Scientific Committee on Consumer Safety

SCCS

OPINION on

Salicylic Acid

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

- Children's exposure -

The SCCS adopted this document
By written procedure on 10 January 2025

ACKNOWLEDGMENTS

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

For the preliminary version of the Opinion

SCCS members

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

SCCS external experts

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

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 conclusions of the SCCS/1646/22 Opinion on children's exposure, does the SCCS consider Salicylic Acid safe for children between 3-10 years of age:

a) *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 not safe when used as preservative at a concentration of 0.5% in all cosmetic products listed under conclusion (b), considering its current restrictions in place. With the exception of body lotion, it is safe in single dermal and oral product categories, when used only in the respective product category.
- this Opinion is not applicable to any sprayable product (including mouth spray) that may lead to exposure of end-user's lungs by inhalation.
- The provided information shows that Salicylic Acid is an eye irritant with the potential to cause serious damage to the eye.

b) when used for purposes other than inhibiting the development of micro-organisms at a concentration up to:

i. 3.0 % for cosmetic rinse-off products

ii. 2.0 % for cosmetic leave-on products except body lotion and oral products, and

iii. 0.5 % for body lotion and oral products

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 not safe at the following concentrations when aggregate exposure is considered:

- up to 3.0% for the cosmetic rinse-off hair products used by children (shampoo, conditioner),
- up to 2.0% for selected other dermally applied products used by children (face moisturizer, hand cream, liquid soap, shower gel), and
- up to 0.5% for body lotion.

With the exception of body lotion, it is safe in single dermal and oral product categories, when used only in the respective product category.

2 *Alternatively, what is according to the SCCS the maximum concentration of Salicylic Acid that is considered safe for children 3-10 years of age?*

Reducing the concentration, for example to 0.1% in dermal products, would make the use safe for dermal products and toothpaste.

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

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.

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

Keywords: SCCS, scientific opinion, salicylic acid, children exposure, 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)- children exposure, preliminary version of 10 January 2025, SCCS/1675/25

About the Scientific Committees

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

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

SCCS

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

Scientific Committee members

Ulrike Bernauer, Laurent Bodin, Qasim Chaudhry, Pieter Jan Coenraads, Janine Ezendam, Eric Gaffet, Corrado Lodovico Galli, Eirini Panteri, Vera Rogiers, Christophe Rousselle, Maciej Stepnik, Tamara Vanhaecke, Susan Wijnhoven

Contact

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

ISSN ISBN

Doi ND

The opinions of the Scientific Committees present the views of the independent scientists who are members of the committees. They do not necessarily reflect the views of the European Commission. The opinions are published by the European Commission in their original language only.

SCCS - Opinions (europa.eu)

TABLE OF CONTENTS

2. MANDATE FROM THE EUROPEAN COMMISSION

Background

The ingredient 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 is currently regulated under Annex III (entry 98) and Annex V (entry 3) with specific maximum concentrations and conditions of use.

Salicylic acid has been subject to safety evaluations by SCCNFP in 2002[1] in the context of the Cosmetic Directive 76/768/EEC for use other than preservative, while in 2018[2] it was assessed in view of its classification as a CMR cat.2 (Reprotoxic category 2) substance under Regulation (EC) No 1272/2008 (i.e., CLP Regulation). In particular, according to Article 15(1) of the Cosmetics Regulation '*the use in cosmetic products of substances classified as CMR substances, of category 2, under Part 3 of Annex VI to Regulation (EC) No 1272/2008 shall be prohibited. However, a substance classified in category 2 may be used in cosmetic products where the substance has been evaluated by the SCCS and found safe for use in cosmetic products'*.

In 2022[3], the SCCS re-assessed the safety of Salicylic Acid in view of its potential endocrine effects following a call for data where stakeholders submitted scientific evidence to demonstrate the safety of Salicylic Acid in cosmetic products. In the SCCS/1646/22 Opinion, the scientific committee confirmed the current allowed maximum concentration limits for Salicylic Acid for the relevant product types. However, the SCCS concluded that '*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)'*.

In November 2023, the Commission received additional information from industry to defend the use of Salicylic Acid in cosmetic products used in children of 3-10 years of age. Cosmetic products intended for children between 3-10 years cover (i) *leave-on* products such as face cream, hand cream, body lotion, (ii) *rinse-off* products such as hand soap, shower gel, shampoo and hair conditioner, and (iii) *oral care* products such as toothpaste and mouthwash with the latter allowed only for children above 6 years. The Commission, therefore, requests the SCCS to carry out a safety assessment on Salicylic Acid in view of the new information provided.

Terms of reference

1. *In light of the data provided and taking under consideration the conclusions of the SCCS/1646/22 Opinion on children exposure, does the SCCS consider Salicylic Acid safe for children between 3-10 years of age:*

[1] https://ec.europa.eu/health/ph_risk/committees/sccp/documents/out170_en.pdf
[2] https://ec.europa.eu/health/sites/default/files/scientific_committees/consumer_safety/docs/sccs_o_223.pdf
[3] https://health.ec.europa.eu/publications/salicylic-acid-cas-no-69-72-7-ec-no-200-712-3_en

a) when used as a preservative in cosmetic products up to a maximum concentration of 0.5 %?

b) when used for purposes other than inhibiting the development of micro-organisms at a concentration up to:

i. 3.0 % for cosmetic rinse-off products

ii. 2.0 % for cosmetic leave-on products except body lotion and oral products, and

iii. 0.5 % for body lotion and oral products

2. Alternatively, what is according to the SCCS the maximum concentration of Salicylic Acid that is considered safe for children 3-10 years of age?

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

3. OPINION

Chapters 3.1, 3.2 and 3.4 are taken from Opinion SCCS/1646/22 for adults. The new Opinion mainly evaluates the newly submitted assessment of the exposure of children between 3 and 10 years old in light of described hazards.

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.

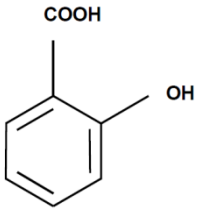
Ref: https://pubchem.ncbi.nlm.nih.gov/compound/338#section=Depositor-Supplied-Synonyms

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

Table 2. Impurities of 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 3. 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 4. Data from a range of kinetics studies in rat and humans, comparing oral dose (in mg/kg/day) with reported Cmax (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 5. 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.

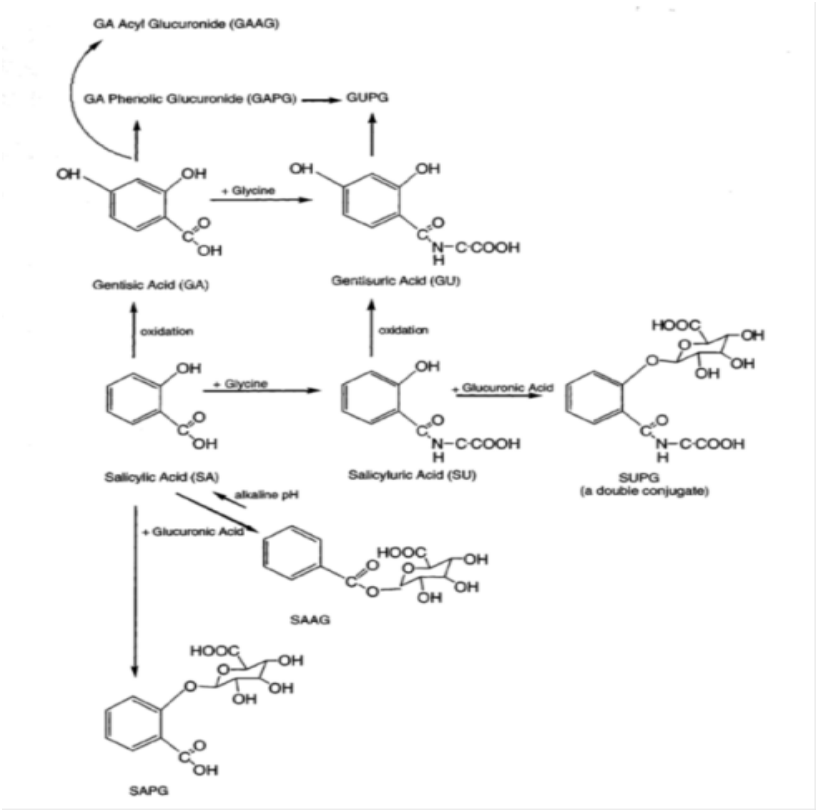


Figure 1. Scheme of the possible major metabolites of salicylic acid, Ref: CIR 2003 review

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

This chapter has been taken over from Opinion SCCS/1646/22.

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 6. 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 7. 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 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, but are not relevant for children 3-10 years old.
Note that there was no reported use of salicylic acid for product types (year 2016): eye pencil, mascara, mouthwash, and toothpaste.

Table 8. 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, there is increasing discussion on children's exposure to products. The OECD published a report in 2019 in which it states '*Children exhibit specific habits and practices that may result in exposure scenarios not considered for other population groups. In addition, there are physiological differences between children and adults, affecting the exposure assessment methodologies. Presently, there is often no structured and harmonised approach for determining when to include a separate children's exposure assessment within risk assessments for chemicals in products*.' A decision tree was provided in the OECD report that acts as a prompt for when a specific children's exposure is necessary, but this still explains that a bespoke approach is needed case by case.

Two main factors that can be considered for cosmetics are smaller surface areas and lower body weights for children as compared to adults, and differences in behaviour that may lead to increased exposure e.g. higher ingestion from swallowing toothpaste and mouthwash.

According to the Applicant, it has been a long-standing view of the SCCS in the Notes of Guidance, and within industry practices, that there is usually no need for a separate cosmetics safety evaluation for systemic toxicity in children via the dermal route. The approach to aggregated dermal exposure assessment for adults and the associated uncertainty factors applied have always implicitly been regarded as also covering children's use of the same products. As detailed below, a MOS of 100 is generally accepted as safe, incorporating an inter-individual safety factor of 10 accounting for human variability in physiologies, thereby covering different age groups including children.

The risk factors for children compared to adults are cited in the SCCS 12th Notes of Guidance as:
(i) Differences in surface area/body weight ratio between children and adults
(ii) Toxicokinetic parameters
(iii) In-use conditions of topical products
(iv) The nappy area
(v) Susceptibility against microorganisms

For the purposes of this case study on salicylic acid for the age group 3-10 years, the risk factors (i), (ii) and (iii) are pertinent.

SCCS comment
The SCCS is currently developing its views on children's exposure in the light of new data regarding endocrine activity and new exposure data that makes it possible to refine aggregate exposure assessments. This will be updated in the next revision of the SCCS Notes of Guidance.

3.3.2.1 Differences in surface area/body weight ratio between children and adults

According to the Applicant, as explained in the SCCS 12th Notes of Guidance (page 112), skin surface area (SSA)/body weight (BW) ratios are different between children and adults: "the ratio between the SSA/BW of children and adults changes from 0 to 10 years and is 2.3 at birth, 1.8 at 6 months, 1.6 at 12 months, 1.5 at 5 years, 1.3 at 10 years (Renwick, 1998). The ratio between the SSA/BW children of 0 to 1 year of age and that of adults is at maximum 2.3. A factor of 3.2 is generally applied by the WHO and also covers variability in human kinetics (see Section 3-5.1.3). Consequently, the inter-individual variation in SSA/BW is covered by the generally accepted default [margin of safety] value of 100 for intact skin". Also, as reiterated in the 12th notes of guidance "the SCCS is of the opinion that there is no need for an additional UF for children when intact skin is present (SCCNFP/0557/02)".

Therefore, the standard way of performing Tier 1 deterministic and Tier 2 probabilistic aggregate exposure calculations for adults are designed to be conservative in adding the intakes from 17 product types (15 dermally applied and 2 oral care products) with the assumptions that all products contain the ingredient in question and all products are used on the same day. When a margin of safety of 100 is obtained from the approach for adults, the long-standing implicit assumption as explained above is that children's potential for exposure, based on SSA and BW differences alone, has also been covered off. Any products targeted and marketed specifically for children have typically been assessed specifically for children, such as specific children's oral care products, where there may be the potential for greater foreseeable and 'accidental' ingestion than in adults, for example.

The values for SSA/BW ratios from Renwick (1998) and WHO (1994) are based on relatively old body weight and skin surface area data and provide a simple way of scaling adult to children's exposure. More up to date information on children's body weights and surface areas according to age are available from authoritative sources.

i) Body weight data
SCCS 12th Notes of Guidance (p115) states "Default values for body weights of different age groups have been published by the European Food Safety Authority (EFSA 2012), infants: 8.8 kg; toddlers: 11.9 kg; children: 23.1 kg; adolescents 10-14 yrs: 43.4 kg; adolescents 14-18 yrs: 61.3 kg)", thereby inferring that these mean body weights are appropriate also to use in cosmetic safety evaluations for the European population. However, using these BW values to convert external applied product/ingredient dose (g/day) to mg/kg/day is applied alongside information about SSA of children relative to adults. In the absence of data specifically on children's g/day product use, a scaling approach is considered applying BW and SSA data to mg/day product use amounts/external applied dose from adult data.

ii) Skin surface area data
There are data on adult skin surface areas for different body parts and the whole body (Table 4 in the SCCS 12th Notes of Guidance); from Bremmer et al., 2006 a,b). The SCCS cite in the footnote to this table the US EPA exposure factors handbook from 1997, but it has been noted on p99 that the most recent US EPA exposure factors handbook is from 2011 (US EPA, 2011). No information on skin surface area datasets to use for children are specifically provided in Appendix 7 of the new guidance for children's exposure assessment in the SCCS 12th Notes of Guidance. There are a number of sources that include a review of children's skin surface area information.

The Nordic Council of Ministers produced a report in 2022 from the Nordic Exposure Group Project, reviewing the most recent sources of evidence for physiological parameters, including data for children's body surface area, by age and by body part. In agreement with the Nordic Council of Ministers Report (2022), it is proposed here that the most relevant data to use for children's SSA is from the RIVM (2014) factsheet on consumer exposure values to use in safety assessment.

Table 9. Default values of the surface area of the total body and different parts of the body for male and female adults (from RIVM, 2014)

	Men		Women		Adults[c]		Q-factor
Surface area	m^2	%	m^2	%	m^2	%	
Total							
Deterministic[a]	1.97		1.73		1.82		4
Probabilistic[b]							
GM	2.09		1.84		1.96		4
CV	1.09		1.09		1.11		
Head	0.13	6.8	0.12	6.7	0.12	6.75	3
Trunk	0.75	38.3	0.60	34.4	0.66	36.35	3
Arms	0.30	15	0.24	13.7	0.26	14.35	3
Hands	0.10	5.2	0.08	4.9	0.09	5.05	3
Legs	0.65	32.8	0.56	32.1	0.59	32.45	3
Feet	0.13	6.7	0.12	6.8	0.12	6.75	3

[a] Deterministic default value is 25th percentile

[b] Body weight distribution for probabilistic calculations (GM: Geometrical Mean and CV: Coefficient of Variation)

[c] For percentage of adults, the average of men and women is assumed

Table 10. Deterministic default values of the skin surface of children of different ages for total body and by body part (from RIVM, 2014).

Age		Body surface area (m^2)		Surface area of parts of the body												
Mon-ths	years	Default	Q-factor	Head (incl. neck)		Trunk (excl. neck)		Arms (excl. hands)		Hands		Legs		Feet		Q-factor
				(%)	(m2)	(%)	(m2)	(%)	(m2)	(%)	(m2)	(%)	(m2)	(%)	(m2)	
0-1[a]		0.20	4	18.2	0.036	35.7	0.071	13.7	0.027	5.3	0.011	20.6	0.040	6.5	0.013	3
1-3[a]		0.28	4	18.2	0.051	35.7	0.100	13.7	0.038	5.3	0.015	20.6	0.058	6.5	0.018	3
3-6[a]		0.34	4	18.2	0.062	35.7	0.121	13.7	0.047	5.3	0.018	20.6	0.070	6.5	0.022	3
6-12[a]		0.41	4	18.2	0.075	35.7	0.146	13.7	0.056	5.3	0.022	20.6	0.084	6.5	0.027	3
	1-2[a]	0.47	4	16.5	0.078	35.5	0.167	13	0.061	5.7	0.027	23.1	0.109	6.3	0.030	3
	2-3[b]	0.57	4	12.3	0.070	37.2	0.212	14.4	0.082	4.7	0.027	25.3	0.144	6.3	0.036	3
	3-6[c]	0.69	4	12.0	0.082	37.3	0.257	14.2	0.098	4.8	0.033	25.5	0.176	6.3	0.044	3
	2-6[b]	0.63	4	12.3	0.077	37.2	0.234	14.4	0.090	4.7	0.029	25.3	0.159	6.3	0.039	3
	6-11[d]	0.93	4	10.2	0.094	36.9	0.343	14	0.130	4.9	0.046	27.5	0.256	6.7	0.062	3
	11-16[e]	1.40	4	7.4	0.105	36.9	0.517	14.1	0.198	4.6	0.064	30.1	0.421	6.8	0.095	3
	16-18[f]	1.68	4	6.2	0.104	38.6	0.648	14.7	0.246	4.5	0.075	29.9	0.501	6.4	0.108	3

[a] Mean per cent of total surface area from (US-EPA 2011). Note that head includes neck.

