



Scientific Committee on Consumer Safety

SCCS

**OPINION on**

**Octocrylene**



The SCCS adopted this document  
at its plenary meeting on 30-31 March 2021

## ACKNOWLEDGMENTS

SCCS members listed below are acknowledged for their valuable contribution to the finalisation of this Opinion.

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This Opinion has been subject to a commenting period of eight weeks after its initial publication (from 18 January until 15 March 2021). Comments received during this time period are considered by the SCCS. The final version has been amended, in particular in the following sections: chapter 3.1. Physicochemical properties, SCCS comment under chapter 3.4.10.1 and in the discussion on endocrine activity in chapter 3.6, as well as related discussion section and references. The conclusions remain the same.

## 1. ABSTRACT

### The SCCS concludes the following:

- (1) *In light of the data provided and taking under consideration the concerns related to potential endocrine disrupting properties of Octocrylene, does the SCCS consider Octocrylene safe when used as a UV-filter in cosmetic products up to a maximum concentration of 10% (as acid)?*

On the basis of safety assessment, and considering the concerns related to potential endocrine disrupting properties of Octocrylene, the SCCS is of the opinion 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.

2. *Alternatively, what is according to the SCCS the maximum concentration considered safe for use of Octocrylene as a UV-filter in cosmetic products?*

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.

3. *Does the SCCS have any further scientific concerns with regard to the use of Octocrylene in cosmetic products?*

The SCCS considers that, whilst there are indications from some *in vivo* studies to suggest that Octocrylene may have endocrine effects, the evidence is not conclusive enough at present to enable deriving a specific endocrine-related toxicological point of departure for use in safety assessment.

Contact sensitisation to Octocrylene has been reported, however, taking into consideration the widespread use of Octocrylene in cosmetic products, the number of reported cases of allergic contact dermatitis appears to be negligible.

It should be noted that occurrence of photoallergy to Octocrylene is strongly related to a previous photoallergy to topical ketoprofen.

Exposure to Octocrylene from other products than those in this Opinion has not been considered.

The SCCS mandates do not address environmental aspects. Therefore, this assessment did not cover the safety of Octocrylene for the environment.

Keywords: SCCS, scientific opinion, Octocrylene, UV-filter, Regulation 1223/2009, CAS No 6197-30-4, EC No 228-250-8

Opinion to be cited as: SCCS (Scientific Committee on Consumer Safety), Opinion on Octocrylene (CAS No 6197-30-4, EC No 228-250-8), preliminary version of 15 January 2021, final version of 30-31 March 2021, SCCS/1627/21

### About the Scientific Committees

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), the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) and are made up of independent experts.

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 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 on substances with endocrine disrupting properties

On 7 November 2018, the Commission adopted a review<sup>1</sup> of Regulation (EC) No 1223/2009 on cosmetic products ('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.

The Cosmetics Regulation does not have specific provisions on EDs. However, it provides a regulatory framework with a view to ensuring a high level of protection of human health. Environmental concerns that substances used in cosmetic products may raise are considered through the application of Regulation (EC) No 1907/2006 ('REACH Regulation'). In the review, the Commission commits to establishing a priority list of potential EDs not already covered by bans or restrictions in the Cosmetics Regulation for their subsequent safety assessment. A priority list of 28 potential EDs in cosmetics was consolidated in early 2019 based on input provided through a stakeholder consultation. The Commission then organised a public call for data<sup>2</sup> from 16 May 2019 – 15 October 2019 on 14<sup>3</sup> of the 28 substances (to be treated with higher priority) in order to be able to prepare the safety assessment of these substances. Octocrylene is one of the above-mentioned 14 substances for which the call for data took place.

### Existing information on Octocrylene

In cosmetic products, the ingredient Octocrylene (CAS No 6197-30-4, EC No 228-250-8) with the chemical name 2-Cyano-3,3-diphenyl acrylic acid, 2-ethylhexyl ester is currently regulated as a UV-filter in sunscreen products in a concentration up to 10% (as acid) (Annex VI/10).

Octocrylene has been subject to a safety evaluation from SCCP in 1994, where the SCCP concluded that Octocrylene was not toxic, non-irritant and non-sensitiser (SCCP, 1994). In addition, the SCCP noted that '*no carcinogenicity study was conducted*'.

During the call for data in 2019, stakeholders submitted scientific evidence to demonstrate the safety of Octocrylene as a UV-filter in cosmetic products. The Commission requests the SCCS to carry out a safety assessment on Octocrylene in view of the information provided.

### Terms of reference

- 1 *In light of the data provided and taking under consideration the concerns related to potential endocrine disrupting properties of Octocrylene, does the SCCS consider Octocrylene safe when used as a UV-filter in cosmetic products up to a maximum concentration of 10% (as acid)?*
- 2 *Alternatively, what is according to the SCCS the maximum concentration considered safe for use of Octocrylene as a UV-filter in cosmetic products?*
- 3 *Does the SCCS have any further scientific concerns with regard to the use of Octocrylene in cosmetic products?*

<sup>1</sup> <https://ec.europa.eu/transparency/regdoc/rep/1/2018/EN/COM-2018-739-F1-EN-MAIN-PART-1.PDF>

<sup>2</sup> [https://ec.europa.eu/growth/content/call-data-ingredients-potential-endocrine-disrupting-properties-used-cosmetic-products\\_en](https://ec.europa.eu/growth/content/call-data-ingredients-potential-endocrine-disrupting-properties-used-cosmetic-products_en)

<sup>3</sup> Octocrylene, kojic acid, 4-methylbenzylidene camphor, propylparaben, triclosan, resorcinol, Octocrylene, triclocarban, butylated hydroxytoluene (BHT), benzophenone, homosalate, benzyl salicylate, genistein and daidzein

### 3. OPINION

#### 3.1 CHEMICAL AND PHYSICAL SPECIFICATIONS

##### 3.1.1 Chemical identity

###### 3.1.1.1 Primary name and/or INCI name

INCI Name: Octocrylene  
EC name: Octocrilene

###### 3.1.1.2 Chemical names

CAS name: 2-Propenoic acid, 2-cyano-3,3-diphenyl-, 2-ethylhexyl ester

IUPAC name: 2-ethylhexyl 2-cyano-3,3-diphenylacrylate  
2-Ethylhexyl 2-cyano-3,3-diphenylprop-2-enoate  
2-Ethylhexyl 2-cyano-3,3-diphenyl-2-propenoate  
2-cyano-3,3-diphenyl-acrylic acid 2-ethyl-hexyl ester  
2-Ethylhexyl 2-cyano-3,3-diphenylacrylate

###### 3.1.1.3 Trade names and abbreviations

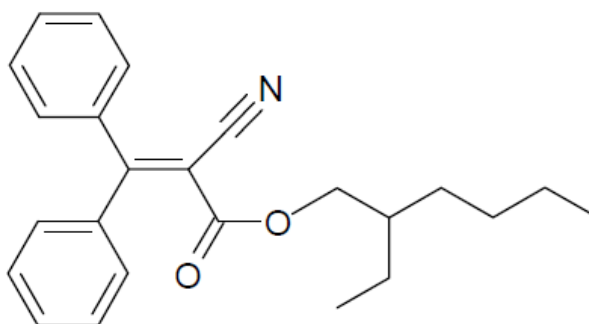
K.SORB 1139, Octocrylene USP, Parsol 340, Sunkem OTC, Sunobel®OCT, Uvinul 3039, UVINUL N 539 T

Ref.: 1

###### 3.1.1.4 CAS / EC number

CAS No 6197-30-4, EC No 228-250-8

###### 3.1.1.5 Structural formula



###### 3.1.1.6 Empirical formula

C<sub>24</sub>H<sub>27</sub>NO<sub>2</sub>



**3.1.2 Physical form**

Liquid (100%) at 20°C and 1013 hPa  
Yellow, clear, viscous liquid

Ref.: 2

**3.1.3 Molecular weight**

361.5 g/mol

**3.1.4 Purity, composition and substance codes**

Chemical characterisation of Octocrylene batch 5132 4997 V0 was performed using IR, <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectroscopies. Its water content was determined by coulometric Karl Fischer titration and was found to be 0.02 g/100 g.

GC fingerprints of the test item, dissolved in acetone or 1,4-dioxane, were recorded on an Rtx-1 MS and DB-17 ht column.

The individual GC purities with respect to the main component are listed in Table 1. No significant difference could be observed between the two solvents.

**Table 1** GC purity

Column	GC purity (area % of main component <sup>1</sup> )
Rtx-1 MS	99.4
DB-17 ht	99.9

<sup>(1)</sup> Corrected for the water content 0.02 g/100 g

The GC purity was conservatively assumed to be 99.4 area %.

Ref.: 3

**SCCS comment**

Only one batch of the test item (batch 5132 4997 V0) was chemically characterized by IR, <sup>1</sup>H-NMR and <sup>13</sup>C-NMR.

**3.1.5 Impurities / accompanying contaminants**

Concentration range: >0 - <2% (w/w); each impurity < 0.5%, sum of impurities < 2.0%

**SCCS comment**

There is no report on the analytical method used to test impurities, or on the chemical nature of these impurities.

Alpha-acetylphenylacetonitrile (CAS 4668-48-8, EC 224-737-4) is reported as an impurity of Octocrylene in one case submitted to ECHA's database of registered substances.

The SCCS is aware that Octocrylene generates benzophenone (CAS 119-61-9, EC 204-337-6) through a retro-aldol condensation and also that benzophenone was detected in the pure Octocrylene manufactured ingredient (Dawns et al. 2020). Benzophenone is a hazardous impurity and degradation product of Octocrylene and it should be monitored and kept at trace levels.

Ref.: 4-5

**3.1.6 Solubility**

Water: 40 µg/L at 20 °C and pH 6.2  
<0.1 µg/L at 20 °C and pH >6.9 -<7.2 (Octocrylene purity 99.2%, EU method A.6, GLP)  
DMSO: 130mg/mL  
n-Octanol: miscible at any ratio at 37 °C (Octocrylene purity 92.6%, OECD Guideline 116, GLP)  
Miscible in methanol, n-butanol, ethyl acetate, mineral oil, hexane, toluene.

Ref.: 2, 6-7

**3.1.7 Partition coefficient (Log Pow)**

LogPow: 6.1 at 23 °C

**3.1.8 Additional physical and chemical specifications**

Where relevant:

- organoleptic properties (colour, odour, taste if relevant): Clear yellow viscous liquid
- melting point: -10 °C at 101.3 kPa
- boiling point: 218 °C at 1.5 mm Hg (Substance decomposes before boiling, at >300 °C)
- flash point: 234 °C at 101.325 kPa
- vapour pressure: 0 Pa at 25 °C
- density: 1.051 g/cm<sup>3</sup> at 25 °C
- viscosity: 637 and 4254 mPa s at 20 °C and 40 °C respectively
- pKa: /
- pH: /
- refractive index: /
- UV/visible light absorption spectrum: /

Ref.: 2, 8-9

**3.1.9 Homogeneity and Stability**

The stability of the test substance (Uvinul N 539, batch 505396-70182) in olive oil dab 9, over a time period of at least seven days, was assessed photometrically at 305nm. It was found to be stable in the carrier for at least seven days.

The stability of Octocrylene (batch 5132 4997 V0) was assessed as part of a dose-range-finding study for an extended one-generation reproductive toxicity study. Samples of the low-dose diet and high-dose diet were analysed in one batch prepared in the study at t=0, after storage in the animal room for approximately four and seven days and after storage in a refrigerator (2-10°C) for at least five weeks. The test item was considered to be stable in the diet if p≥0.01 and/or if the mean concentration after storage was within 90-110% of the mean concentration at t=0.

Octocrylene was stable in the VRF1 (FG) diet for at least one week at room temperature and for at least five weeks when stored at 2 to 10 °C.

Homogeneity was assessed by visual inspection of the test item.

Ref.: 3, 10

**SCCS comment**

Benzophenone is a hazardous impurity and degradation product of Octocrylene and it should be monitored and kept at trace levels.

## 3.2 TOXICOKINETICS

### 3.2.1 Dermal / percutaneous absorption

#### From SPC/1279/94

Five mg of a complex formulation containing 10% of the test substance were applied for a 16 hours period on 12 samples of dermatomized human skin (in-vitro). The amount considered to have penetrated through the skin was  $0.33 \mu\text{g}/\text{cm}^2$ , i.e. 0.08% of the applied dose.

#### New data

Octocrylene was applied for a 16-hour period on human skin *in vitro* using the test substance incorporated into a cosmetic formulation at 8% ( $3 \text{ mg}/\text{cm}^2$ ). Low amounts of the applied dose were found in epidermis ( $0.125\%$ ,  $0.3 \pm 0.7 \mu\text{g}/\text{cm}^2$ ) and dermis ( $0.125\%$ ,  $0.3 \pm 1.0 \mu\text{g}/\text{cm}^2$ ) and nothing was found in the receptor medium whereas 4.3% of the applied dose was found in the *stratum corneum*. Additional studies, applying 8% Octocrylene in a formulation on human skin samples *in vitro* and *in vivo* showed a good correlation in the absorption into the *stratum corneum* between the different experimental setups and the *in vitro* data confirmed the low bioavailability when dermally applied to human skin. The Octocrylene Chemical Safety Report (2010) indicates that dermal absorption rate was found to be low, and a maximum of 0.25% was considered.

