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

Final Opinion on Octocrylene in Cosmetic Products.

1. Introduction

1.1. Octocrylene (2-cyano-3,3-diphenyl acrylic acid 2-ethylhexyl ester; CAS No. 6197-30-4, figure 1) 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 10) of the Cosmetic Products Regulation UK No 1223/2009 (as amended).

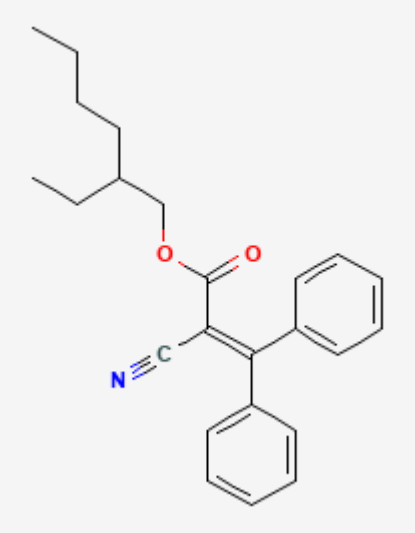

Figure 1: Structure of Octocrylene, CAS No. 6197-30-4 (PubChem, 2023)

1.2. Octocrylene 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 GB mandatory classification and labelling entries exists for octocrylene (databases accessed December 2022). However, it is suspected of being an endocrine

disruptor and is under assessment as persistent, bio-accumulative and toxic (PBT) by the European Chemicals Agency (ECHA, 2022)[1].

1.3. In April 2022, OPSS released a call for data on the safety of cosmetic ingredients with suspected endocrine disrupting properties in which octocrylene was included. Several responses were submitted to OPSS to support the safe use of octocrylene as a UV filter up to a concentration of 10% in cosmetic products. OPSS requested that the SAG-CS review the safety of octocrylene intended to be used as a UV-filter in cosmetic products.

2. Background

Intended function and uses of octocrylene:

2.1. The main function of octocrylene is to act as a UV-B filter and sunscreen stabiliser (when in combination with dibenzoylmethane derivatives) in sunscreen products (Berardesca *et al.,* 2019). Octocrylene is also used in body and face care products, perfumes and fragrances.

3. Potential Endocrine Disrupting Properties

3.1. For the purposes of this assessment the SAG-CS are using the WHO/IPCS definition for endocrine disruption[2] (WHO/IPCS, 2002).

3.2. *In vitro* data (OECD conceptual framework levels 1 and 2): *In vitro* mechanistic studies were undertaken with octocrylene in human sperm cells - these assays were negative and did not show endocrine activity. ToxCast data from the *in vitro* high throughput screening program are available which showed some receptor binding and some endocrine activity was observed in 7/30 assays (*in vitro* human estrogen receptor (hER) and human androgen receptor (hAR) transactivation assays), with 4/7 of these results being flagged as misleading positives by the US EPA automated analysis tool (ToxCast, 2023). Overall, evidence of endocrine activity is weak and octocrylene is unlikely to be an endocrine disrupting chemical according to the WHO definition.

3.3. *In vivo* data (OECD conceptual framework levels 3 and 4): Two *in vivo* mechanistic assays are available, a Hershberger assay and a uterotrophic assay, both conducted in rats; these assays showed no endocrine disrupting

[1] https://echa.europa.eu/pbt/-/dislist/details/0b0236e180a001ed

[2] *'An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations.'*

effects. Several repeated dose toxicity studies providing data on adverse effects on endocrine relevant endpoints are available, including 90-day studies in rats and rabbits and a prenatal developmental toxicity study in rats. No endocrine-relevant adverse effects were observed in these studies.

4 Regulation of Octocrylene in Other Jurisdictions

4.1 In Australia, octocrylene is currently allowed for use up to a maximum concentration of 10% in sunscreen products.

4.2 In Canada, octocrylene is currently allowed for use up to a maximum concentration of 10% in sunscreen products.

4.3 In the European Union, octocrylene is currently allowed for use up to a maximum concentration of 10% in cosmetic products except propellant spray products where 9% is permitted.

