Office for Product Safety & Standards

SCIENTIFIC ADVISORY GROUP ON CHEMICAL SAFETY OF NON-FOOD AND NON-MEDICINAL CONSUMER PRODUCTS (SAG-CS)

Opinion on Homosalate use in Cosmetic Products

1. Introduction

1.1. Homosalate (3,3,5-trimethylcyclohexyl salicylate; CAS No. 118-56-9) is currently included on the list of substances permitted for use as a UV filter in cosmetic products up to a concentration of 10% within Annex VI (Entry 3) of the Cosmetic Products Regulation UK No 1223/2009 (as amended).

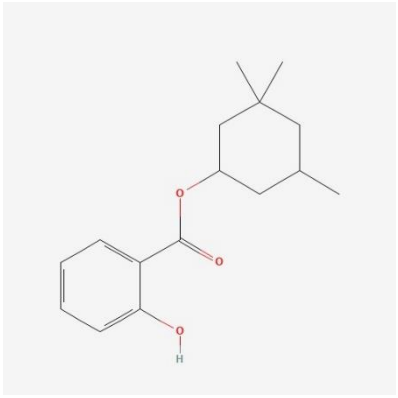

Figure 1: The chemical structure of Homosalate, CAS: 118-56-9. (Source: PubChem).

1.2. Homosalate does not have any human health related harmonised classifications under the GB Classification, Labelling and Packaging (CLP) regulation No 1272/2008 (as amended). Currently no EU harmonised or UK mandatory classification and labelling entries exists for homosalate (databases accessed November 2022). However, it is suspected of having endocrine disrupting activity (ANSES, 2018; European Commission, 2019).

1.3. In April 2022, OPSS released a call for data on the safety of cosmetic ingredients with suspected endocrine disrupting properties in which homosalate was included (OPSS, 2022).

1.4. Several responses were submitted from industry to OPSS to support the safe use of homosalate in cosmetic products up to a maximum concentration of 10% as a UV-filter in sunscreen products. OPSS requested that the SAG-CS assess the safety of homosalate intended to be used within cosmetic products. This assessment took place at the September and November 2022 and July 2024 SAG-CS meetings.

2. Intended function and uses of homosalate.

2.1. Homosalate is currently used in cosmetic products that lead to dermal exposure e.g. sunscreen lotion/cream, face cream, hand cream, lip salve and inhalation exposure e.g. sunscreen pump or propellant spray.

2.2. The predominant use of homosalate is as a broad band UV-filter in sunscreen products. At current usage levels of up to 10%, sun protection products with sun protection factors of 10-50 can be achieved. Homosalate may also be incorporated in cosmetic products to protect the product formulation from UV-induced deterioration (Kao, 2025).

3. Potential Endocrine Disrupting Properties

3.1. *In vitro* assays reported anti-androgenic and estrogenic activities. However, considering the concentrations used in *in vitro* assays, it is difficult to apply these findings to the exposure of homosalate from cosmetic products in humans (Zhang et al, 2024).

3.2. The available databases were extremely limited with respect to *in vivo* assays providing evidence to investigate endocrine activity and adversity. While the uterotrophic assay in the rat was negative it is recognised that this assay is not able to provide information on other potential modes of action (Schlumpf et al, 2001). The repeated dose studies available to the Members were of limited value with respect to the assessment of endocrine disruption, as the majority of endocrine-related effects were not investigated.

4. Previous Scientific Opinions on Homosalate

4.1. Homosalate was initially listed as a permitted UV filter up to a concentration of 10% (*w*/*w*) in Annex VII of the EU Cosmetics Directive 76/768/EEC (repealed 30 Nov 2009).

4.2. In 2001, the Scientific Committee on Cosmetic and Non-Food Products (SCCNFP) reviewed the potential estrogenic effects of homosalate. An E-screen assay[1] in human breast cancer cells (MCF-7) was reviewed and an EC_{50} value of 1.56 µM was reported for homosalate. Additionally, an uterotrophic assay carried out using oral exposure of rats to homosalate

[1]Protocol can be found in Soto et al, 1995; https://pubmed.ncbi.nlm.nih.gov/8593856/

through days 21-24 of life was reported, in which homosalate was reported to be inactive (Schlumpf *et al.*, 2001; SCCNFP, 2001).