[b] Mean per cent of total surface area of 2–year-old boys and girls (Boniol et al. 2008)

[c] Average per cent of total surface area of 2 and 4-year-old boys and girls (Boniol et al. 2008)

[d] Mean per cent of total surface area of 6-year-old boys and girls (Boniol et al. 2008)

[e] Average per cent of total surface area of 10 and 12-year-old boys and girls (Boniol et al. 2008)

[f] Mean per cent of total surface area of 16-year-old boys and girls (Boniol et al. 2008)

Table 11. Skin Surface Area (SSA) data (mean in cm^2) from RIVM (2014) as recommended for use by the Nordic Council of Ministers (2022) and Adult:Child ratios to use in exposure assessment calculations for children.

Body part	3-6 years	6-11 years	3-10 years	Adult
Total body surface	6900	9300	8100	18200
Head/Face	820	940	880	1200
Hands	330	460	395	900
Ratios Adult: Child				
Total body surface	2.6	2.0	2.2	-
Head/Face	1.5	1.3	1.4	-
Hands	2.7	2.0	2.3	-

These ratios in Table 11 will be taken forward into the children's exposure assessment for salicylic acid.

SCCS comment

In the dossier, the Applicant has not explained how the surface area for children 3-10 years has been derived. From number checking, the SCCS assumes that it has been calculated by averaging the averages of the age groups 3-6 and 6-11, which is appropriate for similar sample sizes of the averaged groups.

Boniol *et al*, 2008, used anthropometric data on US children from 1977, which were processed in a computer human model to generate the surface areas. However, since anthropometrics of US children and European children may be different and since the US data are quite old, data on European children would be preferable. Furthermore, with 3D-scanning it is possible to determine actual surface areas directly (Yu et al, 2003; Schloesser et al., 2011), which presumably provides more accurate values.

However, when comparing the SSA approach derived amounts with measured data from Ficheux *et al*., 2016, Ficheux and Roudot, 2017, and Garcia-Hidalgo et al., 2017, for children in France and Switzerland, respectively, the SSA approach amounts tend to be too low. Therefore, whenever adequate measured data are available, the SCCS will use the measured data as explained in chapter 3.3.2.4.

3.3.2.2 Toxicokinetics

According to the Applicant, this safety factor is substance specific and if considered necessary to evaluate, could require human relevant evidence on the fate and transport of the substance in a child's body versus an adult body. This only needs to be considered if there is evidence that there are differences in terms of mode/mechanism of toxicity action in children vs adults. This is not expected to be the case for salicylic acid. On the contrary, the adverse developmental effects taken as pivotal reference point for the safety assessment of salicylic acid for adults may be far less relevant for children at the age group 3 to 10 years. For example, Health Canada considered adverse effects of salicylic acid on liver and kidney, which occurred at much higher doses in an oral repeat-dose study, more relevant for the safety assessment for children up to 11 years (Health Canada, 2020). Salicylate kinetics have been studied for decades and Needs & Brooks (1985) concluded 'No significant differences exist between the pharmacokinetics of the salicylates in the elderly or in children when compared with young adults.' Thus, these conclusions substantially contribute to the fact that the safety assessment for adults based on developmental toxicity is sufficiently protective for children.

3.3.2.3 In use conditions of topical products

In 2023, the SCCS 12th Notes of Guidance was published and includes a new Appendix 7 offering advice on the types of general cosmetic products that can be used by children of different age groups (see Table 4).

Table 12 Different cosmetic product classes to which children of different ages could be exposed (according to Table A.7.2 in SCCS 12th NoG (2023)).

Children between 6 months and 1 year	Children between 1 and 3 years	Children between 3 and 6 years	Children between 6 and 10 years	Children between 10 and 14 years and 14 and 18 years
Shower gel Hand soap Shampoo Body lotion Face cream Hand cream	Shower gel Hand soap Shampoo Body lotion Face cream Hand cream Hair conditioner	Shower gel Hand soap Shampoo Body lotion Face cream Hand cream Hair conditioner	Shower gel Hand soap Shampoo Body lotion Face cream Hand cream Hair conditioner Mouthwash	Same as Adults
Toothpaste (RF 40%)	Toothpaste (RF 40%)	Toothpaste (RF 40%)	Toothpaste (RF 5%) Mouthwash (RF 10%)	Same as Adults

According to the Applicant it is noted in this table that children between 3-6 years use toothpaste and are likely to ingest more (40%) than is assumed for adults. Similarly, 6-10 year-old children use toothpaste and mouthwash and are assumed to ingest 5% and 10%, respectively. For this reason, it is useful to consider 3-6 and 6-10 years separately in overall safety evaluation of dermal and oral care products. The dermal product aggregation of seven products is the same for 3-10 year olds; the differential oral care product calculations will be added for 3-6 years (plus toothpaste), and 6-10 years (plus toothpaste and mouthwash), respectively.

When looking at aggregated exposure it should be noted that in the SCCS 12th NOG p31, "Eproduct for the oral care products is used for calculating the dermal exposure (via mucosa) and not oral (ingestion) exposure per se. Oral exposure (ingestion), if applicable, needs to be calculated separately." A single calculation as aggregated here, covers for the retention of oral care products and includes 100% absorption factor, therefore dermal and oral routes are covered in the single oral care calculations provided.

There are no specific habits and practices data on the actual product amounts g/day used by children aged 3-6 or 6-10 years of each of these product types. Appendix 7 of the SCCS 12th Notes of Guidance proposes a simple scaling approach to modify product amounts for children from adult use g/day levels, using shower gel as an example:
"Exposure data for children could also be deduced from the daily exposure data for adults taking into consideration the body surface area of adults and children, e.g. the exposure to preservatives used in shower gel is considered to be 190 mg/day on a surface of 17 500 cm^2 for an adult (Table 4 in 3-3.4.2.1). For a toddler of 1-3 years of age with a total body surface area of 5 600 cm^2, the daily exposure to preservatives would then result in 190 mg/d X 5 600 cm^2/17 500 cm^2 = 61 mg/day."

This principle in the example cited will be followed in the case study for salicylic acid.

3.3.2.4 Exposure calculation children 3-10 years old: Aggregate dermal exposure

3.3.2.4.1 Tier 1 Deterministic Calculations of dermal Systemic Exposure Dose (SED)

According to the Applicant:

As per the selection of products to be aggregated according to Appendix 7 in the SCCS 12th Notes of Guidance (2023), face cream, hand cream, body lotion, handwash soap, shower gel, hair conditioner and shampoo are included in the Tier 1 Scenario A3 deterministic children's dermal exposure assessment for maximum %use levels of salicylic acid in Table 13 (below); similar calculations using reported maximum % use levels (as determined from a Cosmetics Europe survey in 2016) are presented in Table 14 (below).

The daily amounts of product use in g/day for each product in adults has been used as the starting point. The SSA ratios for adult: child from Table 11 above have been applied to reduce the g/day product use proportionate to a smaller skin surface area. The retention factors for dermal exposure are assumed to be the same as in adults. The $E_{product}$ calculated in mg/kg/day is calculated using the default body weight of 23.1kg for children aged 3-10 years.

In a Tier 1 Scenario A assessment, the regulatory maximum %w/w use levels of salicylic acid have been applied: 2% (face cream, hand cream, hand wash soap, shower gel); 3% (hair conditioner and shampoo); 0.5% in body lotion.

The dermal absorption value of 60% for salicylic acid is the same as used in the SCCS Opinion 2023.

These conservative parameters and assumptions yield a systemic exposure dose (SED) for children of 1690 µg/kg/day (Table 5) for the seven dermally applied products.

A Tier 1 Scenario A deterministic exposure assessment for adults, as reported in SCCS Opinion (2023) generated an SED of 1670 µg/kg/day (dermal and oral care products aggregated). This outcome considering a scaling approach using BW and SSA data, corroborates the longstanding implicit understanding that an adult aggregated exposure assessment already generates an exposure estimate that is sufficiently protective for the safety of children.

Overall, the factors that are applied to account for the differences in both skin surface area and body weight between adults and children, cancel each other out. This always results in a similar SED estimate for adults and children aged 3-10 years after dermal exposure.
In practice, considering the difference in skin surface area between adults and children, for example, 18200 cm^2 (adults)/8100 cm^2 (3-10 children average) = 2.2, one divides the adult product use g/day by this factor.

In considering the body weight difference (e.g. adult default 60kg/3-10 year old child 23.1kg) ratio of approx. 2.6, one effectively multiplies the adult g/day product use values.
Impacts on the SED estimate may come with oral care products for which accidental ingestion is potentially greater in young children. But this is factored in as a separate calculation, as advised in the SCCS Notes of Guidance, and has routinely been the case.

Table 13. Salicylic Acid exposure for children aged 3-10 years –products applied dermally – Tier 1 Scenario A

Tier 1 Scenario A Max regulatory %w/w Levels Deterministic Systemic Exposure Dose estimation							23.1	Default Body Weight (kg) (for children Aged 3-10 years: EFSA, 2012)		
							60%	Dermal absorption as per SCCS Opinion 2022 for salicylic acid		
		Product Exposure					Ingredient exposure			
Category of Product	Product type - Exposure from DERMALLY applied products	Daily amount (DA) of product use (g/d)* (SCCS 12th NoG 2023)	Skin Surface Area (SSA) Ratio (Adult:child)#	Daily amount of product use (Age 3-10 years) (g/d) Scaled by SSA ratio	Retention factor for dermal exposure	Eproduct by body weight per product (mg/kg/d)	Maximum use (w/w%) in the finished product	% absorbed dermally	Calculated SED per product (µg/kg/d)	MOS calculation (NOAEL 75000 µg/kg/day)
Leave-on products	Face cream	1.540	1.4	1.100	1	47.62	2.000	60	571.4	131
	Hand cream	2.160	2.3	0.939	1	40.65	2.000	60	487.9	154
	Body lotion	7.820	2.2	3.555	1	153.88	0.500	60	461.6	162
Rinse-off skin & hair cleansing products	Hand wash soap	20.000	2.3	8.696	0.01	3.76	2.000	60	45.2	1660
	Shower gel	18.670	2.2	8.486	0.01	3.67	2.000	60	44.1	1701
	Hair conditioner	3.920	1.4	2.800	0.01	1.21	3.000	60	21.8	3438
	Shampoo	10.460	1.4	7.471	0.01	3.23	3.000	60	58.2	1288
	TOTAL								**1690.2**	**44**

*Adult values as per used in SCCS 12th Notes of Guidance 2023; #Ratios based on using adult and children SSA data from RIVM (2014)

To note, the Margin of Safety for Adults exposure to salicylic acid was 45 from a Tier 1 Scenario A assessment (SCCS, 2023).

Table 14. Salicylic Acid exposure for children aged 3-10 years –products applied dermally – Tier 1 Scenario B

Tier 1 Scenario B Max Reported %w/w Levels Deterministic Systemic Exposure Dose estimation							23.1	Default Body Weight (kg) (for children Aged 3-10 years: EFSA, 2012)		
							60%	Dermal absorption as per SCCS Opinion 2022 for salicylic acid		
		Product Exposure					Ingredient exposure			
Category of Product	Product type - Exposure from DERMALLY applied products	Daily amount (DA) of product use (g/d)* (SCCS 12th NoG 2023)	Skin Surface Area (SSA) Ratio (Adult:child)#	Daily amount of product use (Age 3-10 years) (g/d) Scaled by SSA ratio	Retention factor for dermal exposure	Eproduct by body weight per product (mg/kg/d)	Survey use (w/w%) in the finished product (Cosmetics Europe 2016 Preservatives Use Survey)	% absorbed dermally	Calculated SED per product (µg/kg/d)	MOS calculation (NOAEL 75000 µg/kg/day)
Leave-on products	Face cream	1.540	1.4	1.100	1	47.62	0.500	60	142.9	525
	Hand cream	2.160	2.3	0.939	1	40.65	0.200	60	48.8	1537
	Body lotion	7.820	2.2	3.555	1	153.88	0.200	60	184.7	406
Rinse-off skin & hair cleansing products	Hand wash soap	20.000	2.3	8.696	0.01	3.76	0.100	60	2.3	33206
	Shower gel	18.670	2.2	8.486	0.01	3.67	2.000	60	44.1	1701
	Hair conditioner	3.920	1.4	2.800	0.01	1.21	0.200	60	1.5	51563
	Shampoo	10.460	1.4	7.471	0.01	3.23	2.000	60	38.8	1932
	TOTAL								**462.9**	**162**

*Adult values as per used in SCCS 12th Notes of Guidance 2023; #Ratios based on using adult and children SSA data from RIVM (2014)

To note, the Margin of Safety for Adults exposure to salicylic acid was 121 from a Tier 1 Scenario B assessment (Industry Dossier, 2021).

SCCS comment

As explained in the Notes of Guidance SCCS/1647/22, the SCCS accepts only the use of maximum allowed weight concentrations for the calculation of exposure estimates. Therefore, it will not use the presented Scenario B calculations.

Regarding body weight, the SCCS will use the more conservative median (P50) values from EFSA (2012), which are 8.7 kg, 11.6 kg and 21.7 kg for the 0.5-1 years, 1-3 years and 6-10 years age groups, respectively. While the Applicant uses the same body weight value for both the 3-6 years and 6-10 years age groups, the SCCS recommends applying the more conservative EFSA P5 value of 14.0 kg (for children 3-10 years) for the 3-6 years age group. The SCCS has recalculated (see Table 10) the SEDdermal values following the SSA/BW scaling approach based on the body weights as specified above. Corresponding estimates of children's body surface areas were derived from these body weight values, by following an approach as outlined in Sharkey *et al*. 2001. This same approach was applied in the scientific advice on

Triclocarban and Triclosan (SCCS/1643/22) and Methyl Salicylate (SCCS/1654/23), and the most recent Opinion on Hexyl Salicylate (SCCS/1668/24). Adult data is taken from the SCCS Notes of Guidance 12th revision (SCCS/1647/22).

Table 15. SCCS calculations of SEDdermal for SA using the SSA/BW scaling approach for children (age 3-6 years), and children (age 6-10 years) per product type (Tier 1 Scenario A).

Product type	Body weight[1] (kg)	Skin surface area[2] (cm^2)	Daily exposure[3] (g/day)	Daily exposure (mg/kg bw/day)	Substance concentration (%)	Dermal absorption DAp (%)	SED_{dermal} (µg/kg bw/day)
SHOWER GEL							
Adults	*60*	*17500*	*0.19*				
Children 3 – 6 yrs	14	6200	0.07	4.81	3	60	86.6
Children 6 – 10 yrs	21.7	8500	0.09	4.25	3	60	76.5
HAND SOAP							
Adults	*60*	*860*	*0.20*				
Children 3 – 6 yrs	14	305	0.07	5.06	3	60	91.1
Children 6 – 10 yrs	21.7	418	0.10	4.48	3	60	80.6
SHAMPOO							
Adults	*60*	*1440*	*0.11*				
Children 3 – 6 yrs	14	510	0.04	2.78	3	60	50.0
Children 6 – 10 yrs	21.7	699	0.05	2.46	3	60	44.3
HAIR CONDITIONER							
Adults	*60*	*1440*	*0.04*				
Children 3 – 6 yrs	14	510	0.01	1.01	3	60	18.2
Children 6 – 10 yrs	21.7	699	0.02	0.90	3	60	16.2
BODY LOTION							
Adults	*60*	*15670*	*7.82*				
Children 3 – 6 yrs	14	5552	2.77	198	0.5	60	594
Children 6 – 10 yrs	21.7	7611	3.80	175	0.5	60	525
FACE CREAM							
Adults	*60*	*565*	*1.54*				
Children 3 – 6 yrs	14	200	0.55	39.0	2	60	468
Children 6 – 10 yrs	21.7	274	0.75	34.5	2	60	414
HAND CREAM							
Adults	*60*	*860*	*2.16*				
Children 3 – 6 yrs	14	305	0.77	54.7	2	60	656
Children 6 – 10 yrs	21.7	418	1.05	48.4	2	60	580

[1]P50 body weight values from EFSA 2012 for children (6-10 years); P5 body weight value from EFSA 2012 for children (3-6 years)
[2]Child body surface area values are based on Sharkey *et al*. 2001; other child surface areas for application are calculated as follows: (surface area for application for adults * child body surface area) / adult body surface area
[3]Default values for adults from SCCS Notes of Guidance 12th revision (SCCS/1647/22); child daily exposure values are calculated as follows: (mg/day for adults * body surface area for age category) / surface area for adults (SCCS/1466/11)

In addition, the SCCS has reviewed the SSA/BW scaling approach against available children-specific data (probabilistic assessment based on questionnaire/interview data on use frequency, body weight and amount) from France (Ficheux et al., 2016, Ficheux and Roudot, 2017) and Switzerland (Garcia-Hidalgo et al., 2017) and found that the use amounts extrapolated by the skin surface area-body weight approach consistently results in smaller exposure estimates for children compared to the data reported in these studies. Therefore, in the absence of better exposure data for EU children, the SCCS will rely on the currently available children-specific data where possible, and on the SSA/BW scaling approach where those are lacking. The calculations for SEDs for dermal products with concentrations as requested by the Applicant, 0.5% w/w in all dermal products and 0.1% w/w in all dermal products are presented in Tables 16-18, respectively.

