OPINION OF THE SCIENTIFIC COMMITTEE ON COSMETIC PRODUCTS AND NON-FOOD PRODUCTS INTENDED FOR CONSUMERS

CONCERNING

SALICYLIC ACID

adopted by the SCCNFP during the 20th plenary meeting
of 4 June 2002

1. Terms of Reference

1.1 Context of the question

Cosmetic products marketed in the EU may only contain those preservatives which are listed in Annex VI of the Cosmetics Directive 76/768/EEC, "List of preservatives which cosmetic products may contain".

The preamble of the Annex states that preservatives marked with the symbol (+) may also be added to cosmetic products in concentrations other than those laid down in the Annex for other specific purposes apparent from the presentation of the products.

Salicylic acid and its salts bear the symbol (+) and can therefore be used in cosmetics at higher concentrations, as long as they are not employed as preservatives.

In its opinion of 17 February 1999 concerning the restrictions on materials listed in Annex VI of Directive 76/768/EEC on cosmetic products, the SCCNFP stated that those substances indicated by (+) in Annex VI, when incorporated into cosmetic formulations for non-preservative functions, should be subjected to the same restrictions in usage levels and warnings as when used for preservative effects.

If a preservative marked with the symbol (+) is added for non-preservative purpose to a cosmetic product in a concentration higher than that laid down in the Annex VI, data to substantiate its safety should be submitted to the SCCNFP.

1.2 Request to the SCCNFP

The SCCNFP was requested to review the data submitted to support the safety of salicylic acid and its salts, when used at concentrations other than those laid down in Annex VI to Directive 76/768/EEC as preservatives, for other specific non-preservative purposes apparent from the presentation of the products :

* Submission I : concerns the evaluation of the safety of salicylic acid for other specific non-preservative purposes : leave-on formulations (face and general creams) and rinse-off products (make-up removers, shower gels, shampoos and hair conditioners) at a level of 2 %, leave-on hair care products at 1 % salicylic acid level and the use of salicylic acid as a preservative in other cosmetic products at the 0.5 % concentration.

The SCCNFP was also requested to answer the following question :

* Submission II : can salicylic acid and its salts safely be used for non-preservative purposes in cosmetic rinse-off hair products at a maximum concentration of 3 % ?

1.3 Statement on the toxicological evaluation

The SCCNFP is the scientific advisory body to the European Commission in matters of consumer protection with respect to cosmetics and non-food products intended for consumers.

The Commission's general policy regarding research on animals supports the development of alternative methods to replace or to reduce animal testing when possible. In this context, the SCCNFP has a specific working group on alternatives to animal testing which, in co-operation with other Commission services such as ECVAM (European Centre for Validation of Alternative Methods), evaluates these methods (doc. n° SCCNFP/0546/02).

The extent to which these validated methods are applicable to cosmetic products and its ingredients is a matter of the SCCNFP.

SCCNFP opinions include evaluations of experiments using laboratory animals; such tests are conducted in accordance with all legal provisions and preferably under chemical law regulations. Only in cases where no alternative method is available will such tests be evaluated and the resulting data accepted, in order to meet the fundamental requirements of the protection of consumer health.

In the interest of consumer's health protection, the SCCNFP highlights the important requirement of ensuring that files for evaluation are submitted complete.

The files should include, as well as the results procured by the applicants themselves, all relevant published literature and other findings to the applicant's best ability, and also "grey material" available elsewhere. Subsequently, should additional data or information be acquired by Industry and/or other agencies, this should be transmitted to the Commission, for review as necessary.

2. Toxicological Evaluation and Characterisation

2.1. General

Salicylic acid is a white crystalline powder originally introduced for oral therapeutic purposes by Rev. Edmund Stone in 1763. Wintergreen leaves, willow and sweet birch bark, bacteria, fungi and fruits represent its natural occurrence. Salicylic acid and its derivatives, have been available by a synthetic process since the mid 1800s.

Salicylic acid and its salts are currently in Annex VI part 1 number 3 and are restricted to a maximum concentration of 0.5 % calculated as acid function and submitted to the following restrictions :

- limits and requirements : "do not use in preparations for children under 3 years old, excepting shampoos"

- warnings to be printed on the label : "do not use for children care under 3 years old" (only concerning products which could be in contact with the skin for a long time)

2.1.1. Chemical name

Salicylic acid

2.1.2. Synonyms

o-hydroxybenzoic acid
2-hydroxybenzoic acid

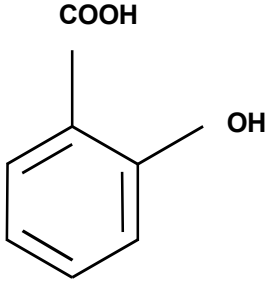
2.1.3. Trade names and abbreviations

No names are available

2.1.4. CAS no.

69-72-7

2.1.5. Structural formula



2.1.6. Empirical formula

Emp. Formula : $C_7H_6O_3$
Mol weight : 138.12

2.1.7. Purity, composition and substance codes

No data are available

2.1.8. Physical properties

Melting point	158-160°C
Boiling point	211°C at 20 mm Hg
Vapor pressure	5 mm Hg at 136°C
Density	1.443 at 20°C
Partition coefficient	Log P_{ow} : 0.35
Flash point	157°C

2.1.9. Solubility

In water 2.17 mg/ml at 20°C
Soluble in : ethanol, diethyl ether

2.2. Function and uses

Cosmetic uses

Salicylic acid used as preservative (up to 0.5 %) in cosmetic products. At a level up to 1 % in leave-on hair products and up to 2 % salicylic acid is used in leave-on cosmetics products (face and general creams) for its exfoliating and cleansing properties and in rinse-off products (shower gels, shampoos, hair conditioners, make-up removers).

Dermatological uses

Salicylic acid is widely used in the treatment of many common dermatological conditions because of its keratoplastic properties.