4.4 In the United States, octocrylene may be used up to 10% in over-the-counter sunscreen products. Local regulations may vary.

5 Previous Scientific Opinions on Octocrylene

5.1 Octocrylene was assessed in 1994 by the Scientific Committee on Consumer Products (SCCP) in which it was deemed to be non-toxic, non-irritating, and not sensitising. The SCCP noted that no carcinogenicity studies were available to be considered..

5.2 Following their call for data on substances considered to be potential endocrine disruptors in 2019, the Scientific Committee of Consumer Safety (SCCS, 2021) were mandated by the European Commission to perform a safety assessment for octocrylene considering the data received. Within this assessment the SCCS performed several Margin of Safety (MoS) calculations using a No Observed Adverse Effect Level (NOAEL) of 153 mg/kg bw/day from an extended one-generation reproductive study in rats and an oral bioavailability of 50%, resulting in an adjusted NOAEL of 76.5 mg/kg bw/day.

5.3 In 2021, the SCCS found that octocrylene used at 10% was safe for use in lipstick, face cream, hand cream, sunscreen cream/lotion, sunscreen propellant spray, and sunscreen pump spray, when used individually. Aggregate exposure of all products (lipstick, face cream, hand cream, and one form of sunscreen) was shown to be safe in scenarios in which sunscreen cream/lotion or sunscreen pump spray was used. However, an insufficiently protective MoS (less than an MOS of 100 according to SCCS Notes of

Guidance (NoG) 2021[3]) was achieved for aggregate exposure when a propellant spray was used as the one form of sunscreen, in addition to lipstick, face cream and hand cream use. A sufficient MoS of greater than 100 was achieved for aggregate exposure when using a sunscreen propellant spray when the octocrylene concentration in the sunscreen propellant spray was reduced to 9%. Overall, the SCCS concluded that:

'*Octocrylene is safe as a UV-filter at concentrations up to 10% in cosmetic products when used individually.*

Octocrylene is also considered safe for a combined use of sunscreen cream/lotion, sunscreen pump *spray, face cream, hand cream and lipstick at a concentration up to 10%. However, the use of octocrylene at 10% or above in sunscreen propellant spray is not considered safe for the combined use.*

The use of octocrylene in sunscreen propellant *spray is considered safe when its concentration does not exceed 9% when used together with face cream, hand cream, and lipstick containing 10% octocrylene*.'

5.4 With respect to endocrine disrupting properties, the SCCS considered that some *in vivo* studies suggested endocrine effects, but the overall data package was not sufficiently conclusive to enable deriving a specific endocrine-related point of departure for use in the safety assessment (SCCS, 2021).

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

6.1 At their July 2022 meeting, the SAG-CS discussed a paper which focussed on risks posed to human health by octocrylene when used as a UV filter in cosmetic products.

6.2 The regulatory background of octocrylene and previous opinions from other risk assessment bodies were discussed (sections 4 and 5). Members noted that octocrylene can degrade to benzophenone (CAS 119-61-9) which is known to be hazardous and should be monitored and kept at trace levels (Downs et al, 2021).

6.3 Members discussed analytical methods for detection and quantification of octocrylene. No analytical difficulties were foreseen. At least one literature high performance liquid chromatographic-ultraviolet detection (HPLC-UV) method exists for octocrylene with reasonable performance characteristics and Limit of Detection (LOD) and Limit of Quantification (LOQ) values. For octocrylene the LOD and LOQ are 1.64×10^{-6} M and 4.97×10^{-6} M, respectively, and are

[3] The 12th SCCS Notes of Guidance (2023) were published after the assessment of octocrylene was completed by the SAG-CS (SCCS, 2023).

anticipated to be replicable in cosmetic product formulations (Berkman and Yazan, 2011).

6.4 Genotoxicity data for octocrylene were discussed. There was a wide range of *in vitro* and *in vivo* studies. The battery of genotoxicity studies covered all three genetic endpoints - gene mutations, structural and numerical chromosome aberrations. Photomutagenicity studies were also conducted. Members were content that octocrylene did not show evidence of genotoxicity (ECHA, 2022).

