were exposed to acetylsalicylic acid at doses of 150, 200 and 250 mg/kg/day from GD 13-21 with caesarean section conducted on GD 21. For dose-response analysis, anogenital distance (AGD) in male foetuses and testosterone production by testes were measured. The findings regarding testosterone and AGD provide strong evidence of an anti-androgenic MoA after Aspirin exposure. The *ex vivo* part focusing on intrauterine exposure to ASA. Testes from male rat foetuses (n=8) obtained by caesarean section on GD 14.5 were incubated with two testes in each experiment, for 3 days in a media with or without Aspirin at concentrations of 1 µM and 10 µM. The media concentration of prostaglandin D2 (PGD2) and testosterone were measured after 24, 48 and 72 h. The result from the study shows a dose dependent reduction in testosterone and PGD2 with a significant result for testosterone at 10 µM Aspirin at all time points and a significant result for PGD2 at 48 and 72 h. The study is well-described although no information on CAS number and purity of the substance used could be found. The quality is assessed to be high, and it provides strong evidence for an anti-androgenic MoA of ASA.

Gupta *et al.* (2003): The aim of this study was to compare the developmental toxicity of Aspirin (CAS 50-78-2) in rats using selected dosing paradigms. To allow a direct comparison between the responses of Sprague-Dawley (SD) rats (in this study) and Wistar rats (from Kimmel *et al.*1971), the study design and dose levels were based on the work of Kimmel et al (1971). The study was conducted in two parts with a single dose study and a multiple dose study and in both cases, timed-mated SD rats were assigned. In the first study (single dose) groups of 7 rats were orally exposed (by gavage) to acetylsalicylic acid (ASA) on gestation day 9 (0, 250, 500 or 625 mg/kg), 10 (0, 500, 625 or 750 mg/kg) or 11 (0, 500, 750, 1000 mg/kg). In the second study (multiple doses) groups of 20 rats were orally (by gavage) treated with ASA from gestation day 6 to 17 at concentrations of 0, 50, 125 or 250 mg/kg. On gestation day 21 all rats were killed, and foetuses were examined and following parameters were noted: numbers of corpora lutea, implantation sites, late and early resorptions, viable and dead foetuses, individual foetus weight, placenta weight and finally all foetuses' were examined for external and visceral anomalies and developmental variations with focus on ventricular septal defects (VSD) and midline defects (MD). The results from the study showed a high concordance between Wistar and SD rats regarding developmental anomalies with the exception to hydrocephalus in Wistar rats and the VSD in

the SD rats. Whether ASA was administrated as a single dose or during the organogenesis (GD 6-17), the malformations were similar. All registrations of malformations are presented in a Table and only in the high dose-group are they statistically significant. Hypoplastic testes were seen in 2 out of 137 foetuses' and only in the highest dose group and along with ectopic adrenals, ablepharia was only detectable in the multiple dose study and not in the single dose study. **This paper is included in the REACH registration dossier for Salicylic acid on developmental toxicity / Teratogenicity.** *Study quality and assessment*: The study is well-written, thoroughly described and contains details on both animal housing conditions, and CAS number of the substance used, and it is assessed to be of high quality. The results provide weak evidence for ED-related adverse effects after exposure to Aspirin.

Conte *et al.* (1999): The aim of this study was to examine the effect of Aspirin on plasma testosterone, pregnenolone, progesterone, 17OH-progesterone, androstenedione, dehydroepiandrosterone and 17β-estradiol in response to human chorionic gonadotropin (hCG). Healthy 20-30-years old men (n=8) age were examined in a placebo-controlled, single-blinded study and to test the efficacy of Aspirin as a prostaglandin-blocker an additional study was conducted where seminal prostaglandin E2 (PGE2) were determined at the same doses and times used in the experimental protocol. The study is assessed to be of high quality and because of the significant results it provides strong evidence that the androgen response to hCG is inhibited by Aspirin treatment.

Davis *et al.* (1996): This study has a two-fold purpose. One part investigates the effect on maternal reproduction in rats after oral exposure to salicylic acid. The other part looks at the structure-toxicity relationship between acetylsalicylic acid (ASA) and sodium salicylate with respect to the effects measured in part one. Sprague-Dawley virgin female rats (n=105) at the age of 63 days was mated and the presence of a copulating plug marked gestation day 0. Randomly assigned animals were divided into dose groups receiving sodium salicylate at the level of 0 mg/kg/day, 20 mg/kg/day, 80 mg/kg/day, and 200 mg/kg/day. A single group received a dose of ASA at 260 mg/kg/day. All groups were exposed by oral gavage on day 15-21 during gestation and administration of the compound was conducted twice a day (one half morning / one half 6-8 h after). Parameters recorded from the dams were body weight (measured on day: 0, 6 and 15-21), duration of gestation, labor time (time between the first and last born) and gross examination of uterus and ovaries (post-mortem). Registrations from pups included examination for external abnormalities, number of viable/non-viable, sex determination and weight. The results of the study showed that the groups exposed to SA 200 mg/kg/day and ASA 260 mg/kg/day had a delay in the onset of labor, an increase in labor time and a significantly increase in maternal perinatal mortality. Regarding the treatment-associated fetotoxicity only the group exposed to ASA 260 mg/kg/day showed a significant increase in stillborn pups and peripartum death. Additionally, ASA and SA were well-tolerated in all treatment groups No substantial potency difference between the salicylate congeners, ASA and SA could be established only the differences in toxicity profile were evident. *Study quality and assessment:* The study is well-described but no information about CAS no. and purity could be found regarding sodium salicylate and acetylsalicylic acid. Overall, the quality of the study is assessed to be high and from the result found it provides moderate evidence of adverse effect on maternal reproduction and fetotoxicity including prolongation of labor and gestation after salicylic acid exposure. Although it is reported in the DK report that animals were exposed to salicylic acid, animals received 3 doses of sodium salicylate.