Table 16: SCCS calculations of deterministic SED for SA for children (age 3-6 years), and children (age 6-10 years) per product type (Tier 1 Scenario A) **with concentrations requested by the Applicant**.

Product type	Data source used for SED derivation	Daily exposure SSA/BW approach (mg/kg bw/day)	Daily exposure experimental (mg/kg bw/day)	Substance concentration (%)	Dermal absorption DAp (%)	SED_{dermal} (µg/kg bw/day)
SHOWER GEL						
Children 3 – 6 yrs	Ficheux and Roudot 2017, gel douche	4.81	**5.33**	3	60	95.9
Children 6 – 10 yrs		4.25	**5.33**	3	60	95.9
HAND SOAP						
Children 3 – 6 yrs	Ficheux and Roudot 2017, gel douche f	5.06	**5.33**	3	60	95.9
Children 6 – 10 yrs		4.48	**5.33**	3	60	95.9
SHAMPOO						
Children 3 – 6 yrs	Ficheux and Roudot 2017, shampoing	2.78	**3.23**	3	60	58.1
Children 6 – 10 yrs		2.46	**3.23**	3	60	58.1
HAIR CONDITIONER						
Children 3 – 6 yrs	Ficheux and Roudot 2017, shampoing*	1.01	**3.23**	3	60	58.1
Children 6 – 10 yrs		0.90	**3.23**	3	60	58.1
BODY LOTION						
Children 3 – 6 yrs	Garcia-Hidalgo *et al*. 2017 body lotion**	198	**620**	0.5	60	1860
Children 6 – 10 yrs		175	**409**	0.5	60	1227
FACE CREAM						
Children 3 – 6 yrs	SSA/BW scaling approach	**39.0**	n.a.	2	60	468
Children 6 – 10 yrs		**34.5**	n.a.	2	60	414
HAND CREAM						
Children 3 – 6 yrs	SSA/BW scaling approach	**54.7**	n.a.	2	60	656
Children 6 – 10 yrs		**48.4**	n.a.	2	60	580
AGGREGATE DERMAL						
Children 3 – 6 yrs						**3292**
Children 6 – 10 yrs						**2529**

*Garcia-Hidalgo *et al*. 2017 data suggest that use of shampoo and conditioner is comparable for children
**calculated by multiplying the P95 for female toddler (0-5 y) or children (6-10 y) by the most probable frequency (04, i.e. 2-3 times a week for both age groups)

Table 17: SCCS calculations of deterministic SED for SA for children (age 3-6 years), and children (age 6-10 years) per product type (Tier 1 Scenario A) **with 0.5 % for all dermal products.**

Product type	Data source used for SED derivation	Daily exposure SSA/BW approach (mg/kg bw/day)	Daily exposure experimental (mg/kg bw/day)	Substance concentration (%)	Dermal absorption DAp (%)	SED_{dermal} (µg/kg bw/day)
SHOWER GEL	Ficheux and Roudot 2017, gel douche					
Children 3 – 6 yrs		4.81	**5.33**	0.5	60	16.0
Children 6 – 10 yrs		4.25	**5.33**	0.5	60	16.0
HAND SOAP	Ficheux and Roudot 2017, gel douche f					
Children 3 – 6 yrs		5.06	**5.33**	0.5	60	16.0
Children 6 – 10 yrs		4.48	**5.33**	3	60	16.0
SHAMPOO	Ficheux and Roudot 2017, shampoing					
Children 3 – 6 yrs		2.78	**3.23**	0.5	60	9.7
Children 6 – 10 yrs		2.46	**3.23**	0.5	60	9.7
HAIR CONDITIONER	Ficheux and Roudot 2017, shampoing*					
Children 3 – 6 yrs		1.01	**3.23**	0.5	60	9.7
Children 6 – 10 yrs		0.90	**3.23**	0.5	60	9.7
BODY LOTION	Garcia-Hidalgo *et al*. 2017 body lotion**					
Children 3 – 6 yrs		198	**620**	0.5	60	1860
Children 6 – 10 yrs		175	**409**	0.5	60	1227
FACE CREAM	SSA/BW scaling approach					
Children 3 – 6 yrs		**39.0**	n.a.	0.5	60	117
Children 6 – 10 yrs		**34.5**	n.a.	0.5	60	103
HAND CREAM	SSA/BW scaling approach					
Children 3 – 6 yrs		**54.7**	n.a.	0.5	60	164
Children 6 – 10 yrs		**48.4**	n.a.	0.5	60	145
AGGREGATE DERMAL						
Children 3 – 6 yrs						**2192**
Children 6 – 10 yrs						**1527**

*Garcia-Hidalgo *et al*. 2017 data suggest that use of shampoo and conditioner is comparable for children
**calculated by multiplying the P95 for female toddler (0-5 y) or children (6-10 y) by the most probable frequency (04, i.e. 2-3 times a week for both age groups)

Table 18: SCCS calculations of deterministic SED for SA for children (age 3-6 years), and children (age 6-10 years) per product type (Tier 1 Scenario A), **with 0.1% for all dermal products.**

Product type	Data source used for SED derivation	Daily exposure SSA/BW approach (mg/kg bw/day)	Daily exposure experimental (mg/kg bw/day)	Substance concentration (%)	Dermal absorption DAp (%)	SED_{dermal} (µg/kg bw/day)
SHOWER GEL	Ficheux and Roudot 2017, gel douche					
Children 3 – 6 yrs		4.81	**5.33**	0.1	60	3.2
Children 6 – 10 yrs		4.25	**5.33**	0.1	60	3.2
HAND SOAP	Ficheux and Roudot 2017, gel douche f					
Children 3 – 6 yrs		5.06	**5.33**	0.1	60	3.2
Children 6 – 10 yrs		4.48	**5.33**	0.1	60	3.2
SHAMPOO	Ficheux and Roudot 2017, shampoing					
Children 3 – 6 yrs		2.78	**3.23**	0.1	60	1.94
Children 6 – 10 yrs		2.46	**3.23**	0.1	60	1.94
HAIR CONDITIONER	Ficheux and Roudot 2017, shampoing*					
Children 3 – 6 yrs		1.01	**3.23**	0.1	60	1.94
Children 6 – 10 yrs		0.90	**3.23**	0.1	60	1.94
BODY LOTION	Garcia-Hidalgo *et al*. 2017 body lotion**					
Children 3 – 6 yrs		198	**620**	0.1	60	372
Children 6 – 10 yrs		175	**409**	0.1	60	245
FACE CREAM	SSA/BW scaling approach					
Children 3 – 6 yrs		**39.0**	n.a.	0.1	60	23.4
Children 6 – 10 yrs		**34.5**	n.a.	0.1	60	20.7
HAND CREAM	SSA/BW scaling approach					
Children 3 – 6 yrs		**54.7**	n.a.	0.1	60	32.8
Children 6 – 10 yrs		**48.4**	n.a.	0.1	60	29.0
AGGREGATE DERMAL						
Children 3 – 6 yrs						**438.5**
Children 6 – 10 yrs						**305.4**

*Garcia-Hidalgo *et al*. 2017 data suggest that use of shampoo and conditioner is comparable for children
**calculated by multiplying the P95 for amount per application of female toddler (0-5 y) or children (6-10 y), respectively, by the most probable frequency of application (0.4, i.e. 2-3 times a week for both age groups)

3.3.2.4.2 Tier 2 Probabilistic Calculations of Systemic Exposure Dose (SED)

According to the Applicant, in the SCCS Opinion for salicylic acid published in 2023, using a tiered approach to exposure assessment (as described in Alexander-White et al., 2022), the Tier 2 Scenario A probabilistic exposure assessment was accepted as the key approach to assuring the safety of salicylic acid at current % use levels. Tier 1 Scenario A exposure assessments, as can be seen above, are similarly yielding MOS of approximately 45 for both adults and children aged 3-10 years. When considering survey % w/w use levels as reported of salicylic acid in products, MOS above 100 are observed.

However, the SCCS does not currently accept that % w/w use survey levels are indicative of potential future uses, and in theory the industry can always use up to the regulatory maxima. Therefore, the next step of refinement comes from a Tier 2 Scenario A (max % use levels) probabilistic exposure assessment using habits and practices data for product use.
Such a probabilistic exposure assessment was performed by Creme Global™ using the Crème RIFM model for salicylic acid as submitted with the industry dossier in 2021. This modelling used the aggregation of 17 product types as per SCCS 12th Notes of Guidance, with the inclusion of body weights and habits and practices data for adult populations aged 11-94 years.
A specific model is not yet set up for calculating probabilistic exposure assessment for children aged 3-10 years, in terms of the product types to aggregate and the relevant body weight information included in the model. There are currently no specific habits and practices data to use for children aged 3-10 years.
However, some approximations can be made considering the scaling of the aggregated outputs from probabilistic modelling. It is expected that the outputs from this approach provide reassurance that children's exposure is not likely to be significantly greater than the adult Tier 2 outputs.
There is an assumption that children use the 7 listed cosmetic products at the same frequencies as adults (as per the SCCS 12th Notes of Guidance). Another assumption is that the habits and practices data can also be used for children in a conservative way i.e., it is assumed children are likely to use products to a lesser extent than adults. One cannot separate out the SSA of body parts doing this generic scaling. From Table 3, we can see that SSA ratios for adults:children range from 1.4-2.2 for age 3-10 years. As a conservative approximation, we will use a default SSA of 2-fold lower to apply to the probabilistic outputs from adults. We will assume a default adult body weight of 60kg to convert from mg/kg/day to mg/day; a body weight of 23.1kg is used for children aged 3-10 years.

i) Creme RIFM model (submitted to the SCCS in 2021)
Adult exposure modelling was performed for 17 products as per the SCCS 12th Notes of Guidance. Using adult body weight ranges and habits and practices data from adult use surveys.

Total exposure Tier 2A (Exposed Population) (Max % use levels in regulation) = 0.459 mg/kg/day
Total exposure Tier 2B (Exposed Population) (P95 % use levels in survey) = 0.066 mg/kg/day

Scaling these values for children aged 3-10 years:

Total exposure Tier 2A (Exposed Population) (Max % use levels in regulation) = 0.459 mg/kg/day

Multiplied by 60kg (default adult BW) and divided by 23.1kg (Child BW) = 1.19 mg/kg/day
Assuming the same g/day product use as adults considering 17 products, which is an overestimate for the 9 products to be aggregated for children.

Accounting for smaller SSA reducing product use, divide by 2 = 0.596 mg/kg/day

Total exposure Tier 2B (Exposed Population) (Max % use levels in regulation) = 0.066 mg/kg/day

Multiplied by 60kg (default adult BW) and divided by 23.1kg (Child BW) = 0.171 mg/kg/day
Assuming the same g/day product use as adults considering 17 products.

Accounting for smaller SSA reducing product use, divide by 2 = 0.086 mg/kg/day

It has not been possible to design a specific model using the Creme Global approach for children at this point in time.

ii) PACEM webtool (run on 16 October 2023)

A web-based aggregate exposure modelling tool is available from RIVM as of 2023 at https://www.rivm.nl/en/consumer-exposure-to-chemical-substances/exposure-models/Pacem
N.B. the model included adult population body weight and habits and practices data. This tool was used to tailor an aggregation for the 7 dermal products and 2 oral care products. The reports from the PACEM webtool are provided in Appendices in the Applicant's dossier, and an example included below.

Table 19. PACEM input/output values for probabilistic exposure calculation with 7 dermal product categories and 2 oral for adults

	Concentration data		Exposure fractions (g/g substance used)		
Selected Products	% Products with substance	Concentration in product (%)	Inhalation	Dermal	Oral
Body lotion	100	0.5	0	1	0
Face moisturiser	100	2	0	1	0
Hand cream	100	2	0	1	0
Liquid soap	100	2	0	0.01	0
Mouthwash	100	0.5	0	0	0.1
Rinse-off conditioner	100	3	0	0.01	0
Shampoo	100	3	0	0.01	0
Shower gel	100	2	0	0.01	0
Toothpaste	100	0.5	0	0	0.05

Systemic dose per route

Percentile	25	50	75	90	95	99
Inhalation	0	0	0	0	0	0
Dermal	1.22×10^{-2}	2.99×10^{-2}	1.23×10^{-1}	2.44×10^{-1}	3.39×10^{-1}	5.74×10^{-1}
Oral	3.48×10^{-3}	6.47×10^{-3}	3.07×10^{-2}	9.32×10^{-2}	1.33×10^{-1}	2.02×10^{-1}
Total	2.15×10^{-2}	6.14×10^{-2}	1.61×10^{-1}	2.92×10^{-1}	3.96×10^{-1}	6.51×10^{-1}

Percentiles of systemic dose per route (mg/kg bw)

Tier 2 Scenarios A and B for Seven Dermal Products
included for children aged 3-10 years (see PACEM reports 2A and 2B)

Adult exposure modelling was performed for 7 dermally applied products as per the SCCS 12th Notes of Guidance Appendix 7 for children's assessment. The input parameters are provided in PACEM reports 2A and 2B.

Total exposure Tier 2A (Exposed Population) (Max % use levels in regulation) = 0.342 mg/kg/day
Total exposure Tier 2B (Exposed Population) (P95 % use levels in survey) = 0.095 mg/kg/day

Scaling these PACEM values for seven products in children (c.f. as above)
Total exposure Tier 2A (Exposed Population) (Max % use levels in regulation) = 0.342 mg/kg/day
Multiplied by 60kg (default adult BW) and divided by 23.1kg (Child BW) = 0.888 mg/kg/day
Assuming the same g/day product use as adults.
Accounting for smaller SSA reducing product use, divide by 2 = 0.444 mg/kg/day

Total exposure Tier 2B (Exposed Population) (Max % use levels in regulation) = 0.095 mg/kg/day
Multiplied by 60kg (default adult BW) and divided by 23.1kg (Child BW) = 0.245 mg/kg/day
Assuming the same g/day product use as adults.
Accounting for smaller SSA reducing product use, divide by 2 = 0.123 mg/kg/day

Table 20. Applicant's summary of Salicylic Acid SED and MOS calculations for children aged 3-10 compared to those for adults

Risk Assessment Scenario	Systemic Exposure Dose (SED) mg/kg/day Children 3-10y[&]	Margin of Safety (using a POD of 75 mg/kg/day) Children 3-10y	Systemic Exposure Dose (SED) mg/kg/day Adults	Margin of Safety (using a POD of 75 mg/kg/day) Adults
Tier 1 Scenario A Maximum % use levels of salicylic acid and deterministic aggregate assessment (see Table 5 dermal only)	1.69	44	1.67*	45
Tier 1 Scenario B P95 % use levels of salicylic acid (Cosmetics Europe 2016 survey) deterministic aggregate assessment (See Table 6 dermal only)	0.46	162	0.62*	121
Tier 2 Scenario A Creme RIFM model Probabilistic Assessment; P95 output using maximum % salicylic acid concentrations in all 17 product categories.	0.60	125	0.46*	163[#]
Tier 2 Scenario B Creme RIFM model Probabilistic Assessment; P95 output using salicylic acid survey % use concentrations in all 17 product categories.	0.086	872	0.066*	1136
Tier 2 Scenario A[$] PACEM webtool (2023) Probabilistic Assessment; P95 output using maximum % salicylic acid concentrations in 7 dermal product categories as per Appendix 7 12th NOG.	0.44	170	0.34	221
Tier 2 Scenario B[$] PACEM webtool (2023) Probabilistic Assessment; P95 output using salicylic acid survey % use concentrations in 7 dermal product categories as per Appendix 7 12th NOG.	0.12	625	0.095	789

* As per aggregated exposure method for 17 products in SCCS 12th Notes of Guidance (2023) including oral care
#This assessment was considered as an acceptable Tier 2 evaluation for adults by SCCS in the 2023 Opinion
$See Appendix 1 for PACEM webtool reported outputs in reports 2A and 2B.
&Children's SED calculated from adult values and scaled for SSA and BW differences.

