Scientific Committee on Consumer Safety

SCCS

SCIENTIFIC ADVICE ON

the safety of Homosalate (CAS No 118-56-9, EC No 204-260-8) as a UV-filter in cosmetic products

The SCCS adopted this scientific advice
by written procedure on 2 December 2021

ACKNOWLEDGMENTS

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The scientific advice is not subject to a commenting period.

1. ABSTRACT

The SCCS concludes the following:

1. *In light of the information provided and taking under consideration the concerns related to potential endocrine disrupting properties of Homosalate, does the SCCS consider Homosalate safe when used as a UV-filter in face products (face cream and pump spray) up to a maximum concentration of 7.34 %?*

   On the basis of safety assessment, and considering the concerns related to potential endocrine disrupting properties of Homosalate, the SCCS is of the opinion that Homosalate is safe as a UV-filter at concentrations up to 7.34% in face cream and pump spray.

2. *Alternatively, what is according to the SCCS the maximum concentration considered safe for use of Homosalate as a UV-filter in face products (face cream and pump spray)?*

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Keywords: SCCS, scientific advice, Homosalate, UV-filter, Regulation 1223/2009, CAS No 118-56-9, EC No 204-260-8

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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.).

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2. MANDATE FROM THE EUROPEAN COMMISSION

Background

Homosalate (CAS No 118-56-9, EC No 204-260-8) with the chemical names 'Benzoic acid, 2-hydroxy-, 3,3,5-trimethylcyclohexyl ester' and '(3,3,5-trimethylcyclohexyl) 2-hydroxybenzoate' has been evaluated for its safety by the SCCP in 2007 (SCCP/1086/07)1 and is currently regulated as a UV-filter in sunscreen products in a concentration up to 10 % (Annex VI/3).

On 7 November 2018, the Commission adopted a review2 of Regulation (EC) No 1223/2009 (i.e. 'Cosmetics Regulation') regarding substances with endocrine disrupting properties. The review concluded that the Cosmetics Regulation provides the adequate tools to regulate the use of cosmetic substances that present a potential risk for human health, including when displaying ED properties.

In the review, the Commission established a priority list of potential EDs for their subsequent safety assessment. A priority list of 28 potential EDs was established in early 2019 based on stakeholder consultation. The Commission then organised a public call for data3 from 16 May 2019 to 15 October 2019 on 144 of the 28 substances in order to mandate the SCCS on the safety of these substances. Homosalate was among the 14 substances for which the call for data took place.

On 24-25 June 2021, the SCCS adopted an Opinion (SCCS/1622/20)5 concluding that Homosalate could not be considered safe at concentrations of up to 10%. According to the SCCS's opinion, the use of Homosalate is safe for the consumer up to a maximum concentration of 0.5% in the final product.
On 30 July 2021, in order to ensure broad availability of UV-filters and consequently adequate sun protection for consumers, industry submitted a re-calculation of the Margin of Safety (MoS) based only on the use of Homosalate in face products (face cream and pump-spray products).

Terms of reference

(1) In light of the information provided and taking under consideration the concerns related to potential endocrine disrupting properties of Homosalate, does the SCCS consider Homosalate safe when used as a UV-filter in face products (face cream and pump spray) up to a maximum concentration of 7.34 %?

(2) *Alternatively, what is according to the SCCS the maximum concentration considered safe for use of Homosalate as a UV-filter in face products (face cream and pump spray)?*

[1] https://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_097.pdf
[2] https://ec.europa.eu/transparency/regdoc/rep/1/2018/EN/COM-2018-739-F1-EN-MAIN-PART-1.PDF
[3] https://ec.europa.eu/growth/content/call-data-ingredients-potential-endocrine-disrupting-properties-used-cosmetic products_en
[4] Benzophenone-3, kojic acid, 4-methylbenzylidene camphor, propylparaben, triclosan, Homosalate, octocrylene, triclocarban, butylated hydroxytoluene (BHT), benzophenone, homosalate, benzyl salicylate, genistein and daidzein
[5] https://ec.europa.eu/health/sites/default/files/scientific_committees/consumer_safety/docs/sccs_o_244.pdf

3. SCIENTIFIC ADVICE

3.1 CHEMICAL AND PHYSICAL PROPERTIES

Homosalate (CAS no. 118-56-9) is a clear, colourless to pale yellow liquid with a molecular weight of 262.3 g/mol and a partition coefficient of 6.34 (at 40°C). The substance is miscible in paraffin oil, isopropyl myristate and ethanol (at 20°C), and immiscible in propylene glycol (at 20°C). Solubility in water (at 25°C) is 0.4 mg/L.