Abend *et al.* (1991): The aim of this study was to examine the feedback mechanism from T3/T4 on TSH by looking at the role of type II 5'Deiodinase (5'D-II). Three groups of male Sprague-Dawley rats were exposed to 1) Intraperitoneal injection of 40 nM NaOH vehicle (control), 2) Intraperitoneal injection of 2 µmol/100g 3-methyl-4',6-dihydroxy-3',5'-dibromo-flavone (EMD 21388) and 3) 30 mg/100 g sodium salicylate administrated by oral gavage. All rats were sacrificed 1 h after exposure by decapitation and trunk blood and

pituitaries was collected. The study is assessed to be of medium quality, and it provides moderate evidence for a thyroid disrupting MoA after exposure to sodium salicylate.

Overman and White (1983): The aim of this study was to compare the teratogenic effect of methyl salicylate in hamsters after oral and topical exposure. Virgin female hamsters were individually mated and the pregnant rats were grouped into either an oral or topical treatment group. For Oral exposure (by intubation) two dose levels were established at 0 mg/100 g bw (control) and 175 mg/100 g bw. For the topical application four groups were established at levels of 0 mg/100 g bw (control, shaved and treated with saline solution and washed after 2 h.), 0 mg (control, anesthetized with Nembutal and shaved), 350 mg/100 g bw (applied to a clipped area and washed after 2 h), 525 mg/100 g bw (applied to a clipped area and washed after 2 h). All exposures to methyl salicylate were conducted once at 7 days and 9 hours into the pregnancy and at day 9-12 all animals were sacrificed. The study provides moderate evidence for developmental adverse effects on skeletal malformations after oral and topical exposure to methyl salicylate and no evidence for ED related adverse effects.

Didolkar *et al.* (1980): This study examines the effect of Aspirin (acetylsalicylic acid) on spermatogenesis in rats. The study examined two age-groups of male albino rats (n=12), Norwegian strain. The study is well-described but assessed to be of medium quality due to the lack of information regarding CAS no. and purity of the substance used, and there is no information on general toxicity in the animals. The study provides strong evidence for adverse effects on spermatogenesis after Aspirin exposure.

Balasubtamanian and Ramakrishnan (1979): The aim of the study was to investigate the effect of acetylsalicylic acid (Aspirin) individually and in combination of prostaglandins (PGs) on carbohydrate and thyroid metabolism in rats. The study is assessed to be of low quality (lack of information) but it provides moderate evidence for a thyroid disrupting MoA of Aspirin.

Beall and Klein (1977): This study was designed to determine if maternal food restriction would enhance the teratogenic effects of salicylic acid. Charles River, CD rats were mated and day 0 of pregnancy was determined by sperm in vagina. From a group of 49 pregnant rats, four groups of similar size were established and received I) Food Ad Libitum (control), II) Food Ad Libitum + 250 mg/kg acetylsalicylic acid administered orally by gavage (0.5 ml/100 g bw) suspended with vehicle (2,5% aqueous Tween 80) from day 7-10 of pregnancy, III) Restricted food (6 g/day) from day 6-15 after mating along with vehicle (control) and IV) Restricted food + 250 mg/kg acetylsalicylic acid administration orally by gavage (0.5 ml/100 g bw) from day 7-10 of pregnancy. The study is assessed to be of medium quality, and it provides moderate evidence for developmental adverse skeletal and soft tissue effects induced by Aspirin.

Wilson *et al.* (1977): This study investigates the embryo toxicity and comparative distribution of acetylsalicylic acid in pregnant rats and rhesus monkeys. In the rat study, a weight adjusted volume of acetylsalicylic acid (suspended in 0.3% aqueous solution of carboxymethyl-cellulose) was administrated orally (by gavage) twice a day on gestation day 9-12 at doses of 0 (control), 100, 150, 175 and 200 mg/kg (2-8 litters/dose gr). Embryo removal was conducted at 1, 2, 4, 8 or 17 h after last exposure on GD12 or they were allowed to continue their pregnangy and removed on GD20. Blood samples for preparation of plasma were taken by cardiac puncture under light ether anesthesia at 1, 2, 4, 8 and 17 h after exposure. For the pregnant monkeys (n=8) acetylsalicylic acid was administrated orally (by gavage) twice a day on gestation day 23-32 at doses of 100 and 150 mg/kg (no report of a control group). Blood sample for serum preparation was taken by venipuncture at day 4, 5 or 10 at1, 2, 4, 8 and 17 h after gavage. Hysterectomy was performed at same intervals after the last gavage. The study is assessed to be of medium quality and since the exposure doses were well tolerated by the maternal animals at levels below 200 mg/kg, the study provides high evidence for adverse effects on embryonic development, growth and

survival in rats and moderate evidence for adverse effects on embryonic growth and survival in monkeys.

Tuchmann-Duplessis *et al.* (1975): The aim of the study is to look at the effects of prenatal administration of acetylsalicylic acid (ASA) in rats. Two groups of pregnant rats (COBS CD Charles River) were established and randomly divided in two dose groups (n=16/group), 0 mg/kg/day and 200 mg/kg/day. ASA, suspended in 1% tragacanth gum, was administered by gastric intubation twice a day starting on day 15 until the end of pregnancy. The study is assessed to be of medium quality, and it provides strong evidence for adverse effects on gestation length and parturition after exposure to 200 mg ASA/kg/day.

Larsen, P.R. (1972): This study was conducted to clarify the effect of SA on the protein binding of the two thyroid hormones triiodothyronine (T3) and thyroxine (T4). Aspirin was administrated to humans (n=2) for a period of 8-10 days in quantities sufficient to obtain a serum salicylate level of 20-25 mg/100 ml. Three baseline determinations were obtained during a 6-day control period prior to the study. During the period of treatment samples of serum were collected every other day and the free T3 and free T4 was estimated by ultrafiltration (UF). The results from the study showed an immediate and persistent increase in the UFT3 and UFT4 in both humans. *Study quality and assessment:* The study is not described in a structured way, and it contains several references to earlier studies for description of methods used. There was no report of batch number of the Aspirin used. The *in vivo* part is assessed to be of medium quality. Although only two subjects were assigned to the study, it provides moderate evidence for thyroid ED MoA after Aspirin exposure.