4.3. In 2007, the Scientific Committee on Consumer Products (SCCP) reviewed a dossier that proposed continued usage of homosalate up to a concentration of 10% (*w*/*w*) following a request for re-evaluation by EU member states. Using a Point of Departure (PoD) which was a No Observed Adverse Effect Level (NOAEL) equal to 100 mg/kg bw/day from a 14-day oral toxicity range-finding study in male and female rats, the SCCP derived a Margin of Safety (MoS) of 167, taking into account a Systemic Exposure Dose (SED) of 0.60 mg/kg bw/day. The SCCP concluded that homosalate did not pose a risk to the consumers' health when used as a UV-filter up to 10% (*w*/*w*) in cosmetic sunscreen products. The SCCP further regarded that homosalate did not pose a risk to the health of consumers when used as a UV-filter up to 10% (*w*/*w*) in other cosmetic products. The SCCP noted that their assessment related only to dermal application and not to spray-type products (SCCP, 2007).

4.4. Following their call for data on substances with potential endocrine disrupting properties in 2019, the Scientific Committee of Consumer Safety (SCCS) were mandated by the European Commission to perform a safety assessment for homosalate considering the data received. Within this assessment, the SCCS performed a MoS calculation using an adjusted NOAEL of 10 mg/kg bw/day. This adjusted NOAEL was derived through application of an adjustment factor of 3 for LOAEL-NOAEL extrapolation in addition to using a 50% assumed oral bioavailability to a Lowest Observed Adverse Effect Level (LOAEL) of 60 mg/kg bw/day which was obtained from a rodent study performed following the OECD test guideline (TG) no. 422: “Combined repeated dose toxicity study with reproduction/developmental toxicity screening test” (Dettwiler, 2013). A systemic exposure dose of 1.59 mg/kg bw/day was derived utilising a dermal absorption value of 5.3%, resulting in a Margin of Safety of 6.3. The SCCS therefore concluded that homosalate was not safe when used as a UV-filter in cosmetic products at concentrations of up to 10%. In order to derive a safe usage level where MoS > 100, a SED of 0.1 mg/kg bw/day should be achieved, hence a maximum permissible usage concentration of homosalate was derived at 0.5% when used in sunscreen, hand cream and face cream. The SCCS therefore concluded that the use of homosalate as a UV filter in cosmetic products was safe for the consumer up to a maximum concentration of 0.5% homosalate in the final product. Regarding suspected endocrine disrupting properties, the SCCS concluded that the available evidence was inconclusive, and at best equivocal. The SCCS considered that, whilst there were indications from some studies to suggest that homosalate may have endocrine effects, the evidence was not conclusive enough to enable a derivation of a specific endocrine-related toxicological point of departure for use in safety assessment (SCCS, 2021a).

4.5. Following publication of their 2021 opinion on homosalate, a recalculated MoS was submitted to the SCCS to defend the use of homosalate as a UV-filter in face products only (face cream dermal exposure and pump spray dermal and inhalation exposure only) up to a maximum concentration of 7.34%. A SED for

face creams and face pump sprays containing 7.34% homosalate was derived as 0.0998 mg/kg bw/day for dermal exposure and 0.0001 mg/kg bw/day for inhalation exposure, result in an aggregate SED of 0.0999 mg/kg bw/day. Utilising these SED values and the previous described adjusted PoD of 10 mg/kg bw/day, a MoS was calculated at 100.2 for face cream (dermal only) and 100.1 for face pump spray (dermal + inhalation). The SCCS concluded that homosalate was safe as a UV-filter at concentrations up to 7.34% in face cream and pump spray (SCCS, 2021b).

5. Discussion by the Scientific Advisory Group on Chemical Safety of Non-Food and Non-Medicinal Consumer Products (SAG-CS)

5.1. At their September and November 2022 meetings, the SAG-CS discussed the papers prepared by OPSS which focussed on risks posed to health by homosalate when used as a UV filter in cosmetic products.

5.2. Members commented that the data in relation to the endocrine disrupting potential of homosalate were mixed, with both positive and negative results. Positive results were largely observed *in vitro*.

5.3. Members discussed the metabolism of homosalate to salicylic acid via esterase activity and potential effects of salicylic acid on human health. Members noted evidence of metabolism *in vitro* but not *in vivo*.

5.4. Members discussed the read-across of data on methyl salicylate to homosalate. Members agreed that based on chemical structure, the two chemicals are not sufficiently structurally similar to support read across. In addition, as data on homosalate is available, read-across is not required. Further, the limited read-across case submitted is not sufficient to evaluate.