Ref.: 4

Guidelines:	OECD Test Guideline 428 (2004), OECD Guidance Document No. 28, SCCS/1358/10 SCCS Basic criteria for the in vitro assessment of dermal absorption of cosmetic ingredient
Test system:	Dermatomed human skin preparations (319 to 380 $\mu\text{m}$ )
Number of donors:	12 skin samples from 6 female donors (aged between 22 and 63 years)
Membrane integrity:	Measurement of trans-epithelia electrical resistance ( $>2 \text{ k}\Omega$ )
Test substance:	10% w/w Octocrylene (Uvinol N 539 T)/ 14C-Octocrylene
Batch:	51324997V0 (Octocrylene) / 933-2009 (labelled)
Vehicle:	Cosmetic formulation (representative of a cosmetic oil/water emulsion)
Purity:	Labelled test substance: chemical purity 97.4%, radio chemical purity $>98\%$ ; Non-labelled test substance: 99.4 area %
Specific activity:	64.2 MBq/g test substance solution
Dose applied:	3 mg formulation/ $\text{cm}^2$ (equivalent to 300 $\mu\text{g}$ of Octocrylene / $\text{cm}^2$ )
Exposed area:	1 $\text{cm}^2$
Exposure period:	24 hours
Sampling period:	Pre-dose (collection about 15 minutes), 0-0.5; 0.5-1; 1-2; 2-3, 3-4; 4-6; 6-8; 8-10; 10-12; 12-14; 14-16; 16-18; 18-20; 20-22; 22-24 hours after application
Receptor fluid:	NaCl with 5% bovine serum albumin (BSA) and 0.01% (w/w) $\text{NaN}_3$
Solubility:	8.91 mg/L
Mass balance:	Provided
Tape stripping:	20 strips in total (Scotch Crystal Tape 600)
Method of analysis:	LSC and/or HPLC
GLP:	Yes

Study period: 17 June 2020 – 2 July 2020

Split-thickness human skin (12 samples from abdominal surgery of 6 female donors) was mounted onto modified Franz cells containing receptor fluid (physiological saline solution with about 5% BSA and 0.01% (w/w)  $\text{NaN}_3$ ). The skin surface temperature was maintained at  $32 \pm 1^\circ\text{C}$  throughout the experiment. The cosmetic formulation was applied to the mounted skin with  $3 \text{ mg}/\text{cm}^2$ .

After an exposure period of 24 hours, skin membranes were washed. The upper layers of *stratum corneum* were removed by tape stripping. The remaining skin was heat separated to epidermis and dermis and both were analysed. Receptor fluid sample and solvents used for extraction of the diffusion cell parts were analysed by liquid scintillation counting (LSC).

The experimental results and mean recoveries from the different compartments of the diffusion cell are presented in the Tables 2 and 3. Dermal delivery (0.15%) is calculated as the sum of the absorbed dose, the epidermis (0.14%) and dermis (0.01%). The mean total recovery was 98.80 % (90.73-107.18%) of the applied dose.

**Table 2** Experimental results and mean recovery data

<b>Dose group / human</b>		
Target concentration [%]		10.0
Target concentration [mg/mL]		100.0
Target dose level of test substance [ $\mu\text{g}/\text{cm}^2$ ]		300.0
Mean actual nominal dose level test substance [ $\mu\text{g}/\text{cm}^2$ ]		297.3
	<b>Mean amount of test substance [<math>\mu\text{g}</math>]</b>	<b>Mean % of applied dose</b>
<b>Dislodgeable dose</b>		
Membrane washing after 24 hours	286.31	96.30
Donor chamber washing	4.93	1.66
<b>Sum</b>	<b><math>291.24 \pm 14.32</math></b>	<b><math>97.96 \pm 4.93</math></b>
	<b>Mean amount of test substance [<math>\mu\text{g}</math>]</b>	<b>Mean % of applied dose</b>
<b>Dose associated to tape strips</b>		
Tape strips 1+2	1.16	0.39
Tape strips 3-5	0.59	0.20
Tape strips 6-10	0.25	0.08
Tape strips 11-15	0.05	0.02
Tape strips 16-20	0.00	0.00
<b>Sum</b>	<b><math>2.06 \pm 0.94</math></b>	<b><math>0.69 \pm 0.18</math></b>
<b>Dose associated to remaining skin</b>		
Epidermis excluding tape strips	0.41	0.14
Dermis	0.03	0.01
<b>Sum</b>	<b><math>0.45 \pm 0.52</math></b>	<b><math>0.15 \pm 0.18</math></b>
<b>Absorbed dose</b>		
Sum receptor samples 0 - 24 h	0.00	0.00
Receptor fluid	0.00	0.00
Receptor chamber washing	0.00	0.00
<b>Sum</b>	<b><math>0.00 \pm 0.00</math></b>	<b><math>0.00 \pm 0.00</math></b>
<b>Total</b>	<b><math>293.75 \pm 14.31</math></b>	
<b>Total recovery</b>		<b><math>98.80 \pm 4.92</math></b>

**Table 3** Distribution/absorption of test substance and absorption kinetic parameters ( $\pm$  one standard deviation (SD))

Distribution/absorption	Amount mean $\pm$ SD [ $\mu\text{g}/\text{cm}^2$ ]	% of applied dose mean $\pm$ SD
Tape stripping	2.06 $\pm$ 0.94	0.69 $\pm$ 0.31
Epidermis (excluding tape strips) and dermis	0.45 $\pm$ 0.52	0.15 $\pm$ 0.18
Receptor fluid, receptor chamber washing	0.00 $\pm$ 0.00	0.00 $\pm$ 0.00
Absorption kinetics <sup>1</sup>	-	-

<sup>1</sup>Negligible amounts of test substance in the receptor sample of one cell. Therefore, kinetic parameters could not be calculated.

At 24 hours post-dose, the amount considered as absorbed (epidermis, dermis and receptor fluid) was estimated to be a maximum of  $0.45 \pm 0.52 \mu\text{g}/\text{cm}^2$ , corresponding to  $0.15\% \pm 0.18\%$  of the applied dose.

Ref.: 11

### SCCS comment

Based on all dermal absorption studies described above, no clear relationship between applied dose and dermal absorption could be established for Octocrylene.

Based on Fabian & Landsiedel (2020), a dermal absorption of  $0.97 \mu\text{g}/\text{cm}^2$  (mean + 1SD:  $0.45 \pm 0.52 \mu\text{g}/\text{cm}^2$ ) was therefore considered a worst case scenario and was used in the calculation of SED.

## 3.2.2 Other studies on toxicokinetics

### New data

Matta *et al.* (2019) determined in healthy volunteers whether Octocrylene was absorbed into the systemic circulation. A randomized clinical trial, which was conducted at a phase 1 clinical pharmacology unit in the United States, enrolled 24 healthy volunteers. Octocrylene was applied to participants using spray 1 (n = 6 participants), spray 2 (n = 6), a lotion (n = 6), and a cream (n = 6). The Octocrylene concentration was 2.35% in spray 1, 6% in lotion and 10% in spray 2 and cream. Two milligrams of sunscreen per  $\text{cm}^2$  were applied to 75% of body surface area 4 times per day for 4 days, and 30 blood samples were collected over 7 days from each participant. Twenty-three participants (96%) completed the trial. Plasma concentrations of the parent compounds were measured by LC/MS methods.

Maximum plasma concentrations of Octocrylene on Day 1, overall systemic Octocrylene concentrations, residual concentration at day 7, the overall time to maximum concentration and plasma half-lives are shown in Table 4. Area under the curve (AUC) increased from day 1 to day 4 for all four products, and maximum plasma concentration was numerically higher on day 4 compared with day 1. Octocrylene sunscreen was applied without exposure to heat or direct sunlight, i.e., not under typical "real-life" conditions.

**Table 4** Toxicokinetic data after dermal exposure to Octocrylene (modified from Matta *et al.*, 2019)

	Spray 1	Spray 2	Lotion	Cream
<b>Octocrylene (%)</b>	2.35	6	10	10
<b>N=6</b>	<b>Geometric mean (CV%) [95% CI]</b>			
<b>c<sub>max</sub> (ng/mL) Day 1</b>	0.8 (53.0) [0.5-1.7]	3.7 (126) [1.1-18.5]	2.6 (65.6) [1.2-6.3]	2.9 (39.9) [1.6-4.2]
<b>Overall c<sub>max</sub> (ng/mL)</b>	2.9 (102) [1.0-9.8]	7.8 (113) [2.5-20.4]	5.7 (66.3) [2.8-13.4]	5.7 (47.1) [2.9-10.3]
<b>Residual plasma concentration (ng/mL) Day 7</b>	0.6 (28.4) [0.4-0.9]	1.2 (66) [0.6-2.6]	1.7 (87.3) [0.5-4.4]	1.3 (50.9) [0.8-2.6]
	<b>Geometric mean [95% CI]</b>			
<b>Overall t<sub>max</sub> (hours)</b>	74.5 [8-78]	65 [14-84]	54.5 [33-78]	72 [33-81]
	<b>Geometric mean (CV%) [95% CI]</b>			
<b>t<sub>1/2</sub> (hours)</b>	84.4 (53.3) [59.3-120]	43.3 (50.7) [26.9-75.2]	45.2 (20.7) [36.9-55.6]	45.9 (27.9) [33.9-62.8]

c<sub>max</sub>: max plasma concentration; t<sub>max</sub>: time to maximum concentration; t<sub>1/2</sub>: half-life

Matta *et al.* (2020), assessed the systemic absorption and pharmacokinetics of Octocrylene in four sunscreen products under single- and maximal-use conditions. In a randomized clinical trial, healthy participants were exposed to sunscreen products containing Octocrylene, formulated as lotion (6%), aerosol spray (10%), and non-aerosol spray (10%) (n=12 for each formulation). Sunscreen product was applied at 2 mg/cm<sup>2</sup> to 75% of body surface area during 4 days of the study, with a total of 13 applications. The study product was applied 1 time on day 1 (0 hours) and 4 times per day for the remaining 3 days. Thirty-four blood samples were collected over 21 days. Octocrylene was measured by a validated LC/MS method.

Maximum plasma concentrations of Octocrylene on Day 1, overall plasma concentrations, residual concentration at day 7, the time to maximum concentration on Day 1, overall time to maximum concentration and plasma half-lives are shown in Table 5. AUC increased from day 1 to day 4 for all four products, and maximum plasma concentration was numerically higher on day 4 compared with day 1.

**Table 5** Toxicokinetic data after dermal exposure to Octocrylene (modified from Matta *et al.*, 2020)

	Aerosol spray	Non-aerosol spray	Lotion
<b>Octocrylene (%)</b>	10	10	6
<b>N=12</b>	<b>Geometric mean (CV%) [95% CI]</b>		
<b>c<sub>max</sub> (ng/mL) Day 1</b>	1.3 (438) [0-12.3]	1.4 (73.9) [0.4-3.1]	1.5 ng/mL (67.8 [0.3.6]),
<b>Overall c<sub>max</sub> (ng/mL)</b>	6.6 (78.1) [1.4-16-2]	6.6 (104) [1.7-34.4]	7.8 (87.1) [2.6-38-7]
<b>t<sub>max</sub> (hours) Day 1</b>	8.7 (1067) [0-23]	12.5 (147.5) [0.5-23]	18.7 (32.4) [10-23]
<b>Overall t<sub>max</sub> (hours)</b>	65.3 (38.4) [33-95]	69 (21.6) [47-95]	72 (15) [57-82]
<b>t<sub>1/2</sub> (hours)</b>	48.4 (36.7) [28.9-70.9]	79.1 (40.1) [41.2-118.8]	49.5 (59.1) [23.7-121.8]

c<sub>max</sub>: max plasma concentration; t<sub>max</sub>: time to maximum concentration; t<sub>1/2</sub>: half-life

Hiller *et al.* (2019) explored whether and to what extent UV filters (including 10.85% Octocrylene) were absorbed through the skin into the human body. Plasma and urine samples from 20 healthy volunteers were collected before, during and after a real-life

exposure scenario (1<sup>st</sup> application: 2 mg/cm<sup>2</sup>; 2<sup>nd</sup> and 3<sup>rd</sup> (after 2 and 4 hours): 1 mg/cm<sup>2</sup> each) using a commercial sunscreen formulation. Only the parent Octocrylene and the main metabolite 2-cyano-3,3-diphenylacrylic acid (CDAA; representing 45% of the Octocrylene dose after oral administration) were analysed in plasma by LC-MS/MS and in urine by using two-dimensional LC/LC-MS/MS procedures.

Following dermal sunscreen exposure, Octocrylene and CDAA could be detected in all samples investigated, however amounts were below LOD in 17% of the plasma samples for Octocrylene and in 6 % of the samples for CDAA. Maximally achieved plasma concentrations were 11.7 µl/L (max 25 µg/L) for Octocrylene and 570 µg/L (max 1352 µg/L) for CDAA (Table 6). In urine, detection rates of Octocrylene were low (< 20% of the samples, 81% of samples were below LOD). In contrast, CDAA showed a high detection rate and a median concentration of 2072 µg/g creatinine (min-max: 1128–5207 µg/g creatinine).

Kinetic models could be fitted for Octocrylene and CDAA in plasma and CDAA in urine. The authors reported maximal plasma concentrations at 10 hours for Octocrylene and 14.5 hours for CDAA, and 15.9 hours in urine for CDAA (Table 6). Plasma half-lives of 43.9 and 36.1 hours were reported for Octocrylene and CDAA, respectively. The half-life of CDAA in urine was 37.7 hours, whereas for Octocrylene it was not determinable. Thus, concentration peaks were reached between 10 and 16 h after first application and half-life periods were in the range of 1.5 to 2 days. The CDAA metabolite showed a markedly increased renal excretion over the whole sampling period and indicated high internal exposure to Octocrylene. The authors stated that the pharmacokinetic results should be considered exploratory due to several limitations of the study, amongst them low creatinine levels and the high number of samples below LOD in the follow up.