Other fields of use

Salicylic acid is used: as a preservative in food, as a chemical raw material for the synthesis of dye and salicylates derivatives (aspirin), as an antiseptic and antifungal by topical application in veterinary medicine.

TOXICOLOGICAL CHARACTERISATION

Important note :

Following oral administration, acetylsalicylic acid (aspirin) is rapidly hydrolysed to salicylic acid. Considering the great number of available and published toxicological data concerning acetylsalicylic acid, when compared to salicylic acid, the studies performed with this ingredient have been considered to have also some importance for salicylic acid.

However, concerning pharmacokinetic data, studies have shown a different mechanism of action between acetylated *versus* non-acetylated salicylates. Acetylsalicylic acid inhibits prostaglandin synthesis by irreversible acetylation of the cyclo-oxygenase, whereas the interaction of salicylic acid with the cyclo-oxygenase is transient and reversible, suggesting a minimal inhibiting activity.

2.3. Toxicity

2.3.1. Acute oral toxicity

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. : 6, 66

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

Ref. : 82, 83, 84

Human data

In human the oral lethal dose for sodium salicylate is estimated between 20 and 30 g in adults.

Ref. : 32

Toxic effects were reported when 10 g or more of salicylates are given orally in single dose or divided doses within a period of 12 to 24 hours. Children under the age of 3 years are more sensitive than adults to salicylates.

Ref. : 25

2.3.2. Acute dermal toxicity

The topical application of acetylsalicylic acid powder at a dosage of 2 g/kg to Rabbit did not induced any sign of erythema or oedema on both the intact and abraded skin of the animals. The dermal LD50 was estimated greater than 2 g/kg in Rabbit.

Ref. : 85

2.3.3. Sub-chronic toxicity

2.3.3.1 Sub-chronic dermal toxicity

Animal data

A 14-day percutaneous study was performed in four groups of 3 male and 3 female New Zealand White rabbits administered topically at 2 g/kg/day of salicylic acid-containing solutions. The concentrations tested were 0%, 2%, 10% and 25% (corresponding to 0, 40, 200 et 500 mg/kg/day) of salicylic acid in a vehicle solution (8% propylene glycol butyl ether in ethanol). After a 7-hour period of daily exposure, the application site was washed with water and dried.

No death was 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 on or 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. : 110

Two 91-day studies were performed in New Zealand White rabbits in order to assess the subchronic cutaneous and systemic toxicity of two cleansing formulations containing 0.5% salicylic acid. 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, behavior), 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 death was observed during the study. No statistical differences were found in mean body weight and 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 skin of Rabbit.

Ref. : 111, 112

A 91-day subchronic 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. 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 on study to the 91-day termination. 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 28 days and 91 days of treatment. There were no test article-related effects on appearance, behaviour, body weights or ophtalmoscopic 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. 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.

Ref. : 113, 114

Human data

Mild chronic salicylate intoxication is defined as salicylism and was described after topical application.

Ref. : 15, 29, 50, 151, 162, 183

This event is rare 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, the surface of application. Ointments containing salicylic acid 3 to 6 % have caused nausea, dyspnaea, hearing loss, confusion and hallucinations in 3 patients with extensive psoriasis. They had two soap and water baths daily combined with UV therapy and six ointment applications. Under these conditions, the symptoms developed in 4 days and were associated with significant salicylic acid plasma levels (46 to 64 mg/100 ml). Symptoms disappeared rapidly after discontinuation of the ointment applications.

Ref. : 175

Two fatal cases of percutaneous salicylate poisoning, caused by the treatment of a fungal infection with an alcoholic solution containing 20 % salicylic acid, were described.

Ref. : AR3

Salicylism can be developed within a short period of treatment. A case was reported after 2 days of treatment, with 10 % salicylic acid, in a man with a widespread psoriasis that covered 80 % of his body surface.

Ref. : AR2

The application of salicylic acid to extensive areas, particularly in children, may involve a risk of toxicity from absorption. Children are particularly susceptible.

Ref.: 79, AR4, AR5

Salicylate plasma levels can be indicative of salicylic acid intoxication. Symptoms occur at plasma level of 35 mg/100 ml or higher.

Ref. : 14

The correlation between body salicylate and clinical severity of the intoxication is poor, that can be associated with the variability of the protein binding and the blood pH. Severe manifestations are linked with diseased skin, multiple applications on large body areas of formulations containing high concentrations of salicylic acid.

2.3.4. Chronic toxicity

2.3.4.1 Chronic oral toxicity

Animal data

In the submission, there is only information on acetylsalicylic acid-related toxicity following oral administration. With regard to the rapid hydrolysis of acetylsalicylic acid to salicylic acid after oral absorption, the available animal data concerning acetylsalicylic acid have been considered.

Ref. : 69, 76

A 200-day comparative study was performed in rats (2 groups of 10 animals) in order to assess the long term toxicity of acetylsalicylic acid *versus* acetaminophen, and their possible interaction when combined. Acetylsalicylic acid alone is discussed in this report. This ingredient was administered orally by gavage at the concentration of 200 mg/kg/day, a volume of 10 ml/kg was administered. Clinical tests, as body weight gain, were performed at monthly intervals ; during that time, alkaline phosphatase, lactic dehydrogenase analysis, volume, pH and osmolarity of urine were recorded ; aspartate and alanine aminotransferase were measured from blood samples. Macroscopic and microscopic examinations were performed after dosing for 200 days.

Two deaths were observed during the study with acetylsalicylic acid and were not considered related to the treatment. A mildly toxic effect on the kidney (without any sign of pathology) was recorded ; the osmolarity of the treated group was significantly higher than control in the fourth

and fifth months. No significant changes compared to the control were related to a potential toxicity of acetylsalicylic acid at the dose level used.