Ref.: ECHA 2020a, 2020b; Symrise 2002, 2004

3.2 TOXICOKINETICS

Taken from SCCS/1622/20

Several *in vitro* dermal penetration studies using rat and human skin have been performed. For MoS calculation, the SCCS selected a new skin penetration study using human skin from which a dermal absorption of 5.3% (mean + 1SD: 3.86±1.43) was derived. Systemic bioavailability of Homosalate after dermal application was confirmed by the detection of Homosalate in plasma of volunteers after topical application of sunscreen products containing Homosalate but also by the detection of Homosalate human milk samples. Maximum plasma concentrations of Homosalate after topical application varied between 13.9 and 23.1 ng/ml and terminal half-lives varied between 46.9 and 78.4 h in an explorative study. *In vitro*, Homosalate was hydrolysed into salicylic acid and 3,3,5-trimethylcyclohexanol. In addition, conjugation and hydroxylation of intact Homosalate was observed.

Ref.: Finlayson 2021; Guesmi 2019; Matta 2020; Schlumpf 2010

3.3 EXPOSURE ASSESSMENT

3.3.1 Function and uses

Taken from SCCP/1086/07

Homosalate is used as a broad-band UV filter in concentrations of up to 10% in the EU or 15% depending upon where the product is used (e.g. in the USA) in sunscreen products alone or in combination with other UV absorbers to protect the skin against harmful effects of the UV radiation.

Ref.: Symrise 2002, 2004

Taken from SCCS/1622/20

A survey on the occurrence of organic UV filters in personal care products in Switzerland revealed that Homosalate can be also found in such products. In a survey performed by the Danish Environmental Protection Agency from October 2013 to August 2015, Homosalate was found in 27 products out of 291, including 18 sunscreens. Products include face cream, body wash, cream; day cream, eau de toilette, foundation, hand cream, lip balm, makeup, perfume, sun oil and sunscreen.

Ref.: Manová 2013; The Danish Environmental Protection Agency 2015

3.3.2 Calculation of SED

An OECD Test Guideline 428 study (Finlayson, 2021) described in SCCS/1622/20, topical application of 2 mg/cm^2 of [^{14}C]-Homosalate in an oil/water-based formulation at 10% (w/w) to human skin *in vitro* resulted in the dermal delivery of 3.86±1.43% (7.50±2.79 µg

equiv./cm^2) after a 24-hour exposure period. The SCCS decided to use 5.3% (mean +1SD) from this properly performed skin penetration study for SED and MoS calculation.
The calculation of the systemic exposure dose (SED) was carried out as laid down in the SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation, 11th revision, was adopted during the plenary meeting of 30-31 March 2021 (SCCS/1628/21).

SED for dermal and inhalation exposure were calculated for face creams and face pump spray containing 7.34% Homosalate. SED after dermal and inhalation exposure are shown in Tables 1 and 2, respectively. Table 3 shows the SED for aggregated exposure for face cream including face pump screen.

Table 1. SED calculation for dermal exposure to face cream

Description	**Parameter**	**Value**	**Unit**
Daily amount applied	A	1.54	g/day
Concentration of substance	C	7.34	%
Dermal absorption	DA_p	5.3	%
Bodyweight	bw	60	kg
SED_{dermal}	Ax1000 x C/100 x DA_p/100	**0.0998**	**mg/kg bw/day**

Table 2. SED calculations for inhalation exposure after the use of face pump spray

Description	**Parameter**	**Value**	**Unit**
Sprayed amount of product	$a_{product}$	1540	mg/day
Concentration of substance in the product	$C_{product}$	0.0734	fraction
Airborne fraction	f_{air}	0.2	fraction
Amount of substance available for inhalation	**a_{expo}** ($a_{product}$ x $C_{product}$ x f_{air})	**22.61**	**mg**
Near-field, 1 m^2			
Volume of Box 1	V_1	1000	L
Inhalation rate	r_{inh}	13	L/min
Duration of exposure in Box 1	t_1	2	min
Potential substance amount inhaled during Box 1	**a_{inh-1}** (a_{expo} x r_{inh} x t_1/V_1)	**0.5878**	**mg**
Second step: 10 min in far field			
Volume of Box 2	V_2	10000	L
Inhalation rate	r_{inh}	13	l/min
Duration of exposure in Box 2	t_2	10	min
Potential substance amount inhaled during Box 2	**a_{inh-2}** (a_{expo} x r_{inh} x t_2/V_2)	**0.2939**	**mg**
Fraction of substance retention in the lung (inhaled – exhaled; 25% exhaled)	f_{ret}	0.75	
Respirable fraction	f_{resp}	0.01	
Frequency of application*	f_{appl}	/	
Bodyweight	bw	60	kg
SED_{inhal}	**((a_{inh-1}+ a_{inh-2}) x f_{ret} x f_{resp} x f_{appl})/bw**	**0.0001**	**mg/kg bw/day**

*Sprayed amount of product ($a_{product}$) is given as mg/day, hence frequency of application (f_{appl}) was not included in the present SED calculation.

Table 3. SED calculations of aggregated exposures to face cream including face pump spray

SED (mg/kg bw/day)		
Dermal	**Inhalation**	**Total**
0.0998	0.0001	0.0999

3.4 TOXICOLOGICAL EVALUATION

A brief summary of Homosalate toxicity is given below. For more details, SCCS/1622/20 should be consulted.