SCCS comment
Since the probabilistic calculations are based on surface area extrapolated use amounts only, that for some products are considerably lower than experimental values determined by Ficheux and Roudot, 2017, the SCCS does not accept the probabilistic calculations.

3.3.2.5 Exposure calculation children 3-10 years old: Oral exposure assessments

According to the Applicant, salicylic acid is not currently used as an ingredient in any oral care products. An industry-wide usage survey was conducted, and at the present time salicylic acid is not used in toothpaste, but so as not to hinder innovation calculations are performed below as if 0.5% salicylic acid were used.

The SCCS in Appendix 7 Table A.7.2 in the Notes of Guidance, differentiate between 3-6 years and 6-10 years in the inclusion of mouthwash products in the older age group, as mouthwash is not recommended for use below the age of 6 years. In the absence of any specific ADME data, there is a highly conservative assumption that 100% of the retained 40% applied dose could in theory be absorbed across the gut (including oral mucosa) and enter the systemic circulation.
The use of toothpaste starts with first erupted teeth and may occur with a high percentage of dentifrice ingestion. Therefore, the amount of toothpaste to be used by children aged 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 considered to be 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 take into account 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 or mouthwash, but so as not to hinder innovation a calculation is performed as if 0.5% salicylic acid were used. Table 21 shows the intake of salicylic acid in mg/person/day for any potential use in toothpaste in age 3-6 year-olds; Table 22 is similarly for 6-11 year-olds; Table 23 is for use of mouthwash in 6-11 year-olds.

Table 21. Calculation of intake levels from use of toothpaste in children aged 3-6 years

3-6 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**	
Intake (mg/kg/day)*		**0.043**	

*Assuming the default body weight of 23.1 kg for children aged 3-10y

Table 22. Calculation of intake levels from use of toothpaste in children aged 6-10 years

6-10 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 (mg/kg/day)*		**0.030**	

*Assuming the default body weight of 23.1 kg for children age 3-10y

Intake from Mouthwash 6-10 years

The use of mouthwash starts at age 6 (it is generally recommended that children under 6 should not use mouthwash)(www.ada.org; Zuanon, 2005). The amount for adults of 21.62 g/day and retention factor of 10 % from SCCS's 2023 12th Notes of Guidance is used. This is appropriate, considering published literature on the ingestion of mouthwash by children aged 6, with a reported 8% retention (Zuanon, 2005). An industry-wide usage survey was conducted, and actually 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.

Table 23. Calculation of intake levels from use of mouthwash in children aged 6-10 years

6 years of age to 10: 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**	
Intake (mg/kg/day)*		**0.467**	

*Assuming the default body weight of 23.1 kg for children aged 3-10y

According to the Applicant, these calculations are very conservative as it is assumed that adult amounts of mouthwash are used 2 times a day and it is unlikely that a child of 6-10 years would use that amount.

SCCS comment

Data on toothpaste use from Garcia-Hidalgo *et al.* (2017) and Gomez-Berrada *et al.* (2018) show that 0.25 g/use is an underestimation of toothpaste use for children. Therefore, the SCCS recalculated the oral exposure to SA in toothpaste for children 3-6 years and 6-10 years with an amount of 1.92 g/day and 2.63 g/day, respectively (P95 from Gomez-Berrada *et al*., 2018). Furthermore, as explained earlier, for 3-6 year old children the P5 bodyweight of the EFSA 3-10 year olds (14 kg bw) and for 6-10 years old the median for 3-10 years olds (21.4 kg bw) is used by SCCS (EFSA, 2012).

Applying retention factors of 40% for 3-6 year and 5% for 6-10 year old children and an SA concentration of 0.5% yield **oral exposures from toothpaste of 274 µg/kg bw/d and 30 µg/kg bw/d for 3-6 and 6-10 year old children**, respectively.

Adjusting the Applicant's mouthwash exposure calculation for the age group 6-10 years with the median bodyweight for 3-10 years old yields an oral exposure of **498 µg/kg bw/ d from mouthwash**, which results in an **aggregate oral exposure for 6-10 year olds of 528 µg/kg bw/ d**.

3.3.2.6. Aggregation dermal and oral exposure

According to the Applicant, the next step is to add in the separate oral care product assessments (for 3-6 and 6-10 years, respectively in Table 11 and Table 12 below), noting that in reality there is currently no reported use of salicylic acid in oral care. Creme Global modelling already includes toothpaste and mouthwash products with adult retention factors, and at this point in time these input parameters cannot be changed here, a new model would need to be built for children. However, the modelling in PACEM was done for the 7 dermally applied products, so it is valid to add in the Tier 1 deterministic oral care outputs to this for an overall assessment.
The value of 0.043 mg/kg/day for use of toothpaste for 3-6 year-olds is added in Table 20. This shows there is minimal impact of the additional toothpaste use.

The values of 0.030 (toothpaste) and 0.467 (mouthwash) is added for 3-10 year-olds in Table 12, noting that the mouthwash value is only relevant for age 6-10 years, but including this evaluation using the relevant parameters ensures that all 3-10 years are protected using this single assessment combining dermal and oral care.

Table 24. SED and MOS calculations for Children Aged 3-6 years for dermal and oral routes

Risk Assessment Scenario	Systemic Exposure Dose (SED) mg/kg/day Children 3-10y Dermal only	Oral care SED from toothpaste mg/kg/day 3-6 year#	Total SED 3-6 years mg/kg/day	Margin of Safety (using a NOAEL of 75 mg/kg/day)
Tier 1 Scenario A Maximum % use levels of salicylic acid and deterministic aggregate assessment (see Table 5 dermal only)	1.69	0.043	1.73	43
Tier 1 Scenario B P95 % use levels of salicylic acid (Cosmetics Europe 2016 survey) deterministic aggregate assessment (See Table 6 dermal only)	0.46	0.043	0.50	150
Tier 2 Scenario A$ PACEM webtool (2023) Probabilistic Assessment; P95 output using maximum salicylic acid concentrations in 7 dermal product categories as per Appendix 7 12th NOG.	0.44	0.043	0.48	156
Tier 2 Scenario B$ PACEM webtool (2023) Probabilistic Assessment; P95 output using salicylic acid survey % use concentrations in 7 dermal product categories as per Appendix 7 12th NOG.	0.12	0.043	0.16	469

$See Appendix 1 for PACEM webtool reported outputs; #Deterministic Tier 1 calculation

Table 25. SED and MOS calculations for Children Aged 3-10 years for dermal (Tier 1 and Tier 2 probabilistic) and oral care (Tier 1 deterministic only)

Risk Assessment Scenario	Systemic Exposure Dose (SED) mg/kg/day Children 3-10y Dermal only	Oral care SED from toothpaste mg/kg/day 6-10 year[#]	Total SED 6-10 years mg/kg/day	Margin of Safety (using a NOAEL of 75 mg/kg/day)
Tier 1 Scenario A Maximum % use levels of salicylic acid and deterministic aggregate assessment (see Table 5 dermal only)	1.69	0.030 (toothpaste) + 0.467 (mouthwash) = 0.497	2.19	34
Tier 1 Scenario B P95 % use levels of salicylic acid (Cosmetics Europe 2016 survey) deterministic aggregate assessment (See Table 6 dermal only)	0.46	0.497	0.96	78
Tier 2 Scenario A[$] PACEM webtool (2023) Probabilistic Assessment; P95 output using maximum salicylic acid concentrations in 7 dermal product categories as per Appendix 7 12th NOG.	0.44	0.497	0.94	80
Tier 2 Scenario B[$] PACEM webtool (2023) Probabilistic Assessment; P95 output using salicylic acid survey % use concentrations in 7 dermal product categories as per Appendix 7 12th NOG.	0.12	0.497	0.62	121

[$]See Appendix 1 for PACEM webtool reported outputs; [#]Deterministic Tier 1 calculation

SCCS comment

As explained above, the SCCS has calculated the aggregate exposure to SA deterministically by applying for 3–6-year-old children the P5 bodyweight of the EFSA 3-10 year olds and for 6-10 years old the median for 3-10 years olds (EFSA, 2012) and using use data where available. The SEDs with different concentration scenarios are listed in **Tables 26-28.**

Table 26. Aggregate dermal and oral exposure for children 3-6 and 6-10 years old with SA **concentrations requested by the Applicant**

	children 3-6 (µg/kg bw/d)	children 6-10 (µg/kg bw/d)
dermal exposure	3292	2529
oral toothpaste	274	30
oral mouthwash	-	498
Aggregate dermal/oral	**3566**	**3057**

Table 27. Aggregate dermal and oral exposure for children 3-6 and 6-10 years old with SA used as preservative **at max. 0.5% in all products**

	children 3-6 (µg/kg bw/d)	children 6-10 (µg/kg bw/d)
dermal exposure	2192	1527
oral toothpaste	274	30
oral mouthwash	-	498
Aggregate dermal/oral	**2467**	**2055**

Table 28. Aggregate dermal and oral exposure for children 3-6 and 6-10 years old with concentrations of **0.1% SA in dermal products, 0.5% in toothpaste and mouthwash**

	children 3-6 (µg/kg bw/d)	children 6-10 (µg/kg bw/d)
dermal exposure	438	305
oral toothpaste	274	30
oral mouthwash	-	498
Aggregate dermal/oral	**713**	**834**

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

/

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

/

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 of 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 29. 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 24.

Table 30. 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 stands by the conclusions reached in 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*

/

3.5.6.2 Mutagenicity / genotoxicity *in vivo*

/

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 according to 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

/

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

/

SCCS comment from previous Opinion
Although safety assessment within the SCCS remit is based on assessment of the ingredients and not on 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

/

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 31: 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 32: 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 disrupting 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.

Many 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. The Applicant has presented two probabilistic exposure calculations for adults that were extrapolated to children 3-10 based on surface area ratios and body weight. Since one of the approaches includes also products only used by adults, the SCCS has based the aggregate SEDs on the approach using 7 dermal products and 2 oral products, calculated with PACEMweb.

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 3.3.2.6. 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 oral care products, a worst-case value of 100% absorption is used for passage across the oral mucosa.

Table 33: MoS for single and aggregate systemic exposure to cosmetic products containing Salicylic Acid for children 3-10 years old, **calculated by the SCCS**

MOS calculated with POD: 75'000 µg/kg bw/d)	SED as requested (µg/kg bw/d)	MoS	SED with 0.5% in all products (µg/kg bw/d)	MoS	SED with 0.1% in dermal products (µg/kg bw/d)	MoS
SHOWER GEL						
children 3-6 y	95.9	782	16.0	4690	3.2	23452
children 6-10 y	95.9	782	16.0	4690	3.2	23452
HAND SOAP						
children 3-6 y	95.9	782	16.0	4690	3.2	23452
children 6-10 y	95.9	782	16.0	4690	3.2	23452
SHAMPOO						
children 3-6 y	58.1	1290	9.7	7740	1.9	38700
children 6-10 y	58.1	1290	9.7	7740	1.9	38700
HAIR CONDITIONER						
children 3-6 y	58.1	1290	9.7	7740	1.9	38700
children 6-10 y	58.1	1290	9.7	7740	1.9	38700
BODY LOTION						
children 3-6 y	1860	40	1860	40	372.0	202
children 6-10 y	1227	61	1227	61	245.4	306
FACE CREAM						
children 3-6 y	468	160	117	642	23.4	3208
children 6-10 y	414	181	103	725	20.7	3626
HAND CREAM						
children 3-6 y	656	114	164	457	32.8	2287
children 6-10 y	580	129	145	517	29.0	2585
AGGREGATE DERMAL	0					
children 3-6 y	3292	23	2192	34	438.5	171
children 6-10 y	2529	30	1527	49	305.4	246
TOOTHPASTE						
children 3-6 y	274	273	274	273	274	273
children 6-10 y	30	2475	30	2475	30	2475
MOUTHWASH						
children 3-6 y	-	-	-	-	-	-
children 6-10 y	498	151	498	151	498	151
AGGREGATE ORAL						
children 3-6 y	274	273	274	273	274	273
children 6-10 y	528	142	528	142	528	142
AGGREGATE DERMAL AND ORAL						
children 3-6 y	3566	21	2467	30	713	105
children 6-10 y	3057	25	2055	36	834	90
children 6-10 y (without mouthwash)	2559	29	1557	48	469	160

Salicylic Acid is not safe for 3-10 years old children in the concentrations requested by the Applicant, when considering aggregate exposure. With the exception of body lotion, it is safe in single products, when used alone.

Salicylic Acid is safe for 3-10 years old children at a reduced concentration of 0.1% in dermal products and 0.5% in toothpaste. It is not safe when used additionally in mouthwash.

Sprayable products that could lead to exposure of the consumer's lungs by inhalation are excluded from this opinion.

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

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

In the dossier, the Applicant has not explained how the surface area for children 3-10 years has been derived. From number checking the SCCS assumes that it has been calculated by averaging the averages of the age groups 3-6 and 6-11, which is appropriate for similar sample sizes of the averaged groups.

Boniol et al, 2008 used anthropometric data on US children from 1977, which were processed in a computer human model to generate the surface areas. However, since anthropometrics of US children and European children may be different and since the US data are quite old, data on European children would be preferable. Furthermore, with 3D-scanning it is possible to determine actual surface areas directly (Yu et al, 2003; Schloesser et al., 2011), which presumably provides more accurate values.

However, when comparing the SSA approach derived amounts with measured data from Ficheux et al., 2016, Ficheux and Roudot, 2017 and Garcia-Hidalgo et al., 2017 for children in France and Switzerland, respectively, the SSA approach amounts tend to be too low. Therefore, whenever adequate measured data are available, the SCCS will use the measured data as explained in chapter 3.3.2.4.

As explained in the Notes of Guidance SCCS/1647/22, the SCCS accepts only the use of maximum allowed weight concentrations for the calculation of exposure estimates, i.e. will not use the presented Scenario B calculations.

Regarding body weight, the SCCS will use the more conservative median (P50) values from EFSA (2012), which are 8.7 kg, 11.6 kg and 21.7 kg for the 0.5-1 years, 1-3 years and 6-10 years age groups, respectively. While the Applicant uses the same body weight value for both the 3-6 years and 6-10 years age groups, the SCCS recommends applying the more conservative EFSA P5 value of 14.0 kg (for children 3-10 years) for the 3-6 years age group. The SCCS has recalculated (see Table 10) the SEDdermal values following the SSA/BW scaling approach based on the body weights as specified above. Corresponding estimates of children's body surface areas were derived from these body weight values, by following an approach as outlined in Sharkey et al. 2001. This same approach was applied in the scientific advice on Triclocarban and Triclosan (SCCS/1643/22) and Methyl Salicylate (SCCS/1654/23), and the most recent Opinion on Hexyl Salicylate (SCCS/1668/24). Adult data is taken from the SCCS Notes of Guidance 12th revision (SCCS/1647/22).

In addition, the SCCS has reviewed the SSA/BW scaling approach against available children-specific data (probabilistic assessment based on questionnaire/interview data on use frequency, body weight and amount) from France (Ficheux et al., 2016, Ficheux and Roudot, 2017) and Switzerland (Garcia-Hidalgo et al., 2017) and found that the use amounts extrapolated by the skin surface area-body weight approach consistently results in smaller exposure estimates for children compared to the data reported in these studies. Therefore, in the absence of better exposure data for EU children, the SCCS will rely on the currently available children-specific data where possible, and on the SSA/BW scaling approach where those are lacking. The calculations for SEDs for dermal products with concentrations as requested by the Applicant, 0.5% w/w in all dermal products and 0.1% w/w in all dermal products are presented in Tables 16-18, respectively.