Ref. : 169

Human data

Ingestion of acetylsalicylic acid tablets is the major cause of salicylate poisoning in adults. In children, infants and neonates other causes were described in the literature (teething gels to gums, breast milk, placental transfer)

Ref. : 1, 16, 63, 81

Oral doses of acetylsalicylic acid of 100 mg/kg or higher induce salicylism. Plasma levels are indicative of salicylic intoxication, symptoms are occuring at plasma levels of 35 mg/100 ml or greater.

Ref. : 14

2.4. Irritation & corrosivity

2.4.1. Irritation (skin)

Animal data

The compound salicylic acid was moderately irritant to minimally irritant when applied up to 2 % product formulations or alcohol solutions to intact or abraded rabbit skin under occlusion or semi-occlusion for up to 24 hours. The pH of the tested products was between 2.8 and 4.0.

Ref. : 88, 91, 93, 94

Skin irritation studies in rabbit

salicylic acid % pH	Test conditions	Results	Reference
Not indicated (laundry additive) pH 4.0	0.5 g semi-occlusive patch for 4 hours	Moderately irritating	91
2% in alcohol solution pH 2.65	0.5 g occlusive patch for 24 hours	Minimally irritating	88
2% in alcohol solution pH not indicated	0.5 ml occlusive patch for 24 hours	Non irritating	93

0.25% in hydroalcoholic cleanser pH not indicated 0.5% in hydroalcoholic cleanser pH 2.81	0.5 ml occlusive patch for 24 hours	Non irritating	94

Repeated open applications of 0.25% to 5% hydroalcoholic solutions (no correspondence available between weight of tested substance and surface unit) of salicylic acid with pH between 2.3 and 3.0 were performed to the skin of guinea pigs for up to 5 consecutive days. Mild to no irritation was noted.

Ref. : 86, 87, 89

Skin irritation studies in guinea pig

salicylic acid % pH	**Test conditions**	**Results**	**Reference**
2.5% in alcohol solution ; pH 2.34 5% in alcohol solution pH 2.32	0.15 ml open application for 3 hours, twice a day for 4 consecutive days	Mildly irritating No peak for skin irritation noted	86
0.5% in hydroalcoholic cleanser ; pH 2.90 0.25% in hydroalcoholic cleanser ; pH 2.7-2.3	0.25 ml open application for 23 hours, once daily for 5 consecutive days	Minimal skin irritation	87
0.5% in hydroalcoholic cleanser ; pH 2.70	0.25 ml open application for 23 hours, once daily for 5 consecutive days	Non irritating	89

Human data

After repeated application of formulations containing up to 2 % salicylic acid, it is possible to categorize salicylic acid as a mild transient irritant.

Duration Matrix	**salicylic acid % pH**	**Test conditions**	**Results (classified as)**	**Reference**
5 days cream no alcohol	2 % pH not indicated	Occlusive and semi occlusive patches diluted	Test substance (15 %) non irritating	137

12 days surfactant based product	Concentration not indicated pH not indicated	Occlusive patch 24 hours 7 times/week	Probably mildly irritanting in normal use conditions	41
12 days surfactant based product	2 % pH 3.8	Occlusive patch diluted 24 hours 7 times/week	Mildly irritanting No experimental irritation	42
14 days surfactant based product	2 % pH 3.8	Occlusive patch diluted 24 hours 6 times/week	Probably mildly irritanting in normal use conditions	43
21 days cream no alcohol	1.5 % pH not indicated	Occlusive undiluted 5 times/week	Slightly irritating versus control	135
21 days gel hydroalcoholic	2 % pH not indicated	Semi-Occlusive undiluted 5 times/week	Slightly irritating versus control	136
21 days cream no alcohol	2 % pH not indicated	Occlusive undiluted 5 times/week	Moderately irritating versus control	143
21 days cream no alcohol	2 % pH not indicated	Occlusive undiluted 5 times/week	Non irritating versus control	144
14 days cream no alcohol	2 % pH not indicated	ROAT undiluted skin of the back 2 times/day 5 times/week 1 time/week-end	No difference between test article and control in irritation	138

In submission II additional human skin irritation data are provided for the use of salicylic acid in rinse-off products at an increased concentration from 2 % to 3 %.

In a 12 days cumulative irritation study with a shampoo containing 3 % salicylic acid applied continuously under a patch test (as a 4 % dilution) the formulation showed a potential for irritation under the drastic test conditions..

Ref. : 187

When shampoos (prototype or commercial formulations) containing 3 % salicylic acid were compared in exaggerated use repeat application patch test (4 studies were conducted) to shampoo formulations containing up to 2 % of salicylic acid versus placebo, there were no statistical differences in combined irritation or transepidermal water loss (measured with an Evaporimeter™). So at 3 % in a rinse-off shampoo formulation salicylic acid does not appear to be more irritant than the other components of the formulations.

Ref. : 188, 189, 190, 191

2.4.2. Irritation (mucous membranes)

Animal data

Numerous formulations (non-alcoholic "NA" and hydroalcoholic) containing salicylic acid 0,5 % to 2 % have been evaluated in a modified Draize test : the Low Volume Eye Test.
The formulations tested were considered by the investigators as mild irritant when instilled into the Rabbit eye.