6.5 Members regarded the risk of skin sensitisation as low and noted a substantial history of the safe use of octocrylene up to 10% in cosmetic products.

6.6 Systemic Exposure Dose (SED) calculation and safety assessment is based on the most recent *in vitro* dermal absorption study by Fabian and Landsiedel (2020) giving a dermal absorption value of 0.33% (equivalent to 0.97 µg/cm^2; mean + one standard deviation) for a 10% octocrylene application.

6.7 Metabolism of octocrylene was concluded to be via hydrolysis by esterase enzymes, oxidation and conjugation.

6.8 Repeat dose toxicity studies were conducted and did not indicate concern for carcinogenicity.

6.9 No long-term toxicity and/or carcinogenicity studies were submitted or identified for octocrylene.

6.10 No observable adverse effect levels (NOAELs) were determined in reproductive and developmental toxicity studies.

6.11 An extended one generation reproductive toxicity study (EOGRTS; Triskelion, 2019) was performed to comply with the EU REACH regulation (EC No. 1907/2006) from which a NOAEL of 153 mg/kg bw/day was determined for parental toxicity (based on effects on body weights at the next highest dose, the lowest observed adverse effect level (LOAEL) of 534 mg/kg bw/day), fertility and reproductive performance (based on implantations and number of pups delivered at the LOAEL) and developmental toxicity (based on effects on pup body weights at the LOAEL). This NOAEL of 153 mg/kg bw/day was used as the basis for the Point of Departure (PoD) in the safety assessment. According to the SCCS NoG (SCCS, 2023), section 3-5.1.2: *'in the absence of data, 50% of the administered dose is used as the default oral absorption value for a cosmetic ingredient and the PoDsys is derived from the PoD by dividing with a factor 2.'* Therefore, the NOAEL is adjusted by the default oral absorption value (50%), resulting in a systemic PoD (PoDsys) of 76.5 mg/kg bw/day. Members agreed with the application of this approach in this situation.

6.12 Committee members discussed the Margin of Safety (MoS) calculations in depth; the following SED and MoS values were calculated:

Table 1. SED and MoS calculations using a default body weight of 70kg. All products containing 10% octocrylene.

Route of Exposure		SED (mg/kg bw/day)	PoD_{sys} (mg/kg bw/day)	MoS
Dermal exposure to sunscreen (whole body)		0.485[1]	76.5	158
Dermal exposure to face cream		0.0168	76.5	4566
Dermal exposure to hand cream		0.0238[1]	76.5	3210
Inhalation exposure to sunscreen	*using Propellant spray*	0.150[2]	76.5	509
Inhalation exposure to sunscreen	*using Pump spray*	0.00150[2]	76.5	50855
Oral exposure to lip salve		0.0450[3]	76.5	1700
Aggregated exposure to sunscreen spray (body, face and hands) + lip salve (dermal + inhalation + oral exposure)	*using Propellant spray*	0.485 + 0.0168 + 0.0238 + 0.0450 + 0.150 = 0.721	76.5	106
Aggregated exposure to sunscreen spray (body, face and hands) + lip salve (dermal + inhalation + oral exposure)	*using Pump spray*	0.485 + 0.0168 + 0.0238 + 0.0450 + 0.00150 = 0.572	76.5	134

SED – systemic exposure dose. MoS – margin of safety
Notes: SED values stated are rounded to the nearest 3 significant figures. Calculation of the MoS used unrounded numbers and therefore sometimes resulted in different final MoS values compared to those the rounded figures would lead to.
[1] = derived in appendix, table 2
[2] = derived in appendix, table 3
[3] = derived in appendix, table 4

6.13 Safety assessment calculations submitted by the applicants were evaluated (see Appendix), and the safety assessment calculations, using a body weight of 70kg[4], demonstrate that octocrylene is considered to be safe as a UV-filter at concentrations up to 10% in sunscreen lotion, cream, propellant spray, pump spray and lip products, when used individually and in combination with a propellant sunscreen spray and a lip product used in combination in a Tier

1 aggregate deterministic exposure assessment giving a MoS of 106, which meets acceptable risk criteria according to SCCS 12th Notes of Guidance, (SCCS, 2023), which the SAG-CS are following[4].