5.5. Members discussed the available data with respect to identifying a dermal absorption value. Members agreed that the Finlayson (2021) study was the most appropriate study from which to derive the dermal absorption value for homosalate, as it is a well conducted (according to the OECD TG no. 428, meets GLP guidelines and the SCCS 'basic criteria' (2010)) study. In addition, based on this reasoning, the mean dermal delivery value plus one standard deviation was appropriate to derive the final dermal absorption value. Members agreed on a dermal absorption value of 5.3% for use in the safety assessment based on mean experimental results from Finlayson (2021) plus one standard deviation. Members did note that the PBPK modelling used a dermal absorption value of 2.48% which was derived following comparison between measured and simulated C_{max} values. The higher dermal absorption figure was used in the SED and MoS calculations (found in Annex 1 to this opinion) to be more precautionary.

5.6. Members discussed the pivotal study by Dettwiler (2013), used to identify a critical NOAEL and PoD for use in the safety assessment. They noted that further studies (a 90-day oral repeated dose study in rats, a pre-natal developmental toxicity study in the rat or rabbit, an extended one-generation reproductive toxicity study in rats) have been requested for REACH regulation

purposes for submission by September 2021 (ECHA, 2018) and may be available for evaluation in the future if required.

5.7. In the study conducted by Dettwiler (2013), homosalate was administered at 0, 60, 120, 300 and 750 mg/kg bw/day to Han Wistar rats for 67 days in males and 14 days in females prior to pairing. Effects on male fertility were noted including changes in sperm motility and morphology at 750 mg/kg bw/day. Effects on reproductive outcome were noted at 300 mg/kg bw/day with increased post implantation loss. No effects were observed in the 60 and 120 mg/kg bw/day groups, but the low number of pregnant females makes it difficult to draw firm conclusions in these groups.

5.8. Members agreed that there were deficiencies in the study (i.e. constant lighting rather than a light-dark cycle and low numbers of pregnant females) which limited its potential usefulness for consideration in the safety assessment.

5.9. However, despite the shortcomings of this study, members concluded that, whilst the reproductive rate was low, effects were observed across the two top groups and therefore they were happy to accept the results from this study. The NOAEL of 120mg/kg bw/day was therefore accepted as the point of departure for homosalate

5.10. Members discussed the rat and human PBPK models (Najjar, 2021; Najjar *et al.*, 2022) and proposal by the applicant to use the model estimates as the basis for the safety assessment. Members also asked an independent expert for their opinion on the modelling used by the applicant. Members discussed limitations, uncertainties and confidence in the models. Members agreed that the level of confidence in the models was high and they were reassured that the model platform and code used had been approved for use by the US FDA for the safety assessment of pharmaceuticals, food ingredients, additives and contaminants to predict human exposure.

5.11. Both models sufficiently described the proposed biological events with respect to the mode of action of homosalate and the strengths and limitations of the available parameters and data. The human model was considered valid because the prediction of the mean plasma C_{max} and the 95% confidence interval values after a single application of 163 µg/cm^2/day (assuming both 2% and 2.48% dermal penetration) were within the range reported in a human clinical trial by Matta et al, (2020).

5.12. The Members were reassured by the conservatism built into the results through the oral absorption assumptions. Models of oral absorption have predicted almost 100% absorption whereas the oral bioavailability has been predicted to be 83%. The applicant has been more conservative than this in their calculations by using the 50% absorption assumption used in the SCCS notes of Guidance.

5.13. The Members worked through the OECD guidance checklist for PBPK model evaluation and were reassured by the outcome. In conclusion, the Members were content that the PBPK model was adequately representative of the

actual exposures likely to be reached following use of homosalate-containing cosmetic products and was robust and predictive.

5.14. The Members agreed with the applicant's use of the PBPK modelling to calculate the internal consumer exposure to homosalate following use of sunscreens containing a maximum of 10% homosalate and the internal exposure in rats at the PoD of 120mg/kg bw/day from the Dettwiler (2013) study. Calculations used the assumption of 18 g per day for sunscreen exposure as described in the SCCS Notes of Guidance 2023.

5.15. The usual 100-fold uncertainty factor used in the safety assessment of cosmetics can be reduced to 25 in this case because the interspecies kinetics factor of 4 can be reduced to 1 because use of the PBPK model has removed this uncertainty.

5.16. Using both the C_{max} and $AUC_{(0-24)}$ exposure metrics from the rat and human PBPK models, the applicant calculated the following margins of safety for dermal exposure alone.