Hansen and Mogensen (1964): This study investigated the effect of sodium salicylate on the uptake of [^{131}I]-1-triiodothyronine by human erythrocytes. Human patients (n=9) were given 1 g sodium salicylate three times a day for 4 days and serum concentrations of salicylic acid were measured). The study is assessed to be of medium quality. No information on CAS number and purity of the substance used was given and there is no report of any control group. The evidence for a thyroid disrupting MoA is moderate.

Warkany and Takacs (1959): The aim of the study was to conduct an experimental production of congenital malformations in rats by salicylate exposure. The study was composed of two experimental parts. In the first part 116 female rats were mated and the presence of sperm in vagina marked the first day of pregnancy. One single dose of 0.1-0.5 cc (cubic centimetre) methyl salicylate was administrated subcutaneously on gestation day (GD) 9, 10 or 11. In the second study 43 pregnant rats received a single dose of 60-180 mg sodium salicylate also administrated subcutaneously on gestation day 9, 10 or 11. For control group, 105 females were used. The study quality is assessed to be low and due to the number of dead dams and resorptions it provides weak evidence for adverse effect on fetal development.

SCCS comments

Although there are indications from the literature that salicylic acid may have endocrine properties, most of these studies are not focused on salicylic acid alone, and therefore need to be viewed with caution regarding the conclusions. Indeed, the effects of salicylic acid are not the only ones evaluated in most of these studies. For example, although salicylic acid is the major metabolite of aspirin, other metabolites of aspirin may have confounded the results reported in the articles.

Although no *in vivo* or *in vitro* studies are available that have explicitly examined the potential endocrine mode of action of salicylic acid, the available data do not support an adverse effect of salicylic acid from an endocrine mechanism.

Similarly, sodium/natrium salicylate may have different pharmacokinetics from salicylic acid and therefore for the purpose of data read-across it needs to be considered a compound that is not completely similar to salicylic acid.

4) Epidemiological studies

Information taken from Hass *et al.* 2018

Kristensen *et al.* (2011): This study consisted of 3 parts (*in vivo*, ex vivo and epidemiology) and the epidemiology part will be described here. The focus of the study was to evaluate maternal use of mild analgesics during pregnancy in relation to congenital cryptorchidism in humans. A prospective birth cohort study was conducted in collaboration between the university hospital of Copenhagen (Rigshospitalet and Hvidovre Hospital) and the Turku University Central Hospital in Finland with the use of a self-administrated questionnaire (assessing the use of mild analgesic by indication, name, dosage, and gestational week of administration), completed by 2297 women from both countries and a computer-assisted interview over the telephone (addressing the use of analgesic), where 491 of the Danish mothers participated. Following criteria were established to obtain a genetically well-defined population: both the parents and grandparents of the unborn child should have been born and raised in Finland or Denmark with a maximum residence abroad of 10 years for the grandparents and father and 3 years for the mother. A total of 2521 mothers entered the Danish part of the study, and 1071 boys were examined, of those 5 were excluded as dependent cases and 26 excluded due to missing data. From Finland a total of 2728 mothers participated where 1499 boys were examined and from that group 25 were excluded as dependent cases along with 4 due to missing data. The assessment of the testicular position in the new-borns was performed by trained paediatricians. In the Danish part, findings in the self-administrated questionnaire indicated that many mothers strongly under-reported their use of analgesic unless they were specifically asked and for that reason only the results from the computer-assisted telephone interview were taken into account. The data from that part, showed that the use of mild analgesic was dose-dependently associated with congenital cryptorchidism and especially the use during the second trimester increased the risk - for acetylsalicylic acid data was reported to be significant. In the finish cohort the same association could not be identified, only a trend was seen in the second trimester. *Study quality and assessment:* The study is well-described and is assessed to be of high quality. The study provides strong evidence of adverse effects of acetylsalicylic acid on male sexual development leading to congenital cryptorchidism.

Labib, 2018: These authors published a kinetic-based safety assessment of consumer exposure to salicylic acid from cosmetic products demonstrating no evidence of a health risk from developmental toxicity. Briefly, they performed a safety reassessment in which margins of safety (MoS) were calculated based on literature data on the NOAEL plasma exposure levels from animal reproductive toxicity studies with acetylsalicylic acid, rapidly converted to salicylic acid in plasma, human salicylic acid plasma levels from oral exposure to acetylsalicylic acid and human dermal exposure to salicylic acid-containing cosmetic products. In addition, they performed a literature review and showed that there are no adverse developmental effects despite extensive human clinical oral use of acetylsalicylic acid up to the maximum recommended therapeutic doses. The plasma exposure-based safety assessment for salicylic acid, combined with an absence of any clinical health risk with oral acetylsalicylic acid use in the literature supports that there is an acceptable MoS for the consumer exposure to salicylic acid as authorized in the current EU cosmetic regulation.

Taken from Hass *et al.* 2018- Summary of the plausible link between adverse effects and endocrine mode of action

The androgenic activity is also investigated *in vitro* and ex vivo and the studies showed decreased testosterone production after acetylsalicylic acid exposure in all cases except one. The three studies showing a decrease includes investigations in H295 cells (Albert *et al.*2013) and *ex vivo* rat foetal testicular tissue (Kristensen *et al.* 2012 and Kristensen *et al.* 2011). However, *ex vivo* studies in human testis did not show clear reductions in testosterone production after acetylsalicylic acid exposure. One study showed a reduction in testosterone levels in adult testis, but it did not reach statistical significance (Albert *et al.* 2013) and another study found results showing that Aspirin stimulated testosterone production in testis from gestation week 8-9 but no effects were seen in older fetal testis

(Mazaud-Guittot *et al.* 2013). It is unclear whether the differences in effects on ex vivo testosterone levels are due to species differences or if there is a difference in either the methods used or the sensitivity of the testis at different time-points. Taken together, both the *in vitro* and the *ex vivo* data provide moderate evidence of an anti-androgenic mode of action of acetylsalicylic acid. The human studies available show that Aspirin significantly inhibit the androgen response to hCG stimulation in humans (Conte *et al.* 1991) and a significant decrease in testicular weight together with a decrease in the activity of testicular enzymes and an impairment of the later stages in the spermatogenesis were found by Didolkar *et al.*1980. The adverse effects observed in human testis are likely related to the anti-androgenic MoA of acetylsalicylic acid. When all results are taken into consideration the data provide moderate evidence for an anti-androgenic ED MoA and adverse effects after exposure to acetylsalicylic acid.