Ref. : 33, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104

Test material	Average Score	Median days to clear	Results	Reference
NH cleansing milk with 0.05% SA pH 5.4	2.7	1	Redness and discharge	95
NH toner with 0.2% SA pH 5.7	2.7	2	Redness and discharge	
NH moisturizer with 2% SA	5.3	4	Conjunctivitis	96
Hydrogel with 2% SA	3.3	3	Conjunctivitis	97
NH cleanser with 2% SA pH 3.09	4.3	4	Iritis (1/3), conjunctivitis (2/3)	98
NH cleanser with 2% SA pH 3.09	2.0	3	Conjunctivitis (2/3)	
NH cleanser with 2% SA pH 3.09	6.3	4	Iritis (1/3), conjunctivitis (3/3)	
NH moisturizer with 2% SA	1.3	2	Conjunctivitis (2/3)	99
NH cream with 1.5% SA	2.7	3	Conjunctival swelling and redness (2/3)	100
NH cream with 1.5% SA	0.7	1	Conjunctivitis (1/3)	
NH cream with 1% SA	0.7	1	Conjunctivitis (1/3)	

Low Volume Eye Tests in rabbit *(continued)*

Test material	Average Score	Median days to clear	Results	Reference
NH moisturizer with 2% SA, pH 2-3	2	2	Conjunctivitis (2/3)	101
NH moisturizer with 2% SA, pH 4-5	2	2	Conjunctivitis (2/3)	
NH moisturizer with 2% SA	0.7	1	Conjunctival redness (1/3)	102
NH moisturizer with 2% SA	1.3	1	Conjunctival redness and swelling (1/3)	
NH moisturizer with 1.5% SA	2	3	Conjunctival redness (3/3)	
NH moisturizer with 0.5% SA	0	0	No effects observed	
NH cream with 2% SA,	3.3	2	Conjunctivitis (3/3)	103
Hydro after-shave with 2% SA	1.3	4	Conjunctival discharge and redness (2/3)	104
Hydro after-shave with 2% SA	1.3	2	Conjunctival redness (2/3)	

SA: salicylic acid ; NH: Non Hydroalcoholic

Human data

Different formulations containing salicylic acid were evaluated for their eye irritation potential :

- 2 % salicylic acid in cream after a single periocular application induced a transient subjective irritation (stinging, burning, itching) that was confirmed by ophthalmic investigation. The irritation resolved within 96 hours. The applied cream to the periocular area was able to migrate into the eyes.

Ref. : 118

- A twice daily application for five days of a 2 % salicylic acid cream to normal and sensitive eye volunteers induced mild to moderate bulbar conjunctival inflammation and a mild to moderate corneal superficial punctuate keratopathy. Irritation increases as the length of exposure. All eyes returned to normal within two days after the end of exposure.

Ref. : 150

- From a cream containing 1.5 % salicylic acid, with a pH of 2.5 to 2.8, after a 3 day periocular study, a mild conjunctival inflammation and mild or no superficial punctate keratopathy were reported.

Ref. : 117, 118

- The same formulation was evaluated in a 4 week in-use study, with application around the eyes twice a day for 28 days. Results indicated a mild ocular irritation.

Ref. : 148

- In a 14 day in-use study comparing a 1.5 % salicylic acid cream and a cream without salicylic acid, the superficial conjunctival and corneal superficial keratopathy were mild and similar for all the formulations (including the one without salicylic acid).

Ref. : 149

- In a large 6 week home use-test study with a cosmetic formulation containing up to 2 % salicylic acid (pH 3.0 to 3.09) 4 volunteers in a group of 64 users of salicylic acid were subject to a mild, transient irritation, in a group of 48 volunteers using the control product without salicylic acid 3 were subject to similar effects.

Ref. : 119

From these studies, it can be concluded that the intensity of the eye irritation with salicylic acid containing formulation is strongly related to the composition and formulation of the matrix and the capacity to migrate into the eyes.

2.4.3. In-use skin test

Human data

Under the conditions of use in the market place, the studied products have demonstrated to have a low potential for skin irritation on the face of the panellists.

Duration Matrix	salicylic acid % pH	Test conditions	Results (classified as)	Reference
2 weeks hydroalcoholic solution	0.5 % pH 2.82	Daily application forehead and nose	No evidence of skin irritation	142
6 weeks no alcoholic lotion	2 % pH not indicated	Home use test	Mild, transient and/or sporadic reactions even for the products without salicylic acid	140
6 weeks cream no alcohol	2 % pH not indicated	Home use test 50 % of the included panellists had self assessed sensitive skin	Little or no irritation potential	147

12 weeks cream with no alcohol hydroalcoholic gel and lotion	not indicated pH not indicated	Neat product 2 times/day 5 days/week	The cream showed improvement in irritation and dryness versus lotion	141
14 weeks non alcoholic lotions and moisturizers with/without salicylic acid	2 % pH 2.28	Home use test	12/194 adverse effects : itching, stinging, redness, mild erythema, burning feeling, irritated upper eye-lid, skin reaction on finger	139

2.5. Sensitisation

Animal data

Potential allergic contact sensitization 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**.**

Taking into account the available data, the mentioned references seem to correspond to only one performed study.

Ref. : 105, 106, 107, 108, 156

Human data

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. 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. ** pH value not given.

Vehicle	Salicylic acid Concentration / pH	Patch test	Positive responses	Reference
Hydroalcoholic lotion	0.5 %/ **	Occlusive	3/84*	121
Non alcoholic cream	1 % / 2.87	?	0/86	122
Hydroalcoholic gel	0.5 % / **	Occlusive	0/89	123
Hydroalcoholic foam	0.5 % / 4.5-5.5	Occlusive	0/101	120
Hydroalcoholic cleanser	0.5 % / 2.82	Occlusive	1/86*	124
Non alcoholic liquid make up	0.55 % / **	Occlusive	0/98	125

Hydroalcoholic gel	2 % / **	Occlusive	0/102	126
Non alcoholic cream	2 % / 3.15	Occlusive	0/108	127
Non alcoholic moiturizer	2 % / 3.17	Occlusive	0/99	128
Non alcoholic lotion	0.06 % / **	Occlusive	0/113	129
Non alcoholic cleanser	0.3 % / **	Semi-occlusive	0/99	130
Non alcoholic cleanser	0.3 % / 3.0	Semi-occlusive	0/104	131
Non alcoholic cream	0.3 % / 3.04	Semi-occlusive	0/105	132
Non alcoholic moisturizer	0.2 % / 7.28	Occlusive	0/99	133
Non alcoholic moisturizer	1.5 % / **	Occlusive	0/114	134
Non alcoholic rinse off	unknown /**	Occlusive	0/25	44
Non alcoholic cleanser	0.02 % / **	Occlusive	0/26	45
Non alcoholic cream	2 % / **	Occlusive	0/178	46
Non alcoholic rinse off	0.08 % / **	Occlusive	0/34	47
Non alcoholic cream	2 % / 3.8	Occlusive	0/193	48
Non alcoholic cream	2 % / 3.8	Occlusive	0/198	49
Non alcoholic cream	2 % / **	Occlusive	0/101	145
Non alcoholic cream	2 % / 2.6-2.7	Occlusive	1/102*	146

Other published data suggest that topically applied salicylic acid is not a contact allergen.