**Table 6** Toxicokinetic data after dermal exposure to Octocrylene (modified from Hiller *et al*, 2019)

	Octocrylene	CDAA
<b>Octocrylene (%)</b>	10.85	
<b>N=20</b>	<b>Mean (max)</b>	
<b>c<sub>max</sub> plasma (µl/L)</b>	11.7 (25)	570 ( 1352)
	<b>Median (min-max)</b>	
<b>c in urine (µg/g creatinine)</b>	n.d.	2072 (1128–5207)
	<b>Median (95% CI)</b>	
<b>t<sub>max</sub> plasma (hours) Day 1</b>	10 (6.9-13.4)	14.5 (13.2-15.9)
<b>t<sub>max</sub> urine (hours) Day 1</b>	n.d.	15.9 (15.2-16.7)
<b>t<sub>1/2</sub> plasma (hours)</b>	43.9 (19.0-68.7)	36.1 (31.0-41.2)
<b>t<sub>1/2</sub> urine (hours)</b>	n.d.	37.7 (35.1-40.4)

\*81% of samples <LOD

c: concentration; c<sub>max</sub>: max plasma concentration; n.d.: not determinable; t<sub>max</sub>: time to maximum concentration; t<sub>1/2</sub>: half-life

In another study, Bury *et al.* (2019) investigated human Octocrylene metabolism and urinary excretion after oral administration of approximately 5 mg Octocrylene in three healthy males. Six urinary Octocrylene metabolites were identified. CDAA was the major urinary metabolite, representing 45% (range 40-50%) of the Octocrylene dose. 2-ethyl-5-hydroxyhexyl 2-cyano-3,3-diphenyl acrylate (5OH-OC) and 2-(carboxymethyl)butyl 2-cyano-3,3-diphenyl acrylate (dinor OC carboxylic acid; DOCCA) were only minor metabolites with low, but highly consistent, renal conversion factors of 0.008% (0.005-0.011%) and 0.13% (0.11-0.16%), respectively. Peak urinary metabolite concentrations were observed between 3.2 and 4.2 hours post dose and reach peak concentrations of 1.85, 10.6 and 2450 µg/g creatinine for 5OH-OC, DOCCA and CDAA, respectively (Table 7). All three metabolites were excreted with biphasic elimination kinetics, with considerably longer elimination half-lives for DOCCA and CDAA compared to 5OH-OC (Table 7). Within 24 hours, 99% of all 5OH-OC was excreted compared to 82% of DOCCA and 77% of CDAA. CDAA was eliminated in its free form, only. For DOCCA, 9–27% were excreted non-conjugated, and 5OH-OC was



only found in its glucuronidated form. In terms of mass balance, approximately 50% of the oral dose was recovered in urine. Therefore, most probably, a relevant share of the oral dose is also excreted via feces.

After a single dermal application of a commercial sunscreen containing 2% Octocrylene on one male volunteer, peak urinary metabolite levels (0.14, 1.15 and 71.4 µg/g creatinine for 5OH-OC, DOCCA and CDAA, respectively, Table 7) were only 2.5–5.4-times as high as the predose background levels. Thus, compared to oral exposure, the same metabolites were detected with similar ratios in urine, however, at much lower concentrations. In relation to the oral dose (approx. 5 mg), the amount of dermally applied Octocrylene (217 mg) was much higher (factor > 25), but urinary peak metabolite levels were much lower (factor > 9) in the dermal study. In addition to these differences in urinary metabolite concentrations between the oral and dermal exposure, pronounced differences in metabolite elimination kinetics were observed. For CDAA and 5OH-OC, a slow but clear increase in urinary concentrations was observed following the dermal application, whereas for DOCCA no clear excretion profile was observed (probably due to its small renal conversion factor and long excretion half-lives similar to CDAA). For CDAA and 5OH-OC, in contrast to the oral study with peak urinary concentrations ~ 3 to 4 h post-dose, peak concentrations in the dermal study occurred only around 24 h (5OH-OC) and between 24 and > 48 h (CDAA) post application. This indicates a slower uptake of Octocrylene through the skin, compared to resorption from the digestive tract. 5OH-OC returned to baseline levels within 60–96 h, whereas CDAA levels were still elevated after 96 hours. Accordingly, the authors state that an accumulation of Octocrylene in the skin, following repeated applications, can be expected.

**Table 7** Toxicokinetic data in urine after oral or dermal exposure to Octocrylene (modified from Bury *et al.*, 2019)

		CDAA	5OH-OC	DOCCA
<b>Oral (N=3)</b>		<b>Median (range)</b>		
<b>c (µg/g creatinine)</b>		2450 (1150-4410)	1.85 (1.62-2.11)	10.6 (9.94-11.1)
<b>t<sub>max</sub> (hours)</b>		4.2 (2.7-5.0)	3.2 (1.4-4.4)	3.6 (1.4-5.0)
<b>t<sub>1/2</sub> (hours)</b>	1 <sup>st</sup> phase	5.7 (3.8-7.1)	1.3 (1.1-1.5)	3.0 (2.1-3.6)
	2 <sup>nd</sup> phase	16 (14-20)	6.4 (5.7-7.5)	16 (10-21)
<b>Dermal (N=1)</b>				
<b>c (µg/g creatinine)</b>		71.4	0.14	1.15

c: concentration; t<sub>max</sub>: time to maximum concentration; t<sub>1/2</sub>: half-life

Guesmi *et al.* (2019) performed a study designed to examine the oxidative metabolism of Octocrylene. *In vitro* incubations with Octocrylene were performed with human and rat liver microsomes in the presence of β-nicotinamide adenine dinucleotide phosphate (NADPH) and glutathione (GSH) to form oxidative metabolites and adducts. GSH was used as the trapping agent for reactive metabolites in order to detect the unstable electrophilic species. LC/HRMS/MS was used to qualitatively identify the parent compound, metabolites and GSH adducts. The ester bond of Octocrylene can be hydrolysed to form 3,3-diphenyl-cyanoacrylate (DPCA) and 2-ethylhexanol. Peaks for DPCA, a single oxidation metabolite and a GSH adduct were detected. The authors propose that the oxidation site is on the alkyl group of Octocrylene, which is in agreement with the single hydroxylated metabolite 5OH-OC reported in Bury *et al.* (2019).

Concerning metabolism, oral repeated dose and reproductive/developmental toxicity studies have identified the capacity of Octocrylene to induce xenobiotic-metabolising enzymes (ECHA registration dossier). Therefore, a significant metabolism of Octocrylene in the liver can be expected when being absorbed from the gastrointestinal tract. Based on the chemical structure of Octocrylene, the metabolism may consist of:



- Hydrolysis of the ester binding by esterases and formation of 2-cyano-3,3-diphenyl-2-propenoic acid and 2-ethylhexanol.
- Oxidation of both hydrolysis products by cytochrome P450-dependent monooxygenases.
- Cytochrome P450-dependent decarboxylation of 2-cyano-3,3-diphenyl-2-propenoic acid.
- Glucurono-/ Sulfo- or GSH-conjugations of metabolic oxidation products.

Ref.: 4, 12-16

**SCCS comment**

Octocrylene is a lipophilic substance (logPow 6), and it is reported to be metabolised to a variety of metabolites where CDAA is the main metabolite. Information is lacking on whether the most important toxic agent is Octocrylene, CDAA or other metabolites.

Based on the cited studies, internal exposure doses and half-life of Octocrylene and CDAA after dermal exposure can be summarised as follows:

- The maximum plasma levels of Octocrylene varies between 0.5-11.7 ng/mL with peak concentrations after 10-74.5 hours and with a half-life of between 43.3-84.4 hours.
- The level of Octocrylene in urine is low.
- The maximum plasma concentration of CDAA has been reported to be 570 ng/mL with a peak concentration after 15 hours and a half-life of 36 hours.
- In urine, the maximum concentration of CDAA varies between 71.4-2072 µg/g creatinine with a peak concentration after 16 to more than 48 hours and a half-life of 38 hours.

The SCCS notes that due to the relatively long half-life of both Octocrylene and CDAA in plasma and the low elimination rate of CDAA in urine, an accumulation of Octocrylene and CDAA in the human body following repeated dermal applications may occur. On the other hand, the reported plasma levels of Octocrylene and CDAA are low (in the ng/mL range) and it can be questioned whether these substances may reach toxic levels due to accumulation after repeated applications.

Due to the lack of data on the volume of distribution, this data cannot be used to calculate systemic uptake after dermal exposure to the product types relevant for this Opinion.

### 3.3 EXPOSURE ASSESSMENT

#### 3.3.1 Function and uses

Octocrylene can be used as a UV-B filter in sunscreen products at a concentration up to 10% (as acid) and is often used together with dibenzoylmethane derivatives to stabilise sunscreen products. Octocrylene is also used in body and face care products, perfumes and fragrances.

**3.3.2 Calculation of SED**

Systemic exposure doses (SED) are calculated for dermal, inhalation and oral exposure to product types containing 10% Octocrylene (Tables 8-10) separately and as aggregate exposure (Table 11).

**Dermal exposure**

The systemic exposure dose for Octocrylene used as a UV filter in cosmetic products was calculated using a dermal absorption value of 0.97  $\mu\text{g}/\text{cm}^2$  based on the *in vitro* dermal absorption study by Fabian & Landsiedel (2020) with an Octocrylene concentration of 10% (Table 8).

**Table 8** SED calculations after dermal exposure

Description	Parameter	Sunscreen	Face cream	Hand cream	Unit
Absorption through the skin	DA <sub>a</sub>	0.97	0.97	0.97	µg/cm <sup>2</sup>
Skin surface area	SSA	17 500	565	860	cm <sup>2</sup>
Dermal absorption per application	DA <sub>a</sub> *SSA*0.001	17.0	0.55	0.83	mg
Frequency of application	F	2	2.14	2	Application/day
Default bodyweight	BW	60	60	60	kg
<b>SED<sub>dermal</sub></b>	SSA*DA <sub>a</sub> *0.001*F/BW	<b>0.566</b>	<b>0.020</b>	<b>0.028</b>	<b>mg/kg bw/day</b>

**Inhalation exposure**

The systemic exposure dose by the inhalation route was calculated using an adapted deterministic 2-box model (Rothe *et al.*, 2011) (Table 9).

It was assumed that for both pump spray and propellant spray the same amount of sunscreen needs to reach the skin to ensure the necessary level of sun protection. For a propellant spray, this means that the additional amount of propellant gas needs to be added to the default value of 9 g/application, resulting in 15 g/application. By applying a factor of 0.6 for the proportion of non-propellant in the formulation based on information by the Applicant, this results in an amount of 9 g/application on the skin.

**Table 9** SED calculations after inhalation exposure

Description	Parameter	Propellant spray	Pump spray	Unit
Amount by application <sup>1</sup>	A	15 000	9 000	mg/application
Fraction of Octocrylene in non-propellant	C	0.1	0.1	(w/w)
Proportion of non-propellant in formulation	P	0.6	1	-
Airborne fraction	AF	1	0.2	-
Potential amount to be inhaled	EA (A*C*P*AF)	900	180	mg
First step: Near-field, 1 m <sup>3</sup>	V <sub>1</sub>	1 000	1 000	L
Breathing rate	BR	13	13	L/min
2 min in near-field	t <sub>1</sub>	2	2	min
Potential amount inhaled during t <sub>1</sub>	IA <sub>1</sub> (EA/V <sub>1</sub> *BR*t <sub>1</sub> )	23.4	4.68	mg
Second step: Far-field 10 m <sup>3</sup>	V <sub>2</sub>	10 000	10 000	L
Breathing rate	BR	13	13	l/min
10 min in far-field	t <sub>2</sub>	10	10	min
Potential amount inhaled during t <sub>2</sub>	IA <sub>2</sub> (EA/V <sub>2</sub> *BR*t <sub>2</sub> )	11.7	2.34	mg
Substance availability fraction	G	0.75	0.75	-
Respirable fraction	RF	0.2	0.01	-
Frequency of application	F	2	2	d <sup>-1</sup>
Default bodyweight	BW	60	60	kg
<b>SED<sub>inhal</sub></b>	(IA <sub>1</sub> *IA <sub>2</sub> )*G*RF*F/BW	<b>0.176</b>	<b>0.002</b>	<b>mg/kg bw/day</b>

<sup>1</sup>Adjusted for the proportion of propellant to achieve a final "on-body" amount of 9 000 mg

The airborne fraction AF was assumed following Bremmer *et al.*, 2006. The near-field zone of the two-compartment model was assumed to have a volume  $V_1$  of 1 m<sup>3</sup> (Sahmel *et al.*, 2009) and the duration of staying in the near-field zone  $t_1$  as 2 min. For the far-field a volume  $V_2$  of 10 m<sup>3</sup> and a duration of 10 min ( $t_2$ ) was assumed (Bremmer *et al.*, 2006, Rothe *et al.*, 2011).

The factor for substance availability G is based on Guidance from the European Commission, 1996. The respirable fraction of 0.2 is based on Applicant information on the spray can types used for sunscreen sprays.

### Oral exposure

The systemic exposure dose from lipstick was corrected for a 50% oral availability of Octocrylene (Bury *et al.*, 2019) (Table 10).

**Table 10** SED calculation after oral exposure

Description	Parameter	Lipstick	Unit
Relative daily exposure	$E_{\text{product}}$	0.9	mg/kg bw/d
Concentration of Octocrylene	C	10	%
Retention factor <sup>1</sup>	$F_{\text{ret}}$	100	%
Adjustment for oral bioavailability		50	%
<b>SED<sub>oral</sub></b>	$E_{\text{product}} * (C/100) * (F_{\text{ret}}/100) * (50/100)$	<b>0.045</b>	<b>mg/kg bw/day</b>

<sup>1</sup>Potential amount available for oral exposure

### Aggregated exposure

**Table 11** Calculation of total SED for aggregated exposures

SED <sub>dermal</sub>	SED <sub>inhal</sub>	SED <sub>dermal</sub>	SED <sub>dermal</sub>	SED <sub>oral</sub>	SED <sub>total</sub>
Sunscreen (lotion)		Face cream	Hand cream	Lipstick	
0.566	-	0.020	0.028	0.045	<b>0.659</b>
Sunscreen (propellant spray)					
0.566	0.176	0.020	0.028	0.045	<b>0.835</b>
Sunscreen (pump spray)					
0.566	0.002	0.020	0.028	0.045	<b>0.661</b>

Ref.: 11, 15, 17-19

### SCCS comment

The parameter value of 0.2 for the respirable fraction (corresponding to 20%) was used by the Applicant based on an internal, unpublished survey of Cosmetics Europe that was not made available to the SCCS. The spray container, its nozzle, the amount of propellant and the viscosity of the formulation together influence the respirable fraction, so that this value may be specific to sunscreen sprays. However, this assumption could not be evaluated by the SCCS. The responsible person has to ensure that the final product generates a spray with a respirable fraction that does not exceed 0.2.