The ED MoA of Salicylic acid has been investigated in several *in vivo*, *ex vivo* and *in vitro* studies (Table 19 and Annex B - I). Starting with the results from *in vitro* studies concerning the thyroid function, some of the studies found that exposure to salicylates increased the free fraction of T3 and T4 (Larsen *et al.*1972). Going further into details, other studies found that salicylate affects the binding capacity between T4 and TBPA (Wolff *et al.*1961) and that T4 then is displaced to TBG (Wolff *et al.*1961). A similar action of salicylate on the binding of T3 to TBPA and TBG was shown (Larsen *et al.* 1972) and it appears that this leads to an increased binding to erythrocytes *in vivo* (Hansen and Mogensen, 1964). Available human studies provide results that back up the *in vitro* findings. A human study showed an increase in free T3 and T4 after Aspirin exposure and this was in line with their *in vitro* results (Larsen *et al.*1972). Furthermore, studies showed a decrease in total serum T4 concentration (Abend *et al.* 1991) and increased uptake of T3 by erythrocytes after salicylate treatment in humans (Hansen and Mogensen, 1964). Together, both the *in vitro* and the human studies provide strong evidence of a thyroid disrupting mode of action of salicylates and when all data are taken together, they provide strong evidence of a thyroid disrupting MoA of salicylates. No studies investigated endpoints relevant for evaluation of adverse effects related to thyroid disruption were found. In conclusion, salicylates meet the WHO definition of an endocrine disruptor with anti-androgenic ED MoA leading to adverse effects.

Table 19: Overview of *in vitro* and *in vivo* endocrine disrupting (ED) mode(s) of action (MoA(s)) of Salicylic acid (SA) and analogues (adapted from Hass *et al.* 2018 on salicylic acid)

Reference	**Molecule tested**	**MoA**		**Quality of study**	**Evidence for ED MoA**
		In Vitro	*In Vivo*		
Albert *et al.* 2013	Aspirin	The production of testosterone by human test is revealed a decreased level but did not reach statistical significance. In the NCI-H295R cell line, exposure to 10^{-5} and 10^{-4} M Aspirin significantly reduced testosterone production. A reduction was also seen in the levels of INSL3, PGD_2, PGE_2 and Inhibin B production.		High	Moderate
Mazaud-Guittot *et al.* 2013	Aspirin		Aspirin showed a significant dose-response relationship by increasing the level of testosterone in the youngest fetal testis (8-9.86 GW). Anti-Müllerian Hormone production was strongly stimulated. PGE_2 was significantly inhibited	High	Strong
Kristensen *et al.* 2012	Aspirin		Decreased testosterone levels in rat fetal testis were found at all aspirin concentrations. For PGD_2, aspirin led to a modest decrease in the production at all time-points	High	Strong
Kristensen *et al.* 2011	Aspirin		The results showed reduced AGD compared to control but due to fetal growth retardation AGD was undetectable in a number of fetuses and statistical data are not presented. A significant reduction of testosterone was measured.	High	Strong
Kristensen *et al.* 2011	Aspirin		Dose dependent reduction in testosterone and PGD_2 production in rat fetal testis with a significant result for testosterone at 10 µM Aspirin at all time points and a significant result for PGD_2 at 48 and 72 h.	High	Strong

Reference	Molecule tested	MoA		Quality of study	Evidence for ED MoA
		In Vitro	*In Vivo*		
Conte *et al.* 1999	Aspirin		Aspirin significantly lowered the seminal level of PGE_2 and significantly inhibited the androgen response of testosterone, 17 OH-progesterone, androstenedione and dehydroepiandrosterone to hCG stimulation in humans.	High	Strong
Balasubramanian and Ramakrishnan 1979	Aspirin		Decreased percentage uptake of injected $Na^{131}I$ and plasma PBI by the thyroid gland in the groups exposed to Aspirin (acute and chronic) and Aspirin + PGs.	Low	Moderate

Insulin-like growth factor 3 (INSL3), Prostaglandin D2 (PGD2), Prostaglandin E2 (PGE2), anogenital distance (AGD), hCG, protein-bound iodine (PBI), triiodothyronine (T3), thyroxine (T4), thyroxine-binding pre- albumin (TBPA), thyroxine binding globulin (TBG).

Table 20: Overview of potential endocrine-related adverse effects of salicylic acid and analogues (adapted from Hass *et al.* 2018 on salicylic acid)