Ref. : 13, 74, 152

In submission II additional human skin irritation data are provided for the use of salicylic acid in rinse-off products at an increased concentration from 2 % to 3 %. A 12 days cumulative irritation study with a shampoo containing 3 % salicylic acid applied continuously under a patch test (as a 4 % dilution) showed no evidence of sensitization in a challenge patch test applied after a resting period of 16 days.

Ref. : 187

2.6. Reproduction toxicity

In the submission, there is only information on acetylsalicylate-related reproductive toxicity following oral administration. Taking into account the rapid hydrolysis of acetylsalicylic acid to salicylic acid after oral absorption, the available animal data concerning acetylsalicylic acid have been considered.

Ref. : 69, 76

Effects of prenatal administration of 200 mg/kg/day acetylsalicylic acid suspended in 1% tragacanth gum have been studied in rat. The substance has been administered twice daily by gastric intubation during the last 6 days of gestation. The control group received the vehicle. Behaviour and weight were recorded, gross examinations of the dams were performed after delivery.

A good tolerance of the treatment was noted during pregnancy. A prolongation of pregnancy and parturition time was observed. Two dams died during the labour period. A lethal effect on the

foetuses has been recorded: 7 dead pups out of 65 in the treated group. Only one dead pup out of 112 was seen in the control group. Foetal deaths were attributed to prolonged parturition caused by the effects of acetylsalicylic acid on prostaglandins synthesis.

Ref. : 173

The effects of sodium salicylate on parturition and neonatal viability were studied in mated female rats. The animals were administered orally by gavage twice daily on gestation days 15 through 21 at dosage levels of 20, 80 and 200 mg/kg/day, at a volume of 20 ml/kg. The positive control group received acetylsalicylic acid at a total daily dosage of 261 mg/kg, the control group received the vehicle only : 0.5% low viscosity carboxymethylcellulose.

Administration of 200 mg/kg/day sodium salicylate and of 261 mg/kg/day acetylsalicylic acid induced maternal toxicity : agonal clinical signs and/or reduction of body weights and food consumption. These signs were generally associated with prolonged parturition and difficulty in delivery. A significant increase in mean gestation length was noted with acetylsalicylic acid. Corresponding adverse effects on offspring survival for the affected dams were noted. However, there was no evidence of systemic or maternal toxicity, and no adverse effects on offspring survival or growth in the mid-dose group (80 mg/kg/day) and in the low-dose group (20 mg/kg/day).

Under the experimental conditions adopted, the NOAEL (No-Observable-Adverse-Effect-Level) of sodium salicylate has been found to be 80 mg/kg/day when administered orally to mated rats corresponding approximately to 69 mg/kg/day of salicylic acid.

Ref. : 115

2.6.1 Two-generation reproduction toxicity

No data are available

2.6.2 Teratogenicity

Numerous studies concerning fetotoxic and teratogenic potential of acetylsalicylic acid and salicylic acid have been performed in animals. When these compounds were administered by oral or by parenteral route at various time during pregnancy at daily doses of 75 to 500 mg/kg in rats, mice and monkeys, fetal malformations (skeletal anomalies, cleft lip), resorptions and perinatal death were recorded.

Ref. : 27, 54, 166, 167, 172, 176, 181, 182

Teratogenicity studies :

Species	Test article	Route of exposure	Dosage	Results	Ref.
Rats	Methyl salicylate	Subcutaneous Injections Days 9, 10 and 11 of gestation	0.1 to 0.5 ml (*no detail about concentration dosage*)	47/116: reabsorbtion of the young 45/298 offspring: cleft lip, eye defects, hydrocephaly, exencephaly 75/298 offspring: skeletal deformities	176

Mice	Acetyl salicylate	Oral Days 8 and 9, or 9 and 10 of gestation	500 mg/kg/day	Cleft lip: increase incidence Various malformations Effect level: 500 mg/kg/day	172
Rats	Sodium salicylate	Oral Days 9 and 11 of gestation	250 or 500 mg/kg/day after metal salt treatment (Fe, Mn, Cu)	Dose dependent malformations Increased maternal serum concentration of salicylic acid Effect level: 250 mg/kg/day Teratogenic effect of sodium salicylate potentiated by metal salts (Mn)	55
Rats	Acetyl salicylate or salicylate	Oral Days 8 to 14 of gestation	75, 150, 300 mg/kg/day	Rapid death after 300 mg/kg/day dosing Significant abnormalities for both test article at 150 mg/kg/day 75 mg/kg/day: low incidence of skeletal (3/26 extra ribs, 2/29 in controls) and external malformations (1.8%) LOEL: 75 mg/kg/day (Lowest dose Observable Effect Level)	166
Rats	Salicylic acid	Oral Days 8 to 14 of gestation	0.06% to 0.4% in diet (50 to 200 mg/kg/day)	0.4% group: body weight loss, toxic symptoms, significant mortality and growth retardation in fetuses 0.2% group: growth retardation 0.1% and 0.06% groups: no significant effects	167
Rats	Acetylsalicylic acid	Oral Days 9 to 12 of gestation	100 and 150 mg/kg twice daily	100 mg/kg: no foetotoxicity 150 mg/kg: death and reabsorption in 34% of the embryos	182