## 3.4 TOXICOLOGICAL EVALUATION

### 3.4.1. Irritation and corrosivity

#### From SPC/1279/94

Instillation of 0.1 ml undiluted substance in the eyes of six albino rabbits (Draize test) produced no discernible effects. In the skin irritation test carried out with six albino rabbits, the effects observed were minimal.

Summarizing these results, the substance can be classified as non-irritant.

No new data was submitted.

#### 3.4.1.1 Skin irritation

/

#### 3.4.1.2 Mucous membrane irritation / eye irritation

/

### 3.4.2 Skin sensitisation

#### From SPC/1279/94

In a sensitisation test according to Magnusson/Kligman, 20 guinea pigs were challenged after previous induction by cutaneous application of the test substance. No cutaneous reaction was observed at the challenge site.

Summarising these results, the substance can be classified as a non-sensitiser.

#### New data

##### *Animal studies*

The sensitising potency of Octocrylene was investigated in a local lymph node assay (LLNA) at the following concentrations (wt/vol): 1.0%, 2.5%, 5.0%, 15%, and 30%. Female CBA/CA mice (3/group) received 25 µl of a solution of the test compound, dissolved in acetone/olive oil (4:1 vol/vol), on the dorsum of the ears daily for three consecutive days. A control group

with three mice was treated with vehicle alone. All mice were injected intravenously five days

after the first treatment with 20 µCi of [3H]thymidine. Five hours later, the mice were killed and the draining lymph nodes were excised and pooled for each group. The thymidine incorporation was measured. Octocrylene was found to be a moderate sensitizer, with an EC3 value of 7.7%. It should be noted that this study has several limitations. The study was not performed under quality assurance according to the OECD GLP Guideline and deviated from the current OECD guideline (e.g. three animals/group, no information on variability within the groups is available, the test concentrations were not evenly spaced 2-fold, possible UV-irradiation from windows or laboratory lighting was not controlled).

Ref.: 20

##### *Human studies*

Studies on patch testing of patients have shown positive reactions to Octocrylene in 0.7-5% of the patients. However, a percentage of 4.4% was found in a study with some weaknesses in its design, and a percentage of 5% was found in a small study with only one patient reacting to Octocrylene. In the general population, contact allergy is considered to be rare.

In a European multicentre photopatch test study comprising 1031 patients patch tested with 10% Octocrylene for suspected photoallergic contact dermatitis, positive reactions attributed to Octocrylene were reported in only 0.7%. The occurrence of photoallergy to Octocrylene is strongly related to a previous photoallergy to topical ketoprofen. Studies show that 27–80% of patients who were photoallergic to ketoprofen co-reacted to Octocrylene. The mechanism of this reaction is unknown. Patients with positive photopatch tests to Octocrylene are mainly reported in France, Belgium, Italy and Spain, all countries where topical ketoprofen is widely used. Photoallergy to Octocrylene is considered to be rare in the general population.

Contact allergy to Octocrylene appears to be more frequent in children than in adults, whereas photoallergy to Octocrylene is more frequent in adults than in children (in whom few cases have been reported).

Ref.: 21-22

### SCCS comment

Literature both on LLNA results and on human sensitisation cases published since 1994 suggests that Octocrylene is a moderate skin sensitiser and a skin photosensitiser. When taking into consideration the widespread use of Octocrylene in cosmetic products, the number of reported cases of allergic contact dermatitis appears to be small. Photoallergy is seen mainly in adult patients who have previously used topical products containing the non-steroidal anti-inflammatory drug ketoprofen. Thus, the majority of photoallergic reactions are probably not induced by Octocrylene itself but occur as a result of previous photosensitisation to ketoprofen.

## 3.4.3 Acute toxicity

### 3.4.3.1 Acute oral toxicity

#### From SPC/1279/94

The acute oral median lethal dose (LD<sub>50</sub>) in the rat was found to be greater than 5000 mg/kg body weight.

No new data was submitted in 2019.

### 3.4.3.2 Acute dermal toxicity

#### New data

Guideline:	OECD Guidelines for Testing of Chemicals (1981) No. 402
Species/strain:	Rat, Sprague-Dawley
Group size:	5/sex/dose
Test substance:	Octocrylene (HR 92/600154)
Batch:	2010002
Purity:	98.5%
Vehicle:	/
Dose levels:	2000 mg/kg bw
Dose volume:	10% of body surface area
Route:	Semi-occluded dermal application on intact skin
Duration:	24-hour exposure, 14-day observation period
GLP:	In compliance
Study period:	April 8-22 1992

A group of ten animals (five males and five females) was given a single 24-hour, semi-occluded dermal application to intact skin at a dose level of 2000 mg/kg bodyweight. The animals were observed for fourteen days after the day of treatment and were then killed for gross pathological examinations.

There were no deaths. No signs of systemic toxicity or skin irritation were noted during the study. All animals showed an expected gain in bodyweight during the study. No abnormalities were noted at necropsy.

The acute dermal median lethal dose (LD<sub>50</sub>) of the test material in the Sprague-Dawley strain rats was found to be greater than 2000 mg/kg bodyweight.

Ref.: 23

### SCCS comment

The SCCS agrees that the acute dermal median lethal dose (LD<sub>50</sub>) in the rat is greater than 2000 mg/kg body weight.

#### 3.4.3.3 Acute inhalation toxicity

No new data was submitted.

### 3.4.4 Repeated dose toxicity

#### 3.4.4.1 Repeated dose (28 days) oral / dermal / inhalation toxicity

#### New data

Guideline: Equivalent or similar to OECD Guideline 407  
Species/strain: Rat, Wistar  
Group size: 5/sex/dose  
Test substance: Octocrylene (00/0495-13)  
Batch: 51324997V0  
Purity: 99.5%  
Vehicle: Test substance provided via feed  
Dose levels: 0, 1000ppm, 3000ppm, 10000ppm  
Route: Oral  
Duration: Subset A: 28 days; Subset B: 14 days (continuously via feed)  
GLP: In compliance  
Study period: January 2018 – February 2019

This study was performed to comply with the REACH regulation (EC) No 1907/2006.

Octocrylene was administered via diet to groups of five male and five female Wistar rats at concentrations of 0 (test group 00), 1000 (test group 01), 3000 ppm (test group 02), 10000 ppm (test group 03) over a period of 28 days (Subset A) as well as to 5 male and 5 female Wistar rats at concentrations of 0 (test group 10), 1000 (test group 11), 3000 ppm (test group 12), 10000 ppm (test group 13) over a period of 14 days (Subset B).

The concentrations in the diet corresponded to calculated test substance intake values of:

- about 65 (Subset A) and 63 mg/kg bw/d (Subset B) in males and about 72 (Subset A) and 69 mg/kg bw/d (Subset B) in females of test groups 01 and 11 (1000 ppm);
- about 188 (Subset A) and 193 mg/kg bw/d (Subset B) in males and about 215 (Subset A) and 207 mg/kg bw/d (Subset B) in females of test groups 02 and 12 (3000 ppm);
- about 650 (Subset A) and 630 mg/kg bw/d (Subset B) in males and about 720 (Subset A) and 690 mg/kg bw/d (Subset B) in females of test groups 03 and 13 (10 000 ppm).

During the course of the study, blood samples were taken and examined for thyroid hormone levels (T3, T4 and TSH; Subsets A and B). Shortly before necropsy, blood samples were taken for the examination of hematology and clinical chemistry parameters (Subset A, only). At necropsy, organ weights were determined, and histopathological examinations of selected organs were performed (Subsets A and B). In addition, liver microsomes were prepared for assessment of certain enzyme amounts/activities (Subset B, only).

The following test substance-related, relevant findings were noted:

*Test groups 03 and 13: 10000 ppm*

Clinical Examinations

Significantly lower mean body weights were observed in male animals of test groups 03 and 13 and in females of test group 03 (10000 ppm). The most prominent deviations to the control groups were observed in male animals of test group 03 on study day 21 (-9.3%), in female animals of test group 03 on study day 7 (-7.3%) and in male animals of test group 13 on study day 14 (-8.6%).

Clinical Pathology (Subset A, only)

- Increased urea levels in both sexes
- Increased total white blood cell (WBC) and absolute lymphocyte counts in females
- Increased  $\gamma$ -glutamyl transferase (GGT) activities in females
- Increased cholesterol, triglyceride and inorganic phosphate levels in females
- Increased TSH levels in females on study day 14 and in rats of both sexes on study days 21 and 29

Pathology

- Significant increase of relative liver weight (+23.69%) in females of test group 03
- Diffuse hypertrophy (graded minimal) in livers of 3 out of 5 females of test group 03
- Hypertrophy/hyperplasia of follicular cells in the thyroid glands of 2 out of 5 males and 3 out of 5 females (graded minimal), accompanied by altered colloid (graded minimal to slight) of test group 03
- Significant increase of absolute and relative liver weights, i.e. in males (+12.85%/+23.05%) and in females (+21.88%/+27.20%) of test group 13
- Diffuse hypertrophy (graded minimal) in livers of 1 out of 5 males and 3 out of 5 females of test group 13
- Hypertrophy/hyperplasia of follicular cells in the thyroid glands of 2 out of 5 males and 3 out of 5 females (graded minimal), accompanied by altered colloid (graded minimal) in 2 out of 5 males and 1 out of 5 females of test group 13

Bioanalytical Examinations (Subset B, only)

- In male rats in test group 13, total CYP 450 content was significantly increased when compared to untreated controls
- 7-Ethoxyresorufin O-deethylase (EROD)-activities were significantly increased for male rats of test group 13
- 7-Pentoxeresorufin-O-dealkylation (PROD)-activities were significantly increased for male and female animals of test group 13
- 7-Benzoyloxyresorufin oxidation (BROD)-activities were significantly increased for male and female rats of test group 13
- For male and female rats of test group 13, 4-Methylumbelliferone glucuronosyltransferase (MUF-GT)-activities were significantly increased.
- For male and female rats of test group 13, 4-Hydroxybiphenyl-glucuronosyltransferase (HOB-GT)-activities were significantly increased.
- For male and female rats of test group 13, T4-specific UDP-glucuronosyltransferase activities were significantly increased.



- Significant reduction of Thyroxin 5'-deiodinase type D1 (Iodothyronine deiodinase type D1) activity in male but not in female animals.
- Significant induction of Thyroxin 5'-deiodinase type D3 (Iodothyronine deiodinase type D3) activity in male but not in female animals.

*Test groups 02 and 12: 3000 ppm*

(about 188 [Subset A] and 193 mg/kg bw/d [Subset B] in males and about 215 [Subset A] and 207 mg/kg bw/d [Subset B] in females)

Clinical Examinations, Clinical Pathology (Subset A, only) and Pathology

No treatment-related, adverse effects were observed.

Bioanalytical Examinations (Subset B, only)

- PROD-activities were significantly increased for male animals of test group 12
- BROD-activities were significantly increased for male and female rats of test group 12
- T4-specific UDP-glucuronosyltransferase-activities were significantly increased in female animals of test group 12.
- Significant induction of Thyroxin 5'-deiodinase type D3 (Iodothyronine deiodinase type D3) activity in male but not in female animals.

*Test groups 01 and 11: 1000 ppm*

(about 65 [Subset A] and 63 mg/kg bw/d [Subset B] in males and about 72 [Subset A] and 69 mg/kg bw/d [Subset B] in females)

Clinical Examinations, Clinical Pathology (Subset A, only) and Pathology

No treatment-related, adverse effects were observed.

Bioanalytical Examinations (Subset B, only)

No treatment-related effects were observed.

The mechanistic study in Wistar rats with oral administration of Octocrylene up to 10000 ppm showed an induction of liver enzymes (PROD, BROD, T4-specific UDP-glucuronosyltransferase) accelerating the thyroid hormone clearance in both sexes. As a result, a compensating positive feedback mechanism was installed, leading to higher TSH levels and hypertrophy/hyperplasia of follicular thyroid gland cells. Accordingly, T3 and T4 levels remained in a physiological range when Octocrylene was administered nearly at limit dose (10000 ppm).

Ref.: 24

3.4.4.2 Sub-chronic (90 days) oral / dermal / inhalation toxicity
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**From SPC/1279/94**

Octocrylene was administered to Wistar rats in doses from 750-15000 ppm in the diet over a period of 3 months. Substance-related effects were observed at 1085 and 340 mg/kg body weight per day. Target organs were liver, thyroid and pituitary gland. Additional changes were observed in hematological parameters, i.e. the red blood cells of the high dose females. Based upon the above-mentioned findings, the NOAEL under the conditions of this study is 175 mg/kg body weight per day for males and females.

**New data**

Guideline: /  
Species/strain: Rabbit, New Zealand White  
Group size: 5/sex/dose  
Test substance: Octocrylene  
Batch: /  
Purity: /

Vehicle: Mixture of petrolatum and C12-15 alkylbenzoate (Finsolv TN) at differing ratios  
Dose levels: 0, 130, 264, 534 mg/kg bw/day  
Control: 80% (w/w) petrolatum and 20% (w/w) Finsolv  
Route: Dermal (open, clipped area on the back)  
Duration: 91 days (5 days per week, totally 65 applications)  
GLP:  
Study period: 1994

In the dermal subchronic study, five male and five female New Zealand white rabbits per group were treated topically (open) with Octocrylene (130, 264, 534 mg/kg/day) for 13 weeks (5 days per week, 65 applications in total).