Reference	Molecule tested	Species, n	Adverse effects	Quality of study	Evidence for adverse effects
Gupta *et al.* 2003	Aspirin	Rats	The results from the study showed a high concordance between Wistar and SD rats regarding developmental anomalies with the exception to hydrocephalus in Wistar rats and the VSD in the SD rats. Whether acetylsalicylic acid was administrated as a single dose or during the organogenesis (GD 6-17), the malformations were similar. Hypo-plastic testes were seen in 2 out of 137 fetuses and only in the highest dose group	High	Weak
Beall and Klein 1977	Aspirin	Rats n= 49	Increase in resorption sites for group IV, reduced mean body weight of pups in group II and increase in developmental defects (rib abnormalities, craniorachischisis and umbilical hernia, eye defects) in both Aspirin- treated groups. The combination of food restriction and exposure to Aspirin increased the incident of abnormalities from 24.4% in group II (=32 pups) to 66,3% (=59 pups) in group IV.	Medium	Moderate
Wilson *et al.* 1977	Aspirin	Rats (n= 4-8) Monkeys (n= 8)	The study results from the rat part showed a significant effect on intrauterine death, growth and malformation (cardiac, brain and skeletal) at doses of 150 and 200 mg/kg and for the monkey part the results showed that both exposure doses (100 and 150 mg/kg) resulted in a slight increase in intrauterine death and transitory growth retardation.	High	Rat study: Strong Monkey study: Moderate
Tuchmann-Duplessis *et al.* 1975	Aspirin	Rats n=32	The results revealed a statistically significant difference in the two groups with a prolongation of pregnancy for the treated dams. The parturition time was also observed to be prolonged and in the treated group 2/16 dams died due to extended period of contractions.	Medium	Strong
Didolkar *et al.* 1980	Aspirin	Rats n= 24	The result from the study shows that Aspirin caused a significant decrease in testicular weight in the group of immature rats. A decrease in the activity of testicular enzymes was observed for hyaluronidase and sorbitol dehydrogenase in both groups. Regarding spermatogenesis, for both groups, Aspirin caused an impairment of the later stages	Medium	Strong

SCCS comments
Only a few studies have specifically investigated the properties of salicylic acid relating to endocrine mode of action. A published report by Hass *et al.* 2018 has evaluated that there is scientific evidence that salicylates (salicylic acid esters, including aspirin) have endocrine disruptor properties (Table 20, Annexes B-I and B-II)). However, there is a current lack of specific data to demonstrate endocrine properties of salicylic acid itself.
A lot of the available studies have been performed on acetylsalicylic acid (aspirin) to infer endocrine effects of salicylic acid. It is, however, not possible for the SCCS to associate the effects observed in these studies specifically to salicylic acid. More specific studies using salicylic acid need to be performed to conclude on the ED properties of salicylic acid.

3.5 SAFETY EVALUATION (INCLUDING CALCULATION OF THE MoS)

According to the Applicant, salicylic acid can be used in 17 product categories (the standard 17 product types of cosmetic products that could lead to exposure by different routes – dermal and oral (but not by inhalation) – therefore, aggregated exposure must be taken into consideration.

For MoS calculation, SCCS has used the developmental NOAEL of 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 in agreement with the previous SCCNFP Opinion (2002), the previous SCCS Opinion (SCCS/1601/2018) and it is also supported by Tanaka *et al.* (1973b). Because of the evidence for rapid and almost complete absorption of salicylic acid from the oral route, the SCCS has not applied any adjustment for bioavailability to this NOAEL value.

Details of the calculation of systemic exposure dose (SED) are given in the Tables presented in section 3.3.2. A generic maximal value for skin penetration of salicylic acid of 60% (see section 3.2.1) has been used for all products in these calculations where dermal absorption needs to be factored in to calculate a systemic exposure dose (SED). For lipstick and oral care products, a worst-case value of 100% absorption is used for passage across the oral mucosa.

The SCCS considers that for this case, the probabilistic approach Scenario 2A, presented in Table 12, section 3.3.2, can be used in the safety assessment of salicylic acid.

The outcomes for aggregate exposures from the different risk assessment approaches are summarised in Table 21.

Table 21: MoS for aggregate systemic exposure to cosmetic products containing salicylic acid, **calculated by the SCCS**

Risk Assessment Scenario	**Basis for exposure assessment**	**Aggregate Systemic Exposure Dose (SED) (mg/kg/day)**	**Margin of Safety (using a NOAEL of 75 mg/kg/day)**
Probabilistic Assessment for adults 18-94: Scenario 2A (Table 12); uses maximum salicylic acid concentrations in all product categories.	Crème Care and Cosmetics model; probabilistic habits & practices; maximum % level	**0.45**	**167**
Maximum use levels of salicylic acid and associated worst case deterministic aggregate assessment - Scenario 1A	According to SCCS notes of guidance (11th revision) (2021); deterministic approach	**1.67**	**45**

The Applicant excluded mouth spray in the aggregate assessment on the basis that the test substance is not used in these products. The SCCS accepts the argumentation of the Applicant. The Applicant also did not include any other spray applications in the aggregate exposure. Therefore, for systemic aggregate exposure calculation, only the product categories of dermally non-sprayed products have been considered because salicylic acid is not used in sprayable products.

The probabilistic approach combines currently allowed maximal concentrations of salicylic acid with population data on habits and practices. For the assessment of the MoS, the 95th percentile is used. The derived MoS with scenario 2A is 167 and thus demonstrates the safety of salicylic acid for cosmetics, excluding mouth spray products. Sprayable products that could lead to exposure of the consumer's lungs by inhalation are also excluded.

From the Applicant scenario (cf. Annex AIII), the SCCS did not note any safety concern for adolescents (between 11 and 18 years).

3.6 DISCUSSION

Physicochemical properties
The analytical methods used for the determination of purity and impurities in the test substance were not provided by the Applicant.

Function and uses
Salicylic acid is used in cosmetic products as a denaturant, a hair and skin conditioning agent, an exfoliant, an anti-acne cleansing agent, an anti-dandruff agent and a product preservative.
It can be used in 17 product categories (the standard 17 product types of cosmetic products that could lead to exposure by different routes – dermal and oral). Oral care products are included in this updated Opinion up to a maximum concentration of 0.5%.

According to Annex III of Regulation 1223/2009/EC, salicylic acid is allowed for use at (a) 3% in rinse off hair products, (b) 2.0% in other products except body lotion, eye shadow, mascara, eyeliner, lipstick, roll-on deodorant, and (c) 0.5% in body lotion, eye shadow, mascara, eye liner, lipstick and roll-on deodorant. Salicylic acid is not allowed to be used in preparations for children under 3 years of age. Not to be used in applications that may lead to exposure of end-user's lung by inhalation. It is also not allowed to be used in oral products for purposes other than the inhibition of development of micro-organisms in the products. This purpose has to be apparent from the presentation of the product. These levels are inclusive for any use of salicylic acid.