Teratogenicity studies (*continued*):

Species	**Test article**	**Route of exposure**	**Dosage**	**Results**	**Ref.**
Monkey	Acetylsalicylic acid	Oral Days 23 to 32 of gestation	100 and 150 mg/kg twice daily	Transient growth retardation with both dosages 150 mg/kg/day: malformations in 3/15 fetuses 100 mg/kg/day: no malformations	182
Rats	Acetylsalicylic acid	Oral Days 7 to 17 of gestation	50, 100 and 200 mg/kg/day	Decrease in maternal body weight gain in all groups 200 mg/kg/day: increase in resorption and fetal malformations dose-related decrease in average fetal body weight for the 100 and 200 mg/kg groups 50 and 100 mg/kg groups: no abnormal foetuses, reduced fetal weights	73

2.7. Toxicokinetics (incl. Percutaneous Absorption)

2.7.1. Metabolism and pharmacokinetics

Human data

Salicylic acid and derivatives are weak acids, after oral administration they are found in the unionized form in the stomach. They are well absorbed in human from the gastrointestinal tract and rapidly distributed throughout the extracellular fluid and most tissues. High concentrations are found in the liver and the kidneys (organs of biotransformation and excretion) and 50 to 80 % of salicylic acid in plasma is bound to albumin and other proteins. 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 %).

Ref. : 30

Pharmacokinetics of acetylsalicylic is largely documented. Acetylsalicylic acid is hydrolyzed in the stomach and in the blood to salicylic acid and acetic acid. The biological half life of acetylsalicylic acid is only 20 minutes. After the oral administration of 0.6 g of acetylsalicylic acid, only 27 % of the total plasma salicylate are still acetylated after 30 minutes.

Ref. : 30

2.7.2. Percutaneous Absorption

Animal data

Salicylic acid percutaneous absorption was studied in several animal species which are mainly non relevant according to the methodology for prediction of human skin permeability:

- Rabbits : salicylic acid was applied at the concentration of 6 % incorporated in several formulations : hydrophilic ointment (O/W), hydrophilic petrolatum (W/O), petrolatum, polyethylene glycol. Salicylic acid was most effectively absorbed from the hydrophilic ointment. The dose applied was 7.5 g/animal ,the plasma level pick was 12 mg/100 ml at 4.5 hours after the application of the hydrophilic ointment, it was 8 mg/100 ml at 6 hours for the hydrophilic petrolatum and 6.5 mg/100 ml at 4 hours with petrolatum. No absorption was detected from the propylene glycol excipient Sodium salicylate was studied in parallel from the same excipients, its absorption is considerably smaller than the acid salicylic one, but is also better from the hydrophilic ointments than from the others.

  Ref. : 165

- Rabbits : 10 g of a 10 % salicylic acid hydrophilic ointment with or without urea were applied on the ventral skin of the animals (91 cm^2). Peak plasma salicylic concentrations were between 10 and 18 mg/100 ml and were attained within four to six hours. Urea had not the percutaneous absorption enhancer effect that was initially expected.

  Ref.: 7

- Guinea pigs : percutaneous absorption of salicylic acid was studied from four oily vehicles applied on 2.25 cm²: liquid paraffin, oleic acid, hexadecyl alcohol and isopropyl myristate. When salicylic acid had a strong affinity to the vehicle (high solubility), the absorption was poor. The higher flux was reached from liquid paraffin (14.6 % of the dose between 1 and 6 hours - 500 µg/ml for a volume of 25 ml). The absorption was about 10 times greater when the skin was damaged by tape stripping.

  Ref. : 177

- Guinea pigs :percutaneous absorption was investigated in vivo from solutions at different pH. The absorption rate of the non ionised form (pH 2 and pH 3) is respectively 10 times and 5 times higher than the rate of the ionised form (pH 4 solution).

  Ref. : 3

- Rats : various concentrations (1, 5 and 10 %) of salicylic acid in hydrophilic ointment were applied repeatedly at daily or weekly intervals during 7.5 hours. The surface of application was 3 cm², the amount applied under occlusion was 2 g. A gradual decrease in the salicylic acid penetration was observed following weekly applications of either 5 or 10 % concentrations. The penetration flux of 1 % was nor modified under the same conditions. For the daily dosage with 5 and 10 %, the penetration flux increased after 2 days of treatment and declined thereafter. For the 1 % salicylic acid concentration, the penetration increased slightly after 3-4 days of treatment. These data were related to skin histological modifications.

  Ref. : 155

Human data :

- *In vitro* across human skin the absorption of salicylic acid at a concentration of 2 % was studied from 6 different formulations (hydro-alcoholic and non-alcoholic vehicles). Diffusion was greater for the hydro-alcoholic (35 %) than from the non alcoholic excipients (propylene glycol, cream)

  Ref. : 109

- A comparative pharmacokinetics study, oral dosing *versus* topical administration, was conducted in order to determine the systemic salicylic acid burden after topical use of a leave-on formulation containing 2 % salicylic acid (hydro-alcoholic vehicle, non-alcoholic cream). The application sites were the face and the neck, the amounts applied were 1.25 g to 1.50 g (i.e. 25 mg of salicylic acid). 40 subjects received the topical formulations daily during 16 days. A group of 12 volunteers received one daily dose of a "baby aspirin formula" containing 81 mg of acetylsalicylic acid. Plasma salicylate levels were compared (peak plasma level, time to peak, area under the curves). The peaks of salicylate levels for the topical application were $1/20^{th}$ for the cream to $1/10^{th}$ for the hydro-alcoholic formulation of the one obtained after oral dosing. The AUC were respectively $1/8^{th}$ to $1/5^{th}$ that of the oral treatment. The topical pharmacokinetics was not affected by the skin type

  Ref. : 116

Conclusion on percutaneous absorption

Salicylic acid is readily absorbed when applied on the skin. The absorption is strongly dependent on the vehicle composition, pH, structure of the skin, conditions of the application on the skin (single dose, repeated doses, occlusion). The absorption from topically applied 2 % salicylic acid containing products is in the range of 20 % of the applied dose.