Irritation/skin sensitisation
Homosalate is not considered as a skin irritant. The limited data available for eye irritation do not point to eye irritation of Homosalate when used in concentrations up to 10% in sunscreen formulations. Furthermore, the substance is considered not to present any concern for skin sensitisation.

Acute toxicity
Homosalate is of low acute oral and dermal toxicity.

Repeated dose toxicity
For repeated dose toxicity, an oral study performed according to OECD TG422 (Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test) is available, where the following dose levels of Homosalate were administered to male and female RccHanTM: WIST(SPF) rats: 0 (control), 60, 120, 300 and 750 mg/kg bw/d.
Based on this study, the Applicant derived a NOAEL of 300 mg/kg bw/day for general toxicity based on mortality in high-dose females and decreased food consumption. However, it should be noted that at this dose, effects on kidneys, liver, thyroid and thymus had already occurred. In male animals, histopathological kidney findings occurred from the lowest dose level. Immunohistochemical analysis did not support the conclusion that kidney toxicity is not of relevance for humans. It is of note that in males, higher kidney weights were also observed from the lowest dose (but without dose-dependency). As effects were noted from the lowest dose of 60 mg/kg bw/d the SCCS considered this dose as LOAEL, in particular as human relevance of the kidney findings could not be ruled out due to inconclusive results from immunohistochemical reanalysis of kidneys.

Reproductive toxicity
Fertility and developmental toxicity of Homosalate were addressed in the same Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test according to OECD TG 422.
A NOAEL for general toxicity was established at 300 mg/kg bw/day for both sexes based on maternal effects and developmental toxicity (adverse effects on food consumption and body weights in both sexes and mortality of females noted at higher dose).
No indication of any effect on reproduction was noted at the dose levels of 60 and 120 mg/kg bw/day (changes in sperm morphology and sperm motility correlating with reduced weights of prostate and seminal vesicles and increased post-implantation loss were noted at 750 and 300 mg/kg/day). However, because of low numbers of pregnant females, none of these dose levels could be conclusively confirmed as NOAEL.
The possible effects on fertility (increased infertility, sperm changes), development (higher post-implantation loss) and thyroid (hypertrophy of the follicular epithelium) noted in this study cannot be considered as conclusive and reliable due to a technical error that maintained the animals under a constant light.

Mutagenicity/genotoxicity
Homosalate was investigated in valid GLP genotoxicity tests for the three types of genotoxic endpoints: gene mutations, structural and numerical chromosome aberrations.

Homosalate did not induce gene mutations in bacteria and it did not induce gene mutations at the HPRT locus in V79 Chinese hamster cells. Homosalate did not induce chromosomal aberrations in CHO cells. Overall, the SCCS is of the opinion that Homosalate can be considered to have no genotoxic potential.

Endocrine activity
The available data on Homosalate provide some indications for potential endocrine effects. However, the current level of evidence is not sufficient to regard it as an endocrine disrupting substance, or to derive a toxicological point of departure based on endocrine disrupting properties for use in human health risk assessment.

Ref.: SCCS/1622/20

3.5 SAFETY EVALUATION

In SCCS/1622/20, a LOAEL of 60 mg/kg bw/d, based on a combined repeated dose toxicity study with the reproduction / developmental toxicity screening test (OECD Guideline 422) was used. Since the point of departure was based on a LOAEL, an assessment factor of 3 was added to account for LOAEL-NOAEL extrapolation. Furthermore, due to lack of information on oral bioavailability, 50% of the administered dose was used as the default oral absorption value, resulting in an adjusted NOAEL of 10 mg/kg bw/day.

Product	**Exposure route**	**$NOAEL_{adj}$ (mg/kg bw/day)**	**SED**	**MoS**
Face cream	Dermal	10	0.0998	**100.2**
Face pump spray	Dermal + inhalation	10	0.0999	**100.1**

$NOAEL_{adj}$: Adjusted NOAEL value

Combined exposure to salicylic acid either formed by metabolic transformation from Homosalate, other salicylates (e.g. methylsalicylate) or directly from salicylic acid itself has not been considered in this Opinion.

4. CONCLUSION

1. In light of the information provided and taking under consideration the concerns related to potential endocrine disrupting properties of Homosalate, does the SCCS consider Homosalate safe when used as a UV-filter in face products (face cream and pump spray) up to a maximum concentration of 7.34 %?

On the basis of safety assessment, and considering the concerns related to potential endocrine disrupting properties of Homosalate, the SCCS is of the opinion that Homosalate is safe as a UV-filter at concentrations up to 7.34% in face cream and pump spray.

2. Alternatively, what is according to the SCCS the maximum concentration considered safe for use of Homosalate as a UV-filter in face products (face cream and pump spray)?

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5. MINORITY OPINION

None

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7. GLOSSARY OF TERMS

See SCCS/1628/21, 11th Revision of the SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation – from page 181

8. LIST OF ABBREVIATIONS

See SCCS/1628/21, 11th Revision of the SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation – from page 181