Toxicokinetics
SCCS maintains its conclusion from the previous Opinion (SCCS/1601/18) and agrees to use a dermal absorption rate of 60% for the calculation of the internal dose and the safety assessment.
Regarding salicylic acid kinetics in rats and humans, no robust data have been provided to enable comparison of the kinetic parameters of the test substance between species (rat and human). For these reasons, the SCCS has not been able to compare the kinetics of salicylic acid in rats and humans. Therefore, the SCCS is of the opinion that a factor of 4 accounting for inter-species toxicokinetic differences is necessary and the acceptable MoS should be 100.
In addition, and based on the studies provided, the SCCS is of the opinion that the metabolism of salicylic acid in rats and humans follow a similar route. It is metabolised mainly to salicyluric acid and conjugated salicylic acid compounds, with a small proportion of oxidative metabolites. Salicylic acid has been reported to be almost completely excreted

via urine both in rats and humans. From the provided studies, the SCCS has also noted that salicylic acid has the potential to cross the placenta.

Exposure Assessment
For the dermal and oral aggregate exposure assessment of salicylic acid for adults, the SCCS has considered it appropriate to use the probabilistic scenario 2A (Table 12) that assumes maximum allowed concentrations of salicylic acid in all cosmetics where it is used.

Salicylic acid is also used as a preservative in food and as a biocide in some consumer products or in various pharmaceutical formulations such as anti-acne products. As no specific exposure data were made available to SCCS to assess exposure following these non-cosmetic uses, it was not possible to include them in the aggregated exposure scenarios. Therefore, the actual total exposure of the consumer may be higher than exposure from cosmetic products alone. However, this has not been considered in this safety evaluation.

Toxicological Evaluation

Irritation and corrosivity

Skin irritation
Based on previous animal skin irritation studies using alcoholic solutions of salicylic acid, the SCCNFP had considered in its Opinion (SCCNFP/0522/01 of 2002) that salicylic acid is mildly to non-irritating to skin. Based on the TLK 2008 study, the SCCS had concluded in its Opinion (SCCS/1601/18) that neat salicylic acid is not irritating to skin.

Mucous membrane irritation / eye irritation
In its previous Opinion (SCCS/1601/18), the SCCS considered salicylic acid as being able to cause serious damage to the eye. Salicylic acid is also classified as Eye Dam. 1 (H318 Causes serious eye damage) and was included in annex VI of CLP (Regulation 2018/1480).

Skin sensitisation
Based on the studies provided, the SCCS considers that salicylic acid has no skin sensitising potential.

Acute toxicity

Acute oral
Salicylic acid is (Regulation 2018/1480) included in annex VI of CLP and as regards acute oral toxicity, it is classified as Acute Toxicity Category 4, H302 (Harmful if swallowed). Even though all the studies and publications submitted have certain shortcomings, the available data support this classification.

Acute dermal
Based on the results of an animal study covering the acute dermal toxicity of salicylic acid, the SCCS considers salicylic acid as a low dermal acute toxicant.

Acute inhalation
No data have been provided on acute toxicity by inhalation. According to the Applicant, salicylic acid is not intended for use in spray or aerosol cosmetics.

Repeated dose toxicity
The SCCS considers that the assessment from SCCNFP (2002) and SCCS (2018) concerning the toxicity of salicylic acid after repeated exposure remains valid. In particular that:
- No systemic toxicity was noted from sub-chronic dermal toxicity studies conducted in rabbit at the highest dosage of 120 mg/kg bw/day salicylic acid formulations; dermal irritation was the main recorded observation.

- In humans, toxic effects have been reported after topical application of salicylic acid to extensive areas of the body with diseased skin. Children are more sensitive than adults to develop salicylism, and the topical application of salicylic acid may thus involve a risk of toxicity in children. Reye's syndrome in children has been associated with the use of acetylsalicylic acid during a viral illness.
- No robust data have been provided to enable proper assessment of the repeated dose toxicity by inhalation. However, since the use salicylic acid is not intended in spray/aerosol products, this Opinion has not assessed inhalation toxicity of salicylic acid.

Fertility and reproductive toxicity
Most of the available studies have been performed on aspirin (acetyl salicylic acid), which is mainly metabolised to salicylic acid, along with other metabolites. Since some of the metabolites may confound the effects reported in these studies, it is difficult to ascertain whether or not the effects are due to salicylic acid alone. Further studies specifically using salicylic acid are needed in this regard. Based on the currently available data, the SCCS considers that salicylic acid should not be regarded as a reproductive toxicant for the fertility endpoints.

Developmental Toxicity
As mentioned in the previous Opinion, SCCS maintains its opinion and agrees with RAC 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, the SCCS has used the developmental NOAEL of 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 also supported by Tanaka *et al.* (1973b).

Mutagenicity / genotoxicity
The SCCS comments are based on available, *i.e.* currently and previously submitted data on mutagenicity testing of salicylic acid. The genotoxicity of salicylic acid was investigated with valid genotoxicity tests for *in vitro* gene mutations, in both bacterial (Ministry of Labour/Japan, 2000) and mammalian test systems (RCC, 2008b). Although no valid *in vitro* test results on chromosomal aberrations were provided, the *in vivo* chromosomal aberration and sister chromatid exchange tests in mice showed no mutagenic activity of salicylic acid (Giri *et al.*, 1996).
Based on the results provided, the SCCS is of the opinion that salicylic acid can be considered to pose no genotoxic hazard.

Carcinogenicity
No additional studies have been provided by the Applicant in this submission. However, on the basis of the evidence available on the negative results of genotoxicity and some evidence on the absence of carcinogenicity, the SCCS considers salicylic acid as unlikely to be a carcinogen.

Photo-induced toxicity
Although risk assessment of cosmetic ingredients in the remit of the SCCS is based on the assessment of the ingredient and not of cosmetic formulations, test results of phototoxicity studies which use commercial (probably cosmetic) formulations have been reviewed by the SCCS. The SCCS agrees that, based on the submitted studies (in human and in mice), salicylic acid does not have photo-irritant, photosensitising or photocarcinogenic properties.