All of the animals survived until termination of the study without showing any signs of adverse clinical responses to Octocrylene, other than those noted at or near the site of compound application. In terms of histopathological effects, Octocrylene-treated rabbits showed consistently greater incidence of skin abnormalities (erythema and desquamation) than control counterparts.

In both sexes, mid- and high-dose treatments significantly depressed body weight gain relative to the corresponding controls. At the low dose, no significant body weight effect was noted in females (NOEL, 130 mg/kg/day), whereas in male animals, a statistically significant depression of body weight gain was still observed (NOEL not established). The data also indicated no significant effects in kidney weights of male or female rabbits at any of the Octocrylene doses tested. Absolute liver weights of male animals were reduced at all Octocrylene dose levels, but the effect was no longer evident when organ weights were corrected for Octocrylene-associated effects on body weight. In females, on the other hand, absolute liver weights were unaltered at all Octocrylene dose levels, but the organ to body weight ratio increased significantly at the mid- and high-Octocrylene concentrations.

Regardless of sex or applied concentration (data not shown), none of the Octocrylene-treated rabbits showed any evidence of macroscopic or histopathological abnormalities in any organs examined, which included kidney, liver, and all other internal organs. In addition, clinical hematology values, including differential leukocyte counts, erythrocyte counts, hemoglobin levels, and cell morphology, were within historical control limits for this strain of rabbit.

In male rabbits, morphological examination of epididymis and testicles showed no signs of Octocrylene-associated abnormalities. In these same animals, epididymal sperm concentrations were (mean  $\pm$  SD; n = 5; sperm/g caudal tissue) 311  $\pm$  57 (control), 380  $\pm$  211 (130 mg/kg/day), 467  $\pm$  301 (264 mg/kg/day), and 245  $\pm$  58 (534 mg/kg/day); percentage sperm motility in these same groups was (mean  $\pm$  SD; n = 5) 92  $\pm$  4 (control), 91  $\pm$  5 (130 mg/kg/day), 88  $\pm$  8 (264 mg/kg/day), and 86  $\pm$  6 (534 mg/kg/day). Thus, no evidence was obtained of adverse Octocrylene effects on these measures of male reproductive system integrity.

Overall, no signs of significant toxicity were noted in male or female rabbits after 13 weeks of topical treatment with various doses of Octocrylene.

Ref.: 25

#### 3.4.4.3 Chronic (> 12 months) toxicity

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#### Overall SCCS comment on repeated dose toxicity

The newly submitted repeated dose toxicity studies do not provide new data that support a change of the NOAEL of 175 mg/kg body weight per day for males and females described in the previous SCCS Opinion.

### 3.4.5 Reproductive toxicity

#### 3.4.5.1 Fertility and reproduction toxicity

##### New data

##### Dose-range-finding study

Guideline:	No guideline (Dose-range-finding (DFR) study for extended one-generation reproductive toxicity study (EOGRTS) described below)
Species/strain:	Rat/Wistar Crl:WI(Han)
Group size:	12/sex/dose
Test substance:	Octocrylene
Batch:	5132 4997 V0
Purity:	99.4%
Vehicle:	Feed
Dose levels:	0, 5000 and 15000 ppm (nominal)
Route:	Oral
Exposure period:	<i>Males</i> : pre-mating period (4 weeks), mating (1 week) and post-mating up to the day of sacrifice (42 days) <i>Females</i> : pre-mating period (4 weeks), mating (1 week), gestation and lactation until (or shortly after) postnatal day 21 (PN 21) 10-week pre-mating period, during mating up to the day of sacrifice (approx. 13 weeks).
GLP:	In compliance
Study period:	March 2017 – September 2018

This study was performed to comply with the REACH regulation (EC) No 1907/2006.

The concentration of the test substance in the diet was 0, 5000 and 15000 mg/kg diet for the control, low- and high-dose groups, respectively. These concentrations were halved during the lactation phase due to the considerable higher food consumption of the dams during this phase. The test substance intake of male animals during the entire study ranged from 279-399 and 812-1271 mg/kg body weight/day in the low- and high-dose group, respectively. The test substance intake of the female animals during the entire study ranged from 323-618 and 796-1740 mg/kg body weight/day in the low- and high-dose group, respectively.

There was no treatment-related mortality.

Daily clinical observations of male animals and female animals during the pre-mating period did not reveal any treatment-related clinical signs.

During the gestation and lactation period, the incidences of female animals of the high-dose group showing piloerection was 5 of 10 and 6 of 10, respectively. Body weights and body weight gains were markedly decreased in the high-dose group in both sexes. Slight, but statistically significant, effects on these parameters were also seen at the low-dose group. Food consumption was decreased in the high-dose group in both sexes. Food consumption in the animals of the low-dose group was comparable to controls. Hematological and clinical chemistry examinations revealed lower hemoglobin concentrations and eosinophil counts in females in the high-dose group. Males in the high-dose group showed higher albumin concentrations. Increased GGT activities as well as higher urea values were observed in females in the high-dose group. Higher urea values were also measured in females in the

low-dose group. Liver weights were dose-dependently increased in males and females. Higher thyroid weights were observed in both sexes of both treatment groups. The low- and high-dose animals showed an increased incidence of activated appearance of the thyroid gland (18/24 low-dose animals and 21/24 high-dose animals) in comparison with the controls. It was characterized by loss of colloid from the follicles, hypertrophy and hyperplasia of follicular epithelial cells.

Lower mean numbers of implantation sites and pups per litter were observed in the high-dose group. Birth weight and postnatal body weight development of male and female pups of the high-dose group were decreased. No compound-related effects on these parameters were observed in the low-dose group.

In conclusion, 15000 mg/kg diet was considered to be too high as a high dose in the upcoming Extended One-Generation Reproductive Toxicology Study based on maternal toxicity, since body weights were 21% lower at the end of gestation in this group. Effects on offspring (lower litter size, decreased body weights) occurred in the presence of marked maternal toxicity.

Ref.: 3

**Extended one-generation reproductive toxicity study (EOGRTS)**

Guideline:	OECD 443 (with F2 and developmental neurotoxicity (Cohorts 1A, 1B with extension, 2A and 2B))
Species/strain:	Rat/Wistar Crl:WI(Han)
Group size:	28/sex/dose
Test substance:	Octocrylene
Batch:	5132 4997 V0
Purity:	99.4%
Vehicle:	Feed
Dose levels:	750, 2100, 7000 ppm (nominal). Anticipated doses: 50 mg/kg bw/d overall mean dose: 55 mg/kg bw/d males and 58 mg/kg bw/d females; 135 mg/kg bw/d overall mean dose: 153 mg/kg bw/d males and 163 mg/kg bw/d females; 450 mg/kg bw/d overall mean dose: 534 mg/kg bw/d males and 550 mg/kg bw/d females, respectively
Route:	Oral
Exposure period:	<i>Males</i> : 10-week premating period, during mating up to the day of sacrifice (approx. 13 weeks). <i>Females</i> : P: 10-week premating period, during mating, gestation and lactation up to the day of sacrifice after lactation day 21. <i>F1</i> : from weaning up to sacrifice (approx. 10 weeks in Cohort 1A, approx. 13 weeks (males) and approx. 18 weeks (females) in Cohort 1B; approx. 8 weeks in cohort 2A). <i>F2</i> : indirectly exposed until weaning.
GLP:	In compliance
Study period:	July 2017 – February 2019

This study was performed to comply with the REACH regulation (EC) No 1907/2006.

The objective of this study was to provide data on the possible effects of the test substance Octocrylene on reproductive performance of Wistar rats and the development of pups consequent to daily oral administration of various dietary concentrations of the test substance to male and female rats during a premating period of 10 weeks and during mating (max. 2 weeks), gestation and lactation until postnatal day 21. At weaning, pups were distributed to different cohorts and were exposed to the same dose levels of the test substance as their parents during their growth into adulthood. Cohorts 1A and 1B of this study assessed reproductive performance and Cohorts 2A and 2B focused on

neurodevelopmental endpoints. Animals of Cohort 1B were used for breeding a second generation.

#### *General observations*

In total, two animals (one high-dose male animal of Cohort 1A and one high-dose female of Cohort 1B) were sacrificed in a moribund condition. The macro- and micro-observations in these animals were not considered to be related to treatment. Furthermore, no treatment-related clinical signs were observed during the study.

Body weights of the male and female animals of the high-dose group were lower than the corresponding control animals throughout almost the entire study (maximally, during pre-mating: F0 males 7%, F0 females 11%; F0 females during gestation 13%, F0-females during lactation 11% and F1-Cohort 1A males 8%, females 14%). In general, food consumption of the male and female animals of the high-dose group was slightly but statistically significantly lower than of the control animals (during the F0-generation maximally 10% in males and 19% in females and in F1-Cohort 1A maximally 6% in males and 13% in females). The observed effects on body weight and food consumption in the high-dose group were considered to be related to treatment.

During the gestation periods of the F0- and Cohort 1B F1-generation, the mean test substance intake was slightly lower than intended, most probably due to the higher body weights of the pregnant females. In general, however, the mean test substance intake was higher than the anticipated dose, reaching a maximum of 67, 187 and 636 mg/kg body weight/day.

Except for the increase in gamma glutamyl transferase activity (GGT) in male and female animals of the high-dose group of both the F0- and Cohort 1A F1-generation, no treatment-related effects were observed on hematology, clinical chemistry and urinalysis in F0-generation and Cohort 1A animals.

The decreased terminal body weights (~5 to 10% below controls) and the increased relative liver (males ~20%, females ~30%) and thyroid weight (males ~25 to 30%, females F0 ~25%) as observed in male and female animals of the high-dose group of the F0- and Cohort 1A F1-generation were considered to be related to treatment. The decreased terminal body weights were considered to be adverse, whereas the increased liver and thyroid weights were considered to be adaptive changes in rats. All other findings observed on organ weight were considered of no toxicological relevance and not related to treatment. No effects were observed on the weight of the reproductive organs of Cohort 1B F1-generation animals.

At necropsy of F0-generation and Cohort 1A F1-generation animals, no treatment-related macroscopic changes were observed. In F0-generation animals of the mid- and high-dose group and in Cohort 1A animals of the high-dose group an increased incidence of activated appearance of the thyroid gland in comparison with the controls was observed. It was characterised by loss of colloid from the follicles and hypertrophy and hyperplasia of follicular epithelial cells. These findings were considered to be related to treatment but to be adaptive changes in rats. Other organs and tissues did not reveal treatment related histopathological changes.

#### *Fertility and reproductive parameters*

No treatment-related effects were observed on parameters related to the estrus cycle in female animals of the F0-generation or in animals of Cohort 1A of the F1-generation. No treatment-related effects were observed on epididymal and testicular sperm parameters in male animals of the F0-generation or in animals of Cohort 1A of the F1-generation.

The lower mean number of implantation sites, and consequently, a lower number of pups delivered in female animals of the high-dose group of the F0-generation (implantation sites: 10.7 *versus* 12.3 in controls; pups: 9.6 *versus* 11.4 in controls) and of Cohort 1B of the F1-generation (implantation sites: 9.3 *versus* 10.7 in controls; pups: 9.3 *versus* 10.3 in controls) was considered to be related to treatment and adverse. Furthermore, no treatment-related effects were observed on fertility or the reproductive performance of male and female animals of the F0-generation and of Cohort 1B of the F1-generation.

No effects were observed on TSH and T4 analysis in animals of the F0-generation and in adult F1-generation animals of Cohort 1A. No effects were observed on T4 concentrations in serum of pups culled on PN day 4 and, in addition, no treatment-related effects were observed on T4-and TSH concentrations in serum of pups sacrificed on PN day 21.

#### *General and sexual developmental parameters*

The mean number of live pups on postnatal day 0 was lower in the high-dose group of the F0-generation and in the high-dose group of Cohort 1B of the F1-generation. This finding was considered to be related to the lower number of implantation sites and the lower number of pups delivered as observed in the animals of these groups. The effects were considered to be related to treatment. No other relevant effects were observed on implantation loss, stillborn pups, dead, missing and/or cannibalized pups, litter loss, pup viability indices and sex ratio.

No treatment-related effects were observed on clinical signs of pups nor on macroscopic observations at sacrifice and of dead pups in F1-generation pups and Cohort 1B F2-generation

pups. Overall, in the high-dose group, the body weight of F1-generation pups and of Cohort 1B F2-generation pups was lower than of the corresponding control pups (~10% on postnatal day 21), which is considered due to relatively high compound intake via food. This finding was considered to be related to treatment.

Preputial separation (control: 43.0 days, high dose 46.4 days), vaginal opening (control: 31.4 days, high dose: 33.9 days), and first estrus stage occurred later in Cohort 1A-generation offspring. However, these differences were not considered as delayed sexual development but as a consequence of delayed general development (lower pup weights).

No direct effects were observed on the organ weights of F1-generation pups. No effects were observed on nipple retention in male F1-generation pups or Cohort 1B F2-generation pups. No treatment-related effects were observed on the development of the ovarian follicles from primordial small follicles into corpora lutea. No treatment-related effects were observed on the splenic lymphocyte subpopulation analysis in Cohort 1A F1-generation animals.