Since the probabilistic calculations are based on surface area extrapolated use amounts only, that for some products are considerably lower than experimental values determined by Ficheux and Roudot, 2017, the SCCS does not accept the probabilistic calculations.

Data on toothpaste use from Garcia-Hidalgo et al. (2017) and Gomez-Berrada et al. (2018) show that 0.25 g/use is an underestimation of toothpaste use for children. Therefore, the SCCS recalculated the oral exposure to SA in toothpaste for children 3-6 years and 6-10 years with an amount of 1.92 g/day and 2.63 g/day, respectively (P95 from Gomez-Berrada et al., 2018). Furthermore, as explained earlier, for 3-6 year old children the P5 bodyweight of the EFSA 3-10 year olds (14 kg bw) and for 6-10 years old the median for 3-10 years olds (21.4 kg bw) is used by SCCS (EFSA, 2012).

Applying retention factors of 40% for 3-6 year and 5% for 6-10 year old children and an SA concentration of 0.5% yield **oral exposures from toothpaste of 274 µg/kg bw/d and 30 µg/kg bw/d for 3-6 and 6-10 year old children**, respectively.

Adjusting the Applicant’s mouthwash exposure calculation for the age group 6-10 years with the median bodyweight for 3-10 years old, yields an oral exposure of **498 µg/kg bw/ d from mouthwash**, which results in an **aggregate oral exposure for 6-10 year olds of 528 µg/kg bw/ d**.

As explained above, the SCCS has calculated the aggregate exposure to SA deterministically by applying for 3–6-year-old children the P5 bodyweight of the EFSA 3-10 year olds and for 6-10 years old the median for 3-10 years olds (EFSA, 2012) and using use data where available. The SEDs with different concentration scenarios are listed in **Tables 26-28.**

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)

Salicylic Acid is not safe for 3-10 years old children in the concentrations requested by the Applicant, when considering aggregate exposure. With the exception of body lotion, it is safe in single products, when used alone.

Salicylic Acid is safe for 3-10 years old children at a reduced concentration of 0.1% in dermal products and 0.5% in toothpaste. It is not safe when used additionally in mouthwash.

Sprayable products that could lead to exposure of the consumer's lungs by inhalation are excluded from this opinion.

4. CONCLUSION

The SCCS concludes the following:

1) In light of the data provided, and taking under consideration the conclusions of the SCCS/1646/22 Opinion on children's exposure, does the SCCS consider Salicylic Acid safe for children between 3-10 years of age:

a) *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 not safe when used as preservative at a concentration of 0.5% in all cosmetic products listed under conclusion (b), considering its current restrictions in place. With the exception of body lotion, it is safe in single dermal and oral product categories, when used only in the respective product category.
- this Opinion is not applicable to any sprayable product (including mouth spray) that may lead to exposure of end-user's lungs by inhalation.
- The provided information shows that Salicylic Acid is an eye irritant with the potential to cause serious damage to the eye.

b) when used for purposes other than inhibiting the development of micro-organisms at a concentration up to:

i. 3.0 % for cosmetic rinse-off products

ii. 2.0 % for cosmetic leave-on products except body lotion and oral products, and

iii. iii. 0.5 % for body lotion and oral products

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 not safe at the following concentrations when aggregate exposure is considered:

- up to 3.0% for the cosmetic rinse-off hair products used by children (shampoo, conditioner),
- up to 2.0% for selected other dermally applied products used by children (face moisturizer, hand cream, liquid soap, shower gel), and
- up to 0.5% for body lotion.

With the exception of body lotion, it is safe in single dermal and oral product categories, when used only in the respective product category.

2) Alternatively, what is according to the SCCS the maximum concentration of Salicylic Acid that is considered safe for children 3-10 years of age?

Reducing the concentration, for example to 0.1% in dermal products, would make the use safe for dermal products and toothpaste.

3) Does the SCCS have any further scientific concerns with regard to the use of Salicylic Acid in cosmetic products and children's exposure?

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.

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

5. MINORITY OPINION

/

6. REFERENCES

NEW references (related to children exposure)

Adé DC, Filippi C, Filippi A (2024). A survey on toothbrushing practices and dosing of fluoridated toothpaste among preschool children in the cantons of Basel-Stadt and Berne, Switzerland. Swiss Dent J 133(2): 18-34. doi: 10.61872/sdj-2024-07-08-01

Alexander-White C, Bury D, Cronin M, Dent M, Hack E, Hewitt NJ, Kenna G, Naciff J, Ouedraogo G, Schepky A, Mahony C, Europe C. (2022) A 10-step framework for use of read-across (RAX) in next generation risk assessment (NGRA) for cosmetics safety assessment. Regul Toxicol Pharmacol;129:105094. doi: https://doi.org/10.1016/j.yrtph.2021.105094 . PMID: 34990780.

Boniol M., Verriest J.P., Pedeux R., Doré J.F. 2008. Proportion of skin surface area of children and young adults from 2 to 18 years old. J Invest Dermatol 28: 461-464.

Bremmer, H. J. (2006a). Cosmetics Fact Sheet to assess the risks for the consumer. Updated version for ConsExpo 4. RIVM Report 320104 001/2006 (2006a). https://www.rivm.nl/bibliotheek/rapporten/320104001.pdf

Bremmer, H. J. (2006b). General Fact Sheet – Limiting conditions and reliability, ventilation, room size, body surface area. Updated version for ConsExpo 4, RIVM report 320104002/2006 https://www.rivm.nl/bibliotheek/rapporten/320104002.pdf NB RIVM 2014 General Fact Sheet by te Biesebeek et al now replaces this document online.

EFSA (2012) (European Food Safety Authority). Guidance on selected default values to be used by the EFSA Scientific Committee, Scientific Panels and Units in the absence of actual measured data. In *EFSA Journal, 10*(3), 2579. https://doi:10.2903/j.efsa.2012.2579.

Ficheux AS, Chevillotte G, Wesolek N, Morisset T, Dornic N, Bernard A, Bertho A, Romanet A, Leroy L, Mercat AC, Creusot T, Simon E, Roudot AC (2016). Consumption of cosmetic products by the French population second part: Amount data. Food Chem Toxicol 90: 130-41. doi: 10.1016/j.fct.2016.02.008

Ficheux RA-C, Roudot A-S (2017). Exposition de la population française aux produits cosmétiques. LERCCo, UBO, Brest, France

Garcia-Hidalgo E, von Goetz N, Siegrist M, Hungerbühler K (2017). Use-patterns of personal care and household cleaning products in Switzerland. Food Chem Toxicol 99: 24-39. doi: 10.1016/j.fct.2016.10.030

Gomez-Berrada MP, Ficheux AS, Boudières I, Chiter M, Rielland A, De Javel D, Roudot AC, Ferret PJ (2018). Consumption and exposure assessment to toothpaste in French families. Food Chem Toxicol 118: 24-31. doi: 10.1016/j.fct.2018.04.061

Hass, U., Christiansen, S., Andersen MD, Rosenberg SA, Egebjerg KM, Brandt S, Nikolov NG, Holbech H, Morthorst JE; List of Endocrine Disrupting Chemicals, Report from Danish Centre on Endocrine Disrupters for Danish EPA, 2018. link to report: http://cend.dk/files/DK_ED-list-final_2018.pdf;
link to appendix:
http://cend.dk/files/DK_ED-list-final_appendix1_2018.pdf

Health Canada (2020). Draft Screening Assessment - Salicylates Group, Chemical Abstracts Service Registry Numbers 69-72-7; 87-22-9; 118-56-9; 68917-75-9; 84012-15-7. March 2020 https://www.canada.ca/content/dam/eccc/documents/pdf/pded/salicylates/Draft-screening-assessment-salicylates- group.pdf
Needs CJ & Brooks PM (1985) Clinical pharmacokinetics of the salicylates 10: 164-177.

Nordic Council of Ministers (2022) Existing Default values and recommendations for exposure assessment – Revision of the 2011 report, a Nordic Exposure Group Project. Report available online at https://pub.norden.org/temanord2023- 508/

OECD (2019) CONSIDERATIONS WHEN ASSESSING CHILDREN'S EXPOSURE TO CHEMICALS FROM PRODUCTS Series on Testing and Assessment No. 310 ENV/JM/MONO(2019)29

Renwick, A. G. (1998). Toxicokinetics in infants and children in relation to the ADI and TDI. In *Food Additives and Contaminants*, *15 Suppl*, 17–35. https://doi.org/10.1080/02652039809374612

RIVM (2014) General Fact Sheet General default parameters for estimating consumer exposure - Updated version 2014 RIVM report 090013003/2014 J.D. te Biesebeek et al. https://www.rivm.nl/bibliotheek/rapporten/090013003.pdf

Sharkey I, Boddy AV, Wallace H, Mycroft J, Hollis R, Picton S; Chemotherapy Standardisation group of the United Kingdom Children's Cancer Study Group (2001). Body surface area estimation in children using weight alone: application in paediatric oncology. Br J Cancer 85(1): 23-8. doi: 10.1054/bjoc.2001.1859

SCCNFP (2003). The Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers. Opinion concerning The Safety Of Fluorine Compounds In Oral Hygiene Products For Children Under The Age Of 6 Years. Adopted by the SCCNFP during the 24th Plenary Meeting of 24-25 June 2003. SCCNFP/0653/03, Final.

Schloesser RL, Lauff M, Buxmann H, Veit K, Fischer D, Allendorf A (2011) Three-Dimensional Body Scanning: A New Method to Estimate Body Surface Area in Neonates. Neonatology 100 (3):260-264.

Scientific Committee on Consumer Products (2005) Opinion on the safety of fluorine compounds in oral hygiene products for children under the age of 6 years. SCCP/0882/05

SCCS (2023) Opinion on Salicylic Acid (CAS No. 69-72-7, EC No. 200-712-3) SCCS/1646/22 Available online at https://health.ec.europa.eu/latest-updates/sccs-final-opinion-salicylic-acid-2023-06-09_en

US EPA (2008), Child-Specific Exposure Factors Handbook, EPA/600/R-06/096F, Washington DC.

US EPA (2011) Exposure Factors Handbook 2011 Edition (Final Report). U.S. Environmental Protection Agency, Washington, DC, EPA/600/R-09/052F, 2011.

WHO (World Health Organization) - Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits. Environmental Health Criteria, 170, WHO, Geneva (1994).

Yu C-Y, Lo Y-H, Chiou W-K (2003) The 3D scanner for measuring body surface area: a simplified calculation in the Chinese adult. Applied Ergonomics, 34 (3):273-278.

Zuanon AC, Aranha AM (2005) Mouthwash ingestion by preschool children. J Clin Pediatr Dent; 30(1):15-7

DTU Foods

Abend, S.L., Feng, S.L., Alex, S.,Braverman, L.E. and Leonard, J.L. (1991) 'Rapid alteration in circulating free thyroxine modulates pituitary type II 5' deiodinase and basal thyrotropin secretion in the rat', *J.Clinical Investigation.88, pp.898-903,*doi: 10.1172/JCI115392.

Albert, O., Desdoits-Lethimonier. C., Lesné, L. Legrand, A., Guille, F., Bensalah, K., Dejucq-Rainsford, N. and Jègou, B. (2013) 'Paracetamol, aspirin and indomethacin display endocrine disrupting properties in the adult human testis n hypospadiaitro', *Human Reproduction.28(7), pp.1890-1898* doi:10.1093/humrep/det112*.*

Balasubramanian, A. and Ramakrishnan, S. (1979) 'Effect of acetyl salicylic acid (aspirin) & prostaglandins on thyroid tissue & carbohydrate metabolism in liver of male albino rats', *Indian Journal of Biochemistry and Biophysics.16, pp.88-92.*

Beall, J.R. and Klein, M.F. (1977) 'Enhancement of aspirin-induced teratogenicity by food restriction in rats', *Toxicology and applied pharmacology. 39, pp.489-495,* doi: 10.1016/0041-008X(77)90140-5

Belsito, D., Brickers, D., Broze, M., Calow, P., Greim, H., Hanifin, J.M., Rogers, A.E., Saurat, J.H., Sipes, I.G. and Tagami, H. (2007) 'A toxicologic and dermatologic assessment of salicylates when used as fragrance ingredients', *Food and Chemical Toxicology.45, S318-S361*

Cappon, G.D., Gupta, U., Cook, J.C., Tassinari, M.S. and Hurtt, M.E. (2003) 'Comparison of the developmental toxicity of aspirin in rabbits when administrated throughout organogenesis or during sensitive windows of development', *Birth Defects Research (Part B).68, pp.38-46*.

Chapin, R.E., and Sloane, R.A. (1997) 'Reproductive Assessment by Continuous Breeding: Evolving Study Design and Summaries of Eighty-Eight Studies', *Enviromental Health Perspectives.104, sup.2, pp.*

Collins, T.F.W., Hansen, W.H. and Keeler, H.V. (1971) 'Effect of Methyl Salicylate on rat reproduction', *Toxicology and applied pharmacology.18, pp.755-765,* doi: 10.1016/0041-008X(71)90227-4

Conte, D., Romanelli, F., Fillo, S., Isidori, A., Franceschi, F., Latini, M. and Luigi, L.D. (1999) 'aspirin inhibits androgen response to chorion gonadotropin in humans', *Am.J. Physiol. 277 (Endocrinol. Metab. 40): E1032–E1037*.

Davis, D.P., Daston, G.P., Odio, M.R., York, R.G. and Kraus, A.L. (1996) 'Maternal reproductive effects of oral salicylic acid in Sprague-Dawley rats.', *Toxicology Letters.84, pp.135-14.*

Didolkar, A.K., Patel, P.B. and Roychowdhury, D. (1980) 'Effect of aspirin on spermatogenesis in mature and immature rats', *International Journal of Andrology.3, pp.585-593*.

Eriksson, M. (1970) 'Salicylate-induced foetal damage during late pregnancy in mice', *Acta Paediatrics Scandinavia.59, pp.517-522.*

Gupta, U., Cook, J.C., Tassinari, M.S., and Hurtt, M.E. (2003) 'Comparison of developmental toxicology of aspirin (Acetylsalicylic Acid) in rats using selected dosing paradigms', *Birth Defects Research (Part B).68, pp.27-37.*doi: 10.1002/bdrb.10007

Hansen, H.H. and Mogensen, E.F. (1964) 'The effect og sodium salicylate on the uptake of ^{131}I-labelled 1-triiodothyronine by human erythrocytes', *Acta Medica Scandinavia.175(6), pp.687-690.*

Hass, U., Christiansen, S., Andersen MD, Rosenberg SA, Egebjerg KM, Brandt S, Nikolov NG, Holbech H, Morthorst JE; List of Endocrine Disrupting Chemicals, Report from Danish Centre on Endocrine Disrupters for Danish EPA, 2018. link to report: http://cend.dk/files/DK_ED-list-final_2018.pdf; link to appendix: http://cend.dk/files/DK_ED-list-final_appendix1_2018.pdf

Kristensen, DM., Mazaud-Guittot, S., Gaudriault, P., Lesné, L., Serrano, T., Main, K, M., Jégou, B. (2016) 'Analgesic use - prevalence, biomonitoring and endocrine and reproductive effects', *Nat.Rev.Endocrinol. 12(7), pp.381-93*, Doi: 10.1038/nrendo.2016.55

Kristensen, D.M., Lesne, L., Fol, V.L., Desdoits-Lethimonier, C., Dejucq-Rainsford, N., Leffers, H. and Jègou, B. (2012) Paracetamol (acetaminophen), aspirin (acetylsalicylic acid) and indomethacin are anti-androgenic in the rat foetal testis', *International Journal of Andrology.35, pp.377-384.* doi:10.1111/j.1365-2605.2012.01282.x

Kristensen, D.M., Hass, U., Lesne´, L., Lottrup, G., Jacobsen, P.R.,Desdoits-Lethimonier, C., Boberg, J., Petersen, J.H., Toppari, J., Jensen, T.K., Brunak, S., Skakkebæk, N.E., Nellemann, C., Main, K.M., Je´gou, B. and Leffers, H. (2011) 'Intrauterine exposure to mild analgesics is a risk factor for development of male reproductive disorders in human and rat', *Human Reproduction.26(1), pp.235-244.* Doi:10.1093/humrep/deq323

Lapczynski AJones, L., McGinty, D., Bhatia, S.P., Letizia, C.S., Api, A.M. (2007) Fragrance material review on methyl salicylate (2007), *Food Chem Toxicology.45, Suppl 1: S428-5.* Doi:10.1016/j.fct.2007.09.053

Larsen, P.R. (1972) 'Salicylate-induced increases in free triiodothyronine in human serum. Evidence of inhibition of triiodothyronine binding to thyroxine-binding globulin and thyroxine-binding prealbumin', *The Journal of Clinical Investigation.51, pp.1125-1134*

Mazaud-Guittot, S., Nicolaz, C.N., Desdoits-Lethimonier, C., Coiffec, I., Maamar, M.B., Balaguer, P., Kristensen, D.M., Chevrier, C., Lavoué, V., Poulain, P., Dejucq-Rainsford, N. and Jégou, B. (2013) 'Paracetamol, aspirin and idiometacin induce endocrine disturbances in the human fetal testis capable of interfering with testicular descent', *J. Clin. Endocrinol. Metab. 98: E1757–E1767,* Doi: 10.1210/jc.2013-2531

Overman, D.O. and White, J.A. (1983) 'Comparative teratogenic effects of methyl salicylate applied orally or topically to hamsters', *Teratology.28, pp.421-426,* Doi: 10.1002/tera.1420280313

SCCNFP (2002) 'Opinion of the scientific committee on cosmetic products and non-food products intended for consumers concerning salicylic acid'*, SCCNFP/0522/01, final*

Schardein, J.L., Blatz, A.T., Woosley, E.T. and Kaump, D.H. (1969) 'Reproduction studies on sodium meclofenamate in comparison to aspirin and phenylbutazone', *Toxicology and applied Pharmacology.15, pp.46-55,* Doi:10.1016/0041-008X(69)90130-6

Tuchmann-Duplessis, H., Hiss, D., Mottot, G. and Rosner, L. (1975) 'Effects of prenatal administration of acetylsalicylic acid in rats', *Toxicology.3(2), pp.207-2011.*

Warkany, J.M.D. and Takacs, E. (1959) Experimental production of congenital malformations in rats by salicylate poisoning', *The American Journal of Pathology.35(2), pp.315-330*

WHO (2017) Homepage

https://www.whocc.no/atc_ddd_index/?showdescription=yes&code=N02BA in November 2017.