After topical human administration of 1.25 g-1.50 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 $1/10^{th}$ and $1/20^{th}$ those obtained after the oral administration of 81 mg of acetyl salicylic acid (aspirin baby dose).

2.8. Mutagenicity/Genotoxicity

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 1, 2 and 3.

2.8.1. *In vitro* mutagenicity in Bacteria and Yeast (Table 1)

Methods	Test article	Metabolic activation	Results	Reference
Ames tests	salicylic acid acetylsalicylic acid 500 µg/ml	with without	negative	66 53
Ames tests	salicylic acid 3 to 8 10^{-5} M	No data available	negative	66
Bacillus subtilis assay	salicylic acid acetylsalicylic acid	without	positive	53

2.8.2. In vitro mammalian clastogenicity and DNA damage (Table 2)

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	164
Chinese hamster lung cells (*48 hour exposure*)	salicylic acid 1.0 and 1.25 mg/ml	Without	positive	40

The *in vitro* submitted studies for salicylic acid and for acetylsalicylic acid 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.

2.8.3. *In vivo* clastogenicity/mutagenicity (Table 3)

Method	Test article	Animal species	Results	Reference
Drosophila sex-linked recessive letal assay	Acetylsalicylic acid 10 mM	*Drosophila Melanogaster*	negative	56

2.9. Carcinogenicity

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 evaluation of possible carcinogenic properties of the substance.

  Ref. : 9

- 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. : 77

  Salicylic acid is the main metabolite of acetylsalicylic acid (aspirin) and there is sufficient evidence in animal models that acetylsalicylic acid prevents cancer.

  Ref. : AR 6

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. : AR 6

- Thun *et al*. reported that chronic use of acetylsalicylic acid decreases susceptibility to bowel cancer.

  Ref. : 57

- 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. :58

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

Ref. : AR1

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.

2.10. Special investigations

In vitro eye irritation studies were performed. The ocular irritation potential for prototype anti-dandruff shampoo formulations containing 2% or 3% salicylic acid was compared to marketed anti-dandruff shampoos (1.8 to 3% salicylic acid) and regular shampoos formulations. Two types of *in vitro* assays were performed: Bovine Corneal Opacity and Permeability assay (BCOP) and Cell Viability Assays (NRR and MT).

- **Bovine Corneal Opacity and Permeability assay (BCOP)** : Products were applied to excised bovine corneas under either in-use or maximalizing conditions for an assessment of ocular irritation relative to that of currently marketed products. Opacity changes of the test cornea or changes in corneal permeability after exposure to the product were measured to assess the ocular irritation potential.
  The results are summarized in the table: In Vitro Eye Irritation Results.

Ref. : 192

- **Cell viability assays** : Two assays were used to measure viability of normal human keratinocytes after exposure to products relative to that of currently marketed products: the Neutral Red Release Assay (NRR) and the Mat-Tek Epi-ocular ^{TM} (MT).

In both assays, BCOP and NRR, no significant differences were noted between shampoos formulations containing or not salicylic acid. In the Epi-ocular assay, the prototype formulations showed a higher predicted eye irritation potential, comparatively to the commercial shampoo formulations with or without salicylic acid. The results are summarized in the table: In Vitro Eye Irritation Results.

Ref. : 193, 194

In Vitro Eye Irritation Results :

Product ref.	Description	salicylic acid (%)	BCOP (*In vitro* score/classification)	NRR_{50} (mg/ml)	MT (ET_{50}) (minutes)
	« TEST » Shampoos				
1622	2.0% salicylic acid	2.0	0.57/non-irritant	0.76	11.3
1853	3.0% salicylic acid	3.0	1.7/non-irritant	0.80	<10
	Commercial Shampoos				
1516	Baby Shampoo	0	0.6/non irritant	3.87	47.8
2012	Adult Shampoo « A » (Normal)	0	0.74/non-irritant	0.82	27.5
2014	Adult Shampoo « A » (Dry/damaged)	0	1.8/non-irritant	0.80	33.6
2247	Adult Shampoo « B » (Normal)	0	1.8/non-irritant	1.11	27.2
2248	Adult Shampoo « B » (Dry/damaged)	0	1.6/non-irritant	0.82	23.3
1570	Adult Shampoo « C » (Normal/oily)	0	1.5/non-irritant	0.79	24.8
1039	1.8% salicylic acid	1.8	2.91/non-irritant	1.65	27.9
1034	3.0% salicylic acid	3.0	0.9/non-irritant	1.04	21.6

In the experimental conditions adopted, the obtained results showed that the concentration of salicylic acid, up to a level of 3%, and used in rinse-off shampoo formulations does not appear to significantly influence the ocular irritation potential.

2.11. Conclusions

In cosmetics salicylic acid is currently used at concentrations up to 2 % in leave-on formulations (face and general cream) and in rinse-off products (make-up removers, shower gels, shampoos and hair conditioners), at concentrations up to 1 % in leave-on hair care products and at 0.5 % as preservative in other cosmetic products. Studies have been submitted to support the use of salicylic acid at a level of 3% in rinse-off hair-care formulations.

Irritant potential :

- Product formulations or alcohol solutions containing up to 5% salicylic acid (skin irritation studies) and up to 2% salicylic acid (low volume eye tests) with pH between 2.3 and 5.7 were mildly to no irritating to the skin or to the eye of the animals treated. These results were confirmed by *in vitro* eye irritation studies using formulations containing salicylic acid at a concentration up to 3.0%.