6.14 Members were of the opinion that risk assessments for children and adolescents should be conducted when appropriate data on usage patterns become available.

6.15 Members considered that octocrylene is endocrine active in some *in vitro* assays but stated that the available evidence from *in vivo* studies is not sufficiently conclusive to suggest that octocrylene may be an endocrine disruptor according to the WHO/IPCS definition[5] (WHO/IPCS, 2002). Members considered there was insufficient information available to derive an endocrine-specific PoD.

6.16 Members discussed a potential interaction with ketoprofen, namely initial sensitisation with ketoprofen and subsequent interaction with octocrylene degradation products (benzophenone). Studies show that 27–80% of patients who were photoallergic to ketoprofen co-reacted to octocrylene. The mechanism of this reaction is unknown (De Groot & Roberts, 2014).

6.17 Members noted that the consideration of environmental effects is outside the remit of the group.

[4] Except that the SAG-CS advises on the use of a default adult body weight of 70kg, where the SCCS would use 60kg.

[5] *'An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations.'*

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7. SAG-CS Conclusions

Members agreed that octocrylene is acceptable when used as a UV-filter in cosmetic products up to a maximum concentration of 10% when used:

- *Individually.*
- *In combination.*

The Committee were of the opinion that a full risk assessment in children and adolescents should be conducted when adequate data and an appropriate methodology become available (children's bodyweights p5 3.2 – 14 kg, p95 6.4 – 37 kg; adolescents bodyweights p5 29.4 - 45 kg, p95 62 – 83 kg; EFSA 2012).

Members considered that the available data were inconclusive regarding endocrine disruption according to the WHO definition and the information is not sufficient to conclude that the observed effects in the one-generation reproductive toxicity study were as a result of an endocrine mode of action.

Members noted potential interactions between ketoprofen and octocrylene.

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

December 2023

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Appendix – Safety Assessment Calculations

These calculations followed the SCCS NoG (SCCS, 2023) principles and calculations for dermal, inhalation and oral exposure[6]. The equations used were as follows:

$$\mathbf{SED_{dermal}} = \frac{\mathbf{\text{Dermal absorption } (\mu g/cm^2)} \times \mathbf{10^{-3}} \times \mathbf{\text{Skin surface area } (cm^2)} \times \mathbf{\text{Frequency of application}}}{\mathbf{\text{Body weight (70 kg)}}}$$

Where:

- The dermal absorption value of 0.97 µg/cm^2 is used; based on the in vitro dermal absorption study by Fabian and Landsiedel (2020) with an octocrylene concentration of 10% (paragraph 5.6 above).
- 10^{-3} is used to convert the dermal absorption units from µg/cm^2 to mg/cm^2.
- Values for skin surface area, frequency of application (Table 4 of the SCCS NoG 2021) and the default human body weight value of 70 kg is used, according to the SCCS NoG (SCCS, 2023) which, at the time of calculation, applies in GB.

For inhalation exposure, the 2-box inhalation model was used, as set out in the SCCS NoG (SCCS, 2023), sections 3-3.4.1.3, 3-3.4.2.3 and Appendix 11.

$$\mathbf{\text{Potential amount inhaled}} = \mathbf{\text{amount per application}} \times \mathbf{\text{content octocrylene}} \times \mathbf{\text{proportion propellant}} \times \mathbf{\text{air-borne fraction}}$$

$$\mathbf{\text{Potential amount inhaled in box 1 or 2}} = \frac{\mathbf{\text{potential amount inhaled}}}{\mathbf{\text{box 1 or 2 volume}}} \times \mathbf{\text{duration in box 1 or 2}} \times \mathbf{\text{inhalation rate}}$$

[6] Except that the SAG-CS advises on the use of a default adult body weight of 70kg, where the SCCS would use 60kg.

