Scientific Committee on Consumer Safety

SCCS

OPINION ON

salicylic acid (CAS 69-72-7)
Submission I

The SCCS adopted the final Opinion
by written procedure on 21 December 2018

Corrigendum of 20-21 June 2019

ACKNOWLEDGMENTS

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

For the preliminary and the final Opinion

The SCCS members:

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

External experts:

Dr A. Simonnard
Dr A. Koutsodimou
Prof. W. Uter

The additional contribution of the following external expert is gratefully acknowledged:

Dr. N. von Goetz

All Declarations of Working Group members are available on the following webpage:
http://ec.europa.eu/health/scientific_committees/experts/declarations/sccs_en.htm

This Opinion has been subject to a commenting period of a minimum eight weeks after its initial publication (from 10 September until 14 November 2018). Comments received during this time were considered by the SCCS.
For this Opinion, comments received resulted in the following main changes: *sections 3.3.1.1. - 3.3.2.1 - 3.3.6.2. (SCCS comment), 3.3.2.2. (SCCS conclusion), 3.3.10, and 3.4.1. Changes in the discussion part and in the SCCS conclusions have been made accordingly.*
Corrigendum made in the conclusion number 2, only for clarity of SCCS position regarding percentage and coverage of oral products (lipstick).

1. ABSTRACT

The SCCS concludes the following:

1. *In light of the new data provided, does the SCCS still consider Salicylic acid (CAS 69-72-7) safe when used as a preservative in all cosmetic products up to a maximum concentration of 0.5% (acid) considering its current restriction as reported above?*

   The SCCS considers salicylic acid (CAS 69-72-7) safe when used as preservative at a concentration of 0.5 % in cosmetic products considering its current restrictions in place.
   This Opinion is not applicable to any oral product (such as toothpaste and mouthwash) with the exception of lipsticks. Sprayable products that could lead to exposure of the consumer's lung by inhalation are also excluded. The provided information shows that salicylic acid is an eye irritant with the potential to cause serious damage to the eye.

2. *In addition, does the SCCS still consider Salicylic acid (CAS 69-72-7) safe when used for purposes other than inhibiting the development of micro-organisms at a concentration up to 3.0 % for the cosmetic rinse-off hair products and up to 2.0 % for other products considering its current restrictions as reported above?*

   Based on the data provided and available literature, the SCCS considers salicylic acid (CAS 69-72-7) safe when used for purposes other than preservative at a concentration up to 3.0 % for the cosmetic rinse-off hair products and up to 2.0 % for other products, considering its current restrictions in place. However, in body lotion, eye shadow, mascara, eyeliner, lipstick and roll on deodorant applications, salicylic acid is considered safe up to 0.5 %. The SCCS position is that these levels are inclusive of any use of salicylic acid, i.e. should not exceed the stated levels with additional use as a preservative.
   This Opinion is not applicable to any oral product (such as toothpaste and mouthwash) with the exception of lipsticks. Sprayable products that could lead to exposure of the consumer's lung by inhalation are also excluded.

3. *Does the SCCS have any further scientific concerns with regard to the use of Salicylic acid (CAS 69-72-7) in cosmetic products?*

   Salicylic acid is also used as a preservative in food and as a biocide in some consumer products (see section 3.2.3) or in various pharmaceutical formulations such as anti-acne products. As no specific exposure data were made available to SCCS to assess exposure following these non-cosmetic uses, it was not possible to include them in the aggregated exposure scenarios. Therefore, the actual total exposure of the consumer may be higher than exposure from cosmetic products alone.
   The conclusions of this Opinion refer only to Salicylic Acid and should not be applied to other salicylates or salicylic acid salts.

Keywords: SCCS, scientific opinion, salicylic acid, Regulation 1223/2009, CAS 69-72-7, EC 200-712-3, SCCS/1601/18

Opinion to be cited as: SCCS (Scientific Committee on Consumer Safety), Opinion on salicylic acid (CAS 69-72-7) - Submission I, SCCS/1601/18, preliminary version of 10 September 2018, final version of 21 December 2018, CORRIGENDUM on 20-21 June 2019

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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.
They are: the Scientific Committee on Consumer Safety (SCCS) and the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) and 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 all types of 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

Contact
European Commission
Health and Food Safety
Directorate C: Public Health, Country Knowledge, Crisis Management
Unit C2 – Country Knowledge and Scientific Committees
L-2920 Luxembourg
SANTE-C2-SCCS@ec.europa.eu

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2. MANDATE FROM THE EUROPEAN COMMISSION

Background

Salicylic acid (CAS 69-72-7) and its salts, as Calcium salicylate, Magnesium salicylate, MEA-salicylate, Sodium salicylate, Potassium salicylate and TEA- salicylate (CAS 824-35-1/ 18917-89-0/ 59866- 70-5/ 54-21-7/ 578- 36-9/ 2174-16-5) are currently listed in Annex V (entry 3) of the Regulation (EC) No. 1223/2009[1] (Cosmetics Regulation) as preservative to be used in all cosmetic products up to a maximum concentration of 0.5% (acid). The following restriction applies: Not to be used for children under 3 years old, except for shampoos.

Salicylic acid (CAS 69-72-7) is also listed in Annex III (entry 98) of the Cosmetics Regulation to be used up to a maximum concentration of 3.0 % for the cosmetic rinse-off hair products and of 2.0 % for other products.
The following restrictions apply:
Not to be used for children under 3 years old, except for shampoos.
For purposes other than inhibiting the development of micro-organisms in the products.
This purpose has to be apparent from the presentation of the product.

The SCCNFP published an opinion on the safety of Salicylic acid (CAS 69-72-7) in June 2002 (SCCNFP/0522/01)[2].

ECHA's Risk Assessment Committee (RAC) adopted its opinion on the harmonised classification for Salicylic acid (CAS 69-72-7) on 10 March 2016, with a proposed classification as CMR2 [3] under Regulation (EC) No. 1272/2008. This proposed classification does not cover the salts of Salicylic acid.[4]

Art. 15 (1) of the Cosmetics Regulation states that '*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. To these ends the Commission shall adopt the necessary measures in accordance with the regulatory procedure with scrutiny referred to in Article 32(3) of this Regulation*'.

In December 2017, Cosmetics Europe transmitted a safety dossier on Salicylic acid (CAS 69-72-7) intended to demonstrate the safety of the ingredient for its current uses and restrictions.

Terms of reference

1. *In light of the new data provided, does the SCCS still consider Salicylic acid (CAS 69-72-7) safe when used as a preservative in all cosmetic products up to a maximum concentration of 0.5% (acid) considering its current restriction as reported above?*

2. *In addition, does the SCCS still consider Salicylic acid (CAS 69-72-7) safe when used for purposes other than inhibiting the development of micro-organisms at a concentration up to 3.0 % for the cosmetic rinse-off hair products and up to 2.0 % for other products considering its current restrictions as reported above?*

3. *Does the SCCS have any further scientific concerns with regard to the use of Salicylic acid (CAS 69-72-7) in cosmetic products?*

[1] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:342:0059:0209:en:PDF
[2] http://ec.europa.eu/health/ph_risk/committees/sccp/documents/out170_en.pdf
[3] Repr. 2; H361d (Suspected of damaging the unborn child) (ECHA 2016)
[4] Harmonized classification of salicylic acid was published in the official journal (L251) on 5 October 2018 (regulation 2018/1480). Salicylic acid is classified as Repr. 2 (H361d Suspected of damaging the unborn child), Acute Tox. 4 (H302 Harmful if swallowed), Eye Dam. 1 (H318 Causes serious eye damage).

3. OPINION

3.1 CHEMICAL AND PHYSICAL SPECIFICATIONS

3.1.1 Chemical identity

3.1.1.1 Primary name and/or INCI name

Salicylic acid

3.1.1.2 Chemical names

IUPAC: 2-hydroxybenzoic acid

3.1.1.3 Trade names and abbreviations

A. MeSH entry names:

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

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

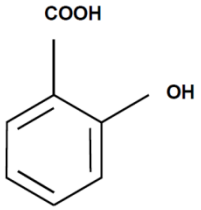
Ref: https://pubchem.ncbi.nlm.nih.gov/compound/338#section=Depositor-Supplied-Synonyms

3.1.1.4 CAS / EC number

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

Ref: Analytical Dossier; PubMed; ECHA, SigmaAldrich

3.1.1.5 Structural formula



3.1.1.6 Empirical formula

$C_7H_6O_3$

3.1.2 Physical form

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

3.1.3 Molecular weight

138.12 g/mol

3.1.4 Purity, composition and substance codes

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

Table 1. Physicochemical properties (purity) of salicylic acid

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

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

SCCS comment
The analytical methods used for the determination of purity of the test substance should be provided, according to the SCCS Notes of Guidance.

3.1.5 Impurities / accompanying contaminants

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 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. The SCCS is of the opinion that the method described in European Pharmacopoeia is the method of choice for the impurity testing of Salicylic Acid (EP7, pp2284-2285).

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 P_{ow})

Octanol/water partition coefficient ($logP_{o/w}$)= 2.25

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

3.1.8 Additional physicochemical specifications

Table 2. Physicochemical properties of salicylic acid,

Property	**Salicylic Acid**
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.

- 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 FUNCTION AND USES

3.2.1 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.
Salicylic acid is currently listed in Annex V (entry 3) of the Cosmetics Regulation (EC) No. 1223/2009 as preservative to be used in all cosmetic products up to a maximum concentration of 0.5% (acid). The following restriction applies: Not to be used for children under 3 years old, except for shampoos.
Salicylic acid is also listed in Annex III (entry 98) of the Cosmetics Regulation to be used up to a maximum concentration of 3.0 % for the cosmetic rinse-off hair products and of 2.0 % for other products. The following restrictions apply: Not to be used for children under 3 years old, except for shampoos. Not to be used for purposes other than inhibiting the development of micro-organisms in the products. This purpose has to be apparent from the presentation of the product.

3.2.2 Cosmetic product uses as per Cosmetics Europe 2017 Survey

According to the survey, the salts of salicylic acid are used as preservatives in all cosmetic products except toothpaste or mouthwash products. Salicylic acid according to the survey is not used at all in mouthwash, toothpaste, eye liner and mascara.

In the submitted dossier, no data is provided to support the use of salicylic acid in sprayable products.

3.2.3 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 TOXICOLOGICAL EVALUATION

The toxicology evaluation is focused on the data available for salicylic acid.

3.3.1 Acute toxicity

3.3.1.1 Acute oral toxicity

From SCCNFP/0522/01/2002

Animal data
Acute toxicity has been investigated following various routes.
The oral LD50 of salicylic acid were 400-3700 mg/kg for the rat.
Ref.: Biofax 21-3/1971, McCann J., et al. 1975

The oral LD50 of formulations containing salicylic acid up to 2% were 10-20 g/kg for the rat, which is equivalent to 200 to 400 mg/kg bw for the pure substance.

Ref.: Procter & Gamble (1993a), (1993b) and (1989a)

New information

Animal Data

Guideline:	similar to OECD TG 401
Species/strain:	male Albino rats (strain not specified)
Group size:	5 per group (4 groups)
Test substance:	salicylic acid
Batch:	/
Purity:	/
Vehicle:	corn oil
Dose levels:	464, 681, 1000 and 1470 mg /kg bw
Route:	oral, unspecified
Administration:	single administration
GLP:	No

Observation period: 14 days
Study period: /

In the Biofax study (1971) which has been considered by RAC as the key study for assessing acute toxicity by oral route, salicylic acid (purity unknown) was tested in a test similar to OECD guideline 401. Five male Albino rats per group (4 groups) were administrated a single dose of the test substance in a corn-oil suspension. The doses were 464, 681, 1000 and 1470 mg/kg bw. The animals were then observed for 14 days. Under the conditions of this test, the LD50 was 891 mg/kg bw. Signs of intoxication were hypoactivity and muscular weakness. At necropsy, no significant findings were observed in survivors, whereas inflammation of the gastrointestinal tract was observed in deceased animals. Based on the results of this study, salicylic acid would be classified as harmful in male rats by oral route, according to the Directive (67/548/EEC) on dangerous substance.

Ref: Biofax, 1971;
https://echa.europa.eu/el/registration-dossier/-/registered-dossier/14544/7/3/2

In the more recent study from Hasegawa et al., 1989, n=10 Wistar rats were administrated a single dose of an aqueous solution of the test substance in a gum arabic. LD50 values were also in the range of 500 to 2000 mg/kg bw, demonstrating that salicylic acid is harmful *via* the oral route.

Ref: Hasegawa et al. (1989)

Human Data

In humans, the oral lethal dose for sodium salicylate or aspirin is estimated between 20 and 30 g in adults, but much higher amounts (130 g of aspirin in one case) have been ingested without a fatal outcome (Goodman & Gilman, 2006). Children under the age of 3 years are more sensitive than adults to salicylates.

SCCS comment
Salicylic acid was recently (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 with this dossier have certain shortcomings, the available data support this classification.