Special investigation

Endocrine activity
Only a few studies have investigated the properties of salicylic acid relating to endocrine mode of action. A published report by Hass *et al.* 2018 has evaluated that there is scientific

evidence that salicylates (salicylic acid esters, including aspirin) have endocrine disruptor properties. However, there is a current lack of specific data to demonstrate endocrine properties of salicylic acid itself.

A lot of the available studies have been performed on acetylsalicylic acid (aspirin) to infer endocrine effects of salicylic acid. It is, however, not possible for the SCCS to associate the effects observed in these studies specifically to salicylic acid. More specific studies using salicylic acid need to be performed to conclude on the ED properties of salicylic acid.

Safety evaluation (including calculation of the MoS)
The evaluation of safety carried out by the SCCS for the use of salicylic acid in cosmetic products for adults has been detailed in section 3.5.
The Cosmetic Regulation does not allow the use of salicylic acid in products for children under 3 years of age. As the concerns for this opinion is on ED, which may lead to some specific effects in vulnerable populations such as children, specific exposure calculations for children (above 3 years old), by age categories are needed for a specific evaluation for children. In the absence of exposure data of Salicylic acid in cosmetic products for children, some safety concerns are noted for the younger age groups.

From the Applicant scenario (cf. Annex AIII), the SCCS did not note any safety concern for adolescents (between 11 and 18 years).

4. CONCLUSION

The SCCS concludes the following:

(1) In light of the data provided and taking under consideration the concerns related to potential endocrine disrupting properties of Salicylic acid,

a) does the SCCS consider Salicylic acid safe when used as a preservative in cosmetic products up to a maximum concentration of 0.5%?

Based on the safety assessment carried out in consideration of all available information, including the potential endocrine effects:

- the SCCS is of the opinion that salicylic acid (CAS 69-72-7) is safe when used as preservative at a concentration of 0.5 % in cosmetic products, considering its current restrictions in place. The provided information shows that salicylic acid is an eye irritant with the potential to cause serious damage to the eye.

- this Opinion is not applicable to any sprayable product (including mouth spray) that may lead to exposure of end-user's lungs by inhalation.

b) does the SCCS consider Salicylic acid safe when used in cosmetic for purposes other than inhibiting the development of micro-organisms at a concentration up to:

i. 3.0% for the cosmetic rinse-off hair products,

ii. 2.0% for other products except body lotion, eye shadow, mascara, eyeliner, lipstick, non-spray deodorant, and

iii. 0.5% for body lotion, eye shadow, mascara, eyeliner, lipstick, oral products and non-spray deodorant

The SCCS assessment has shown that:

The use of salicylic acid as a restricted ingredient for purposes other than inhibiting the development of micro-organisms is safe at a concentration:

- up to 3.0 % for the cosmetic rinse-off hair products,
- up to 2.0 % for other products, except body lotion, eye shadow, mascara, eyeliner, lipstick, non-spray deodorant, and
- up to 0.5% for body lotion, eye shadow, mascara, eyeliner, lipstick, oral products and non-spray deodorant.

This Opinion is not applicable to any sprayable product (including mouth spray) that may lead to exposure of end-user's lungs by inhalation.

(2) Alternatively, what is according to the SCCS the maximum concentration considered safe for use of Salicylic acid in cosmetic products?

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(3) Does the SCCS have any further scientific concerns with regard to the use of Salicylic acid in cosmetic products?

In the absence of exposure data of Salicylic acid in cosmetic products for children, safety concerns have been noted for the younger age groups (between 3-10 years).

Since the Cosmetic Regulation does not allow the use of salicylic acid in products for children under 3 years of age, this age category has not been considered in this Opinion.

The conclusions of this Opinion refer only to Salicylic Acid as a cosmetic ingredient and not to other salicylates or salicylic acid salts.

5. MINORITY OPINION

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7. GLOSSARY OF TERMS

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

8. LIST OF ABBREVIATIONS

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. ANNEXES

ANNEX A

Annex A-I: Probabilistic P95 of the systemic exposure doses for salicylic acid **calculated by the Applicant** with the Crème RIFM model for the exposed population by using allowed maximum concentrations for all products and 100% occurrence (**Scenario 2A, 11-94 years old**).

Aggregation	P95 Systemic Exposure Dose (ug/kg bw/day)	95% Confidence Interval
All Products	458.7166	(448.5506, 462.5267)
BodyLotionMass	354.9598	(349.6343, 395.3753)
BodyLotionOther	351.9108	(310.1705, 513.7109)
BodyLotionPrestige	366.7547	(350.5823, 400.4199)
DeoRollOn	45.2664	(44.0725, 46.1023)
EyeShadow	0.2477	(0.2458, 0.2547)
Eyeliner	0.0272	(0.0267, 0.0275)
FaceMoisturizer	257.0628	(250.6014, 266.2350)
HairStyling	85.7814	(81.1536, 88.2325)
HandCream	519.5270	(497.2577, 547.7133)
Lipstick	1.6471	(1.5877, 1.6959)
LiquMakeupFoundation	110.9006	(108.2773, 113.6455)
LiquidHandSoap	10.5925	(10.1814, 10.8552)
MakeupRemoverCreamWipeOff	90.4969	(82.0614, 105.1568)
Mascara	1.0623	(1.0452, 1.0768)
Mouthwash*	255.0191	(251.6929, 261.3142)
RinseoffConditioner	33.8704	(33.4383, 34.7560)
Shampoo	28.2082	(28.0023, 28.6759)
Showergel	41.8090	(41.2206, 42.2507)
Toothpaste*	12.5422	(12.3671, 12.6166)

Annex A- II: Probabilistic P95 systemic exposure dose for salicylic acid **calculated by the Applicant** using survey distributional data, (**Scenario 2B, 11-94 years old**)