- After repeated application in human under occlusive or semi-occlusive patches of formulations containing up to 3 % salicylic acid with a pH range 2.5 – 3.8, it can be possible to categorized salicylic acid as a mild transient irritant.

Allergenic potential :

- According to the modified Buehler test protocol using the Guinea pig, salicylic acid was not considered as a sensitising agent. However there are neither data related to the experimental potential risk under maximising conditions nor to the confirmation of absence of risk to Human.
- 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.
- No information is available concerning the phototoxicity or photoallergenic potential of salicylic acid in animal.

Potential systemic toxicity :

- Carcinogenicity studies were performed with acetylsalicylic acid ; this substance was not carcinogenic. Most of the results from genotoxic studies do not comply with the actual SCCNFP notes of guidance.
- No systemic toxicity was noted from subchronic 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 are 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
- Numerous reproductive studies have been performed with acetylsalicylic acid or salicylic acid in various animal species. A NOAEL of sodium salicylate administered orally to mated rats has been established to 80 mg/kg/day corresponding to 69 mg/kg/day of salicylic acid. The results also showed that following oral administration salicylic acid is not teratogenic nor embryotoxic up to 75 mg/kg/day in rodents and up to 100 mg/kg/day in Monkey. Above these dose levels, foetal malformations (skeletal malformations, cleft lip, growth retardation), resorptions and perinatal death were recorded with the compounds salicylic acid or acetylsalicylic acid.
- Salicylic acid is readily absorbed when applied to human skin. . The absorption is strongly dependent on the vehicle composition, pH, structure of the skin, conditions of the application on the skin (single dose, repeated doses, occlusion). The human percutaneous absorption from topically applied 2 % salicylic acid containing products is in the range of 20 % of the applied dose of salicylic acid. The topical application of salicylic acid to extensive areas, particularly in children, may involve a risk of toxicity by absorption due to their specific surface of exposure / body weight ratio.

2.12. Safety evaluation

Calculation of the margin of safety was performed according to the different uses of salicylic acid in cosmetic products.

CALCULATION OF THE MARGIN OF SAFETY
Salicylic acid

(Leave-on skin care product / face cream)
Based on an exposure of 1.6 g, containing at maximum 2 %

Maximum amount of ingredient applied	**I (mg)**	**=**	**32 mg**
Typical body weight of human		**=**	**60 kg**
Maximum absorption through the skin	**A (%)**	**=**	**20 %**
Absorption per treatment	**I x A**	**=**	**6.4 mg**
Systemic exposure dose (SED)	**I x A / 60 kg**	**=**	**0.11 mg/kg bw**

(Leave-on skin care product / hand cream)
Based on an exposure of 2.4 g, containing at maximum 2 %

Maximum amount of ingredient applied	**I (mg)**	**=**	**48 mg**
Typical body weight of human		**=**	**60 kg**
Maximum absorption through the skin	**A (%)**	**=**	**20 %**
Absorption per treatment	**I x A**	**=**	**9.6 mg**
Systemic exposure dose (SED)	**I x A / 60 kg**	**=**	**0.16 mg/kg bw**

(Leave-on hair products)
Based on an exposure of 1 g, containing at maximum 1 %

Maximum amount of ingredient applied	**I (mg)**	**=**	**10 mg**
Typical body weight of human		**=**	**60 kg**
Maximum absorption through the skin	**A (%)**	**=**	**20 %**
Dermal absorption per treatment	**I x A**	**=**	**2.0 mg**
Systemic exposure dose (SED)	**I x A / 60 kg**	**=**	**0.03 mg/kg bw**

(All rinse-off products)
Based on an exposure of 0.72 g, containing at maximum 2 %

Maximum amount of ingredient applied	**I (mg)**	**=**	**14.4 mg**
Typical body weight of human		**=**	**60 kg**
Maximum absorption through the skin	**A (%)**	**=**	**20 %**

Dermal absorption per treatment	**I x A**	**=**	**2.9 mg**
Systemic exposure dose (SED)	**I x A / 60 kg**	**=**	**0.05 mg/kg bw**

(A shampoo) **Based on an exposure of 0.08 g, containing at maximum 3 %**			
Maximum amount of ingredient applied	**I (mg)**	**=**	**0.24 mg**
Typical body weight of human		**=**	**60 kg**
Maximum absorption through the skin	**A (%)**	**=**	**20 %**
Dermal absorption per treatment	**I x A**	**=**	**0.05 mg**
Systemic exposure dose (SED)	**I x A / 60 kg**	**=**	**0.01 mg/kg bw**

(All other remaining cosmetic products / Salicylic acid as a preservative) **Based on an exposure of 12 g, containing at maximum 0.5 %**			
Maximum amount of ingredient applied	**I (mg)**	**=**	**60 mg**
Typical body weight of human		**=**	**60 kg**
Maximum absorption through the skin	**A (%)**	**=**	**20 %**
Dermal absorption per treatment	**I x A**	**=**	**12 mg**
Systemic exposure dose (SED)	**I x A / 60 kg**	**=**	**0.20 mg/kg bw**

Overall SED	**0.11 + 0.16 + 0.03 + 0.05 + 0.01 + 0.20**	**=**	**0.56 mg/kg bw**
No observed adverse effect level (75 mg/kg) (rat oral teratogenicity study)	**NOAEL**	**=**	**75 mg/kg bw**

Margin of Safety	**NOAEL / SED**	**=**	**133**

2.13 Opinion

On the bases of the information provided for consideration, the SCCNFP considers that salicylic acid is safe for "other uses" than as a preservative, at a concentration up to 2.0 % for the leave on and rinse-off cosmetic products and at a concentration up to 3.0 % for the cosmetic rinse-off hair products.

2.13. References

The references in italic were not used for the risk assessment

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