3.3.1.2 Acute dermal toxicity

From SCCNFP/0522/01/2002

The topical application of acetylsalicylic acid powder at a dosage of 2 g/kg to rabbits did not induced any sign of erythema or oedema on both the intact and abraded skin of the animals. The dermal LD_{50} was estimated greater than 2 g/kg in rabbits.

Ref.: Procter & Gamble (1976b)

This submission
There is one animal study covering the acute dermal toxicity of salicylic acid.

Animal Data

Guideline:	OECD Guideline 402 (Acute Dermal Toxicity)
Species/strain:	female and male rats/ Wistar
Group size:	5 male and 5 female
Test substance:	salicylic acid
Batch:	/

Purity:	99.8 %
Vehicle:	cremophor EL®
Dose levels:	2000 mg/kg
Route:	dermal
Administration:	single administration
GLP:	Yes
Observation period:	14 days
Study period:	/
Year study completed:	1989

A single dose of 2000 mg/kg was occlusively applied to the intact clipped skin of 5 male and 5 female young adult rats (242/199g) for an exposure period of 24 hours. The animals were observed for mortality, body weights, clinical signs, and gross pathological changes for 14 days.

Results

No mortality and no local effects were noted. Clinical signs included poor general condition and piloerection. Onset of symptoms was 1 hour post administration. On day 2, all animals were free of signs. Necropsy on day 14 revealed slightly swollen liver in two females. The dermal LD50 in both sexes is greater than 2000 mg/kg bw.

Ref: Bomhard 1996;

https://echa.europa.eu/el/registration-dossier/-/registered-dossier/14544/7/3/4

SCCS comment
The SCCS considers salicylic acid as a low dermal acute toxicant.

3.3.1.3 Acute inhalation toxicity

The Applicant does not intend to use salicylic acid in spray or aerosol cosmetics.

SCCS comment
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.

3.3.1.4 Acute toxicity by the intraperitoneal route

/

3.3.2 Irritation and corrosivity

SSCS 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.

3.3.2.1 Skin irritation

SCCNFP/0522/01/2002
- Single dermal application for 4 hours of alcoholic solutions containing 2% salicylic acid was mildly to non-irritating to rabbit skin.
- Repeated open applications of 2.5 % and 5 % hydroalcoholic solutions of salicylic acid (3 hours exposure twice a day for 4 consecutive days) to guinea pig skin showed mild irritation.

Ref.: Procter & Gamble (1982a), (1979a), (1995a) and (1980)

This submission
Animal data

Guideline:	OECD 404 (2002)
Species/strain:	New Zealand White rabbit
Group size:	1 male and 2 females
Test substance:	Salicylic acid
Batch:	RAS0725500
Purity:	99.9%
Dose:	0.5 g
Exposure:	Single topical application for 4 hours and observation over 14 days
GLP:	In compliance
Study period:	2 April – 28 May 2008

Approximately 0.5 g of the test substance, spread over an area of 6.25 cm^2 and moistened with 0.5 mL of purified water was applied semi-occlusive to the test site for 4 hours. The skin was examined at 1, 24, 48 and 72 hours after patch removal, as well as 7, 10 and 14 days after the exposure.

Results
No death and no clinical signs of systemic toxicity were observed during the study. No staining of the treated skin by the test item was observed. The test item did not elicit any skin reactions at the application site of any animal at any of the observation times.

Conclusion
The study authors conclude that salicylic acid is not irritating to rabbit skin.

Ref: RCC, 2008a
SCCS comment
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. However, the new study provided in the current submission indicates that neat salicylic acid is not irritating to skin.

3.3.2.2 Mucous membrane irritation / eye irritation

This submission
Animal data
The primary eye irritation potential of salicylic acid was evaluated with a method similar to a Draize test. In this study, salicylic acid induced severe eye irritation. Mean scores for cornea, iris and conjunctivae were 51.5, 40.3 and 38.7 at 24 h, 48 h and 72 h, respectively.

Ref: BioFax 1971

Additionally, in a Draize eye irritation test available in open literature, salicylic acid induced severe irritation that did not recover within 21 days of treatment. Draize scores for cornea and conjunctivae were 54.1 and 10.3, respectively.

Ref: Sugai et al. 1991

***In vitro* data**

In an *in vitro* Bovine Corneal Opacity/Permeability (BCOP) test available in open literature, results for opacity but not permeability were reported for salicylic acid tested at up to 10% in MEM + 1% FBS. Based on the following opacity readings in this study, salicylic acid was considered by the RAC as a severe eye irritant: 0.1%: 7.2±1.7; 1%: 70.2±8.4; 5%: 88.2±5.1; 10%: 98.7±7.4.

Ref: Gautheron et al. 1992

Applicants' conclusion on eye irritation

On the basis of a hazard assessment in animals, salicylic acid can induce severe irritation does not recover within 21 days of treatment (Sugai et al 1991). Salicylic acid has therefore been classified by the RAC as irritant for the eyes, with R41: risk of serious damage to eyes, according to EU criteria and is classified category 1 (irreversible effects on the eye) according to the GHS (EU).

SCCS comment

The reference BioFax, 1971 provided to SCCS is only a fax with test results and does not include any details about how the study was conducted.

SCCS conclusion on eye irritation

Based on all available data concerning ingredients, SCCS considers salicylic acid as being able to cause serious damage to the eye. Salicylic acid was recently classified as Eye Dam. 1 (H318 Causes serious eye damage) and was included in annex VI of CLP (Regulation 2018/1480).

3.3.3 Skin sensitisation

From SCCNFP/0522/01/2002

Animal data

Potential allergic contact sensitisation has been investigated according to the modified Buehler test protocol using the guinea pig:

- 20 animals had hydro-alcoholic solutions of salicylic acid, acetyl salicylate, methyl salicylate or hexadienyl acetyl salicylate (25% w/v) applied for 6 hours, once a week, for three weeks. After a 2-week rest period the animals were challenged with the same concentrations. Under the experimental conditions adopted none of the animals exhibited signs of sensitisation.

Ref.: Procter & Gamble (1975), (1976d), (1976e), (1976f), and Robinson (1990)

Human data

The results of human repeated insult patch tests conducted with formulation containing up to 2 % salicylic acid confirm that topical application does not cause skin sensitisation. In 3 studies, some subjects were showing a positive response to an ingredient of the product formulation. None of the subjects were sensitive to salicylic acid.

Ref: Procter & Gamble (1988a), (1993g), (1994k) and Orris L. (1995)

SCCNFP/0522/01/2002 conclusions
-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.

This submission

Local lymph node assays (LLNA)

Guideline:	OECD 429
Species/strain:	Female CBA/J mice
Group size:	4 mice per group (except group 4 (25% salicylic acid): 3 mice per group)
Test substance:	Salicylic acid
Batch:	S2013607
Purity:	99%
Vehicle:	4:1 acetone/olive oil (AOO)
Concentration:	5, 10, 25%
Positive control:	Not included
GLP:	Not in compliance
Study period:	16 - 22 June 1993

Mice were treated by topical application to the dorsal surface of each ear with the vehicle alone or with salicylic acid (5, 10 and 25%) for three consecutive days. Five days after the first topical application, mice were administered with ^{3}HTdR. After sacrifice, the draining auricular lymph nodes were excised and pooled for each experimental group. Single cell suspensions (SCSs) of pooled lymph node cells (LNC) were prepared and ^{3}HTdR incorporation was measured. The proliferative responses of lymph node cells (LNC) was expressed as the number of radioactive disintegrations per minute per lymph node (DPM/NODE) and as the ratio of HTdR incorporation into LNC of test lymph nodes relative to that recorded for control lymph nodes. A test substance was regarded as "a sensitiser" in the LLNA if the test substance resulted in an incorporation of ^{3}HTdR at least 3-fold or greater than that recorded in the control mice.

Results

The ratio between test substance and control lymph node proliferation was: 0.8, 1.5 and 2.5 for 5, 10 and 25% salicylic acid, respectively. Salicylic acid failed to show positive proliferative responses at any of the concentrations assayed. The mice showed no visible signs of toxicity to salicylic acid throughout this study.

Conclusion

Salicylic acid is 'unlikely to be a strong sensitizer' in the LLNA.

Ref: Unilever, 1993

Non-guideline studies

Two publications were provided as well by the Applicant in which the skin sensitising potential of salicylic acid was tested in the LLNA. Gerberick *et al.* (1992) reported on an LLNA that was performed in groups of 5 CBA/J mice dosed once daily for 4 consecutive days

with 12.5 µL of 1, 10 or 20 % salicylic acid in acetone. Stimulation indices (treated vs control ratios) of 0.9, 1.8 and 7.2-fold were observed. This indicated that the test material was sensitising at 20%.

Ref: Gerberick et al., 1992

Boussiquet-Leroux et al. (1995) published an LLNA using 5% to 20% salicylic acid in 4:1 acetone:olive oil (AOO). Groups of four female CD1 mice were dosed for 3 days with 25 µL of test solution or vehicle only. The maximum treated/control (T/C) ratio was 1.74, indicating that the test material was not sensitising.

Ref: Boussiquet-Leroux et al., 1995

Human data

The Applicant provided a new human study in which salicylic acid was tested in a formulation. In SCCNFP/0522/01 as well, only human data were provided based on patch tests using salicylic acid in product formulations. Based on all human data, the Applicant concluded that topical application of formulations containing up to 2% of salicylic acid does not cause skin sensitisation.

Ref: TKL Research, 2008a and 2008b

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.

3.3.4 Toxicokinetics

3.3.4.1 Dermal / percutaneous absorption

SCCNFP/0522/01/2002 conclusion
Salicylic acid is readily absorbed when applied on the skin. The absorption is strongly dependent on the vehicle composition, pH, and structure of the skin, as well as conditions of the application on the skin (single dose, repeated doses and occlusion). The absorption from topically applied 2 % salicylic acid containing products is in the range of 20 % of the applied dose. After topical administration on human skin of 1.25 to 1.5 g of a 2 % salicylic acid containing formulation (corresponding to 25 mg of salicylic acid) daily for 16 days, the peak salicylate levels were between 1/10th and 1/20th of those obtained after the oral administration of 81 mg of acetyl salicylic acid (baby dose aspirin).

This submission

Animal studies

***In vitro* data**

***In vitro* percutaneous absorption**
In vitro percutaneous absorption studies (OECD guideline 428) have been performed using Franz diffusion cells and porcine skin dermatomed to a thickness of 500 ± 50 µm. The receptor chamber was filled with a receptor fluid containing phosphate-buffered saline (pH 7.4) in distilled water, 1% bovine serum albumin, and 0.04% of gentamicin sulfate. The cells were placed in a circulating water bath to ensure that the skin surface was maintained

at 32 °C. The integrity of the skin was checked by measurements of transepidermal water loss. The diffusion experiment was initiated by applying 10 µL of ethanol–water (1:1) solution salicylic acid (about 3%, w/v) to the entire surface. After an exposure time of 24 hours, the test formulation remaining on the skin surface was removed with a specific wash. The *stratum corneum* of the treated area was removed by eight successive tape strippings. After that, the viable epidermis was separated from the dermis. The different compartments, for each active principle, were analysed using high-performance liquid chromatography. Six samples were used for each experimental assay. Dermal absorption of salicylic acid (epidermis, dermis and receptor fluid) on intact skin was found to be **34.48% ± 2.56** (n=6). Total recovery was 99.28% ± 4.31.

Ref: Rubio et al 2011

^{14}C-salicylic acid was topically dosed with either 10% solutions of natural extracts or ethanol (control) using a flow through *in vitro* porcine skin diffusion system. Porcine skin was dermatomed to a thickness of 500 µm. Each square section (1 cm^2) was placed into a two-compartment Teflon flow-through diffusion cell using a well-established protocol. The dermal side of the skin sections were perfused using the receptor fluid consisting of a Krebs–Ringer bicarbonate buffer spiked with dextrose and BSA (4.5% w/v). The temperature of the perfusate and the diffusion cells was maintained at 37 °C. The flow rate of the flow-through receptor solution was 4 mL/h. Salicylic acid was topically dosed either in 10% solution of eight natural extracts or ethanol at a concentration of 1.6 µg/µL as finite (25 µL) volumes to an area of 1 cm^2. Samples of the receptor fluid were collected at the following predetermined intervals post dose application: 0, 15, 30, 45, 60, 75, 90, 105, 120min and then 3, 4, 5, 6, 7, 8, 12, 16, 20 and 24h. At the end of experiment, the dose area was swabbed and then tape-stripped six times. Samples from the perfusate, swabs, stratum corneum tape strips, dosed skin and mass balance samples were analysed with liquid scintillation counter. The dermal absorption of ^{14}C-salicylic acid in ethanol was **40.05%** (**± 7.63**; n=3).