Wilson, J.G., Ritter, E.J., Scott, W.J. and Fradkin, R. (1977) 'Comparative distribution and embryotoxicity of acetylsalicylc acid in pregnant rats and rhesus monkeys', *Toxicology and Applied Pharmacology.41, pp.67-78,* Doi: 10.1016/0041-008X(77)90054-0

Wolff, J., Standaert, M.E. and Rall, J.E. (1961) 'Thyroxine displacement from serum proteins and depression of serum protein-bound iodine by certain drugs', *Journal of Clinical investigation,*10.1172/JCI104368 *40(8 Pt 1-2)*, Doi: 10.1172/JCI104368

REACH registration dossier: https://echa.europa.eu/da/registration-dossier/-/registered-dossier/14544/1 (Link used in November 2017)

Cosmetics Europe

Abdallah HY, Mayersohn M, Conrad KA (1991) The influence of age on salicylate pharmacokinetics in humans. J Clin Pharmacol 31:380-387.

Ahrens KA, Silver RM, Mumford SL, Sjaarda LA, Perkins NJ, Wactawski-Wende J, Galai N, Townsend JM, Lynch AM, Lesher LL, Faraggi D, Zarek S, Schisterman EF. (2016) Complications and Safety of Preconception Low-Dose aspirin Among Women With Prior Pregnancy Losses. Obstet Gynecol. 127(4):689-98. doi:10.1097/AOG.0000000000001301.

Akre K. *et al.*, (2001) Brit. J. Cancer, 84, 965-968.

Alpen EL, Mandel HG, Rodwell VW, Smith PK (1951) The metabolism of C14 carboxyl salicylic acid in the dog and in man. J Pharmacol Exp Ther 102: 150-155.

Arif T (2015) Salicylic acid as a peeling agent: a comprehensive review. Clinical, Cosmetic and Investigational Dermatology 8: 455–461.

Bard (2012) Reproductive and teratogenic risks of low salicylic acid doses in humans. Report prepared by industry for 2013 CLH dossier. Lead contact, NOVACYL.

Bari AU, Iqbal Z, Rahman SB. (2005) Tolerance and safety of superficial chemical peeling with salicylic acid in various facial dermatoses. Indian J Dermatol Venereol Leprol. 2005 Mar-Apr;71(2):87-90.

Benech-Kieffer F, Wegrich P, Schwarzenbach R, Klecak G, Weber T, Leclaire J, Schaefer H. (2000) Percutaneous absorption of sunscreens in vitro: interspecies comparison, skin models and reproducibility aspects. Skin Pharmacol Appl Skin Physiol. 2000 Nov-Dec;13(6):324-35.

Benfeldt E, Serup J, Menne T (1999) Effect of barrier perturbation on cutaneous salicylic acid penetration in human skin: in vivo pharmacokinetics using microdialysis and non-invasive quantification of barrier function. Br J Dermatol 140:739-748.

Beyer PE, Chernoff N (1986) The induction of supernumerary ribs in rodents: role of the maternal stress. Teratog. Carcinog. Mutagen 6: 419-429.

BIOFAX 21-3/1971. BIOFAX Industrial Bio-test Laboratories, Inc., Data Sheets. 1810 Frontage Rd., Northbrook, IL 60062.

Birmingham BK, Greene DS and Rhodes CT (1979a) Percutaneous absorption of salicylic acid in rabbits. Drug. Dev. Indust. Pharm., 5: 29-40.

Birmingham BK, Greene DS, Rhodes CT. (1979b) Systemic absorption of topical salicylic acid. Int J Dermatol. 18(3):228-31

Bochner F, Williams D.B., Morris P.M.A., Siebert D.M., Lloyd, J.V., (1988) Pharmacokinetics of Low-Dose Oral Modified Release Soluble and Intravenous aspirin in Man and Effects on Platelet Function. Eur. J. Clin. Pharmacol. 35, 287-294.

Bojic M, Sedgeman CA, Nagy LD, Guengerich FP (2015) Aromatic hydroxylation of salicylic acid and aspirin by human cytochrome P450. Eur J Pharm Sci 73: 49-56.

Bomhard E (1996). Acute toxicologic evaluation of salicylic acid. J Am Coll Toxicol, Vol. 15, Suppl. 1, p. S81

Boussiquet-Leroux C, Durand-Cavagna G, Herlin K, Holder D (1995) Evaluation of lymphocyte proliferation by immunohistochemistry in the local lymph node assay. J Appl Toxicol 15: 465-475.

Boutwell R.K. and Bosch D.K. (1959) The tumor-producing action of phenol and related compounds for mouse skin. Cancer Res., 19: 413-427.

Bronaugh RL, Collier SW, Storm JE, Stewart RF (1989) In vitro evaluation of skin absorption and metabolism. J Toxicol, Cutaneous and Ocular Toxicol 8: 453-467.

Bucks DA, Hinz RS, Sarason R, Maibach HI, Guy RH (1990) In vivo percutaneous absorption of chemicals: a multiple dose study in rhesus monkeys. Food Chem Toxicol 28:129-132.

Budavari S, Ed (1989) The Merck Index. An encylopedia of chemicals, drugs and biologicals, 11th Ed, 893, 961-962, 1217, 1324, 1367-1368. Rahway, NJ: Merck & Co.

Buelke-Sam J, Kimmel CA, Nelson CJ, Sullivan PA (1984) Sex and strain differences in the developmental activity profile of rats prenatally exposed to sodium salicylate. Neurobehav. Toxicol. Teratol 6: 171-175.

Cappon GD, Gupta U, Cook JC, Tassinari MS, Hurtt ME. Comparison of the developmental toxicity of aspirin in rabbits when administered throughout organogenesis or during sensitive windows of development. Birth Defects Res B Dev Reprod Toxicol 2003; 68(1):38-46.

ChemSpider http://www.chemspider.com/

Chiaretti A., Schembri-Wismayer D. Tortorolo L., Piastra M. and Polidori G. Salicylate intoxication using a skin ointment. Acta Pediatr., 1997, 86:330-331

Clark J.H. and Wilson W.G. A 16-day-old breast fed infant with metabolic acidosis caused by salicylate. Clin. Pediatr., 1981, 20: 53-54.

CLASP (Collaborative Low-dose aspirin Study in Pregnancy) Collaborative Group (1994). CLASP: a randomised trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women. Br J Obstet Gynaecol 102:861-868.

Combrinck J, Otto A, du Plessis J (2014) Whey protein/polysaccharide-stabilized emulsions: Effect of polymer type and pH on release and topical delivery of salicylic acid. AAPS PharmSciTech. 15(3):588-600. doi: 10.1208/s12249- 014-0081-3. Epub 2014 Feb 19.

Commoner B (1976) Reliability of bacterial mutagenesis techniques to distinguish carcinogenic and non-carcinogenic chemicals. Contract No 68-01-2471. National Technical Information Service (NTIS) Report No PB259934.

Cosmetic Ingredients Review (CIR) Expert Panel (Fiume MZ) (2003). Safety Assessment of Salicylic Acid, Butyloctyl-, Calcium-, C12-15 Alkyl Salicylate, Capryloyl Salicylic Acid, Hexyldodecyl-, Isocetyl-, Isodecyl-, Magnesium-, MEA-, Ethylhexyl-, Potassium-, Methyl-, Myristyl-, Sodium-, TEA-, and Tridecyl Salicylate. Int J Toxicol 22S3:1-108

Crème Global (2017) Aggregate Exposure to Salicylic Acid. Final Report, commissioned by Cosmetics Europe, November 2017.

Davis, D.A.P., Kraus, A.L., Thompson, G.A., Olerich, M., Odio, M.R., 1997. Percutaneous absorption of salicylic acid after repeated (14-day) in vivo administration to normal, acnegenic or aged human skin. J. Pharm. Sci. 86, 896–899.

Davison C, Zimmerman EF, Smith PK (1961) On the metabolism and toxicity of methyl salicylate. J Pharmacol Exp Ther 132:207-211.

Dean M, Penglis S, Stock B (1989) The pharmacokinetics of salicylate in the pregnant Wistar rat. Drug Metab Disposit 17:87-90.

ECHA (2016) Committee for Risk Assessment Opinion proposing harmonised classification and labelling at EU level for salicylic acid
https://echa.europa.eu/documents/10162/43e13264-93e1-4d7e-b8d2-64cb649ad324

Emudianughe TS, Oduleye SO, Ebadan EE, Eneji SD (1986) Sex differences in salicylic acid metabolism in Nigerian subjects. Xenobiotica 16: 177-179.

Eriksson M (1971) Salicylate-induced fetal damage during late pregnancy in mice. A comparison between sodium salicylate, acetyl salicylic acid and salicylsalicylic acid. Acta Phamracol. Toxicol 29: 250-255.

Farid NA, Born GS, Kessler WV, Shaw SM, Lange WE (1975) Improved colorimetric determination of salicylic acid and its metabolites in urine. Clin Chem 21: 1167-1168.

Feldmann RJ & Maibach HI (1970) Absorption of some organic compnents through the skin in man. J Invest Dermatol 54:399-404.

Fleischli FD, Morf F, Adlhart C. (2015) Skin Concentrations of Topically Applied Substances in Reconstructed Human Epidermis (RHE) Compared with Human Skin Using in vivo Confocal Raman Microscopy. Chimia (Aarau). 69(3):147- 51. doi: 10.2533/chimia.2015.147

Fritz H & Giese K (1990) Evaluation of the teratogenic potential of chemicals in the rat. Pharmacology 40 (suppl 1):1-28.

Fritz H & Suter HP (1985) Postnatal development of young rats following the treatment of the dams with sodium salicylate during later periods of pregnancy. Arzneim. Forsch 35:937-939.

Fung, W., Orak, D., Re, T.A., Haughey, D.B., 2008. Relative bioavailability of salicylic acid following dermal application of a 30% salicylic acid skin peel preparation. J. Pharm. Sci. 97, 1325–1328.

Gabrielsson J, Paalzow L, Larsson S, Blomquist I (1985) Constant rate of infusion – improvement of tests for teratogenicity and embryotoxicity. Life Sci. 37: 2275-2282.

Galea P. and Goel K.M. Salicylate poisoning in dermatological treatment. Arch. Dis. Child, 1989.65:335

Gautheron P, Dukic M, Alix D, Sin JF (1992). Bovine corneal opacity and permeability test: an in vitro assay of ocular irritancy. Fundam Appl Toxicol, 18, 442-449.

Gerberick GF, House RV, Fletcher R, Ryan CA (1992) Examination of the local lymph node assay for use in contact sensitization risk assessment. Fundam. Appl Toxicol 19:428-445.

Goodman and Gilman (2006) Chapter 26 Salicylates In The Pharmacological Basis of Therapeutics, 11th edition. Pergamon Press New York, 688-692.

Giri AK, Adhikari N, Khan KA (1996) Comparative genotoxicity of six salicylic acid derivatives in bone marrow cells of mice. Mutat Res 370:1-9.

Greenaway J. C., Bark D. H., Juchau M. R., (1984). Embryotoxic effects of salicylates: Role of biotransformation. Toxicol. Appl. Pharmacol., 74, 141-149.

Griffith J.F., Nixon G.A., Bruce R.D., Reer P.J. and Bannan E.A. Dose-response studies with chemical Irritants in the albino rabbit eye as a basis for selecting optimum testing conditions for predicting hazard to the human eye. Toxicol. Appl. Pharmacol., 1980, 55: 501-513.

Gulamhusein AP, Harrison-Sage C, Beck F, Al-Alousi A (1980) Salicylate-induced teratogenesis in the ferret. Life Sci 27:1799-1805.

Gupta U, Cook JC, Tassinari MS, Hurtt ME. (2003). Comparison of developmental toxicology of aspirin (acetylsalicylic acid) in rats using selected dosing paradigms. Birth Defects Research Part B) 68: 27-37.

Hafeez F, Chiang A, Hui X, Maibach H. (2014) Role of partition coefficients in determining the percutaneous penetration of salicylic acid and formaldehyde under varying occlusion durations. Drug Dev Ind Pharm. 40(10):1395- 401. doi: 10.3109/03639045.2013.828218. Epub 2013 Aug 12.

Harada K, Murakamia T, Kawasaki E et al (1993) In vitro permeability to salicylic acid of human, rodent and shed snake skin. J Pharm Pharmacol. 45:414-418.

Hart V.A. One Pilot Test Followed by a 48 Hour Human Patch Test for Skin Irritation of Seven Formulations of CPO/SA Shampoo. Quintiles Consumer Product Evaluation. Study Number STL/041. September 1998.

Hasegawa R, Nakaji Y, Kurokawa Y, Tobe M (1989). Acute toxicity tests on 113 environmental chemicals. Sci. Rep. Res. Inst. Tohoku Univ., -C, Vol. 36 (Nos 1-4), 10-16.

Henderson JT, Whitlock EP, O'Connor E, Senger CA, Thompson JH, Rowland MG. Low-Dose aspirin for the Prevention of Morbidity and Mortality From Preeclampsia: A Systematic Evidence Review for the U.S. Preventive Services Task Force. Evidence Synthesis No. 112. AHRQ Publication No. 14-05207-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2014.

Hertz-Picciotto I, Hopenhayn-Rich C, Golub M, Hooper K. The risks and benefits of taking aspirin during pregnancy. Epidemiol Rev 1990; 12:108-48. PMID:2286215.

Hoffman MK, Goudar SS, Kodkany BS, Goco N, Koso-Thomas M, Miodovnik M, McClure EM, Wallace DD, Hemingway- Foday JJ, Tshefu A, Lokangaka A, Bose CL, Chomba E, Mwenechanya M, Carlo WA, Garces A, Krebs NF, Hambidge KM, Saleem S, Goldenberg RL, Patel A, Hibberd PL, Esamai F, Liechty EA, Silver R, Derman RJ (2017) A description of the methods of the aspirin supplementation for pregnancy indicated risk reduction in nulliparas (ASPIRIN) study. BMC Pregnancy Childbirth. 17(1):135. doi: 10.1186/s12884-017-1312-x.

HRL Inc (1993a). Cumulative irritation test of a gel containing 2% salicylic acid. HRL Panel no 93356. Ref no 18254.05. Project number 7536. Final report dated September 20. Unpublished data submitted by CTFA and cited in CIR 2003.

HRL Inc (1993c) Phototoxicity test of a gel containing 2% salicylic acid. HRL Panel no 93-511T(1) Ref no. 18254.06. Project no 7536. Final report dated July 26. Unpublished data submitted by CTFA.

HRL Inc (1993d) Photoallergy test of a gel containing 2% salicylic acid. HRL Panel no 93-511A(1) Ref no. 18254.07. Project no 7536. Final report dated August 22. Unpublished data submitted by CTFA.