$$SED_{inhalation} = \frac{\text{potential amount in haled in box 1 + 2} \times \text{retention factor in lungs} \times \text{respirable fraction} \times \text{frequency of application}}{\text{Body weight (70 kg)}}$$

$$SED_{oral} = \text{calculated relative daily exposure (mg/kg bw/day)} \times \text{concentration octocrylene (\%)} \times \text{oral absorption (\%)}$$

Where:

- The calculated relative daily exposure is taken from the SCCS NoG (2023) Tables 3A for lipstick.
- According to the SCCS NoG (SCCS, 2023), section 3-5.1.2: *'in the absence of data, 50% of the administered dose is used as the default oral absorption value for a cosmetic ingredient…'*

Table 2. Dermal exposure to sunscreen, face cream and hand cream. All products containing 10% octocrylene. Default bodyweight used is 70kg.

	Sunscreen	Face cream	Hand cream
SED calculations			
Dermal absorption (µg/cm^2)	0.97	0.97	0.97
Skin surface area (cm^2)	17500	565	860
Frequency of application	2	2.14[1]	2
Body weight (kg)	70	70	70
SED_{dermal} (mg/kg bw/day)	0.485	0.017	0.024
MoS calculations			
PoD (mg/kg bw/d)	153	153	153
Oral absorption value (%)	50	50	50
PoD_{sys} (mg/kg bw/day)	76.5	76.5	76.5
SED_{dermal} (mg/kg bw/d)	0.485	0.0168	0.0238
MoS	**158**	**4566**	**3210**

Notes: SED values stated are rounded to the nearest 3 significant figures. Calculation of the MoS used unrounded numbers and therefore sometimes resulted in different final MoS values compared to those the rounded figures would lead to.
[1]Taken from the SCCS Notes of Guidance table 4 (2021).

Table 3. Inhalation exposure to sunscreen propellant and pump sprays. Sunscreens containing 10% octocrylene. Default bodyweight used is 70kg[4].

	Propellant spray	**Pump spray**
SED calculations		
Amount per application (mg/application)	15,000	9,000
Content octocrylene (%)	10.0	10.0
Proportion propellant	0.6	1
Air-borne fraction	1	0.2
Potential amount inhaled (mg)	**900**	**180**
Box 1 volume (L)	1,000	1,000
Duration in box 1 (min)	2	2
Inhalation rate (L/min)	13	13
Potential amount inhaled in box 1 (mg)	**23.40**	**4.68**
Box 2 volume (L)	10,000	10,000
Duration in box 2 (min)	10	10
Inhalation rate (L/min)	13	13
Potential amount inhaled in box 2 (mg)	**11.70**	**2.34**
Retention fraction in lungs (25% exhaled)	0.75	0.75
Respirable fraction	0.2	0.01
Frequency of application (/day)	2	2
Body weight (kg)	70	70
$SED_{inhalation}$ (mg/kg bw/d)	**0.150**	**0.00150**
MoS calculations		
PoD (mg/kg bw/d)	153	153
Oral absorption value (%)	50	50
PoD_{sys} (mg/kg bw/day)	76.5	76.5
$SED_{inhalation}$ (mg/kg bw/d)	0.150	0.00150
MoS	**509**	**50854**

Notes: SED values stated are rounded to the nearest 3 significant figures. Calculation of the MoS used unrounded numbers and therefore sometimes resulted in different final MoS values compared to those the rounded figures would lead to.

Table 4. Oral exposure to lip salve/lipstick. Lip products containing 10% octocrylene. Default bodyweight used is 70kg.

	Lip salve / lipstick
SED calculations	
Calculated relative daily exposure (mg/kg bw/day)	0.90
Concentration octocrylene (%)	10
Oral absorption (or bioavailability) value (%)	50
SED_{oral} (mg/kg bw/day)	**0.0450**
MoS calculations	
PoD (mg/kg bw/d)	153
Oral absorption value (%)	50
PoD_{sys} (mg/kg bw/day)	76.5
SED_{oral} (mg/kg bw/d)	0.0450
MoS	**1700**

Notes: SED values stated are rounded to the nearest 3 significant figures. Calculation of the MoS used unrounded numbers and therefore sometimes resulted in different final MoS values compared to those the rounded figures would lead to.

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