Ref: Muhammad et al. 2017

***In vivo* data**

***In vivo* percutaneous absorption in Rhesus Monkeys**

The effect of daily topical application on the *in vivo* percutaneous absorption of salicylic acid in rhesus monkeys has been investigated (female rhesus monkeys; n=4; aged 7 ± 3 yr; 5±2 kg). In both single- and multiple-dose experiments, salicylic acid was administered dissolved in a small volume of acetone, at a surface dose of 4 mg/cm2 to a lightly clipped area of the abdomen. In the single-dose study the 14C-labelled salicylic acid were applied and the dose site was washed, 24 hr after administration, with soap and water. To quantify absorption, urine was collected for 7 days after dosing and was assayed for 14C radioactivity by liquid-scintillation counting. Urine samples were collected, after dosing, according to the following schedule: day 1: 0-4, 4-8, 8-12 and 12-24 hr; days 2-7: urine for each 24-hr period was combined. In the multiple-application experiments, the animals received a chemical dose of 4 µg/cm2 applied to exactly the same site, every 24 hr for 14 days. The first and eighth applications used 14C-labelled salicylic acid; and other applications involved unlabelled compound at the same chemical dose. The skin site of application was not washed between dosings. No 'contamination' of the excretion kinetics of the second radiolabelled dose by the first was apparent. The kinetics observed are independent of the dosing method. Thus, under the conditions used, measurement of percutaneous absorption after a single application can be predictive of permeation when multiple skin contacts occur. The percutaneous absorption of 14C-salicylic acid after a single topical application was **59 % ± 32**. In the multiple dose study, cumulative absorption was **67 % ± 17** to **78 % ± 18** after the 1st and the 8th dose, respectively. According to the Applicant, this is unusually high, as the vehicle chosen for this study was acetone, which maximises skin penetration.

Ref: Bucks et al, 1990

Human studies

***In vitro* data**

***In vitro* Percutaneous Absorption of ^{14}C-salicylic Acid**

Guideline:	OECD 428/ OECD 28/ SCCS 1358/10
GLP:	No
Test system:	Human abdominal skin samples (Split-thickness)
Sample number:	12 human abdominal skin samples
Test substance:	[phenyl-^{14}C(U)]-Salicylic acid
Batch:	150924
Purity:	99.0 %
Vehicle:	ethanol: water (35% v/v)
Concentration:	2% (w/w)
Route:	topically, dermal
Dose:	40 µg/cm^2
Receptor fluid :	5%, v/v PBS with new-born calf serum, 2.5 µg/mL amphotericin B, 100 units/mL penicillin, and 0.1 mg/mL streptomycin.
Exposure:	Single application 2 mg/cm^2
Exposure period:	1, 2, 4, 6, 8, 10, 12 and 24 h post dose.
Method of analysis:	Liquid scintillation counting
Study period:	1 September 2015 – 11 November 2015

Four samples of full-thickness human skin (abdomen) were obtained from male and female donors. Split-thickness membranes were prepared by pinning the full-thickness skin, stratum corneum uppermost, onto a raised cork board and cutting at a setting equivalent to 200-400 µm depth using a Zimmer® electric dermatome. The surface area of exposed skin within the cells was 3.14 cm^2. Any skin sample exhibiting a resistance less than 4 kΩ was excluded from subsequent absorption measurements. The skin surface temperature was maintained at 32°C ± 1°C throughout the experiment. *Ca* 6.28 mg (2 mg/cm^2) of the test preparation was applied over the stratum corneum surface of the exposed skin of 12 skin samples obtained from four different donors. The exposure period was terminated at 24 h post dose. Receptor fluid was sampled at approximately 1, 2, 4, 6, 8, 10, 12 and 24 h post dose. The highest achievable concentration of the test item in receptor fluid (i.e. if 100% was absorbed) would be 12.6 mg/L. Since water solubility of the test substance is 2.2 µg/mL, the receptor fluid was considered to be acceptable for use. At 24 h post dose, the donor chamber was transferred to a pre-weighed pot containing ethanol. The skin was then removed from the static diffusion cells and dried. The stratum corneum was removed with 20 successive tape strips. The remaining skin was divided into exposed and unexposed skin. The exposed epidermis was separated from the dermis. The skin samples were solubilised with Solvable® tissue solubiliser. All samples were analysed by liquid scintillation counting.
The mass balance for all samples was within 100 ± 10%, with the exception of Cell 28 (mass balance: 89.66%). Similar absorption profiles were observed for all samples. The absorbed dose (50.09%) was the sum of the receptor fluid (47.97%) and the receptor chamber wash (2.12%). Dermal delivery (54.00%) was the sum of the absorbed dose, the epidermis (1.26%) and dermis (2.64%). A summary of the mean results are shown in Table 3.

Table 3. Mean results of salicylic acid application to human skin *in vitro* for 24 hours.		
Test Item	**[^{14}C]- salicylic acid**	
	(% Applied Dose)	**(µg equiv/cm^2)**
Dislodgeable dose	38.60 ± 4.8	15.72 ± 1.96
Unabsorbed dose	39.57 ± 4.88	16.11 ±1.99
Absorbed dose	50.09 ± 5.26	20.41 ± 2.14
Dermal delivery	54.00 ± 5.12	22.00 ± 2.09
Mass balance	93.57± 1.58	38.11 ± 0.61

According to the Applicant, the study provides a high-end estimate of skin absorption for use in risk assessment, as a worst case of **50.09 (±5.12;** n=12) **%** absorption of salicylic acid after a continuous 24 hours of topical exposure in ethanol:water (35% v/v).

Ref: Unilever, 2016.

A single dose of [^{14}C]-salicylic acid was applied onto human skin *in vitro* in diffusion cells under non-occlusion as well as various occlusive time periods (1, 4 and 8 h). The dermatomed human cadaver skin was clamped onto 1.77 cm^2 glass Franz cells in a diffusion cell system. A 12 mL of reservoir fluid volume was filled to capacity with receptor fluid PBS (0.01 M, pH 7.4). The temperature of the glass cell was maintained at 32 ˚C. A 5 µL dose of [^{14}C]-salicylic acid was applied to the surface of the skin. At regular intervals (1, 4, 8, 12 and 24 h), 1.0 mL of the receptor fluid in each cell chamber was manually collected. Upon reaching a pre-defined time of occlusion (1, 4 or 8h of occlusion), the wraps were removed. After 24 hours, skin samples were removed and the skin surface sites were tape-stripped 10 times. The radioactivity in the epidermis and dermis represented the dose absorbed in the skin. Mass balance was between 97-114%. The radioactivity recovery as percent of applied dose of [^{14}C]-salicylic acid was significantly higher under occlusion versus non-occlusion in the epidermis, dermis and receptor fluid after 24 h ($p < 0.05$). Occlusion increases salicylic acid absorption. The total amount of [^{14}C]-salicylic acid absorbed in the skin (epidermis + dermis + receptor fluid), as a percent of applied dose increased from 4.5% (8% including 1SD) under non-occlusion to **50.5%** (**85%** including 1SD) when under 8 h of occlusion.

Ref: Hafeez F, et al (2014)

A number of studies justify that salicylic acid is readily ionised and skin penetration is significantly affected by pH and other properties of the vehicle in which it is applied.

Ref: Harada K et al. (1993); Singh P & Roberts MS, 1994, and Leveque N. et al, 2004

In vivo data

Salicylic acid was applied daily over 14 days at 2% to the face and neck in different vehicles (a hydroalcoholic vehicle and a cream). The effect of facial skin condition (normal, acnegenic or photodamaged) on dermal delivery was also assessed. Subjects with acnegenic skin received topical treatment in a hydroalcoholic vehicle and those with aged or photodamaged skin were treated with salicylic acid in a cream.

Thirty-eight female volunteers, 18 to 65 years of age, were assigned to four treatment groups based on dermatologically assessed facial skin characteristics: two groups of subjects presented normal skin, one group presented mild to moderate acne, a fourth group was selected for evidence of moderate to severely aged or photo damaged skin, and a fifth group, which served as the reference control. The amount of the test material applied was approximately 1.25 to 1.5 g (25-30 mg salicylic acid). Subjects in the oral aspirin reference group received 81 mg of ASA with 8 ounces of water once daily. On day 15 of the study, all subjects were confined to the testing facility for 24 h. For the pharmacokinetic study, blood samples were collected on study days 0, 7, and 12; and for each day of analysis pre-dose

blood samples, as well as post-dose samples at 5, 15, 30, and 45 min, and 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 h have been collected and total urine was also collected to determine salicylate excretion. Table 6 shows the estimated steady-state pharmacokinetic parameters (C_{max}, T_{max}, terminal half-life and AUC) for salicylic acid in plasma after both topical application and oral aspirin administration.

Table 4. Steady-state pharmacokinetic parameters in subjects with normal, aged or acnegenic facial skin after topical application of 2% salicylic acid or in subjects receiving one daily oral dose of 81mg aspirin.

Skin Type	Vehicle	C_{max} (µg/L)	T_{max} (h)	Terminal Half-Life (h)	AUC (µg h/L)
Normal	Cream	293 ± 37	4.30 ± 0.40	5.83 ± 0.73	3108 ± 293
Aged	Cream	275 ± 58	4.11 ± 0.58	5.93 ± 0.83	2636 ± 302
Normal	Hydroalcoholic	525 ± 66[a]	1.89 ± 0.35 [a]	7.62 ± 0.82	4225 ± 425 [a]
Acnegenic	Hydroalcoholic	487 ± 41	1.67 ± 0.24	8.06 ± 1.12	3893 ± 329
N/A	Oral aspirin	5282 ± 457 [b]	0.71 ± 0.25 [b]	2.62 ± 0.46 [b]	22010 ± 3907 [b]

Data presented are mean ± SEM for n=10 (normal/cream) or n =9 (all others groups), a) Significantly different from 'normal' subjects ($p < 0.05$). b) Statistically different from all topical treatments. N/A = not applicable.

Data presented in Table 4 indicate that systemic exposure to salicylic acid from the use of a 2% topical product is approximately 15% of that following an oral administration of 81 mg aspirin. Relative bioavailability for topically applied salicylic acid among normal skin type subjects were 57.6 and 44 % for the hydroalcoholic and cream delivery vehicles, respectively.

According to the Applicant, the lower absorption of topically compared with orally administered salicylates observed in this study is in agreement with earlier reports by other investigators. Moreover, the slower half-life observed after topical compared with oral administration indicated that absorption is the rate limiting step for absorption of topically applied SA.

Ref: Davis et al (1997).

A single-centre, single-sequence, two-period crossover study has been performed to compare systemic exposures following facial application of a 30% salicylic acid cosmetic skin peel formulation applied for 5 min and an oral dose of 650 mg aspirin in nine subjects (2 healthy male and 7 non-pregnant females; age 35-53). For the topical application, a 30% SA /3% glycolic acid hydroethanolic skin peel solution was applied to the full face. The solution was kept on the face for 5 min, and was then removed with warm water using a gauze pad. After a 1-week washout period, the test subjects ingested two 325-mg buffered aspirin tablets with 8 oz. of water. Blood samples were collected at 0.5, 1, 1.5, 2, 2.5, 3.5, 6, 12, and 24 h. The pharmacokinetic parameters are shown in Table 5.

Table 5. Salicylic acid pharmacokinetic parameters in humans after topical skin peel application and oral aspirin

Parameter	Mean	Standard Deviation	Geometric Mean	Range
Topical 30% salicylic acid				
C_{max} (µg/ml)	0.81	0.32	0.77	0.43-1.57
T_{max} (h)	2.33	0.54	2.27	1.40-3.40
AUC_{0-n} (h. µg/ml)	6.22	2.56	5.76	3.01-11.40
$AUC_{0-\infty}$ (h. µg/ml)	6.39	2.58	5.97	3.32-11.65
λ_Z (h^{-1})	0.19	0.05	0.19	0.14-0.30
$T_{1/2}$ (h)	3.82	0.83	3.72	2.29-4.90
650 mg oral aspirin				
C_{max} (µg/ml)	56.40	14.20	54.8	34.3-77.5
T_{max} (h)	1.03	0.39	0.95	0.47-1.50
AUC_{0-n} (h. µg/ml)	319.50	104.80	304.20	86.7-464.1

$AUC_{0-\infty}$ (h. µg/ml)	319.90	105.10	304.50	186.8-464.4
λ_Z (h^{-1})	0.32	0.04	0.31	0.26-0.38
$T_{1/2}$ (h)	2.23	0.27	2.21	1.84-2.72

The mean (SD) maximum SA concentration (C_{max}) was 0.81 (0.32) µg/mL and 56.4 (14.2) µg/mL. The AUC-based safety margin ratio was 50:1. A depot effect was observed during topical application of the skin peel solution as the absorption of SA continued beyond the 5 min application period. Plasma SA C_{max} values were achieved from 1.4 to 3.5 h after topical application and from 0.5 to 1.5 h after oral aspirin.

Ref: Fung et al (2008)

According to the Applicant, the plasma concentrations in the Fung et al. study (30%; 5 min) were similar to that of a low concentration (2%) applied in a leave-on product to the same body surface area. Reviews of the safety of skin peeling agents have been performed by Bari et al., (2005) and Arif et al., (2015).