Aggregation	P95 Systemic Exposure Dose (ug/kg bw/day)	95% Confidence Interval
All Products	66.3617	(66.0572, 67.8677)
BodyLotionMass	117.4708	(115.3536, 120.5004)
BodyLotionOther	151.7554	(125.6789, 153.1195)
BodyLotionPrestige	109.6071	(98.9678, 122.4734)
DeoRollOn	11.4338	(11.4167, 11.7276)
EyeShadow	0.0744	(0.0737, 0.0755)
Eyeliner	0.0110	(0.0109, 0.0112)
FaceMoisturizer	47.2575	(44.9100, 49.0026)
HairStyling	3.2381	(3.0313, 3.2963)
HandCream	46.2688	(43.2975, 48.1418)
Lipstick	0.5795	(0.5541, 0.5937)
LiquMakeupFoundation	10.9377	(10.5573, 11.1607)
LiquidHandSoap	0.5127	(0.4871, 0.5309)
MakeupRemoverCreamWipeOff	61.0004	(58.6882, 67.2114)
Mascara	0.4205	(0.4077, 0.4305)
Mouthwash	0.0000	(0.0000, 0.0000)
RinseoffConditioner	1.8175	(1.7567, 1.8632)
Shampoo	9.0192	(8.6364, 9.0535)
Showergel	29.9120	(29.0986, 30.6339)
Toothpaste	0.0000	(0.0000, 0. 0000)

*Oral care is included here in relation to potential prospective use (up to 0.5%).

Annex A -III Probabilistic P95 systemic exposure dose for salicylic acid **calculated by the Applicant** using survey distributional data, prepared by the Applicant (**Scenario 2A, 11-18 years old**)

Aggregation	P95 Exposure (ug/kg bw/day)	95% Confidence Interval
All Products	541.5623	(524.1841, 555.4095)
BodyLotionMass	642.6042	(611.3905, 678.8857)
BodyLotionOther	798.4712	(687.4375, 809.803)
BodyLotionPrestige	404.1432	(384.6178, 404.1432)
DeoRollOn	73.8843	(70.3932, 77.8628)
FaceMoisturizer	584.2674	(528.8909, 623.7508)
HairStyling	124.9627	(117.9615, 128.9579)
HandCream	473.8491	(411.3311, 514.0928)
Lipstick	0.9937	(0.9731, 1.0591)
LiquidHandSoap	20.3406	(19.6685, 23.0987)
LiquMakeupFoundation	124.2461	(104.5894, 153.0551)
MakeupRemoverCreamWipeOff	88.7652	(85.8307, 128.5699)
Mouthwash	431.5394	(424.8472, 451.9661)
RinseoffConditioner	25.5416	(24.4004, 29.0483)
Shampoo	28.7135	(26.5428, 29.6816)
Showergel	34.4871	(32.6623, 37.1077)
Toothpaste	20.3461	(19.7987, 20.9507)

Annex B -I: Overview of *in vitro* and *in vivo* endocrine disrupting (ED) mode(s) of action (MoA(s)) of Salicylic acid analogues (adapted from Hass *et al.* 2018 report on salicylic acid)

Reference	Molecule tested	MoA	Quality of study	Evidence for ED MoA	Reference
		In Vitro	*In Vivo*		
Abend et al 1991	Sodium salicylate	The result did not provide evidence for the administrated doses of salicylates to directly inhibit enzyme activity.		Medium	none
Abend et al 1991	Sodium salicylate		Administration of salicylates significantly decreased the serum total T4 concentration.	Medium	Moderate
Balasubramanian and Ramakrishnan 1979	Aspirin		Decreased percentage uptake of injected $Na^{131}I$ and plasma PBI by the thyroid gland in the groups exposed to Aspirin (acute and chronic) and Aspirin + PGs.	Low	Moderate
Larsen *et al.* 1972	sodium salicylate	Five smaller studies all confirmed the endpoint that addition of salicylate to human sera caused an increased in free T3 and T4	Increase in free T3 and T4 after administration of Aspirin to humans (n=2)	medium	*In vitro* Strong *In vivo* Moderate
Hansen and Mogensen 1964	sodium salicylate	Increased uptake of [^{131}I]- 1-triiodothyronine by human erythrocytes after addition of sodium salicylate to human donor blood.	Increased uptake of [^{131}I]- 1-triiodothyronine by human erythrocytes in blood from humans exposed to sodium salicylate	Medium	Moderate
Wolff *et al.*1961	natrium salicylate	At low T4 concentrations in human serum most of the T4 was displaced from TBPA onto TBG by addition of natrium salicylate. In the situation where T4 was present in higher amounts TBG became saturated and T4 was further displaced to albumin.		High	Strong

Annex B - II: Overview of potential endocrine-related adverse effects of Salicylic acid analogues (adapted from Hass *et al.* 2018on salicylic acid)

Reference	Molecule tested	Species, n	Adverse effects	Quality of study	Evidence for adverse effects
Overman and white 1983	Methyl salicylate	Hamsters	Failure of closure of the neural tube resulting in cranium bifidum and/or spina bifida	Medium	None
Collins *et al.* 1971	Methyl salicylate	Rats 3 generations	Significant findings were observed at dose levels of 3000 and 5000 ppm regarding a decrease in the average number of litter size, number of live- born progeny, number of survivors to day 4 and number of survivors to day 21. The decrease in number of live-born appeared to be dose-related. At the lower dose levels only a non-significant decrease were observed.	Medium	Moderate
Warkany and Takacs 1959	Methyl salicylate and Sodium Salicylate	Rats n=159	Warkany and Takacs 1959	Methyl salicylate and Sodium Salicylate	Rats n=159
Davis *et al.* 1996	sodium salicylate And Aspirin	Rats n=105	The results of the study showed that the groups exposed to 200 mg/kg/day SA and 260 mg/kg/day ASA had a delay in the onset of labor, an increase in labor time and a significantly increase in maternal perinatal mortality. Regarding the treatment-associated fetotoxicity only the group exposed to ASA 260 mg/kg/day showed a significant increase in the number of stillborn pups and peripartum death.	High	Moderate