HRL Inc (1997b) Phototoxicity test of a gel containing 2% salicylic acid. HRL Panel no 97-502T(1) Ref no. 21544.06. Project no 7696. Final report dated February 14. Unpublished data submitted by CTFA.

HRL Inc (1997c) Photoallergy test of a gel containing 2% salicylic acid. HRL Panel no 97-502A(1) Ref no. 21544.07. Project no 7696. Final report dated March 28. Unpublished data submitted by CTFA.

HRL Inc (2003) Repeated insult patch test. No #03-116

Ishidate M Jr, Sofuni T, Yoshikawa K, Hayashi M, Nohmi T, Sawada M, Matsuoka A. (1984) Primary mutagenicity screening of food additives currently used in Japan. Food Chem Toxicol. 22(8):623-36.

Ivy Laboratories (1993a) Final report on human phototoxicity bioassay of a 2% salicylic acid cream dated August 9. Sponsor study DRD no BCS0070(S) KGL Protocol no 3112. Unpublished data submitted by Procter & Gamble.

Ivy Laboratories (1993b) Final report on the determination of the photocontact allergenic potential of two topically applied test materials (one of which is a 2% salicylic acid cream) by means of the photocontact allergenicity test dated September 14. Sponsor study DRD no BCS0080. KGL protocol no 3111. Unpublished data submitted by Procter & Gamble.

Jabarah A., Gileas L.T., Zlotogorski A., Salicylate intoxication from topically applied salicylic acid. J. Eur. Acad. Dermatol. Venereol., 8, 41-42, 1997.

Janssen K, Hollman PCH, Reichman E et al (1996) Urinary salicylate excretion in subjects eating a variety of diets shows that amounts of bioavailable salicylates in foods are low. Am J Clin NUtr 64: 743-747.

Kamal MAHM, Nabekura T, Kitagawa S (2005) Permeability of ionized salicylate derivatives through guinea-pig dorsal skin. Chem. Pharm. Bull. 53(4) 441—443.

Karadzovska D, Brooks JD, Riviere JE (2012) Experimental factors affecting in vitro absorption of six model compounds across porcine skin. Toxicol In vitro. 26(7):1191-8. doi: 10.1016/j.tiv.2012.06.009. Epub 2012 Jun 28.

Kavlock RJ, Chernoff N, Rogers EH (1985) The effect of acute maternal toxicity on fetal development in the mouse. Teratog. Carcinog. Mutagen 5: 3-13.

Kershaw RA, May DC, Bianchine JR, Gerber N (1987) Disposition of aspirin and its metabolites in the semen of man. J Clin Pharmacol 27:304-309.

Kimmel CA, Wilson JG, Schumacher HJ (1971) Studies on metabolism and identification of the causative agent in aspirin teratogenesis in rats. Teratology 4: 15-24.

Kimmel C.A., Butcher R.E. and Vorhees C.V. Metal-salt potentiation of salicylate-induced teratogenesis and behavioral changes in rats. Teratology, 1974, 10: 293-300.

King M.K. Bovine Corneal Opacity and Permeability Assay. Stephens & Associates Inc. Study Number L99-D058. May 1999.

Koshakji RP, Schulert AR (1973) Biochemical mechanisms of salicylate teratology in the rat. Biochem. Pharmacol. 22: 407-416.

Kozer E, Nikfar S, Costei A, Boskovic R, Nulman I, Koren G. (2002) aspirin consumption during the first trimester of pregnancy and congenital anomalies: a meta-analysis. Am J Obstet Gynecol 187(6):1623-30.

Kozer E, Costei A M, Boskovic R, Nulman I, Nikfar S, Koren G. (2003) Effects of aspirin consumption during pregnancy on pregnancy outcomes: meta-analysis. Birth Defects Research Part B - Developmental and Reproductive Toxicology 68(1): 70-84.

Kuboyama N & Fujii A (1992) Mutagenicity of analgesics, their derivatives, and anti-inflammatory drugs with S-9 Mix of several animal species. J Nihon Univ Sch Dent 34:183-195.

Kurosaki Y, Hisaichi S-I, Hamada C, Nakayama T, Kimura T (1988) Effects of surfactants on the absorption of salicylic acid from hamster cheek pouch as a model of keratinized oral mucosa. Int J Pharm 47:13-19.

Kurosaki Y, Takatori T, Nishimura H, Nakayama T, Kimura T (1991) Regional variation in oral mucosal drug absorption: permeability and degree of keratinization in hamster oral cavity. Pharm Res 8:1297-1301.

Labib R, Bury D, Boisleve F, Eichenbaum G, Girard S, Naciff J, Leal M, Wong J. A kinetic-based safety assessment of consumer exposure to salicylic acid from cosmetic products demonstrates no evidence of a health risk from developmental toxicity. Regul Toxicol Pharmacol. 2018 Apr; 94:245-251. doi: 10.1016/j.yrtph.2018.01.026. Epub 2018 Feb 21. PMID: 29410076.

Lansdown ABG (1970) Histological changes in the skeletal elements of developing rat foetuses following treatment with sodium salicylate. Food Cosmet. Toxicol 8:647-653.

LeFevre ML. (2014) Low-dose aspirin use for the prevention of morbidity and mortality from preeclampsia: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2014;161:819-826.

Leveque N, Makki S, Hadgraft J, Humbert P (2004) Comparison of Franz cells and microdialysis for assessing salicylic acid penetration through human skin. Int J Pharm. 269(2):323-8.

Lewis RJ Sr (1993) Hazardous chemicals desk reference, 3rd Ed, 877, 1124, 1172. New York: Van Nostrand Reinhold.

Lin AN, Nakatsui T. (1998) Salicylic acid revisited. Int J Dermatol. 37(5):335-42.

Lukas JC, Rosenkrantz TS, Raye JR, Porte PJ, Philipps AF (1987) Intrauterine growth retardation after long term maternal salicylate administration in the rabbit. Am J Obstet Gynecol 156: 245-249.

Lynd P.A., Andreasen A.C. and Wyatt RJ. Intrauterine salicylate intoxication in a newborn. Clin. Pediatr. 1976, 15: 912-913.

Ma J, Cai Z, Wei H, Liu X, Zhao Q, Zhang T (2017) The anti-tumour effect of aspirin: what we know and what we expect. Biomedicine & Pharmacotherapy 95, 656-661

Madan RK, Levitt J. (2014) A review of toxicity from topical salicylic acid preparations. J Am Acad Dermatol. 70(4):788-92. doi: 10.1016/j.jaad.2013.12.005. Epub 2014 Jan 25

Marcus F, Colaizzi JL, Barry III H (1970) pH effects on salicylate absorption from hydrophilic ointment. J Pharm Sci 59:1616-1620.

Mateus R, Moore DJ, Hadgraft J, Lane ME. (2014) Percutaneous absorption of salicylic acid--in vitro and in vivo studies. Int J Pharm. 475(1-2):471-4. doi: 10.1016/j.ijpharm.2014.08.061. Epub 2014 Aug 29.

McCann J., Choi E., Yamasaki E. and Aimes B.N. Detection of carcinogens as mutagens in Salmonella/microsome test: Assay of 300 chemicals. Proc. Nat. Acad. Sci., 1975, 72: 5135-5139.

McMahon TF, Diliberto JJ, Birnbaum LS (1990) Effects of age and dose on disposition and metabolism of salicylic acid in male Fischer 344 rats. Drug Metab Dispos. 18:494-503.

Meek ME, Boobis AR, Crofton KM, Heinemeyer G, Raaij MV, Vickers C (2011) Risk assessment of combined exposure to multiple chemicals: A WHO/IPCS framework. Regulatory Toxicology and Pharmacology 60 (2011) S1–S14.

Miaskiewicz SL, Shively CA, Vessell ES (1982) Sex differences in absorption kinetics of sodium salicylate. Clin Pharmacol Ther 31:30-37.

Ministry of Labour/Japan, 2000 genotoxicity study as cited in REACH IUCLID entry.

Miyachi Y, Takigawa M (1983) Mechanisms of contact photosensitivity in mice. III Predictive testing of chemicals with photoallergenic potential in mice. Arch Dermatol 119:736-739.

Moore GS, Allshouse AA, Post AL, Galan HL, Heyborne KD. (2015) Early initiation of low-dose aspirin for reduction in preeclampsia risk in high-risk women: a secondary analysis of the MFMU High-Risk aspirin Study. J Perinatol. 35(5):328-31. doi: 10.1038/jp.2014.214. Epub 2014 Dec 4.

Muhammad F, Riviere JE. Differential effects of some natural compounds on the transdermal absorption and penetration of caffeine and salicylic acid. Int J Pharm. 2015 Apr 10;483(1-2):151-7. doi: 10.1016/j.ijpharm. 2015.02.029. PubMed PMID: 25681718.

Muhammad F, Wiley J, Riviere JE. Influence of some plant extracts on the transdermal absorption and penetration of marker penetrants. Cutan Ocul Toxicol. 2017 Mar;36(1):60-66. doi: 10.3109/15569527.2016.1147456. PubMed PMID: 27027912.

Mumford SL, Silver RM, Sjaarda LA, Wactawski-Wende J, Townsend JM, Lynch AM, Galai N, Lesher LL, Faraggi D, Perkins NJ, Schliep KC, Zarek SM, Schisterman EF (2016) Expanded findings from a randomized controlled trial of preconception low-dose aspirin and pregnancy loss. Hum Reprod. 31(3):657-65. doi: 10.1093/humrep/dev329. Epub 2016 Jan 11.

Nagelschmitz, J., Blunck, M., Kraetzschmar, J., Ludwig, M., Wensing, G., Hohlfeld, T., 2014. Pharmacokinetics and pharmacodynamics of acetylsalicylic acid after intravenous and oral administration to healthy volunteers. Clin. Pharmacol. Adv. Appl. 6, 51-59.

National Toxicology Programme (2007) Technical Report on the Photocarcinogenesis study of glycolic acid and salicylic acid (CAS nos. 79-14-1 and 69-72-7) in SKH-1 Mice (simulated solar light and topical application study). NTR 524, NIH Publication No. 07-4472.

Navarro, S.L., Saracino, M.R., Makar, K.W., Thomas, S.S., Li, L., Zheng, Y., Levy, L., Schwarz, Y., Bigler, J., Potter, J.D., Lampe, J.W., 2011. Determinants of aspirin metabolism in healthy men and women: effects of dietary inducers of UDP-glucuronosyltransferases. J. Nutrigenet. Nutrigenomics 4(2), 110-118.

Neubert R, Partyka D, Wohlrab W et al (1990) Penetration of salicylic acid and salicylate into the multilayer membrane system and into the human horny layer. Dermatol Monschr 176:711-716.

Odashima S. Cooperative programme on long-term assays for carcinogenicity in Japan. In: Molecular and cellular aspects of carcinogen screening tests. Montesano R. Bartsch H. and Tomatis L. (eds.). International Agency for Research on Cancer, Lyon, France, 1979, 315-322.
http://publications.iarc.fr/Book-And-Report-Series/Iarc-Scientific-Publications/Molecular-And-Cellular-Aspects-Of-Carcinogen-Screening-Tests-1980

Odibo AO, Goetzinger KR, Odibo L, Tuuli MG. (2015) Early prediction and aspirin for prevention of pre-eclampsia (EPAPP) study: a randomized controlled trial. Ultrasound Obstet Gynecol. 46(4):414-8. doi: 10.1002/uog.14889. Epub 2015 Aug 31.

Ohno Y, Kaneko T, Inoue T, Morikawa Y, Yoshida T, Fujii A, Masuda M, Ohno T, Hayashi M, Momma J, Uchiyama T, Chiba K, Ikeda N, Imanishi Y, Itakagaki H, Kakishima H, Kasai Y, Kurishita A, Kojima H, Matsukawa K, Nakamura T, Ohkoshi K, Okumura H, Saijo K, Sakamoto K, Suzuki T, Takano K, Tatsumi H, Tani N, Usami M, Watanabe R (1999) Interlaboratory validation of the in vitro eye irritation tests for cosmetic ingredients. (1) Overview of the validation study and Draize scores for the evaluation of the tests. Toxicol In vitro. 13(1):73-98.

Orris L. 12 Day Cumulative Irritancy – Continuous Patch Test with Challenge. Derma Test Laboratories. Final Report A069F, April 1995.

Otto A, Wiechers JW, Kelly CL, Dederen JC, Hadgraft J, du Plessis J. (2010) Effect of emulsifiers and their liquid crystalline structures in emulsions on dermal and transdermal delivery of hydroquinone, salicylic acid and octadecenedioic acid. Skin Pharmacol Physiol. 23(5):273-82. doi: 10.1159/000314702. Epub 2010 May 18.

Paynter A.S. and Alexander F.W. Salicylate intoxication caused by teething ointment. Lancet., 1979, 2: 1132.

Porat-Soldin O & Soldin SJ (1992) Preliminary studies on the in vitro and in vivo effect of salicylate on sperm motility. The Drug Monit 14:366-370.

Pratzel HG, Schubert E, Muhanna N (1990) Pharmacokinetic study of percutaneous absorption of salicylic acid from baths with salicylate methyl ester and salicylic acid. Z Rheumatol 49:185-191.

Procter & Gamble. Delayed contact hypersensitivity in guinea pigs, ECM BTS 206, 1976

Procter & Gamble. Primary skin irritation study in rabbits, P79006, 1979

Procter & Gamble. Primary skin irritation study in rabbits, P80027, 1980

Procter & Gamble. Skin irritation study in guinea pigs, P81081, 1982a

Procter & Gamble. Skin irritation study in guinea pigs, P81069, 1982b

Procter & Gamble. Primary skin irritation study in rabbits, P80087, 1982c

Procter & Gamble. Skin irritation study in guinea pigs, P83012, 1983

Procter & Gamble. HRIPT, BTS 0028, 1988a

Procter & Gamble. HRIPT, BTS 1494, 1988b

Procter & Gamble. HRIPT, BTS 1493, 1988c

Procter & Gamble. HRIPT, IBSE0002, 1989

Procter & Gamble. 91-day subchronic percutaneous toxicity, IBSE0002, 1990a
Procter & Gamble. 91-day subchronic percutaneous toxicity, IBSE0001, 1990b
Procter & Gamble. Low volume eye irritation study in rabbits, BCS0070, 1993c
Procter & Gamble. Low volume eye irritation study in rabbits, BCS0025, 1993d
Procter & Gamble. Low volume eye irritation study in rabbits, BCS0139, 1993e
Procter & Gamble. 14-day percutaneous subchronic toxicity, BCS0062, 1993f
Procter & Gamble. HRIPT, BYCR 1046/02. 1993g
Procter & Gamble. HRIPT, DRD 0030, 1993h
Procter & Gamble. HRIPT, BCS0025, 1993I
Procter & Gamble. HRIPT, HBE BTS 0327/01, 1993j
Procter & Gamble. HRIPT, BCS0070, 1993k
Procter & Gamble. 21-day cumulative irritation, BCS0133, 1993q
Procter & Gamble. 21-day cumulative irritation, BCS0025, 1993r
Procter & Gamble. Facial appearance/irritation, CR93012, 1993s
Procter & Gamble. Facial appearance/irritation, BYCR 1046/03, 1993t
Procter & Gamble. 21-day cumulative irritation, BCS0093, 1993v
Procter & Gamble. 21-day cumulative irritation, BCS0093, 1993w
Procter & Gamble. HRIPT, BCS0080, 1993x
Procter & Gamble. 6-week facial irritation, BCS0070(S3), 1993z
Procter & Gamble. Low volume eye irritation study in rabbits, BS94A056-20, 1994a
Procter & Gamble. Skin penetration study 1994b
Procter & Gamble. 28-day percutaneous study, BCS0062S, 1994c
Procter & Gamble. 91-day subchronic percutaneous toxicity, BCS0062S, 1994d
Procter & Gamble. Perinatal toxicity study in rats, BCS0062(S2), 1994e
Procter & Gamble. Facial appearance/irritation. CR94062, 1994/5h
Procter & Gamble. HRIPT, BCS0138, 1994k
Procter & Gamble. Primary skin irritation/corrosion study in rabbits, ECM BTS 2085/02, 1995a
Procter & Gamble. Low volume eye irritation study in rabbits, SC 95A003, 1995b
Procter & Gamble. Low volume eye irritation study in rabbits, SC95A013, 1995c
Procter & Gamble. Low volume eye irritation study in rabbits, SC95A005, 1995d
Procter & Gamble. Low volume eye irritation study in rabbits, CS95A012, 1995e
Procter & Gamble. Low volume eye irritation study in rabbits, BD94A110-5G, 1995f
Procter & Gamble. Ocular irritancy evaluation study, CRL25895, 1995g
Procter & Gamble. Periocular application study, CR95010, 1995h
Procter & Gamble. Ophthalmologic safety evaluation study, SC95C016, 1995i
Procter & Gamble. HRIPT, BCS0105, 1995j
Procter & Gamble. HRIPT, SC95C014, 1995k
Procter & Gamble. HRIPT, SC95C015, 1995l

Procter & Gamble. HRIPT, SC95C002, 1995m

Procter & Gamble. HRIPT, SC95C008, 1995n

Procter & Gamble. 5-day cumulative cleanser. SC94C006, 1995r

Procter & Gamble. Back irritation, CR94037, 1995s

Procter & Gamble. Dermatologic safety evaluation, SC95C016, 1995v

Procter & Gamble. Periocular application study, CR95039, 1995z

Procter & Gamble. Low volume eye irritation study in rabbits, BTS 0606/01, 1996a

Procter & Gamble. Periocular application study, 1995114, 1996b

Procter & Gamble. Dermatologic and opthalmic safety study, SC95C037, 1996c

Procter & Gamble. HRIPT, CFTSE97/002, 1997

Raabe H.A. and Ruppalt R.R. (1999) Neutral Red Release Bioassay in Normal Human Epidermal Keratinocytes. Institute for In vitro Sciences Gaithersburgh, Maryland. Study Number 99- AE69-AE77, AD 57.110. October.