The percutaneous penetration of salicylic acid was studied after topical application to the forearm of human volunteers. The penetration through the skin was quantitated by measuring ^{14}C salicylic acid appearance in urine. In the experiments, a 4 µg/cm^2 solution of ^{14}C salicylic acid dissolved in acetone was applied to a 13 cm^2 area of the ventral forearm (n=17). The skin site was not protected, and the subjects were asked not to wash the area for 24 hours. The urinary excretion was then measured for 5 days. Total absorption of ^{14}C salicylic acid after topical application was **22.78%** ± 13.25 of the applied dose.

Ref: Feldmann & Maibach 1970

A study compares percutaneous absorption of salicylic acid in the isolated perfused porcine skin flap (IPPSF) system with that in humans *in vivo*. *In vivo* human study included five or six normal volunteer outpatients per group. ^{14}C-salicylic acid was dissolved in 50 µL ethanol and a dose of 39.7 µg/cm^2 was spread over a 10 cm^2 skin surface area, 24 hours, n=6, unoccluded. The subjects were instructed to collect all urine in the containers provided for that day and the subsequent 6 days. At 7 days after application the skin dosing site was tape-stripped 10 times for residual chemical. Percutaneous absorption was determined from the 14C-urinary excretion. The percutaneous absorption values were, for human skin and the isolated perfused porcine skin flap system **6.5%** ± 5.0 and **7.5%** ± 2.6, respectively.

Ref: Wester et al 1998

SCCS comment

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 estimates **a dermal absorption rate of 60 %** for salicylic acid. This value corresponds to the value of 60% absorption rate used by RAC (March 2016).

3.3.4.2 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 6.

Table 6. Data from a range of kinetics studies in rat and humans, comparing oral dose (in mg/kg/day) with reported C_{max} (µg/mL) values.

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

*median values from a range of observed values.

SCCS comments

The SCCS notes that to compare toxicokinetics between different species at least T_{max} associated with C_{max} is needed, along with half-life, AUC and clearance (ref: Miaskiewicz et al 1982). No robust data have been provided on salicylic acid kinetics for both species (rat and human) to enable comparison of the kinetic parameters. Therefore, the SCCS disagrees with the Applicant that a factor of 4 accounting for inter-species toxicokinetic differences is not required.

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).

3.3.4.3 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
SCCS agrees 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 7.

Table 7. 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

3.3.4.4 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.

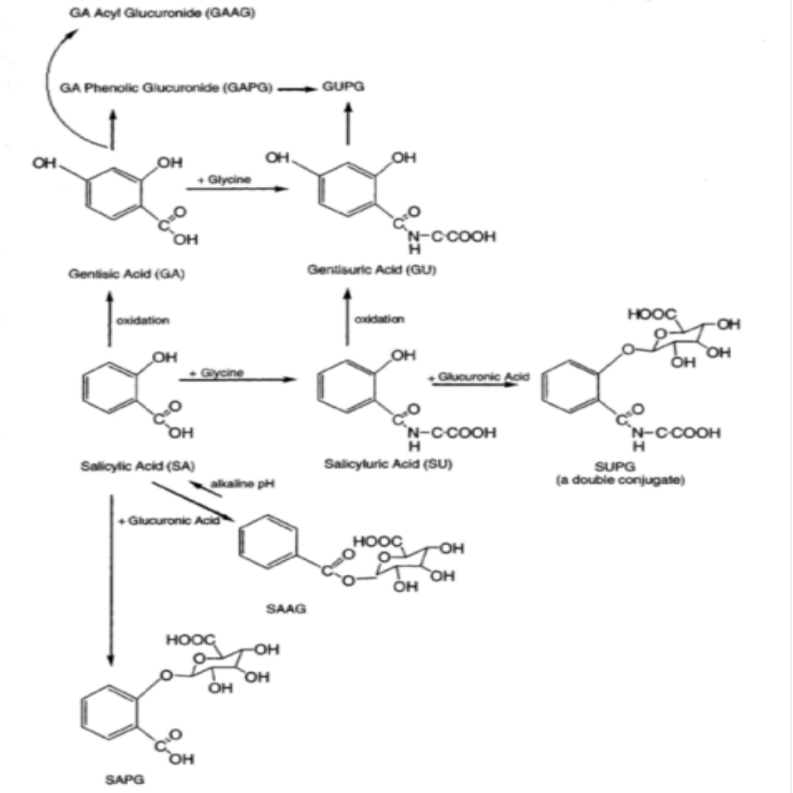


Figure 1. Scheme of the possible major metabolites of salicylic acid, Ref: CIR 2003 review

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

3.3.4.5 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.

3.3.5 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 and inhalation routes.

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

SCCNFP/0522/01/2002

- No systemic toxicity was noted from sub-chronic dermal toxicity studies conducted in the rabbit at the highest dosage of 120 mg/kg/day salicylic acid formulations; dermal irritation was the main recorded observation.
- The chronic oral toxicity study performed in rat with acetylsalicylic acid at a concentration of 200 mg/kg/day during 200 days showed no significant toxic effects compared to the control group at this dose level.
- In humans, toxic effects were reported when 10 g or more of salicylates were given orally in single dose or divided doses within a period of 12 to 24 hours. Children are more sensitive than adults to salicylates. Reye's syndrome in children is associated with the ingestion of acetylsalicylic acid.

Repeated dose dermal toxicity

Animal data

14-days sub-chronic percutaneous toxicity/irritation study

Guideline:	in accordance with IRDC SOPs
Species/strain:	female and male rabbits/ New Zealand
Group size:	4 groups of 3 male and 3 female rabbits
Test substance:	salicylic acid
Physical form:	liquid
Batch:	/
Purity:	/
Vehicle:	8% propylene glycol butyl ether in ethanol
Dose levels:	2 mL/kg day
Route:	topical application for 13 days
Administration:	once daily
GLP:	Yes (1987)
Observation period:	14 days
Study period:	8 April 1993- 8 July 1993

A 14-day sub-chronic percutaneous study was performed in four groups of 3 male and 3 female New Zealand White rabbits administered topically at 2 mL/kg/day of salicylic acid-containing solutions. The concentrations tested were 0%, 2%, 10% and 25% (corresponding to 0, 40, 200 and 500 mg/kg/day) of salicylic acid in a vehicle solution. After a 7-hour period of daily exposure, the application site was washed with water and dried.

Results
No deaths were observed during the study. Dose-related slight to marked erythema and oedema were noted for all dosage groups. Desquamation was most often noted in the 25 % salicylic acid group; fissuring of varying degree was observed in all dosage groups. Eschar was noted in the 10 % and 25 % dosage groups; exfoliation was noted on day 13 in a 25% dosage group. Atonia was predominantly observed in the animals treated with 10 and 25 % salicylic acid. These signs were generally noted between days 7 to 14. The changes in the body weights of animals were considered as not remarkable during the study. Concerning clinical findings, no visible abnormalities were noted at necropsy in any animal beyond the dermal irritation observed at the test sites. Under the experimental conditions adopted, the test articles were considered as dermal irritants by the investigators.

Ref: Procter & Gamble, 1993f

All animals survived after 28 days of treatment. There were no test article-related effects on appearance, behaviour, body weights or ophthalmoscopic examinations. Slight to marked erythema, desquamation, fissuring, oedema and slight to moderate atonia were noted at the site of application. The greatest severity for all findings, particularly scab formation, and desquamation, was observed most predominantly in the high-dose group and during the first 28 days of the treatment. The differences noted in body weight gain and in the body weight change values were not considered treatment-related. No test article-related toxicologic findings were detected in any haematological, biochemical or urological parameters. Serum salicylate was noted in all groups at 1 hour after dosing; the maximum levels occurred between 2.5 and 7 hours after dosing. A low incidence of trace to mild myocardial degeneration was observed in all treatment groups and the vehicle control group at the terminal sacrifice. However no dose-response relationship was retained with respect to either lesion incidence or severity. Under the experimental conditions adopted, the tested formulations were considered irritant.

Ref: Procter & Gamble, 1994&1994d;

Human data

Mild chronic salicylate intoxication is defined as salicylism and cases of this and metabolic acidosis have been described after topical application of salicylic acid. Salicylism can be severe and depends among various factors such as the age of the patient, the intensity of the skin damage, the concentration of salicylic acid in the formulation, and the surface of application. Salicylism symptoms can appear within a short period of treatment.
Ointments containing salicylic acid 3 to 6 % have caused nausea, dyspnoea, loss of hearing, confusion and hallucinations in three patients with extensive psoriasis. The cream was applied six times a day and combined with UV therapy. Salicylism symptoms developed in 4 days and were associated with significant salicylic acid plasma levels of 46 to 64 mg/100 mL. Symptoms disappeared rapidly after discontinuation of the ointment applications (Von Weiss & Lever, 1964). Another salicylism case was reported in a man with a widespread psoriasis that covered 80% of his body surface. The patient was treated with 10% topical salicylic acid on the first 2 days of hospitalization and 20% salicylic acid on the 3rd day on all involved areas of the skin. The serum level of salicylic acid was 93 mg/100 mL (Jabarah et al 1997).
The signs and symptoms of intoxication with salicylic acid vary according to the level of salicylic acid in the plasma. Symptoms may be present with levels of salicylic acid in the plasma as low as 10 mg/100 mL (Von Weiss & Lever, 1964). Ordinarily, symptoms that occur at levels below 35 mg/100 mL are quite mild. Salicylism can be acute or chronic and

usually develops when blood concentrations of salicylate are greater than 35 mg/mL (Madan and Levitt 2014). The most common early symptoms are difficulty in hearing, tinnitus, nausea, and hypernea. The clinical manifestations of intoxication with salicylic acid include gastrointestinal, respiratory, renal, metabolic, neural, and psychic disturbances. Systemic effects of topical salicylic acid are minimal when it is applied to intact skin in low to moderate doses. Conversely, with a break in the stratum corneum, measurable levels of salicylic acid can be found in the body even after application of low concentrations in hydrophilic ointment. Toxicity from the application of as little as 1% to 2% salicylic acid has been reported in neonates. (Madan and Levitt 2014).
In humans, severe salicylism by the dermal route is normally associated with a diseased state of the skin compounded by the multiple applications to large areas of the body. The application of salicylic acid to extensive areas, particularly in children, may involve a risk of toxicity from high levels of dermal absorption (Galea & Goel, 1989; Chiaretti et al., 1997). Children are particularly susceptible.

Repeated dose inhalation toxicity

/

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

SCCS comment
No robust data have been provided to enable proper assessment of the repeated dose toxicity by inhalation. Since the Applicant does not intend to use salicylic acid in spray/aerosol products, inhalation toxicity is not considered in this Opinion.

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

Animal data

Sub-chronic dose dermal toxicity
Two 91-day studies were performed in New Zealand White rabbits in order to assess the sub-chronic cutaneous and systemic toxicity of two cleansing formulations containing 0.5% salicylic acid (Procter & Gamble 1990a, 1990b). 2 mL/kg of the test article, corresponding to 10 mg/kg, was applied to intact skin of the rabbits, with 7 hours daily exposure, 5 times a week. The neat or 50% w/v in distilled water diluted product was applied. Controls were treated with distilled water. The following observations were performed during both studies: clinical data (food consumption, faeces, behaviour), daily dermal irritation observations, body weights records, mean haematology values (neutrophil, monocytes, basophil, leucocytes and lymphocytes counts), gross pathology findings (organ lesions, skin lesions), organ weights and histopathology findings. No deaths were observed during the study. No statistical differences were found in mean body weight or in organ weight. Transient dermal irritation including erythema, oedema, atonia, desquamation and fissuring, varying up to moderate intensity and transient slight to moderate desquamation were observed and considered related to the treatment. No systemic toxicity was observed as confirmed by the clinical evaluation, the clinical chemistry, haematological and histopathological examinations. The tested products were considered slightly and transiently irritating to the skin when applied neat or at a concentration of 50% w/v to the intact rabbit skin.

A 91-day sub-chronic cutaneous toxicity study was performed in New Zealand White rabbits treated with cleansing formulations containing 0.5% to 6% of salicylic acid in propylene glycol butyl ether/ethanol (vehicle), corresponding to topical doses of 10, 20, 40 or 120 mg/kg of salicylic acid (Procter & Gamble, 1994, 1994d). Two controls group were included, one with untreated animals, one with vehicle treated animals. The tested product was applied once daily during a seven hour period, five days per week at a dosage volume of 2

ml/kg to the intact skin of the animals. A first 28-day period was followed by an interim sacrifice of five animals per group; the remaining animals continued to be observed until the end of the 91-day treatment. The observations recorded during the study were: clinical signs, dermal irritation, body weights, opthalmoscopic examinations, haematological parameters (haematocrit, haemoglobin, erythrocyte/leucocyte and platelet counts, coagulation times), biochemical parameters (ASAT, ALAT, alkaline phosphatase, glucose, urea nitrogen, bilirubin, cholesterol, albumin, globulin, total protein, creatinine, electrolytes, phosphorus, calcium), urological parameters (volume, specific gravity), serum salicylate analysis, macroscopic and microscopic examinations, organ weights.