Exposure metric	Rat at POD (120mg/kg bw/day)	Human	Margin of Internal Safety
C_{max} (ng/mL)	1837.8	13.62	135
$AUC_{(0-24)}$ (ng.h/mL)	31979.9	316.49	101

5.17. In both cases, the MoS is well in excess of the required MoS of 25. They also calculated the exposure following inhalation exposure.

Exposure metric	Dermal exposure only	Dermal plus inhalation	Margin of Internal Safety
C_{max} (ng/mL)	13.62	14.22	129
$AUC_{(0-24)}$ (ng.h/mL)	316.49	330.42	96

5.18. Members were content with these margins of safety given the outcome of the PBPK modelling.

5.19. Members discussed the regulatory background of homosalate and relevant opinions from other advisory bodies (the SCCS, 2010 and Health Canada, 2020).

5.20. In addition, the Members noted that following a non-exhaustive overview of the literature published on analytical methods, although sparse, it would appear that routine gas or liquid chromatographic methods are available with adequate performance characteristics that could be validated in an official control laboratory in the UK if required. Confirmatory liquid chromatography

with tandem mass spectrometry (LC-MS/MS) methods are also available, again requiring validation. The cis/trans separation would need to be achieved, and the total content assessed as the sum of both. It seems likely that validated methods capable of addressing limits down to around less than 1% homosalate in sunscreens could be validated.

6. Conclusions

Members agreed that the most appropriate dermal absorption value to use in the safety assessment was 5.3% based on the results of the study by Finlayson (2021).

Members agreed that the pivotal study by Dettwiler, (2013), contained deficiencies which had the potential to limit its usefulness in the safety assessment. However, members concluded that, whilst the reproductive rate was low, adverse effects were observed across the two highest dose groups and therefore they were happy to accept the results from this study. The NOAEL of 120mg/kg bw/day was therefore accepted as the point of departure for homosalate.

Members were content to accept the PBPK modelling presented by the applicant following an independent review provided by an invited expert and therefore the margin of safety could be reduced from 100 to 25 in this case due to removal of the interspecies safety factor of 4.

Calculations based on the exposure metrics from the PBPK modelling (section 5), as well as those using the SED calculation from the SCCS notes of guidance (Annex 1) all give margins of safety in excess of 25.

Members concluded that homosalate is safe at a maximum concentration of 10% in sunscreen products.

An adequate analytical method appears to be available for homosalate.

Scientific Advisory Group on Chemical Safety of Non-Food and Non-Medicinal Consumer Products

March 2025

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Systemic Exposure Dose and Margin of Safety calculations

SED calculations following dermal exposure using the conservative use estimate of 18g/day from the SCCS Notes of Guidance for sunscreens.

Description	Parameter	Value	Unit
Daily amount applied	$E_{product}$	18	g/day
Concentration of substance	C	10	%
Dermal absorption	DAp	5.3	%
Bodyweight	bw	70	kg
SED_{dermal}	($E_{product}$ x 1000) x (C/100) x (Da_p/100)	1.36	mg/kg bw/day
PoD	PoD	120	mg/kg bw/day
MoS (dermal)	PoD_{sys} /SED	88	
SED_{inhal} (see table below)	((a_{inh}-1+ a_{inh}-2) x f_{ret} x f_{resp} x f_{appl})/bw	0.0015	mg/kg bw/day
SED dermal and inhalation	SED_{dermal} + SED_{inhal} = SED_{total}	1.3615	mg/kg bw/day
MoS dermal and inhalation	PoD_{sys} /SED_{total}	88	

SED calculations for inhalation after the use of a pump spray

Description	Parameter	Value	Unit
Sprayed amount of product	$A_{product}$	18000	mg/day
Concentration of substance in product	$C_{product}$	10	%
Airbourne fraction	f_{air}	0.2	
Amount available for inhalation	**a_{expo} ($A_{product}$ x $C_{product}$ x f_{air})**	**360**	**mg**
Near-field 1m^3			
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 amount inhaled in box 1	**a_{inh}-1 (a_{expo} x r_{inh} x t1) /V1**	**9.36**	**mg**
Far-field 10m^3			
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 amount inhaled in box 2	**a_{inh}-2 (a_{expo} x r_{inh} x t2) /V2**	**4.68**	**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	70	kg
SED_{inhal}	**((a_{inh}-1+ a_{inh}-2) x f_{ret} x f_{resp} x f_{appl})/bw**	**0.0015**	**mg/kg bw/day**