Raabe H.A. and Mun (1999). Topical Application Ocular Irritation Screening Assay Using the Epiocular Human Cell Construcy. Institute for In vitro Sciences Gaithersburgh Maryland. Study Number 99-AE69-AE77, AD 57.015004. October.

Radin RG, Mumford SL, Silver RM, Lesher LL, Galai N, Faraggi D, Wactawski-Wende J, Townsend JM, Lynch AM, Simhan HN, Sjaarda LA, Perkins NJ, Zarek SM, Schliep KC, Schisterman EF (2015) Sex ratio following preconception low-dose aspirin in women with prior pregnancy loss. J Clin Invest. 125(9):3619-26. doi: 10.1172/JCI82357. Epub 2015 Aug 17.

Rainsford KD, Schweitzer A, Green P et al (1980). Bio-distribution in rats of some salicylates with low gastric ulcerogenicity. Agents and Actions, 10(5), 457-464.

RCC, 2008a Primary skin irritation study in rabbit. 4 Hour semi-occlusive application. Study number B88582.

RCC, 2008b Cell mutation assay and the thymidine kinase locus in mouse lymphoma L5178Y cells with salicylic acid pharmaceutical grade. Study number 1167700. Dated August 27.

Rhein L, Chaudhuri B, Jivani N, Fares H, Davis A. (2004) Targeted delivery of salicylic acid from acne treatment products into and through skin: role of solution and ingredient properties and relationships to irritation. J Cosmet Sci. 55(1):65-80.

Rizer R. Repeat Application Soap Chamber Test. Stephens & Associates Inc. Study Number C96-0113. September 1996a.

Rizer R. Repeat Application Soap Chamber Test. Stephens & Associates Inc. Study Number C96-0134. September 1996b.

Roberge S, Nicolaides KH, Demers S, Villa P, Bujold E (2013) Prevention of perinatal death and adverse perinatal outcome using low-dose aspirin: a meta-analysis. Ultrasound Obstet Gynecol. 41(5):491-9. doi: 10.1002/uog.12421.

Roberge S, Nicolaides K, Demers S, Hyett J, Chaillet N, Bujold E. (2017) The role of aspirin dose on the prevention of preeclampsia and fetal growth restriction: systematic review and meta-analysis. Am J Obstet Gynecol. 216(2):110-120.e6. doi: 10.1016/j.ajog.2016.09.076. Epub 2016 Sep 15.

Roberts M.S. and Horlock E. Effect of repeated skin application on percutaneous absorption of salicylic acid. J. Pharm. Sci., 1978, 67: 1685-1687.

Robertson RT, Allen HL, Bokelman DL (1979) aspirin: teratogenic evaluation in the dog. Teratology 20(2), 313- 320.

Rubio L, Alonso C, López O, Rodríguez G, Coderch L, Notario J, de la Maza A, Parra JL. (2011) Barrier function of intact and impaired skin: percutaneous penetration of caffeine and salicylic acid. Int J Dermatol. 50(7):881-9. doi:10.1111/j.1365-4632.2010.04819.x.

San RHC & Chan RIM (1987) Inhibitory effect of phenolic compounds on aflatoxin B1 metabolism and induced mutagenesis. Mutat Res 177:229-239.

SCCNFP (2002) Opinion of the scientific committee on cosmetic products and non-food products intended for consumers concerning salicylic acid. SCCNFP/0522/01, final.

SCCS (2016a) Notes of guidance for the testing of cosmetics ingredients and their safety evaluation. 9th revision.

SCCS/1564/15 Revised version of 25 April 2016
http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_190.pdf

SCCS (2016b) Opinion on phenoxyethanol. SCCS/1575/16. Final version 6 October 2016.

SCCS (2018) Opinion on salicylic acid (CAS 69-72-7) - Submission I, SCCS/1601/18, preliminary version of 10 September 2018, final version of 21 December 2018, CORRIGENDUM on 20-21 June 2019)

Schardein J. L., Blatz A. T., Woosley E. T., Kaump D. H. (1969). Reproduction studies on sodium meclofenamate in comparison to acetylsalicylic acid and phenylbutazone. Toxicology and Applied Pharmacology, 15, 46-55.

Schisterman EF, Silver RM, Perkins NJ, Mumford SL, Whitcomb BW, Stanford JB, Lesher LL, Faraggi D, Wactawski- Wende J, Browne RW, Townsend JM, White M, Lynch AM, Galai N. (2013) A randomised trial to evaluate the effects of low-dose aspirin in gestation and reproduction: design and baseline characteristics. Paediatr Perinat Epidemiol. 27(6):598-609. doi: 10.1111/ppe.12088. Epub 2013 Oct 11.

Schisterman EF, Silver RM, Lesher LL, Faraggi D, Wactawski-Wende J, Townsend JM, Lynch AM, Perkins NJ, Mumford SL, Galai N. (2014) Preconception low-dose aspirin and pregnancy outcomes: results from the EAGeR randomised trial. Lancet. 5;384(9937):29-36. doi: 10.1016/S0140-6736(14)60157-4. Epub 2014 Apr 2.

Schlede E, Mischke U, Diener W, Kayser D. (1995) The international validation study of the acute toxic class method (oral). Arch Toxicol. 69(10):659-70.

Schneider H, Panigel M, Dancis J (1972) Transfer across the perfused human placenta of antipyrine, sodium and leucine. Am J Obstet Gynecol. 15;114(6):822-8.

Shapiro S, Siskind V, Monson RR, Heinonen OP, Kaufman DW, Slone D. (1976) Perinatal mortality and birth-weight in relation to aspirin taken during pregnancy. Lancet 1(7974):1375-6.

Shen WW, Santi AG, Bruscata FN (1976) Effect of non-ionic surfactants on percutaneous absorption of salicylic acid and sodium salicylate in the presence of dimethyl sulfoxide. J Pharm Sci 65:1780-1783.

Shen J, Wanwimolruk S,Purves RD, McQueen EG, Roberts MS (1991) Model representation of salicylate pharmacokinetics using unbound plasma salicylate concentrations and metabolite urinary excretion rates following a single oral dsoe. J Pharmacokinet Biopharm 19:575-595.

Sheu CW, Solomon D, Simmons T, Sreevalsan T, Freese E (1975) Inhibitory effects of lipophilic acids and related compounds on bacteria and mammalian cells. Antimicrob. Agents Chemother 7:349-363.

Shintaku K, Arima Y, Dan Y, Takeda T, Kogushi K, Tsujimoto M, Nagata H, Satoh S, Tsukimori K, Nakano H, Hori S, Ohtani H, Sawada Y. (2007) Kinetic analysis of the transport of salicylic acid, a nonsteroidal anti-inflammatory drug, across human placenta. Drug Metab Dispos. 35(5):772-8.

Short CR, Neff-Davis CA, Hsieh LC et al (1991) Pharmacokinetics and elimination of salicylic acid in rabbits. J Vet Pharmacol Ther. 14:70-77.

Sigler M. Repeat Application Soap Chamber Test. Stephens & Associates Inc. Study Number C97-0020. February 1997.

Simonsen L, Petersen MB, Groth L. (2002) In vivo skin penetration of salicylic compounds in hairless rats. Eur J Pharm Sci. 17(1-2):95-104.

Simonsen L, Jørgensen A, Benfeldt E, Groth L. (2004) Differentiated in vivo skin penetration of salicylic compounds in hairless rats measured by cutaneous microdialysis. Eur J Pharm Sci. 21(2-3):379-88.

Singh P, Roberts MS. (1993) Dermal and underlying tissue pharmacokinetics of salicylic acid after topical application. J Pharmacokinet Biopharm. 21(4):337-73.

Singh P, Roberts MS. (1994) Skin permeability and local tissue concentrations of nonsteroidal anti-inflammatory drugs after topical application. J Pharmacol Exp Ther. 268(1):144-51.

Slone D, Siskind V, Heinonen OP, Monson RR, Kaufman DW, Shapiro S. (1976) aspirin and congenital malformations. Lancet 1(7974):1373-5.

Stephens & Associates (1999) Modified 21-day cumulative irritancy. Study no C99-D035.

Stephens & Associates (2001) Modified 21-day cumulative irritancy. Study no C01-D107.

Stich H.F., Rosin M.P. Wu C.H. and Powrie W.D. The action of transition metals on the genotoxicity of simple phenols, phenolic acids and cinnamic acids. Cancer Lett., 1981, 14: 251-260

Stolar ME, Rossi GV, Barr M. (1960) The effect of various ointment bases on the percutaneous absorption of salicylates. I. Effect of type of ointment base. J Am Pharm Assoc Am Pharm Assoc. 49:144-7.

Sugai S, Murata K, Kitagaki T, Tomita I (1991) Studies on eye irritation caused by chemicals in rabbits--II. Structureactivity relationships and in vitro approach to primary eye irritation of salicylates in rabbits. J Toxicol Sci. 16(3):111-30.

Tanaka S., Kawashima K., Nakaura S. Nagao S., Kuwamura T., Takanaka A. and Omori Y. Teratogenic effect of dietary salicylic acid in rats. J. Food. Hyg. Soc., 1973a, 14: 549-557.

Tanaka S_ Kawashima K, Nakaura S., Nagao S., Kuwamura T., Takanaka A. and Omori Y. Studies on teratogenic effects of salicylic acid and aspirin in rats as related to fetal distribution. Congenital Abnormalities. 1973b, 13:73-84.

Tanaka M, Yanagibashi N, Fukuda H, Nagai T (1980) Absorption of salicylic acid through the oral mucous membrane of hamster cheek pouch. Chem Pharm Bull (Tokyo) 28:1056-1061.

Tauber U, Weiss C, Matthes H (1993) Does salicylic acid increase the percutaneous absorption of diflucortolone-21- valerate? Skin Phamracol 6:276-281.

Taylor JR & Halprin KM (1975) Percutaneous absorption of salicylic acid. Arch Dermatol 111:740-743.

Thomas B.H., Nera E.A. and Zeitz W. Failure to observe pathology in the rat following chronic dosing with acetaminophen and acetylsalicylic acid. Res. Commun. Chem. Pathol. Pharmacol., 1977. 17: 663-678

Thun M.L., Namboodiri M.M. and Heath C.W. aspirin use and reduced risk of fatal colon cancer. N. Engl. J. Med., 1991 325: 1593-1596.

Tjälve H, Sjöstrand E, Hansson E. (1973) Whole-body autoradiography of late pregnant mice after intravenous injection of 14C-labelled salicylic acid and acetylsalicylic acid. Arch Int Pharmacodyn Ther. 203(1):142-50.

TKL Research (1993) Repeat Insult Patch Test. Study no 931016-4

TKL Research (1998) 21-day cumulative irritation patch study of a facial cosmetic cream containing 1.5% salicylic acid. Study no. 973015 dated June 22. Unpublished data submitted by the Procter & Gamble Company, as cited in CIR 2003.

TKL Research (2001) Repeat insult patch test. TKL STUDY NO. DS105001-9. Dated Oct 31.

TKL Research (2008a) A 12 consecutive day cumulative irritation patch study. Study no. DS330108, dated July.

TKL Research (2008b) 48 hour. Repeat insult patch test. TKL STUDY NO. DS104708-13. Dated Nov 6.

Tuchman-Dupleissis H., Hiss D., Mottot G. and Rosner 1. Effects of prenatal administration of acetylsalicylic acid in rats. Toxicology, 1975, 3: 207-211.

Ueda S, Mitsugi K, Ichige K, Yoshida K, Sakuma T, Ninomiya S, Sudou T. (2002) New formulation of chemical peeling agent: 30% salicylic acid in polyethylene glycol. Absorption and distribution of 14C-salicylic acid in polyethylene glycol applied topically to skin of hairless mice. J Dermatol Sci. 28(3):211-8.

Unilever (1993) Salicylic Acid: Skin Sensitization Research Studies in Mice (LLNA – Evaluation of Sensitization Potential). Study XL930272. September.

Unilever (2016) The In vitro Percutaneous Absorption of Radiolabelled Salicylic Acid at a Single Concentration Through Human Skin. Study sponsor KSA150066. Study Report No. 37136, performed by Charles RiverLaboratories, Tranent, Scotland. US EPA Chemistry Dashboard https://comptox.epa.gov/dashboard

Vaino H. *et al.*, (1997) Cancer Epidem Biomark Prevent, 6, 749-753.

Varma DR, Yue TL (1984) Influence of age, sex, pregnancy and protein-calorie malnutrition on the pharmacokinetics of salicylate in rats. Br J Pharmacol 82:241-248.

Von Weiss J.F. and Lever W.F. Percutaneous salicylic acid intoxication in psoriasis. Arch. Dermatol. 1964. 90:614-619.

Vree TB, van Ewijk-Beneken Kolmer EWJ, Verwey-Van Wissen CPWGM, Hekster YA (1994a) Direct gradient reversed-phase high performance liquid chromatographic determination of salicylic acid, with the corresponding glycine and glucuronide conjugates in human plasma and urine. J Chromatographr 652:161-170.

Walker RM, Change PK, Martin RA (1989) Effects of salicylate on rat liver in short term toxicity studies. Biochem Pharmacol 38:382-384.

Waltman R, Tricomi V, Shabanah EH, Arenas R (1973) The effect of anti-inflammatory drugs on parturition parameters in the rat. Prostaglandins 4:93-106.

Washitake M, Yajima T, Anmo T, Arita T, Hori R (1973) Studies on percutaneous absorption of drugs. III. Percutaneous absorption of drugs through damaged skin. Chem. Pharm. Bull. 21:2444-2451.

Wester RC, Melendres J, Sedik L, Maibach H, Riviere JE (1998) Percutaneous absorption of salicylic acid, theophylline, 2,4-dimethylamine, diethyl hexyl phtgalic acid, and p-aminobenzoic acid in the isolated perfused porcine skin flap compared to main in vivo. Toxicol Appl Pharmacol 151:159-165.

Wilson J, G., Scott W.J. and Ritters E.S. (1977) Comparative distribution and embryotoxicity of acetylsalicylic acid in pregnant rats and rhesus monkeys. Toxicol. Appl. Pharm., 41: 67-78.

World Health Organisation (2001) Guidance Document for the Use of Data in Development of Chemical-Specific Adjustment Factors (CSAFs) for Interspecies Differences and Human Variability in Dose/Concentration- Response Assessment. WHO/PCS/01.4.

Wurster DE, Kramer SF (1961) Investigation of some factors influencing percutaneous absorption. J Pharm Sci 50:288-293.

Xu TT, Zhou F, Deng CY, Huang GQ, Li JK, Wang XD. (2015) Low-Dose aspirin for Preventing Preeclampsia and Its Complications: A Meta-Analysis. J Clin Hypertens (Greenwich). 17(7):567-73. doi: 10.1111/jch.12541. Epub 2015 Apr 2.

Yoshikawa T, Sugiyama Y, Sawada Y, Iga T, Hanano M (1984) Effect of pregnancy on tissue distribution of salicylate in rats. Drug Metab Disp 12:500-505.

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