All animals survived after 91 days of treatment. There were no test article-related effects on appearance, behaviour, body weights or ophthalmoscopic examinations. Slight to marked erythema, desquamation, fissuring, oedema and slight to moderate atonia were noted at the site of application. After 91 days of treatment, the severity and frequency of hyperkeratosis, acanthosis and dermal inflammation were greatest in the high-dose group. The differences noted in body weight gain and in the body weight change values were not considered treatment-related. No test article-related toxicologic findings were detected in any haematological, biochemical or urological parameters. Serum salicylate was noted in all groups at 1 hour after dosing; the maximum levels occurred between 2.5 and 7 hours after dosing. A low incidence of trace to mild myocardial degeneration was observed in all treatment groups and the vehicle control group at the terminal sacrifice. However no dose-response relationship was retained with respect to either lesion incidence or severity. Under the experimental conditions adopted, the tested formulations were considered irritant.

3.3.5.3 Chronic (> 12 months) toxicity

No chronic data have been submitted.

SCCS overall conclusion of repeated dose toxicity
SCCS considers that the assessment from SCCNFP (2002) concerning the toxicity of salicylic acid after repeated exposure remains valid.
In particular:
- No systemic toxicity was noted from sub-chronic dermal toxicity studies conducted in the rabbit at the highest dosage of 120 mg/kg/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 in diseased skin. Children are more sensitive than adults to develop salicylism, thus the topical application of salicylic acid may involve a risk of toxicity. Reye's syndrome in children is associated with the use of acetylsalicylic acid during a viral illness.

3.3.6 Reproductive toxicity

3.3.6.1 Fertility and reproduction 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 8. 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.

SCCS comments
SCCS agrees that salicylic acid should not be classified as a reproductive toxicant for the fertility endpoints.

3.3.6.2 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 9.

Table 9. 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 0.1% (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/day relating to the most sensitive toxic endpoint i.e. teratogenicity in the rat as the most sensitive species.

Tanaka et al., 1973 a

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 GD 11 day. 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/d, 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/d) for maternal toxicity and 0.1% (75 mg/kg bw/d) for developmental toxicity.

Tanaka et al., 1973 b

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 groups 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 and the NOAEL (development): 75 mg/kg were identified.

Taken from RAC (March 2016)

The results of the studies demonstrated that salicylic acid has an embryo-/foetotoxic effect in **rats** with dose-dependent growth delays, fetal 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
SCCS 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, SCCS uses the developmental NOAEL of 0.1% (75 mg/kg bw/day) derived from Tanaka et al. (1973a). The developmental effects observed in this study are the most sensitive effects after repeated exposure to salicylic acid. This is also in agreement with the previous SCCNFP Opinion (2002) and is also supported by Tanaka et al. (1973b).

3.3.7 Mutagenicity / genotoxicity

3.3.7.1 Mutagenicity / genotoxicity in vitro

From SCCNFP/0522/01/2002

Studies have been performed in order to assess the mutagenic/genotoxic potential of salicylic acid and acetylsalicylic acid. These results are summarised in the following tables 10, 11 and 12.

Table 10. *In vitro* mutagenicity in Bacteria and Yeast

Methods	**Test article**	**Metabolic activation**	**Results**	**Reference**
Ames tests	• salicylic acid acetylsalicylic acid 500 µg/mL	With without	negative	McCann, 1975 Kawachi, 1979
Ames tests	salicylic acid 3 to 8 10^{-5} M	No data available	negative	McCann J., 1975
Bacillus subtilis assay	salicylic acid acetylsalicylic acid	Without	positive	Kawachi T., 1979

Table 11. *In vitro* mammalian clastogenicity

Methods	**Test article**	**Metabolic activation**	**Results**	**Reference**
Cultured CHO cells (*3 hour exposure*)	salicylic acid 1.5 to 25 mg/mL	With and without	negative	Stich HF, 1981

Chinese hamster lung cells (*48 hour exposure*)	salicylic acid 1.0 and 1.25 mg/mL	Without	positive	Ishidate MR, 1983

The *in vitro* studies for salicylic acid and for acetylsalicylic acid that were submitted include results of experiments whose methodology is not reported: they are mainly represented by a list of results related to many chemicals. The results reported do not comply with the guidelines defined by the SCCNFP.

Table 12. *In vivo* clastogenicity/mutagenicity

Method	**Test article**	**Animal species**	**Results**	**Reference**
Drosophila sex-linked recessive lethal assay	Acetylsalicylic acid 10 mM	*Drosophila Melanogaster*	negative	King MT 1979

This submission

A range of studies have been performed in order to assess the mutagenic/genotoxic potential of salicylic acid. These results are summarised in the following sections.

Mutagenicity / genotoxicity *in vitro*
Available *in vitro* data for mutagenicity and genotoxicity for salicylic acid and sodium salicylate are presented in Tables 13 and 14.

Table 13. Bacteria and yeast assays for salicylic acid and sodium salicylate

Methods	**Test Article**	**Metabolic activation**	**Results**	**Reference**
Ames test: TA100, TA98, TA1535, TA1537.	Salicylic acid	With and without	negative	McCann et al 1975
Ames TA98	Salicylic acid 2.5 to 10 mg/mL	With and without	negative	San & Chan, 1987
Ames	Salicylic acid 0.1 mg/disc	With and without	negative	Kuboyama & Fujii, 1992
B subtilis rec assay H17(Rec^+0 and M45(Rec^-)	Salicylic acid (5mg/disc)	NR	positive	Kuboyama & Fujii, 1992
Ames: TA98, TA100.	Sodium salicylate	With and without	negative	Kuboyama & Fujii, 1992
B subtilis rec assay H17(Rec^+0 and M45(Rec^-)	Sodium salicylate 5mg/disc	NR	negative	Kuboyama & Fujii, 1992
OECD guideline 471 Ames: TA1535, TA1537, TA98 and TA100	Salicylic acid 1.22 to 5000	With and without	negative	(Ministry of Labour/Japan, 2000) Reliability 1, Key

and WP2uvrA/pKM101 of *E. coli*	µg/plate			study in REACH dossier.

Applicant's conclusion: On the balance of evidence and giving the OECD guideline test study the most weight, salicylic acid is not genotoxic in bacterial assays.

Table 14. *In vitro* mammalian clastogenicity and gene mutation

Methods	**Test Article**	**Metabolic activation**	**Results**	**Reference**
Chinese Hamster Ovary Cells (cultured for 3 hours) equivalent to OECD guideline 473	Salicylic acid 1.5 to 25 mg/mL	With and without	negative	Stich et al 1981
Chinese Hamster Lung Cells (cultured for 48 hours)	Salicylic acid 1 and 1.25 mg/mL	Without	positive	Ishidate, 1983
OECD Guideline 476 Mouse lymphoma assay	Salicylic acid 87.5, 175.0, 350.0, 1400.0 µg/mL	With and without (4h); without (24h)	Salicylic acid did not induce mutations	RCC, 2008b; key study in REACH dossier.

Applicant's conclusion: In an OECD guideline 476 study, salicylic acid did not induce mutations. Salicylic acid also did not lead to chromosome aberrations in an OECD guideline 473 equivalent study.

3.3.7.2 Mutagenicity / genotoxicity in vivo

From SCCNFP/0522/01/2002

One study by Giri et al. (1996) has investigated mutagenicity / genotoxicity *in vivo*, the findings of which are illustrated in Table 15.

Table 15. Summary of results on chromosomal damage by Giri et al. 1996.

Methods	**Test Article**	**Results**
Sister chromatid exchange (SCE) assay*, n=5 Swiss albino mice	25, 50 or 100 mg/kg salicylic acid in DMSO, injected intraperitoneally. Oral dosing with 350 mg/kg salicylic acid in gum acacia and distilled water.	Salicylic acid did not induce SCE
Chromosome aberration assay**, n =4 or 5 Swiss albino mice	50, 100 or 200 mg/kg salicylic acid in DMSO (n=4), injected intraperitoneally. Oral dosing with 350 mg/kg salicylic acid in gum acacia and distilled water (n =5)	No increase in chromosomal aberration. A significant increase in mitotic index was seen only with the lowest dose (50 mg/kg) *i.p.* and the oral dose.
Sister chromatid	25, 50 or 100 mg/kg sodium	Salicylic acid did not induce

exchange (SCE) assay*, n=5 Swiss albino mice	salicylate in DMSO, injected intraperitoneally. Oral dosing with 350 mg/kg salicylic acid in gum acacia and distilled water.	SCE
Chromosome aberration assay**, n =4 or 5 Swiss albino mice	50, 100 or 200 mg/kg sodium salicylate in DMSO (n=4), injected intraperitoneally. Oral dosing with 350 mg/kg SA in gum acacia and distilled water (n =5)	A significant increase in chromosomal aberrations was seen with 200 mg/kg *i.p.* and the oral dose.
*IP and oral dosing studies taken together, these studies are acceptable, satisfying the requirement of Test Guideline OPPTS870.5915 (*In vivo* Sister Chromatid Exchange Assay). **These tests were carried out according to a scientifically acceptable standard which is similar to EPA OPPTS 870.5915. Although each of these key studies had minor deviations from current guidelines, IP and oral dosing taken together, they are considered as acceptable, satisfying the requirement for Test Guideline OECD 475 (Mammalian Bone Marrow Chromosomal Aberration Test).		

The study by Giri et al 1996, is the key *in vivo* study for mutagenicity cited in the REACH dossier for salicylic acid. Salicylic acid neither induced sister chromatid exchanges (SCE) nor chromosomal aberrations (CA) in *i.p.* or oral studies *in vivo* in mice. This indicates that salicylic acid is not genotoxic in the bone marrow cells of mice.

Applicants' conclusion: The overall conclusion from the weight of evidence *in vitro* and *in vivo* is that salicylic acid is not mutagenic/genotoxic.

SCCS evaluation studies on salicylic acid submitted by the Applicant in SCCNFP/0522/01/2002:

1. Gene mutation assays using bacteria

Guideline: /
Test system: Salmonella typhimurium strains TA100, TA1535, TA98, TA1537
Escherichia coli strain WP2*uvr*A/pKM101
Replicates: Two experiments, duplicate plates
Test substance: Salicylic acid
Batch: GE01 (Tokyo Kasei Kogyo Co, Ltd.)
Purity: >99.5%

Concentrations: Experiment 1:
±S9 mix: all *S. typhimurium* strains and *E. coli*: 0, 1.22, 4.88, 19.5, 78.1, 313, 1250, 5000 µg/plate

Experiment 2:
±S9 mix: all *S. typhimurium* strains: 0, 9.77, 19.5, 39.1, 78.1, 156, 313, 625, 1250, 2500, 5000 µg/plate
±S9 mix: *E. coli* strain: 0, 39.1, 78.1, 156, 313, 625, 1250, 2500, 5000 µg/plate

Vehicles: DMSO

Positive Controls: -S9 mix: 2-aminofluorene (AF-2) for TA100, TA98 and WP2*uvr*A/pKM101; sodium azide (NaN_3) for TA1535; 9-aminoacridine (9-AA) for TA1537
+S9 mix: 2-aminoanthracene (2-AA): for all *S. typhimurium* and WP2*uvr*A/pKM101 strains

Negative controls: Vehicle control (DMSO)
GLP: /
Study period: /

Material and methods
Salicylic acid was tested for mutagenicity in the reverse mutation assay with and without metabolic activation in *S. typhimurium* strains TA100, TA1535, TA98, TA1537, and *Escherichia coli* strain WP2*uvr*A/pKM101, in duplicates, in two separate experiments, both with and without the addition of a S9-mix system (no data on the metabolic system).

Results
There are no data on a preliminary toxicity assay.

Experiment 1
In this experiment, the dose levels tested were 1.22, 4.88, 19.5, 78.1, 313, 1250, 5000 µg per plate in the presence and absence of S9 activation system. No positive mutagenic responses were observed with any of the tester strains in either the presence or absence of S9 activation.
Toxicity was observed beginning at 78.1 µg/plate (TA100 strain), 313 µg/plate (TA1535, TA98 or TA1357 strains) or 1250 µg/plate (*E. coli* WP2*uvr*A/pKM101).

Experiment 2
In this experiment, the dose levels tested were 9.77, 19.5, 39.1, 78.1, 156, 313, 625, 1250, 2500, 5000 µg per plate for all *S. typhimurium* strains and 39.1, 78.1, 156, 313, 625, 1250, 2500, 5000 µg/plate for *E. coli* strain, in the presence and absence of S9 activation system. No positive mutagenic responses were observed with any of the tester strains in either the presence or absence of S9 activation.
Toxicity was observed beginning at 78.1 µg/plate (TA100 and TA1537 strains), 156 µg/plate (TA98 strain), 313 µg/plate (TA1535 strain) or 2500 µg/plate (*E. coli* WP2*uvr*A/pKM101).