#### *Neuro(developmental) parameters*

Functional observation battery (FOB) and spontaneous motor activity analysis did not reveal any effect of the test substance in animals of Cohort 2A of the F1-generation. The results of the auditory startle response did not indicate any neurotoxic potential of the test substance in animals of Cohort 2A of the F1-generation. No treatment-related adverse effects were observed on brain weight, brain length and brain width in animals of Cohort 2A or Cohort 2B. Brain morphometric analysis of the thicknesses of 10 major regions of the brain did not reveal any compound-related adverse effect. Macroscopic observations at sacrifice of animals of Cohort 2A and Cohort 2B did not reveal any treatment-related abnormalities. Microscopic observations of the brains and neuronal tissues of animals of Cohort 2A and the brain of animals of Cohort 2B revealed no treatment-related abnormalities.

#### *Overall conclusion*



Based on the effects on body weights, the NOAEL for parental effects was placed at the mid-dose concentration of 2100 mg test substance per kg diet (this corresponds to a mean test substance of 153 mg per kg body weight per day for males and 163 mg per kg body weight per day for females).

Based on the lower number of implantation sites and the lower number of pups delivered, the NOAEL for fertility and reproductive performance was placed at the mid-dose concentration of 2100 mg test substance per kg diet (this corresponds to a mean test substance of 153 mg per kg body weight per day for males and 163 mg per kg body weight per day for females). The differences in reproductive parameters occurred at a maternally toxic dose level.

Based on the effects on pup body weights, the NOAEL for general and sexual development was placed at the mid-dose concentration of 2100 mg test substance per kg diet (this corresponds to a mean test substance of 153 mg per kg body weight per day for males and 163 mg per kg body weight per day for females).

There were no effects of the test item on neuro(developmental) parameters. The NOAEL for neuro(developmental) parameters was placed at the high-dose concentration of 7000 mg test substance per kg diet (this corresponds to a mean test substance of 534 mg per kg body weight per day for males and 550 mg per kg body weight per day for females).

Ref.: 26

**SCCS comment**

The SCCS agrees on a NOAEL of 153 mg/kg bw/day for general and sexual development.

**3.4.5.2 Developmental Toxicity****From SPC/1279/94**

In a teratogenicity study, pregnant Wistar rats were fed by gavage 100, 400 and 1000 mg/kg bw of the test substance. In the dams receiving 400 and 1000 mg/kg bw, increases in liver weight were noted. No signs of embryo-/fetotoxicity and no indications for a teratogenic effect were observed.

**New data**

Guideline: /  
Species/strain: Rabbit, New Zealand White  
Group size: 17/females/dose  
Test substance: Octocrylene  
Batch: /  
Purity: /  
Vehicle: Mixture of petrolatum and C12-15 alkylbenzoate (Finsolv TN) at differing ratios  
Dose levels: 0, 65, 267 mg/kg bw/day  
Control: 80% (w/w) petrolatum and 20% (w/w) Finsolv  
Route: Dermal (open, clipped area on the back)  
Exposure period: Days 6-18 of gestation  
Duration: Day 29 of gestation  
GLP: /  
Study period: 1994

A percutaneous developmental toxicity study is available as a summary in a publication using New Zealand White does, treated topically with Octocrylene in a mixture of petrolatum and C1-15 alkylbenzoate (65, 267 mg/ kg/day) on days 6 through 18 of gestation.

Body weights, food consumption and further maternal parameters including clinical observations and gross necropsy of thoracic and abdominal viscera, uterus and ovaries were comparable between treated and control animals. Female reproductive parameters addressed by examinations of ovaries and uterine content were unaffected by treatment with Octocrylene. One doe per Octocrylene dose group aborted, being statistically indifferent by respective historical control data. Offspring parameters, covering mortality, survival rates, gender ratios, litter sizes and weights were comparable between treated and control animals, and external, soft tissue, skeletal and head examination yielded no evidence of Octocrylene-associated teratological effects.

Ref.: 25

Guideline: /  
Species/strain: CD-1 mice  
Group size: 12/females/dose  
Test substance: Octocrylene  
Batch: /  
Purity: Corn oil  
Vehicle: Mixture of petrolatum and C12-15 alkylbenzoate (Finsolv TN) at differing ratios  
Dose levels: 0, 100, 300, 1000 mg/kg bw/day  
Control: /  
Route: Oral gavage (0.5 ml)  
Exposure period: Days 8-12 of gestation  
Duration: Lactation day 3  
GLP: /  
Study period: 1994

An *in vivo* teratology screening study in CD-1 mice according to Chernoff-Kavlock was reported (available as a summary in a publication), where Octocrylene (100, 300, 1000 mg/kg bw/d) was administered in corn oil via gavage on days 8-12 of gestation.

All dams survived offspring delivery and maternal body weight changes were comparable across all treatment groups. Pregnancy rates were lower in the high-dose group, which is not attributable to the test substance, which was applied after mating. Litter size and the number of live and dead pups delivered were the same between the test groups. Postnatal survival and body weight gain of pups were unaffected and an observed trend toward decreased survival of pups born to Octocrylene-treated compared to control dams did not achieve statistical significance.

Ref.: 25

#### **Overall SCCS comment on reproductive toxicity**

In the EOGRTS, animals were fed with 750, 2100 and 7000 ppm of the test substance. Based on effects on parental and pup body weights, a lower number of implantation sites and lower number of pups delivered the NOAEL is 2100 ppm (153/163 mg/kg bodyweight per day for males/females) for parental systemic toxicity, fertility/reproduction performance, and general and sexual development. No neuro-/developmental effects were observed at the highest dose level (7000 ppm corresponding to 534/550 mg/kg bw per day for males/females). A NOAEL of 153 mg/kg bodyweight per day will be used as the point of departure in the safety evaluation.

### **3.4.6 Mutagenicity / genotoxicity**

#### **3.4.6.1 Mutagenicity / genotoxicity *in vitro***



/

**3.4.6.2 Mutagenicity / genotoxicity *in vivo*****From SPC/1279/94**

An Ames test using four different strains of *Salmonella typhimurium* yielded negative results. Tests on cytogenetic toxicity performed in mammalian cells *in vitro* (mouse lymphoma cells; CHO-cells) showed negative results as well. There was no indication for a clastogenic potential of the test substance in the micronucleus test.

**New data*****Mutagenesis studies in Mouse L5178Y T/K<sup>+</sup> lymphoma cells***

After a series of preliminary dose-range-finding studies, maximum Octocrylene concentrations of 0.50 µg/mL without S9 activation and 0.16 µg/mL with S9 activation were used. Treatment of cells with 0.29 or 0.58 µg/mL ethyl methanesulfonate resulted in significantly elevated mutant frequencies of 340 and 640x10<sup>6</sup> surviving cells, respectively, compared to control values of 27x10<sup>6</sup> surviving cells. Octocrylene (0.028-0.38 µg/mL) did not increase mutant frequencies compared to those of background. Insufficient cells were obtained for cloning at 0.5 µg/mL Octocrylene.

***Chromosomal aberrations in Chinese hamster ovary cells***

Treatment of CHO cells with triethylenemelamine (positive control) without S9 activation or with cyclophosphamide (positive control) with S9 activation resulted in a significant increase in cells with structural aberrations compared to dimethyl sulfoxide-treated controls. No significant increase in cells with aberrations was observed in any of the Octocrylene-treated groups (0.02-0.04 µl/mL), with or without metabolic activation at any of the harvest times.

Ref.: 25

**SCCS comment**

Both in the previous Opinion from 1994 and in Odio *et al.*, tests on cytogenetic toxicity performed in mammalian cells *in vitro* (mouse lymphoma cells; CHO-cells) showed negative results. It should be noted that there are large differences in the Octocrylene concentrations used in the studies included in the previous Opinion and in Odio *et al.* (4.224-100 µg/mL vs 0.02-0.04 µl/mL).

In the ECHA registration dossier on Octocrylene (last modified April 2020), the *in vitro* AMES test, the *in vitro* gene mutation test and the cytogenicity test in mammalian cells, the *in vitro* chromosome aberrations tests, and the *in vivo* cytogenicity test in mice were evaluated. No genotoxic effects were observed, supporting the previous SCCS conclusion.

**3.4.7 Carcinogenicity****SCCS comment**

No new data was submitted in 2019 and no data on carcinogenicity was available for the ECHA registration dossier on Octocrylene (last modified April 2020).

**3.4.8 Photo-induced toxicity****3.4.8.1 Phototoxicity / photo-irritation and photosensitisation****From SPC/1279/94**

For induction purposes, guinea pigs were treated repeatedly by cutaneous application of the test substance with subsequent irradiation (UVA plus UVB). Challenge procedure consisted of one percutaneous application at another site after a 20-day rest period and included

irradiation as described. No substance-related phototoxic nor photoallergic reactions were observed.

**SCCS comment**

See Chapter 3.4.2 on skin sensitisation for information.

**3.4.8.2 Photomutagenicity / photoclastogenicity****From SPC/1279/94**

In the presence of UV light, the test substance did not induce mutations in *E.coli* strain WP2, nor chromosome aberrations in CHO-cells.

No new data was submitted in 2019.

**3.4.9 Human data**

/

**3.4.10 Special investigations****3.4.10.1 Endocrine activity****New data*****Non-test information, in silico, read across, in chemico***

No data submitted

***In vitro and other assays******Estrogenic /anti estrogenic/androgenic/anti-androgenic activities***

Kunz and Fent (2006) tested a set of 18 UV filters including Octocrylene at non-cytotoxic concentrations with recombinant yeast systems carrying either a human estrogen (hERα) or androgen receptor (hAR). Octocrylene was mainly associated with anti-androgenic/androgenic activities under *in vitro* conditions. The observed *in vitro* effects can be considered as not biologically relevant for the *in vivo* situation.

Ref.: 27

***[Ca<sup>2+</sup>] in human sperm cells***

Rehfeld *et al.* (2016) analysed 29 UV filters including Octocrylene in a series of *in vitro* tests, in order to evaluate their ability to induce the rise in [Ca<sup>2+</sup>] in human sperm cells by interacting with cationic channel of sperm (CatSper) and thereby mimicking the effect of progesterone. The changes in intracellular free calcium levels were measured using a Ca<sup>2+</sup> fluorimetric assay. Octocrylene at 10 µM was found to induce slow rising or sustained Ca<sup>2+</sup> levels, which differed from the fast and transient Ca<sup>2+</sup> signals induced by progesterone, suggesting a different mode of action. The induced Ca<sup>2+</sup> signals were greatly reduced when the sperm cells were kept in a low Ca<sup>2+</sup> HTF+ medium, showing that Octocrylene induced Ca<sup>2+</sup> signals by affecting the uptake of extracellular Ca<sup>2+</sup>. Octocrylene showed a lesser degree of inhibition of Ca<sup>2+</sup> influx in an assay at 50 µM following addition of the CatSper inhibitor, MDL12330A, indicating a mechanism which is separate from CatSper. Furthermore, in another study, no change in pH was induced by Octocrylene, which could have an impact on the activation of the CatSper channel. In a dose-response relationship experiment, Octocrylene showed a saturating dose-response curve, with a mean EC50 value 2.34 µM and the lowest effective dose (EC02) value of 0.0921 µM. Together these findings indicate that Octocrylene might induce Ca<sup>2+</sup> signals via release of Ca<sup>2+</sup> from internal Ca<sup>2+</sup>

stores and not through activation of CatSper, thereby not mimicking the effect of progesterone on human sperm cells.

Ref.: 28

***Acrosome reaction, sperm penetration, hyperactivation, viability of human sperm***

In a follow-up study, Rehfeld (2018) evaluated the 29 UV filters including Octocrylene for their ability to interfere with the human sperm cell functions acrosome reaction, sperm penetration into a viscous medium and hyperactivation, as well as with sperm viability under *in vitro* test conditions in four assays. In each of the assay, the UV filters were tested at 10  $\mu$ M (n = 3–5), along with two positive controls (10  $\mu$ M progesterone and 2  $\mu$ M ionomycin) and a negative control (0.2% DMSO). The acrosome reaction and sperm viability were evaluated using image cytometer-based assays, while the hyperactivation in sperm cells were investigated using computer-assisted semen analysis (CASA). The sperm penetration test was conducted with methylcellulose (1% w/v). Octocrylene was not found to have an impact in either of the sperm function assays, suggesting an absence of effects on male fertility.

Ref.: 29

***In vitro high throughput screening (HTS) assays from the US EPA ToxCast program***

Octocrylene has been tested as part of the ToxCast program of the US EPA, which currently contains 921 ED-specific *in vitro* high-throughput screening (HTS) assays addressing the E (estrogen), A (androgen), T (thyroid) and S (steroidogenesis) modalities being used as part of the US EPA's Endocrine Disruptor Screening Program (EDSP21). Under the EDSP-21 screening program, Octocrylene has been tested in 30 *in vitro* HTS assays. Positive results are considered "active" and are reported as the concentration at which 50% of the maximum response is achieved (AC<sub>50</sub>, in  $\mu$ M). However, a positive result in a specific assay does not necessarily mean an adverse outcome. At times, they may be due to a burst of cellular responses indicative of cytotoxicity and not to a specific chemical-receptor interaction. Octocrylene was found to be active in 7 (E=3; A=2; T=1; S=1) out of 19 ED relevant assays (accessed June 2020), out of which 4 have been flagged as potentially 'false positive' by the automated analysis tool from the US EPA (ToxCast pipeline (tcpl) package). However, the AC<sub>50</sub> values in all 7 assays exceed the cytotoxic concentrations indicating non-specific activity.

Ref.: 30

***Animal data***

***14/28 day repeated dose toxicity***

As referred to in Chapter 3.4.4.1, higher serum TSH levels in high dose rats (10 000 ppm/650 mg/kg bw/day) of both sexes on study days 21 and 29 as well as in high dose females were observed already on study day 14, whereas no significant changes occurred for measured T3- and T4-levels in any test group or time point assessed. The increase in TSH levels in combination with physiological T4 hormone levels was due to a compensation of the increased liver-related thyroid hormone clearance. This resulted in an increased synthesis of the hormones induced by a stimulation of the thyroid via the pituitary gland. Furthermore, the thyroid glands of high dose group males (2/5) and females (3/5) revealed a minimal follicular cell hypertrophy/hyperplasia, accompanied by minimal altered colloid. In females, an association with the increased levels of TSH and the minimal histopathological changes in the thyroid is more evident than in male animals.