Ref.: Ministry of Labour/Japan, 2000

SCCS comment
The results of the study are presented in the pdf file provided to the SCCS in the form of two tables and indicate no mutagenic effect of salicylic acid in the absence or presence of S9 mix in all bacterial strains used.
The SCCS noted that from the information provided it is not certain if the study was performed under GLP standard. Furthermore, it is not clear who performed the study or when it was performed, what concentrations of the positive control substances were used and what the historical values of revertants number for control and positive substances were.

Other studies submitted by the Applicant and available from the open literature are presented in Table 16. They are of limited value for hazard identification.

Table 16. Studies on gene mutations of salicylic acid in bacteria

	Type of test	Tester strain	Test concentrations	S9-mix	Result	Reference	SCCS remarks
1.	Ames test	S. typhimurium: TA100, TA98,	≤ 500 nM/plate	With and without	negative	McCann et al. 1975	- non-GLP study

		TA1535, TA1537					
2.	Ames test	S. typhimurium: TA98	2.5, 5, 10 mg/mL	Without	negative	San & Chan, 1987	- non-GLP study - limited value
3	Ames test Pre-incubation for 30 min	S. typhimurium: TA98, TA100	0.1 mg/plate	With and without	positive	Kuboyama & Fujii, 1992	- non-GLP study - salicylic acid tested positive with rat S9, but sodium salicylate negative; - only one concentration of salicylic acid and two bacterial strains were tested - no TA98 revertants after the exposure to salicylic acid –S9 (probably due to excessive cytotoxicity) - limited value
4	Rec-assay	Bacillus subtilis strains H17 (Rec+) and M45 (Rec-)	1, 2, 3, 4, 5 mg/disc	-	positive	Kuboyama & Fujii, 1992	- Non-GLP study - salicylic acid tested positive (evident concentration-effect relationship) but sodium salicylate was tested negative - Rec-assay is not validated OECD test - limited value

2. *In vitro* gene mutations in mammalian cells

Guideline: OECD 476 (adopted July 21, 1997)
Test system: L5178Y mouse lymphoma cells (Thymidine Kinase Locus $Tk^{+/-}$)
Replicates: Two independent experiments, each two parallel cultures
Test substance: Salicylic acid pharmaceutical grade; CAS: 69-72-7
Batch: RAS0725500 made on Sept. 12th 2007 (purity: >99%)

Concentrations: Preliminary test:
+S9 mix (4 h exposure) and -S9 mix (4 and 24 h exposure): 7.97, 15.94, 31.88, 63.75, 127.5, 255, 510, 1020, 2040 µg/mL

Main test:
Experiment I:
±S9 mix (4 h exposure): 43.8, 87.5, 175, 350, 700, 1400 µg/mL
Experiment II:
-S9 mix (24 h exposure): 43.8, 87.5, 175, 350, 700, 1400 µg/mL
Vehicle controls: deionised water
Positive Controls: -S9 mix: methyl methanesulfonate (MMS), 19.5 µg/mL
+S9 mix: cyclophosphamide (CP), 3 and 4.5 µg/mL
GLP: Yes
Study period: May 2008 – Aug 2008

Material and methods

The *in vitro* mammalian cell gene mutation assay was conducted to investigate the potential of salicylic acid dissolved in water to induce gene mutations at the $TK^{+/-}$ locus of the L5178Y mouse lymphoma cell line.
Prior to the main study, a preliminary toxicity test was performed on cell cultures using a 4-hour exposure time both with and without metabolic activation (S9, liver post mitochondrial supernatant of rats treated with phenobarbital/β-naphthoflavone) and using a 24-hour exposure without S9-mix. The dose range used was 10.9 to 1400 µg/mL for all three exposure groups. The main assay was performed in two independent experiments, using

two parallel cultures each. The first main experiment was performed with and without liver microsomal activation and a treatment period of 4 h. The second experiment was solely performed in the absence of metabolic activation with a treatment period of 24 hours.

Results

In the **pre-test**, following 4 h (±S9-mix). no relevant toxic effects leading to RSG (% Relative Survival Growth) values below 50% were observed up to the maximum concentration (1400 µg/mL, i.e. 10 mM). After continuous treatment (24 hours), a relevant toxic effect occurred at the maximum concentration of 1400 µg/mL. The test medium was checked for precipitation at the end of each treatment period (4 or 24 hours) before the test item was removed. No precipitation occurred with and without metabolic activation.

In the **first experiment,** no relevant toxic effects indicated by a relative cloning efficiency 1 or a relative total growth of less than 50% of survival were observed up to the maximum concentration with and without metabolic activation. In the **second experiment** (24 h treatment solely without metabolic activation) relevant toxic effects were noted at 700 µg/mL and above. The data at the maximum concentration of 1400 µg/mL are considered valid even though the relative total growth fell short of the lower limit of 10 %. The corresponding relative cloning efficiency 1 however, was in a toxic but fully acceptable range. The recommended toxic range of approximately 10 – 20% of survival or RTG was covered in experiment II.

No substantial and reproducible dose dependent increase of the mutation frequency was observed in both main experiments. The threshold of 126 above the corresponding solvent control was not reached at any of the test points. Two minor increases exceeding the historical control range occurred in the second experiment following 24 h exposure at 700 and 1400 µg/mL in culture I. However, no comparable increase of the mutation frequency was noted in the parallel culture under identical conditions. A linear regression analysis (least squares) was performed to assess a possible dose dependent increase of mutant frequencies using SYSTAT® statistics software. A significant dose dependent trend of the mutation frequency indicated by a probability value of <0.05 was solely determined in the first culture of experiment II. However, a certain increase of the mutation frequency is common at cytotoxic concentrations and the threshold of 126 above the corresponding negative control was not reached. Therefore, the isolated significant trend described above was considered as biologically irrelevant.

Conclusion

In conclusion it can be stated that under the experimental conditions reported the test item did not induce mutations in the mouse lymphoma thymidine kinase locus assay using the cell line L5178Y in the absence and presence of metabolic activation.

Ref: RCC, 2008b

SCCS comment

In the first culture of the second experiment a significant trend (p=0.001) was observed, 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 should be regarded as not biologically meaningful. Hence, the study indicates no mutagenic effect of salicylic acid in the mouse lymphoma assay.

3. *In vitro* chromosomal aberrations

SCCS comment

1. Only one study on chromosomal aberrations *in vitro* with salicylic acid is available in the open literature and which was 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 is negative. However, the SCCS emphasizes that the study

is not GLP-compliant, and is of limited value 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 is in contrast to 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).

2. In the second study, i.e. Ishidate et al. (1983) on chromosomal aberration test *in vitro* a Chinese hamster fibroblast cells were exposed to 1 and 1.25 mg/mL salicylic acid for 48h. Although, the result was positive as claimed by the Applicant, the original publication was not provided for verification in the submission II.

4. *In vivo* chromosomal aberrations

SCCS comment
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
The SCCS comments are based on available, i.e. previously and currently 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 salicylic acid can be considered to pose no genotoxic hazard.

3.3.8 Carcinogenicity

From SCCNFP/0522/01/2002

Animal data

- Salicylic acid was tested as part of a skin tumour promotion study using uninitiated mouse skin. Salicylic acid 20% in a dioxane solution was applied topically (one drop of about 25 µl) to 31 female "Sutter" mice, 2-3 months of age, treated twice weekly for 12 weeks. There were no deaths or papillomas throughout the study. However, as no post-mortem examination was performed at the end of the treatment period, the results were considered of limited value for the evaluation of possible carcinogenic properties of the substance.

  Ref.: Boutwell, 1959
- Carcinogenicity studies have been performed to assess the carcinogenic potential of acetylsalicylic acid in mice at 1 and 5% and in rats at 0.25% and 2% in drinking water. The results were negative on both studies. Considering these results, salicylic acid, a metabolite of acetylsalicylic acid, was considered to be devoid of such a potential.

  Ref.: Odashima, 1979
- Salicylic acid is the main metabolite of acetylsalicylic acid (aspirin) and there is sufficient evidence in animal models that acetylsalicylic acid prevents cancer.

  Ref.: Vaino, 1997

Human data
No data are available for salicylic acid.

- Salicylic acid is the main metabolites of aspirin (acetylsalicylic acid). Epidemiological studies have shown that acetylsalicylic acid reduces the risk of colorectal cancer.

  Ref.: Vaino, 1997
- Thun et al. reported that chronic use of acetylsalicylic acid decreases susceptibility to bowel cancer.

  Ref.: La Du, 1971
- In another report, salicylic acid has been shown to interact with phenolsulphotransferase and it has been proposed that this could be one of the pathways by which acetylsalicylic acid reduces cancer risk.

  Ref.: Levy, 1972
- Recently it has also been reported that users of acetylsalicylic acid had a moderately reduced risk of gastric cancer.

  Ref.: Akre, 2001

Hazard evaluation
Only one animal study on the carcinogenicity of salicylic acid has been found. The study is of limited value for evaluation of possible carcinogenic properties of the substance. However, it has been found both in epidemiological studies and in animal experiments that acetylsalicylic acid reduces skin cancer risk. Since salicylic acid is the main metabolite of acetylsalicylic acid, the cancer preventive effect of acetylsalicylic acid may be caused by its metabolite salicylic acid.

Ref: Boutwell and Bosch, 1959

This submission

Animal data
Salicylic acid was tested as part of a skin tumour promotion study using uninitiated mouse skin (Boutwell & Bosch, 1959). Salicylic acid 20% in a dioxane solution was applied topically (one drop of about 25 µL) to 31 female "Sutter" mice, 2-3 months of age, treated twice weekly for 12 weeks. There were no deaths or papillomas throughout the study. However, as no post-mortem examination was performed at the end of the treatment period, the results were considered of limited value for evaluation of possible carcinogenic properties of the substance.
There are no oral carcinogenicity studies on salicylic acid. Carcinogenicity studies have been performed to assess the carcinogenic potential of acetylsalicylic acid in mice at 1 and 5% and in rats at 0.25% and 2% in drinking water (Odashima et al 1979). The results showed acetylsalicylic acid was not carcinogenic in both studies. Considering these results, salicylic acid, a major metabolite of acetylsalicylic acid, is also considered not to be carcinogen. Salicylic acid is the main metabolite of acetylsalicylic acid (aspirin) and there is evidence in animal models that acetylsalicylic acid helps to prevent cancer (Ma et al., 2017).

Human data
Salicylic acid is the main metabolite of aspirin (acetylsalicylic acid). Epidemiological studies have shown that acetylsalicylic acid can reduce the risk of cancer (Ma et al 2017). Thun et al. (1991) reported that chronic use of acetylsalicylic acid decreases susceptibility to bowel cancer. It has also been reported that users of acetylsalicylic acid had a moderately reduced risk of gastric cancer (Akre et al 2001).

Applicant's conclusion: There are no reports of aspirin or salicylic acid acting as a carcinogen. Reported studies discuss the potential anticancer properties of these substances.

Overall SCCS comment on carcinogenicity
No additional studies have been provided by the Applicant in submission II. However, 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.

3.3.9 Photo-induced toxicity

3.3.9.1 Phototoxicity / photo-irritation and photosensitisation

In the previous SCCNFP Opinion, no photo-induced toxicity data have been provided.

This submission
Salicylic acid has been investigated for phototoxic and photosensitising potential, as outlined in the Table below.

Table 17. Phototoxicity studies for salicylic acid

Method	Observations	Reference
5 albino outbred ICR mice Days 0 and 1: 50 µL 50% salicylic acid in acetone applied to clipped abdominal skin, and site irradiated for 2.5 h at 15 cm. Day 5: 50 µL 25% salicylic acid in alcohol applied to either side of the pinna, and site irradiated for 2.5 h at 15 cm.	The degree of the sensitivity was assessed by measuring the ear thickness 24 hours after challenge. Ear thickness was not increased after 24 h. Not photosensitising	Miyachi & Takigawa, 1983
2% salicylic acid in a cream; 2 male and 5 female human subjects. 0.2 g cream applied to lower back. Irradiated with UVA 24 h after application.	No phototoxic potential.	Ivy Laboratories (1993a)
2% salicylic acid in a cream: 8 male and 17 female human subjects. 100 mg applied to lower back (25 mg/cm^2) for 24 h. Solar simulator applied to treated area. 48 hrs later process was repeated. Induction phase, twice weekly exposures over 3 weeks. Challenge patch was applied 10 days after last induction.	Not photosensitising.	Ivy Laboratories (1993b)
2% salicylic acid in gel; 1 male, 9 female human subjects. 0.2g volar forearms. One forearm exposed to UVA 24 h after application.	No phototoxic potential	HRL Inc (1993c)
2% salicylic acid in gel; 4 male and 24 female human subjects. 0.2g volar forearms. One forearm exposed to UVA 24 h after application. Induction phase, twice weekly exposures over 3 weeks. 0.2 g volar forearms. UVA (15 min) and UVB irradiated (135 sec).	Not photosensitising	HRL Inc (1993d)
2% salicylic acid in gel; 2 male and 8 female human subjects. 0.2 g volar forearms. One forearm exposed to UVA 24 h after application. Induction phase, twice weekly exposures over 3 weeks. 0.2 g volar forearms. UVA (17 min) and UVB irradiated (120 sec).	Not photosensitising	HRL Inc (1997b)
2% salicylic acid in gel; 5 male and 23 female human subjects. 0.2 g volar	Not photosensitising	HRL Inc (1997c)

forearms. One forearm exposed to UVA 24h after application. Induction phase, twice weekly exposures over 3 weeks. 0.2 g volar forearms. UVA (17 min) and UVB irradiated (120 sec).		
2 or 4% salicylic acid in cream applied in the morning; 18 male mice, 18 female mice. In the afternoon, skin was exposed to synthetic solar light for four hours, 5 days per week, 40 weeks.	Not photocarcinogenic; photoprotective	National Toxicology Program, 2007

Applicants' conclusion: Salicylic acid is not phototoxic.

SCCS comment
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.

3.3.9.2 Photomutagenicity / photoclastogenicity

/

3.3.10 Special Investigations

Although, the literature search performed by the SCCS has shown some evidence that some salicylates, such as homosalate, may have endocrine properties, only a few studies have investigated the endocrine properties of salicylic acid itself.

Salicylic acid is not listed as an endocrine disrupter candidate in the priority list published in 2007 by the European Commission. This working list of chemicals was compiled from lists of "suspected endocrine disruptors" published by various organisations, supplemented by a search of the scientific literature to identify reports and papers describing effects suggestive of endocrine disrupting activity for specific chemicals.
(http://ec.europa.eu/environment/chemicals/endocrine/strategy/substances_en.htm).

Salicylic acid has also not been identified as an endocrine disrupter by the Pesticide Action Network Pesticide DataBase.
Ref: http://www.pesticideinfo.org/Docs/ref_toxicity5.html#EDSummary

In a newly published report from the Danish Centre on Endocrine Disrupters researchers from the National Food Institute, Technical University of Denmark, and the University of Southern Denmark have evaluated that there is solid scientific evidence that salicylic acid is an endocrine disruptor. In this report different derivatives of Salicylic acid have been used, e.g. acetylsalicylic acid (Aspirin), sodium salicylate and methyl salicylate.
Ref: http://cend.dk/files/DK_ED-list-final_appendix1_2018.pdf

SCCS is also aware that in the framework of the Biocide regulation, specific tests are currently on-going to assess whether salicylic acid has endocrine disrupting

properties. Depending on the outcome of these tests, the potential endocrine disrupting properties of salicylic acid in cosmetics may need to be considered.

3.4 EXPOSURE ASSESSMENT

3.4.1 Single and aggregate exposure to salicylic acid as cosmetic ingredient

The Applicant used three different scenarios and approaches for the consumer exposure assessments, two of which (A and B) are further described and considered in this Opinion. Both scenarios assume 100% occurrence of salicylic acid in all cosmetics products used by an individual in a day. The product concentrations used in both approaches are based on the current legislation that allows SA for use as preservative up to 0.5% and in other applications up to 2 or 3% (Table 18). They are further based on an industry survey provided by the Applicant on concentrations actually used to date (see Appendix). The concentrations used in the assessments are for all products larger than the maximal concentrations found in the survey. In the assessment of the Applicant, all scenarios also factor in a value of 50% for skin penetration of the dermally applied substance from all products, which, according to the Applicant, is likely to be a significant overestimate for most products at neutral pH.
There are literature reports about the use of salicylic acid in toothpaste and mouthwash, however, according to the survey presented by the Applicant, it is not used in any oral products, and therefore not considered in the exposure assessments. Furthermore, the Applicant did not consider any sprayable products for the exposure assessment. Values for the % level of salicylic acid in each of the 17 product types, which were used in the exposure assessment, are presented in Table 18.

Table 18. Salicylic acid concentration values used in the exposure assessment

Product Type (Crème C&C)	Concentration (% w/w)
Shower gel	2
Liquid hand soap	2
Shampoo	3
Rinse-off conditioner	3
Hair styling	2
Body lotion (mass market, prestige, other)	0.5
Face moisturiser	2*
Hand cream	2
Liquid make-up foundation	2
Make-up remover	2
Eye shadow	0.5
Mascara	0.5
Eye pencil	0.5
Lipstick	0.5
Deodorant roll-on	0.5

Deodorant aerosol spray (ethanol-based)	0**
Deodorant spray	0**
Toothpaste	0***
Mouthwash	0***

* For face moisturiser products in Scenario 1, the concentration data and frequency of use of face cream products has been used.
** For both the deterministic and the probabilistic exposure assessment, these products have been excluded, since the Applicant does not intend to use salicylic acid in spray/aerosol products and claims that spray products containing salicylic acid do not exist on the European market.
*** For both the deterministic and the probabilistic exposure assessment, these oral products have been excluded, since the Applicant stated that SA is currently not used in such products on the European market.

The survey of SA use in cosmetic products on the European market also reports the number of formulations with SA on the European market in relation to the total number of respective formulations (see Table 19). This information was NOT used in the approaches A and B that have been selected for SCCS conclusions. It is included in this opinion only for illustrating that to date the assumption of 100% occurrence in cosmetics products in approaches A and B with reference to a whole population is highly conservative. However, considering brand loyalty and possible formulation change in the future, the SCCS considered only the conservative scenarios A and B appropriate for risk assessment.

Table 19. Occurrence (%) of salicylic acid in cosmetic formulations on the European market calculated from tonnage data.

Product Type (Creme C&C)	Formulations total	Formulations with SA[1]	Occurrence (fraction)
Showergel	2985	386	0.121
Liquid hand soap	409	33	1.436
Shampoo	2692	575	6.754
Rinse-off conditioner	2071	39	7.516
Hair styling	2311	20	0.019
Body lotion	3200	61	0.013
Face moisturizer	5218	432	0.958
Hand cream	641	8	0.220
Liquid make-up foundation	8336	194	0.274
Make-up remover	1454	163	0.710
Eye shadow	6140	4	<0.001
Mascara	906	10[2]	0.009[2]
Eye pencil	1599	6[2]	0.029[2]
Lipstick	9751	4	0.001

Deodorant roll-on	1374	16	<0.001
Mouthwash	68	0	0
Toothpaste	517	0	0

[1]Except mascara, eye pencil
[2]No salicylic acid in product type. Refers to formulations containing magnesium salicylate

A) **Deterministic approach according to the SCCS Notes of Guidance, 2016:** This consumer exposure assessment uses maximum allowed % levels of salicylic acid in 17 cosmetic product types (including a calculation of aggregate exposure) according to the deterministic additive methods referred to in the SCCS Notes of Guidance 9th revision (April 2016). This method assumes that everybody in the population uses all the products each day. This is a highly precautionary scenario.
In the SCCS Notes of Guidance 9th revision (April 2016), values are provided for the amount of product exposure an individual consumer could experience daily, for 17 different cosmetic products, and as calculated in mg/kg bw/day.
According to the Applicant, the cosmetics industry does not currently use salicylic acid in toothpaste or mouthwash. Salicylic acid has a bitter taste and is not likely to be palatable in oral care products nor is it likely to be the best preservative for these products. Therefore, oral care products were not included in the exposure assessment. If this situation was to change in the future and salicylic acid was used up to a maximum of 0.5% in an oral care product, the resulting exposures would be very low.

B) **Probabilistic approach**: a consumer exposure assessment using maximum allowed % levels of salicylic acid and taking into account habits and practices data for product use in the European population. Probabilistic distributions of product use data are used according to the Crème Care and Cosmetics exposure model (Ref: Crème Global 2017). This model uses a Monte Carlo approach to solve the exposure equations based on individual based habits and practices and is further described in the following publications: D. Comiskey et al. 2015 &2017, B. Safford et al. 2015 & 2017. The calculations for SA follow the same approach as described in these publications, only differ in the selection of parameter values (assumed occurrence: 100%; specific product concentrations in Table 20).
This approach differs from the deterministic approach only in that product exposure is not based on conservative point estimates for products amounts used, but is based on distributions of product usage data, thus allowing the analysis to reflect that not all subjects are high users of each product. The same concentration and retention values have been used as in the deterministic approach (see Table 18) and the model calculation for the probabilistic approach included also the assumption that salicylic acid is present in every product in the market for cosmetics (occurrence: 100%). Applying these parameters together with the habits and practices data in the Crème Care and Cosmetics exposure model yields the 95th percentile values for systemic exposure dose (SED) and MOS (see Table 20).

SCCS comment
The Applicant considers a dermal absorption fraction of **50%** as a "highly conservative value" to calculate the aggregate exposure. However, in light of the provided absorption studies, the SCCS is of the opinion that a dermal absorption value of **60%** should be used in the calculations (see chapter 3.3.5).

By multiplication with a correction factor, the SCCS updated the SEDs provided by the Applicant to be valid for an absorption fraction of 60%. The updated SEDs for the deterministic approach are given in Table 20 and for the probabilistic approach in Table 21.
The standard errors in Table 21could not be recalculated for uptake of 60%, they refer to the Applicant's calculation with an uptake of 50%.

Table 20. Approach A: Systemic exposure dose (SED) calculation of salicylic acid in various cosmetic products using the deterministic approach according to SSCS Notes of Guidance, 2016

Skin penetration (%):	**60**			
Product	**Maximum concentration (w/w %)**	**Calculated relative daily exposure to product[1] (mg/kg bw/day)**	**Total dermal exposure (mg/kg bw/day)**	**Calculated SED[2] (mg/kg bw/day)**
Shower gel	2	2.79	0.0558	0.0335
Hand wash soap	2	3.33	0.0666	0.0400
Shampoo	3	1.51	0.0453	0.0272
Hair conditioner	3	0.6	0.0180	0.0108
Hair Styling	2	5.74	0.1148	0.0688
Body lotion	0.5	123.2	0.616	0.369
Face cream	2	24.14	0.4828	0.2897
Hand cream	2	32.7	0.654	0.3924
Liquid foundation	2	7.9	0.158	0.0948
Make-up remover for face	2	8.33	0.1666	0.1000
Eye shadow	0.5	0.33	0.0017	0.0011
Mascara	0.5	0.42	0.0021	0.0012
Eyeliner	0.5	0.08	0.0004	0.0002
Lipstick, lip salve	0.5	0.9	0.0045	0.0028
Non-spray deodorant	0.5	22.08	0.1104	0.0662
Deodorant aerosol spray (ethanol-based)*	0			
Deodorant spray*	0			
Toothpaste**	0			
Mouthwash**	0			
Aggregate Exposure				**1.50**

[1]According to values in Table 4 on page 82 of the SCCS Notes of Guidance, 2016
[2]Total dermal exposure x 0.6
* The Applicant does not intend to use salicylic acid in spray/aerosol products.
**The cosmetics industry stated that it does not currently use salicylic acid or its salts in these products

Table 21. Approach B: Probabilistic approach: Estimated 95th percentile and standard error of the systemic exposure dose (SED) of salicylic acid from individual product types, and calculated aggregate exposure from all assessed products (consumers only).

Product	**Concentration (w/w %)**	**SED (95th percentile) (mg/kg bw/day)**	**Standard Error * (mg/kg bw/day)**

Shower gel	2	0.0316	0.0006
Liquid Hand Soap	2	0.0326	0.0003
Shampoo	3	0.0352	0.0005
Rinse-off Conditioner	3	0.0438	0.0013
Hair Styling	2	0.0780	0.0027
Body Lotion	0.5	0.3552	0.0119
Face Moisturiser	2	0.3017	0.0072
Hand Cream[1]	2	0.4130	0.0444
Liquid Makeup Foundation	2	0.1308	0.0072
Makeup Remover	2	0.0840	0.0044
Eye Shadow	0.5	0.0004	0.00001
Mascara	0.5	0.0011	0.00006
Eyeliner	0.5	0.00004	0.000001
Lipstick	0.5	0.0010	0.00005
Deo Roll On	0.5	0.0560	0.00087
Aggregate Exposure[2]		**0.384**	**0.0074**

[1]Note that the P95 of exposure across all products is sometimes exceeded within an individual product category. This is because high users of an individual product are not high users of all products.
[2]This is based upon a probabilistic assessment of habits and practices product use data, therefore this is not a straightforward addition of the SED values for individual products.
* note that the standard errors were not recalculated for uptake of 60%, they refer to the Applicant's calculation with an uptake of 50%.

The Applicant also provided two other probabilistic scenarios ("Scenario 2" and an "Additional Scenario"), where a survey among industry was used to derive distributions for currently used salicylic acid concentrations in products. Since Scenario 2 assumes distributions of current concentrations in products, which may be different in the future, this scenario is not precautionary enough to be used for the assessment of salicylic acid. The "Additional scenario" is even less precautionary as it is based on survey figures that represent actual occurrence of salicylic acid in products, and is therefore likewise not reported here.