Ref.: 24

***90 day repeated dose toxicity***

Octocrylene was administered at doses of 750, 2250, 4500 and 15000 ppm to ten Wistar rats per sex and dose for three months in the diet, corresponding to approx. 58, 175, 340, 1085 mg/kg bw/day ingested test substance, respectively. No changes in absolute and relative testes weights in males and adrenal weights in males/females were observed. Furthermore, no treatment-related microscopic findings were observed in adrenal glands, epididymides, prostate and testes of male animals and in adrenal glands, mammary gland, ovaries, uterus and vagina of female animals. A treatment-related slight or moderate hypertrophy of the follicular epithelium of the thyroid gland, associated with minimal or slight pale staining colloid was observed in the two high-dose groups (340 and 1085 mg/kg bw/day). Based on the indications observed for hepatic enzyme induction, these enzymes are assumed to be responsible for metabolism of thyroid hormones, resulting in an increased removal of circulating T3 and T4 with subsequent elevation of thyroid stimulating hormone secretion. The incidence of hypertrophic cells in the pituitary gland tended to occur in the middle of the pars distalis rather than in the lateral regions suggesting that they may be so called thyroidectomy cells caused by interference in the homeostatic feedback mechanism. Taken together, the observed effects on thyroid and male pituitary gland are considered to have occurred as a secondary consequence of hepatic enzyme induction.

Ref.: 9

As referred to in Chapter 3.4.4.2, none of the Octocrylene-treated rabbits showed any evidence of macroscopic or histopathological abnormalities in any organs examined, which included kidney, liver, and all other internal organs. No evidence was obtained of adverse Octocrylene effects on the measures of male reproductive system integrity (morphological examination of epididymis, testicles abnormalities, epididymal sperm concentrations and percentage sperm motility).

Ref.: 25

**Extended one-generation reproductive toxicity**

As referred to in Chapter 3.4.5.1, the NOAEL for fertility and reproductive performance was placed at the mid-dose concentration of 2100 mg test substance per kg diet (overall mean: 153/163 mg/kg bw/d for males/females) based on the lower number of implantation sites and the lower number of pups delivered. The differences in reproductive parameters occurred at a maternally-toxic dose level.

Ref.: 26

In a supportive uterotrophic assay in immature female Wistar rats (age 20±1 days), Octocrylene in corn oil was administered orally to ten animals per dose group (250 and 1000 mg/kg bw/d) for three consecutive days. Test substance administration led to statistically significantly retarded body weight gain at 1000 mg/kg bw/d, being regarded as sign of systemic toxicity, however no increase in the uterine weights was observed at any dose level. Histopathologically, no changes were detected in the uterus of the Octocrylene-treated animals. Taken together, Octocrylene showed no uterotrophic (estrogenic) effect in rats under the chosen testing conditions, when compared with the carrier control.

Ref.: 31

In a supportive study according to the OECD Protocol and Guidance for the Conduct of the Rodent Hershberger Assay (Phase 2 of the Validation of the Rodent Hershberger Assay) and GLP, Octocrylene was administered in corn oil via gavage to groups of six castrated but testosterone propionate (0.4 mg/kg) substituted male Wistar rats for ten days at dose levels of 300 and 1000 mg/kg bw/day. Substance related findings in the high-dose group (1000 mg/kg bw/day) were increases of absolute and relative liver weights, decreases of absolute and relative ventral prostate weights and weights of the muscle bulbocavernosus/levator ani. In the low-dose group (300 mg/kg bw/day), absolute and relative liver weights were significantly increased. No Octocrylene related effects in clinical examinations, on hormone levels (testosterone, dihydrotestosterone and luteinizing hormone) and the histology of the prostate, seminal vesicle and the bulbo-urethral gland

were observed when compared to animals given testosterone propionate only. The observed decrease in organ weights of ventral prostate and the muscle bulbocavernosus together with the *levator ani* may have been fortuitous or is to be explained by an enzyme induction, indicated by the observed increased liver weights connected with a higher metabolism rate of the substituted androgen testosterone propionate. In contrast, absolute and relative weights of the other accessory sex organs were not significantly reduced. Moreover, the histology of prostate, seminal vesicle and the bulbo-urethral gland was comparable to the control. Therefore, under the conditions of the present study, regarding clinical examinations, hormone investigations as well as pathological evaluations, no indication for an antiandrogen efficacy of Octocrylene was determined.

Ref.: 32

### Human data

No new data was submitted.

### SCCS comment on endocrine activity

Information on endocrine activity of Octocrylene is summarised in Table 12.

In the EOGRT study, the SCCS noted that the increased T4-specific UDP-glucuronosyltransferase-activities in females and the induction of Thyroxine 5'-deiodinase type D3 (Iodothyronine deiodinase type D3) activity in males observed at 3000 ppm (193 mg/kg bw/day) (BASF 2019) were due to a compensation of the increased liver-related thyroid hormone clearance, resulting in an increased synthesis of the hormones induced by a stimulation of the thyroid via the pituitary gland. Since humans, unlike rodents, possess a T4 binding protein that greatly reduces susceptibility to plasma T4 depletion and thyroid stimulation, the effects seen in rats cannot be directly extrapolated to humans. Thus, the SCCS decided not to use these findings in the risk assessment.

The key study was considered to be the EOGRT study (Triskelion B.V. 2019) where a NOAEL of 153 mg/kg bw/day was defined based on general and sexual development. The available data on Octocrylene provide some indications for potential endocrine effects. However, the current level of evidence is not sufficient to derive a toxicological point of departure based on endocrine disrupting properties for use in human health risk assessment.

**Table 12** Summary of studies on endocrine activity and indicated NOAEL's

Study	Route of exposure	Comment	Parameter	NOAEL (mg/kg bw/d)
<b><i>In vitro</i> and other assays</b>				
Kunz and Fent (2006) (27)	//	Recombinant yeast systems carrying either a human estrogen (hER $\alpha$ ) or androgen receptor (hAR)	Octocrylene was mainly associated with anti-androgenic/androgenic activities under <i>in vitro</i> conditions, considered as not biologically relevant for the <i>in vivo</i> situation	//
Rehfeld <i>et al.</i> 2016 (28)	//	Non-standardised tests ( <i>In vitro</i> mechanistic study)	Human sperm cells / 10 $\mu$ M / 3 hours  Octocrylene induced sustained or slow rising of Ca <sup>2+</sup> signals, which did not resemble the Ca <sup>2+</sup> signal induced by progesterone thereby not mimicking the effect of progesterone on	//

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Study	Route of exposure	Comment	Parameter	NOAEL (mg/kg bw/d)
			human sperm cells	
Rehfeld <i>et al.</i> 2018 (29)	//	Non-standardised tests ( <i>In vitro</i> mechanistic study)	Human sperm cells / 10 µM / 3 hours  Octocrylene did not affect sperm functions like sperm acrosome reaction, sperm penetration, proportion of hyperactivated sperm cells or sperm viability indicating absence of effects on male fertility	//
ToxCast 2020 (30)	//	<i>In vitro</i> high throughput screening (HTS) assays	Various human and rat cell lines / from 0.0006 to 90 µM / 0.5 to 48 hours  Octocrylene was found to be active in 7 (E=3; A=2; T=1; S=1) out of 19 ED relevant assays. However, the AC50 values in all 7 assays exceed the cytotoxic concentrations indicating non-specific activity	//
<b>Animal studies</b>				
BASF 2019 (24)	Feed	14/28 day repeated dose toxicity study (rats)	<b>10000 ppm<sup>1</sup></b> <i>Clinical Pathology</i> (28 day study) Increased TSH levels in: -females (day 14) -both sexes (days 21, 29)  <i>Pathology</i> 28 day study: Minimal hypertrophy/hyperplasia of follicular cells in the thyroid glands (2/5 males, 3/5 females), accompanied by altered colloid 14 day study: Minimal hypertrophy/hyperplasia of follicular cells in the thyroid glands (2/5 males, 3/5 females) accompanied by altered colloid (2/5 males, 1/5)  <i>Bioanalytical Examinations</i> (14 day study) -Increased T4-specific UDP-glucuronosyltransferase activity (both sexes) -Reduction of Thyroxin 5'-deiodinase type D1 (Iodothyronine deiodinase type D1) activity in males	215 188  188  193  193 193

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Study	Route of exposure	Comment	Parameter	NOAEL (mg/kg bw/d)
			-Induction of Thyroxin 5'-deiodinase type D3 (Iodothyronine deiodinase type D3) activity in males  <b>3000 ppm<sup>1</sup></b> <i>Bioanalytical Examinations</i> (14 day study) -Increased T4-specific UDP-glucuronosyltransferase-activities in females -Induction of Thyroxin 5'-deiodinase type D3 (Iodothyronine deiodinase type D3) activity in males	193   //  //
BASF AG 1993a (10)	Feed	90-day repeated dose toxicity study (rats)	Slight/moderate hypertrophy of the follicular epithelium of the thyroid gland associated with minimal or slight pale staining colloid in the two high dose groups  Incidence of hypertrophic cells in the pituitary gland (probably thyroidectomy cells caused by interference in the homeostatic feedback mechanism)	175  340
Odio 1994 (25)	Dermal	90-day repeated dose toxicity study (rabbits)	No signs of morphological abnormalities in epididymis and testicles, and in epididymal sperm concentrations  No signs of significant toxicity after 13 weeks treatment	534  534
Triskelion B.V. 2019 (26)	Feed	Key study EOGRTS	<i>F0:</i> -Increased thyroid weight <sup>2</sup> -Incidence of activated appearance of the thyroid gland <sup>3</sup> - Lower no. of implantation sites and number of pups  <i>Cohort 1A F1:</i> -Increased thyroid weight <sup>2</sup> -Incidence of activated appearance of the thyroid gland <sup>3</sup>  <i>Cohort 1B F1</i> - Lower no. of implantation sites and number of pups	// // 153  // // 153
BASF 2001 (31)	Oral	Study period is only three days. No endocrine effects were observed		1 000



Study	Route of exposure	Comment	Parameter	NOAEL (mg/kg bw/d)
BASF 2003 (32)	Gavage	Study period is only ten days	<b>1000 mg/kg bw/day<sup>4</sup></b> Decrease of absolute and relative ventral prostate weights and weights of the muscle bulbocavernosus / <i>levator ani</i>  <b>300 mg/kg bw/day</b> No Octocrylene related effects	300

Remarks by the Applicant:

<sup>1</sup>The increase in TSH levels in combination with physiological T4 hormone levels was due to a compensation of the increased liver-related thyroid hormone clearance, resulting in an increased synthesis of the hormones induced by a stimulation of the thyroid via the pituitary gland.

<sup>2</sup>Considered to be adaptive changes in rats.

<sup>3</sup>Considered to be treatment related but adaptive changes in rats.

<sup>4</sup>The observed decrease in organ weights of ventral prostate and the muscle bulbocavernosus together with the *levator ani* may have been fortuitous or is to be explained by an enzyme induction, indicated by the observed increased liver weights connected with a higher metabolism rate of the substituted androgen testosterone propionate.

### 3.5 SAFETY EVALUATION (INCLUDING CALCULATION OF THE MOS)

MOS calculations for separate product types and aggregated exposures are shown in Table 13. A NOAEL of 153 mg/kg bw/day based on the extended one-generation reproductive toxicity study is used for the calculation of MOS. Information from Bury *et al.* (2019) provide some evidence for an oral bioavailability of 50%, giving an adjusted NOAEL of 76.5 mg/kg bw/day. Details of the calculation of systemic exposure dose (SED) are presented in Table A1 in the Annex.

In order to derive a MOS of 100 for aggregated exposure for lipstick, face cream, hand cream and sunscreen as a propellant spray, the total SED should be maximally 0.765 mg/kg bw/day. Linear extrapolation of the SED for 10% Octocrylene shows that this can be achieved by reducing the Octocrylene concentration from 10% to 9% in the propellant spray (Table 14). Details of the calculation of systemic exposure dose (SED) and safe level are presented in the Tables A2-4 in the Annex.

**Table 13** MOS calculations for the different product types and aggregated exposures

Products	Conc (%)	Surface	Systemic Exposure Dose (SED) (mg/kg bw/day)				NOAEL (mg/kg bw/day)	MOS
			Dermal	Inhalation	Oral	Total		
Lipstick	10	Lips	0	0	0.045	0.045	76.5	<b>1 700</b>
Face cream	10	Face	0.020	0	0	0.020	76.5	<b>3 825</b>
Hand cream	10	Hand	0.028	0	0	0.028	76.5	<b>2 732</b>
Sunscreen cream/lotion	10	Whole body	0.566	0	0	0.566	76.5	<b>135</b>
Sunscreen propellant spray	10	Whole body	0.566	0.176	0	0.743	76.5	<b>102</b>



Sunscreen pump spray	10	Whole body	0.566	0.002	0	0.568	76.5	<b>135</b>
Aggregated exposure (lipstick, face cream, hand cream, sunscreen cream/lotion)			0.614	0	0.045	0.659	76.5	<b>116</b>
Aggregated exposure (lipstick, face cream, hand cream, sunscreen as propellant spray)			0.614	0.176	0.045	0.835	76.5	<b>92</b>
Aggregated exposure (lipstick, face cream, hand cream, sunscreen as pump spray)			0.614	0.002	0.045	0.661	76.5	<b>116</b>

In order to derive a MOS of 100 for aggregated exposure for lipstick, face cream, hand cream and sunscreen as a propellant spray, the total SED should be maximally 0.765 mg/kg bw/day. Linear extrapolation of the SED for 10% Octocrylene shows that this can be achieved by reducing the Octocrylene concentration from 10% to 9% in the propellant spray (Table 14). Details of the calculation of systemic exposure dose (SED) and safe level are presented in the Tables A2-4 in the Annex.