According to the 9th revision of the Notes of Guidance (2016), a probabilistic approach can be accepted, if the robustness has been checked. The probabilistic approach presented above is precautionary in two ways: First, it is assumed that every consumer who uses a product category that may contain salicylic acid, uses salicylic acid containing products. Since there are a number of other preservatives that can be used instead of SA, this is a conservative assumption. Second, it is assumed that all the products contain maximum levels allowed as of today, which is another conservative assumption. Hence, the approach presented above is probabilistic only regarding the use data, which can be assumed to be stable over a longer period of time. The SCCS was given access to the general Crème Care and Cosmetics exposure model and assured that the model assumptions and the realisation are sound and according to the current state of the art.
However, whereas the assumptions and results of the model are clearly reported in the form of text, the presented report for salicylic acid does not include a dated output file of the

Crème Care and Cosmetics exposure model that would contain the major assumptions together with the results. Also, the SCCS would prefer the presentation of 95% confidence limits instead of the standard error.
Spray products and oral care products, such as mouthwash and toothpaste, have not been considered in the exposure assessments. Therefore, this Opinion excludes such product categories.

The Crème Care and Cosmetics exposure model uses habits and practices data for adults. The largest contributions were for hand cream, body lotion and face moisturiser. Garcia-Hidalgo et al, 2017 showed that children and adolescents in Switzerland generally use less of these product categories than adults. Therefore, the presented SEDs most probably are also protective for children and adolescents from 3-18 years of age.

3.4.2 Aggregate exposure with non-cosmetic uses

According to the Applicant, it is useful to consider how the SED for aggregate cosmetics exposures compares to everyday safe use of aspirin, assuming that 100% of aspirin is converted in a day to salicylic acid.
Aspirin is available over the counter for use as a low dose prevention treatment to improve cardiovascular functions and as a commonly used analgesic, used episodically at 1000 mg/day and maximally at 4000 mg/day (4 x 1000 mg/day). For a 60 kg adult, the intake for low dose is 1.35 mg/kg/day and for analgesic level aspirin up to a maximum of 67 mg/kg/day, and is considered safe at this level.
Systemic exposure to salicylic acid from cosmetics use is therefore significantly lower than the safe oral doses of aspirin used daily in the general population, including demonstrated safe use by pregnant women (Bard, 2012).

SCCS comment
The SCCS agrees that exposure to aspirin results in considerably larger doses of SA than the use as preservative in cosmetics. However, the use of a drug includes different risk-benefit considerations than the use in cosmetics, and in recent times also the deliberate use of aspirin has been questioned by medical doctors. Therefore, the fact that aspirin results in much larger doses of salicylic acid cannot be used as an argument for the safety of SA.

Salicylic acid is also used as a preservative in food and as a biocide in some consumer products (see section 3.2.3). As no specific exposure data were made available to SCCS to assess exposure following these non-cosmetic uses, it was not possible to include them in the aggregated exposure scenarios.

3.5 SAFETY EVALUATION (INCLUDING CALCULATION OF THE MOS)

The Margin of Safety is calculated by dividing the toxicological Point of Departure, POD, (in mg/kg/day) by an estimate of the systemic exposure dose (in mg/kg/day) following dermal exposure. The MOS's were updated by the SCCS to include a skin penetration of 60% in all calculations of systemic exposure dose.
The toxicological POD (75 mg/kg/day) is taken in this case as the NOAEL from the pivotal developmental study by Tanaka et al., 1973a, for the most sensitive toxic endpoint observed in the rat as the most sensitive species. Due to the evidence for high (100%) oral bioavailability in humans, the oral NOAEL of 75 mg/kg/day is defined as NOAELsys. The outcomes for aggregate exposures from the different risk assessment approaches are summarised in Table 22.

Table 22. MOS for aggregate systemic exposure to cosmetic products containing salicylic

acid			
Risk Assessment Scenario	**Basis for exposure assessment**	**Aggregate Systemic Exposure Dose (mg/kg/day)**	**Margin of Safety (using a NOAEL of 75 mg/kg/day)**
Scenario 1	Crème Care and Cosmetics model; probabilistic habits & practices; maximum % level	**0.384**	**195**
SCCS 2016 Notes of guidance Approach	SCCS Guidance 9th revision*; deterministic additive; maximum % level	**1.50**	**50**

* Assumes everybody in the population uses all the products each day, and all products contain salicylic acid, aggregate exposure is calculated on the basis of deterministic additive methods.

Applicant's Analysis

In the Applicant's dossier, evidence is presented to show that human and rat toxicokinetics are similar for salicylic acid. Therefore, according to the Applicant, the factor of 4 accounting for inter-species toxicokinetic differences is not required. This leads to a margin of safety of approximately 25 that is needed to account for the uncertainties in this risk assessment. Scenario 1 also ensures that when taking a maximal conservative approach to safety evaluation, the exposed population is safe. The most conservative deterministic approach according to SCCS 2016 Notes of Guidance leads to the conclusion that aggregate exposure is still greater than the required MOS of 25 to assure safety. This indicates that the current permitted uses of salicylic acid in cosmetic products are acceptable in terms of consumer health.

SCCS comment

The Applicant on the basis of the absorption studies considers a dermal absorption fraction of 50% as a "highly conservative value" to calculate the aggregate exposure. However, in light of the high variability of the dermal penetration values provided in the absorption studies, the SCCS considers 50% not conservative enough in this specific case but used a value of 60% instead. The Applicant excluded toothpaste and mouthwash in the aggregate assessment on the basis that the test substance is not used in these products, because of intrinsic product properties of salicylic acid. The SCCS accepts the argumentation of the Applicant. The Applicant also did not include spray applications in the aggregate exposure.

Regarding salicylic acid kinetics for rats and humans, no robust data have been provided to enable comparison of the kinetic parameters of the test substance between species (rats and human). In light of the above, the SCCS cannot compare the kinetics for rat to humans because of species' differences. Hence, the SCCS is of the opinion that the default acceptable **MoS of 100** should be applied.
The SCCS notes that the MoS of 50 derived on the basis of the deterministic approach according to the SCCS 2016 Notes of Guidance is therefore too low to conclude on the safety of salicylic acid.

The SCCS considers that for this case, the probabilistic approach can be used in the safety assessment of salicylic acid.
The probabilistic approach combines currently allowed maximal concentrations of salicylic acid with population data on habits and practices. For the assessment of the MOS, the 95th percentile is used. The derived MOS with this scenario is 195 and thus demonstrates the safety of salicylic acid for cosmetics, excluding oral products such as toothpaste and mouthwash. Sprayable products that could lead to exposure of the consumer's lungs by inhalation are also excluded.

3.6 DISCUSSION

Physicochemical properties

The analytical methods used for the determination of purity and impurities in the test substance along with the results of these studies should be provided, according to the SCCS Notes of Guidance. The SCCS is of the opinion that the method described in European Pharmacopoeia is the method of choice for testing the purity and the impurities of Salicylic Acid.

Function and uses

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Toxicological Evaluation

Acute toxicity

Acute oral

Harmonised classification of salicylic acid was recently published in regulation 2018/1480 and it was classified as Acute Toxicity Category 4, H302 (Harmful if swallowed).

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.

Irritation and corrosivity

Skin irritation

Based on a previous animal skin irritation study, the SCCNFP had considered in its Opinion (SCCNFP/0522/01 of 2002) salicylic acid as mildly to non-irritating to skin. However, the new study provided in the current submission indicates that neat salicylic acid is not irritating to skin.

Mucous membrane irritation / eye irritation

Based on all available ingredient based data, SCCS considers salicylic acid as being able to cause serious damage to the eye. Salicylic acid was recently classified as Eye Dam. 1 (H318 Causes serious eye damage) and was included in annex VI of CLP (regulation 2018/1480). Salicylic acid is eye irritant.

Skin sensitisation

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

Toxicokinetics

In view of the high variability of dermal penetration values reported in the different studies, the SCCS estimates a dermal absorption rate of 60 % for salicylic acid.

Regarding salicylic acid kinetics for rats and humans, no robust data have been provided to enable comparison of the kinetic parameters of the test substance between species (rats and human). In light of the above, the SCCS cannot compare the kinetics for rat to humans because of species' differences. Hence, the SCCS is of the opinion that the default acceptable **MoS of 100** should be applied.

In addition and based on the studies provided, the SCCS is of the opinion that the metabolism for salicylic acid in rats and humans is at least similar. Salicylic acid is metabolised mainly to salicyluric acid and conjugated salicylic acid compounds, with a small proportion of oxidative metabolites. The SCCS agrees that salicylic acid has the potential to cross the placenta, based on the provided studies.

Repeated dose toxicity

Inhalation
No robust data have been provided to enable proper assessment of the repeated dose toxicity by inhalation. Since the Applicant does not intend to use salicylic acid in spray/aerosol products, inhalation toxicity is not considered in this Opinion**.**

Chronic (> 12 months) toxicity
SCCS considers that the assessment from SCCNFP (2002) concerning the toxicity of salicylic acid after repeated exposure remains valid.
In particular:
- No systemic toxicity was noted from sub-chronic dermal toxicity studies conducted in the rabbit at the highest dosage of 120 mg/kg/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 in diseased skin. Children are more sensitive than adults to develop salicylism, thus the topical application of salicylic acid may involve a risk of toxicity. Reye's syndrome in children is associated with the use of acetylsalicylic acid during a viral illness.

Reproductive toxicity
SCCS concludes that there is insufficient evidence that salicylic acid has an adverse effect on sexual function and fertility.

Developmental Toxicity
SCCS agrees that salicylic acid can be considered as 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).As the developmental effects are the most sensitive effects after repeated exposure to SA, the **NOAEL of 75 mg/kg bw/day** has been used for the calculation of the MoS.

Mutagenicity / genotoxicity
The genotoxicity of salicylic acid was investigated with valid genotoxicity tests for *in vitro* gene mutations, in both bacterial and mammalian test system. 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. Based on the submitted studies and available literature, the SCCS is of the opinion that salicylic acid does not pose risk of genotoxicity.

Carcinogenicity
No additional studies have been provided by the Applicant in submission II. However, 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.

Photo-induced toxicity
The SCCS agrees that, based on the submitted studies, salicylic acid does not have photo-irritant, photosensitising or photocarcinogenic properties.

Special investigation

There is some evidence that some salicylates such as homosalate may have endocrine properties but few studies have investigated endocrine properties of salicylic acid itself. In a newly published report from the Danish Centre on Endocrine Disrupters researchers have evaluated that there is solid scientific evidence that salicylic acid is an endocrine disruptor. Salicylic acid is not listed as an endocrine disrupter candidate in the priority list published in 2007 by the European Commission. Salicylic acid has also not been identified as an endocrine disrupter in the Pesticide Action Network Pesticide DataBase.

Exposure Assessment

For the exposure assessment of salicylic acid, the SCCS has considered it appropriate to use the probabilistic scenario that assumes maximum allowed concentrations of salicylic acid in all cosmetics where it is used.

4. CONCLUSION

1. *In light of the new data provided, does the SCCS still consider Salicylic acid (CAS 69-72-7) safe when used as a preservative in all cosmetic products up to a maximum concentration of 0.5% (acid) considering its current restriction as reported above?*

   The SCCS considers salicylic acid (CAS 69-72-7) safe when used as preservative at a concentration of 0.5 % in cosmetic products considering its current restrictions in place.
   This Opinion is not applicable to any oral product (such as toothpaste and mouthwash) with the exception of lipsticks. Sprayable products that could lead to exposure of the consumer's lung by inhalation are also excluded. The provided information shows that salicylic acid is an eye irritant with the potential to cause serious damage to the eye.

2. *In addition, does the SCCS still consider Salicylic acid (CAS 69-72-7) safe when used for purposes other than inhibiting the development of micro-organisms at a concentration up to 3.0 % for the cosmetic rinse-off hair products and up to 2.0 % for other products considering its current restrictions as reported above?*

   Based on the data provided and available literature, the SCCS considers salicylic acid (CAS 69-72-7) safe when used for purposes other than preservative at a concentration up to 3.0 % for the cosmetic rinse-off hair products and up to 2.0 % for other products, considering its current restrictions in place. However, in body lotion, eye shadow, mascara, eyeliner, lipstick and roll on deodorant applications, salicylic acid is considered safe up to 0.5 %. The SCCS position is that these levels are inclusive of any use of salicylic acid, i.e. should not exceed the stated levels with additional use as a preservative.
   This Opinion is not applicable to any oral product (such as toothpaste and mouthwash) with the exception of lipsticks. Sprayable products that could lead to exposure of the consumer's lung by inhalation are also excluded.

3. *Does the SCCS have any further scientific concerns with regard to the use of Salicylic acid (CAS 69-72-7) in cosmetic products?*

   Salicylic acid is also used as a preservative in food and as a biocide in some consumer products (see section 3.2.3) or in various pharmaceutical formulations such as anti-acne products. As no specific exposure data were made available to SCCS to assess exposure following these non-cosmetic uses, it was not possible to include them in the aggregated exposure scenarios. Therefore, the actual total exposure of the consumer may be higher than exposure from cosmetic products alone.
   The conclusions of this Opinion refer only to Salicylic Acid and should not be applied to other salicylates or salicylic acid salts.

5. MINORITY OPINION

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7. GLOSSARY OF TERMS

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8. LIST OF ABBREVIATIONS

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