**Table 14** MOS calculations based on 9% Octocrylene in sunscreen as propellant spray, and 10% Octocrylene in lipstick, face cream and hand cream

Products	Conc (%)	Surface	Systemic Exposure Dose (SED) (mg/kg bw/d)				NOAEL (mg/kg bw/day)	MOS
			Dermal	Inhalation	Oral	Total		
Lipstick	10	Lips	0	0	0.045	0.045	76.5	<b>1 700</b>
Face cream	10	Face	0.020	0	0	0.020	76.5	<b>3 825</b>
Hand cream	10	Hand	0.028	0	0	0.028	76.5	<b>2 732</b>
Sunscreen propellant spray	9	Whole body	0.509	0.158	0	0.667	76.5	<b>115</b>
Aggregated exposure (lipstick, face cream, hand cream, sunscreen propellant spray)			0.557	0.158	0.045	0.760	76.5	<b>101</b>

Ref.: 15, 26

### 3.6 DISCUSSION

#### **Physicochemical properties**

Only one batch of the test item (batch 5132 4997 V0) was chemically characterized by IR, <sup>1</sup>H-NMR and <sup>13</sup>C-NMR. There is no report on the analytical method used to test impurities, or on the chemical nature of these impurities. Alpha-acetylphenylacetone nitrile (CAS 4668-48-8, EC 224-737-4) is reported as an impurity of Octocrylene in one case submitted to ECHA's database of registered substances. Benzophenone is a hazardous impurity and degradation product of Octocrylene and it should be monitored and kept at trace levels.

#### **Toxicokinetics**

A dermal absorption of  $0.97 \mu\text{g}/\text{cm}^2$  (mean + 1SD:  $0.45 \pm 0.52 \mu\text{g}/\text{cm}^2$ ) with an Octocrylene concentration of 10% was used in the calculation of SED.

Octocrylene is a lipophilic substance, and it is reported to be metabolised to a variety of metabolites where CDAA is the main metabolite. Information is lacking on whether the most important toxic agent is Octocrylene or the metabolites.

The SCCS notes that due to the relatively long half-life of both Octocrylene and CDAA in plasma and low elimination rate of CDAA in urine, an accumulation of Octocrylene and CDAA in the human body following repeated dermal applications may occur. On the other hand, the reported plasma levels of Octocrylene and CDAA are low (in the ng/mL range) and it can be questioned whether these substances may reach toxic levels due to accumulation after repeated applications.

### **Exposure**

SEDs for dermal exposures to Octocrylene from sunscreen cream/lotion, face cream and hand cream are 0.566, 0.020 and 0.028 mg/kg bw/day, respectively. SEDs for inhalation exposures to sunscreen sprays are 0.176 and 0.002 mg/kg bw/day for propellant and pump spray, respectively. SED for oral exposure to lipstick is 0.045 mg/kg bw/day.

### **Toxicological Evaluation**

#### *Irritation and corrosivity*

Octocrylene is not expected to be an eye or skin irritant.

#### *Skin sensitisation*

Literature both on LLNA results and on human sensitisation cases published since 1994 suggests that Octocrylene is a moderate skin sensitizer and a skin photosensitizer. When taking into consideration the widespread use of Octocrylene in cosmetic products, the number of reported cases of allergic contact dermatitis appears to be small. Photoallergy is seen mainly in adult patients who have previously used topical products containing the non-steroidal anti-inflammatory drug ketoprofen. Thus, the majority of photoallergic reactions are probably not induced by Octocrylene itself but occur as a result of previous photosensitisation to ketoprofen.

#### *Acute toxicity*

The SCCS agrees that the acute dermal median lethal dose ( $\text{LD}_{50}$ ) in the rat is greater than 2000 mg/kg body weight.

#### *Repeated dose toxicity*

The newly submitted repeated dose toxicity studies do not provide data that support a change of the NOAEL of 175 mg/kg body weight per day for males and females described in the previous SCCS Opinion.

#### *Reproductive toxicity*

In the EOGRTS, animals were fed with 750, 2100 and 7000 ppm of the test substance. Based on effects on parental and pup body weights, a lower number of implantation sites and lower number of pups delivered the NOAEL is 2100 ppm (153/163 mg/kg bodyweight per day for males/females) for parental systemic toxicity, fertility/reproduction performance, and general and sexual development. No neuro-/developmental effects were observed at the highest dose level (7000 ppm corresponding to 534/550 mg/kg bw per day for males/females). A NOAEL of 153 mg/kg bodyweight per day will be used as the point of departure in the safety evaluation.

#### *Mutagenicity / genotoxicity*

The genotoxicity of Octocrylene was investigated in the gene mutation and chromosomal aberration tests *in vitro*. No genotoxic effects were observed supporting the previous SCCS conclusion. The SCCS conclusion is consistent with the ECHA evaluation of the genotoxicity of Octocrylene *in vitro* and *in vivo*.

*Carcinogenicity*

No new data was submitted in 2019 and no data on carcinogenicity was available for the ECHA registration dossier on Octocrylene (last modified April 2020).

*Photo-induced toxicity*

In the presence of UV light, the test substance did not induce mutations in the *E.coli* strain WP2, nor chromosome aberrations in CHO-cells.

Photosensitisation: See skin sensitisation.

*Human data*

/

*Special investigation*

**Endocrine activity**

The key study was considered to be the EOGRT study (Triskelion B.V. 2019) where a NOAEL of 153 mg/kg bw/day was derived based on general and sexual development. The available data on Octocrylene provide some indications for potential endocrine effects. However, the current level of evidence is not sufficient to derive a toxicological point of departure based on endocrine disrupting properties for use in human health risk assessment.

This Opinion did not address the potential impact of Octocrylene on the environment.

#### 4. CONCLUSION

*1. In light of the data provided and taking under consideration the concerns related to potential endocrine disrupting properties of Octocrylene, does the SCCS consider Octocrylene safe when used as a UV-filter in cosmetic products up to a maximum concentration of 10% (as acid)?*

On the basis of safety assessment, and considering the concerns related to potential endocrine disrupting properties of Octocrylene, the SCCS is of the opinion 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.

*2. Alternatively, what is according to the SCCS the maximum concentration considered safe for use of Octocrylene as a UV-filter in cosmetic products?*

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.

*3. Does the SCCS have any further scientific concerns with regard to the use of Octocrylene in cosmetic products?*

The SCCS considers that, whilst there are indications from some *in vivo* studies to suggest that Octocrylene may have endocrine effects, the evidence is not conclusive enough at present to enable deriving a specific endocrine-related toxicological point of departure for use in safety assessment.

Contact sensitisation to Octocrylene has been reported, however, taking into consideration the widespread use of Octocrylene in cosmetic products, the number of reported cases of allergic contact dermatitis appears to be negligible.

It should be noted that occurrence of photoallergy to Octocrylene is strongly related to a previous photoallergy to topical ketoprofen.

Exposure to Octocrylene from other products than those in this Opinion has not been considered.

The SCCS mandates do not address environmental aspects. Therefore, this assessment did not cover the safety of Octocrylene for the environment.

#### 5. MINORITY OPINION

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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

CDA	2-Cyano-3,3-diphenylacrylic acid
5OH-OC	2-Ethyl-5-hydroxyhexyl 2-cyano-3,3-diphenyl acrylate
DOCCA	2-(Carboxymethyl)butyl 2-cyano-3,3-diphenyl acrylate
NADPH	$\beta$ -Nicotinamide adenine dinucleotide phosphate
GSH	Glutathione
DPCA	3,3-Diphenyl-cyanoacrylate
EROD	7-Ethoxyresorufin O-deethylase
PROD	7-Pentoxyresorufin-O-dealkylation
BROD	7-Benzyloxyresorufin oxidation
MUF-GT	4-Methylumbeliferone glucuronosyltransferase
HOBI-GT	4-Hydroxybiphenyl-glucuronosyltransferase
GGT	Gamma glutamyl transferase

**9. ANNEX****SED and MOS calculations****Table A1** MOS calculation based on 10% Octocrylene in all product types

Product type	E <sub>product</sub>	C	F <sub>ret</sub>	Bioavailability		SED	MoS
	mg/kg bw/d	%	%	%		mg/kg bw/d	
Lipstick	0.9	10	100	50		0.045	<b>1 700</b>
	<b>DA<sub>a</sub></b>	<b>SSA</b>		<b>F</b>	<b>BW</b>		
	µg/cm <sup>2</sup>	cm <sup>2</sup>		day <sup>-1</sup>	kg		
Face cream	0.97	565		2.14	60	0.020	<b>3 825</b>
Hand cream	0.97	860		2	60	0.028	<b>2 732</b>
Sunscreen: Dermal	0.97	17 500		2	60	0.566	<b>135</b>
	<b>(IA<sub>1</sub>+IA<sub>2</sub>)</b>	<b>G</b>	<b>RF</b>	<b>F</b>	<b>BW</b>		
	mg			day <sup>-1</sup>	kg		
Sunscreen propellant spray: Inhalation	35.1	0.75	0.2	2	60	0.176	<b>435</b>
Sunscreen propellant spray: Dermal + inhalation						0.742	<b>102</b>
Sunscreen pump spray: Inhalation	7.02	0.75	0.01	2	60	0.002	<b>38 250</b>
Sunscreen pump spray: Dermal + inhalation						0.568	<b>135</b>
Aggregated exposure (lipstick, face cream, hand cream, sunscreen cream/lotion)						0.659	<b>116</b>
Aggregated exposure (lipstick, face cream, hand cream, sunscreen propellant spray)						0.835	<b>92</b>
Aggregated exposure (lipstick, face cream, hand cream, sunscreen pump spray)						0.661	<b>116</b>

**Calculation of a safe levels of Octocrylene in sunscreen propellant spray****Table A2** SED calculations after dermal exposure based on 9% Octocrylene in sunscreen as propellant spray

Description	Parameter	Sunscreen	Face cream	Hand cream	Unit
Absorption through the skin	DA <sub>a</sub>	0.87*	0.97	0.97	µg/cm <sup>2</sup>
Skin surface area	SSA	17 500	565	860	cm <sup>2</sup>
Dermal absorption per application	DA <sub>a</sub> *SSA*0.001	15.3	0.55	0.83	mg
Frequency of application	F	2	2.14	2	applications/day
Default bodyweight	BW	60	60	60	kg
<b>SED<sub>dermal</sub></b>	SSA*DA <sub>a</sub> *0.001*F/BW	<b>0.509</b>	<b>0.020</b>	<b>0.028</b>	<b>mg/kg bw/day</b>

\*linear extrapolation from 0.97 µg/cm<sup>2</sup>



**Table A3** SED calculations after inhalation exposure based on 9% Octocrylene in sunscreen as propellant spray

Description	Parameter	Propellant spray	Unit
Amount by application <sup>1</sup>	A	15 000	mg/application
Fraction of Octocrylene in non-propellant	C	0.09	(w/w)
Proportion of non-propellant in formulation	P	0.6	
Airborne fraction	AF	1	
Potential amount to be inhaled	EA ( $A \cdot C \cdot P \cdot AF$ )	810	mg
Near-field, 1 m <sup>2</sup>	V <sub>1</sub>	1000	L
Breathing rate	BR	13	L/min
First step: 2 min in near-field	t <sub>1</sub>	2	min
Potential amount inhaled during t <sub>1</sub>	IA <sub>1</sub> ( $EA/V_1 \cdot BR \cdot t_1$ )	21.06	mg
Second step: 10 min in far field	V <sub>2</sub>	10000	L
Breathing rate	BR	13	l/min
Far-field, 10 m <sup>2</sup>	t <sub>2</sub>	10	min
Potential amount inhaled during t <sub>2</sub>	IA <sub>2</sub> ( $EA/V_2 \cdot BR \cdot t_2$ )	10.53	mg
Substance availability	G	0.75	
Respirable fraction	RF	0.2	
Frequency of application	F	2	
Default bodyweight	BW	60	kg
<b>SED<sub>inhal</sub></b>	(IA <sub>1</sub> +IA <sub>2</sub> )*G*RF*F/BW	<b>0.158</b>	<b>mg/kg bw/day</b>

**Table A4** MOS calculation based on 9% Octocrylene in propellant spray sunscreen and 10% Octocrylene in lipstick, face cream and hand cream

Product type	E <sub>product</sub>	C	F <sub>ret</sub>	Bioavailability		SED	MoS
	mg/kg bw/d	%	%	%		mg/kg bw/d	
Lipstick (10%)	0.9	10	100	50		0.045	<b>1 700</b>
	<b>DA<sub>a</sub></b>	<b>SSA</b>		<b>F</b>	<b>BW</b>		
	µg/cm <sup>2</sup>	cm <sup>2</sup>		day <sup>-1</sup>	kg		
Face cream (10%)	0.97	565		2.14	60	0.020	<b>3 825</b>
Hand cream (10%)	0.97	860		2	60	0.028	<b>2 732</b>
Sunscreen: Dermal (9%)	0.87	17 500		2	60	0.509	<b>150</b>
	<b>(IA<sub>1</sub>+IA<sub>2</sub>)</b>	<b>G</b>	<b>RF</b>	<b>F</b>	<b>BW</b>		
	mg			day <sup>-1</sup>	kg		
Sunscreen propellant spray: Inhalation (9%)	31.6	0.75	0.2	2	60	0.158	<b>484</b>
Sunscreen propellant spray: Dermal + inhalation (9%)						0.667	<b>115</b>
Aggregated exposure (lipstick, face cream, hand cream, sunscreen propellant spray)						0.760	<b>101</b>