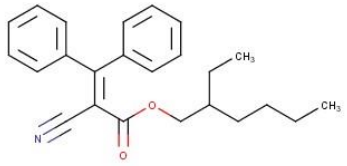
Regulatory Management Option Analysis (RMOA)

Authority: FR- MSCA

Date: March 2023

Substance name: Octocrilene

General structure:



Revision history

Version	*Date*	*Description*
1	March 2023	Initial version

Comments and additional relevant information are invited on this RMOA by XXX.

ANSES would appreciate to receive any information that you are aware of regarding:

- The available alternatives of octocrilene especially when used as a UV filter
- Any information regarding bio-surveillance data
- Any information on uses of octocrilene.

Contents

DISCLAIMER

The author does not accept any liability with regard to the use that may be made of the information contained in this document. Usage of the information remains under the sole responsibility of the user. Statements made or information contained in the document are without prejudice to any further regulatory work that ECHA, the Member States or other regulatory agencies may initiate at a later stage. Assessment of regulatory needs and their conclusions are compiled on the basis of available information and may change in light of newly available information or further assessment.

Foreword

The purpose of the assessment of regulatory needs of a group of substances is to help authorities conclude on the most appropriate way to address the identified concerns for a group of substances or a single substance, i.e. the combination of the regulatory risk management instruments to be used and any intermediate steps, such as data generation, needed to initiate and introduce these regulatory measures.

An assessment of regulatory needs can conclude that regulatory risk management at EU level is required for a (group of) substance(s) (e.g. harmonised classification and labelling, Candidate List inclusion, restriction, other EU legislation) or that no regulatory action is required at EU level. While the assessment is done for a group of substances, the (no) need for regulatory action can be identified for the whole group, a subgroup or for single substance(s).

The assessment of regulatory needs is an important step under ECHA's Integrated Regulatory Strategy. However, it is voluntary, i.e., it is not part of the processes defined in the legislation but aims to support them.

The assessment of regulatory needs can be applied to any group of substances or single substance, i.e., any type of hazards or uses and regardless of the previous regulatory history or lack of such. It can be done based on different level of information. A Member State or ECHA can carry out this case-by-case analysis. The starting point is available information in the REACH registrations and any other REACH and CLP information. However, more extensive set of information can be available, e.g. assessment done under REACH/CLP or other EU legislation, or can be generated in some cases (e.g. further hazard information under dossier evaluation). Uncertainties associated to the level of information used should be reflected in the documentation. It will be revisited when necessary. For example, after further information is generated and the hazard has been clarified or when new insights on uses are available. It can be revisited by the same or another authority.

The responsibility for the content of this assessment rests with the authority that developed it. It is possible that other authorities do not have the same view and may develop further assessment of regulatory needs. The assessment of regulatory needs does not yet initiate any regulatory process but any authority can consequently do so and should indicate this by appropriate means, such as the Registry of Intentions.

For more information on Assessment of regulatory needs please consult ECHA website[1].

[1] https://echa.europa.eu/understanding-assessment-regulatory-needs

Glossary

CLP	Classification, Labelling and Packaging
CoRAP	Community rolling action plan
ED	Endocrine disruptor
EOGRTS	Extended One Generation Reproductive Toxicity Study
LAGDA	Larval Amphibian Growth and Development Assay
LOEC	Lowest Observed Effect Concentration
MoA	Mode of action
NOEC	Non Observed effect Concentration
PBT/vPvB	Persistent, bioaccumulative and toxic/very persistent and very bioaccumulative
RMOA	Regulatory management options analysis
RMM	Regulatory management measure
SEv	Substance evaluation

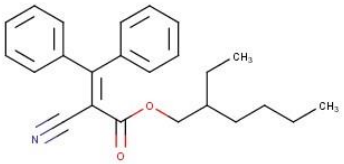
1 Overview of the substance

Table 1: identifiers of the substance

EC name (public):	228-250-8
CAS number	6197-30-4
IUPAC name (public):	2-ethylhexyl 2-cyano-3,3-diphenylacrylate
Index number in Annex VI of the CLP Regulation:	-
Molecular formula:	$C_{24}H_{27}NO_2$
Molecular weight or molecular weight range:	361.47
Synonyms:	Octocrilene

Type of substance ☒Mono-constituent ☐Multi-constituent ☐UVCB

Structural formula:



Other relevant information about Octocrilene:

Octocrilene was originally included in the Community rolling action plan (CoRAP) for substance evaluation in 2012 in order to clarify concerns about:

- Suspected PBT/vPvB,
- Wide dispersive use,
- High (aggregated) tonnage.

During the evaluation, other concerns were identified which were:

- Human health (potential thyroid toxicity, suspected toxicity to reproduction),
- Environment (suspected endocrine activity, exposure of the aquatic environment).

Therefore a decision on substance evaluation published in 2014 required further information to clarify the above mentioned concerns. The results of the tests required were received in 2019. The human health endpoints will be briefly explained in this

RMOA. Regarding the concerns for the environment, they were not totally solved with the results of the tests received in 2019 and led France to request an additional test (LAGDA) in order to clear the potential concern related to Endocrine disruption. The result of this additional test is expected in June 2024.

Nevertheless France, through ANSES, pursued its investigation on octocrilene risk for the environment based on already available data from the evaluation. This particular concern is detailed in the document and potential need for further regulatory risk management actions is discussed.

2 Overview of regulatory processes

2.1 REACH Regulation

Table 2 : Completed or ongoing processes (date of checking: february 2023)

EC/List number	Other REACH related work	RMOA	Evaluation			Authorisation		Restriction	CLH	Actions not under REACH/ CLP(*)
			CCH	TPE	SEV	Candidate List	Annex XIV	Annex XVII	Annex VI (CLP)	
228-250-8	PBT	x			x					

2.2 Regulatory process under CLP

Table 3 : Classification (date of checking: October 2022)

EC/ List No	CAS No	Substance name	Harmonised classification	Classification in registrations	Classification in C&L notifications
228-250-8	*6197-30-4*	*Octocrilene*	_	*Aquatic chronic 1 (H 410)*	*Aquatic chronic 1 (H 410)* *Aquatic chronic 4 (H 413)* *Aquatic chronic 3 (H 412)* *Not classified*

2.3 Other processes/EU legislation

In the EU, the following regulations apply to octocrilene:

- Cosmetic regulation (CE) N° 1223/2009: octocrilene is regulated in the cosmetic regulation for its properties/functions as UV absorber, UV filter and light stabilizer. According to this regulation, octocrilene is allowed in all cosmetic products as UV Filter with a maximum threshold of 10%. According to the SCCS Opinion 1627/21, octocrilene is safe to be used as a UV filter up to 10% regarding its potential ED properties. Moreover, SCCS indicated in its opinion that the maximum concentration of octocrilene in a sunscreen spray must not exceed 9% and in hand cream,

face cream and lipstick up to 10%. SCCS did not investigate the environmental aspects.

- The Food Contact materials regulation (CE) n° 10/2011: octocrilene is listed in the annex I of this regulation indicating that octocrilene can be used as an additive or polymer production aid. Annex I also specifies that the specific migration limit applicable for the substance is 0.05 mg/kg of food. Finally Annex I indicates that octocrilene is not authorized to be used as monomer or other starting substance or macromolecule obtained from microbial fermentation.

3 Information on uses

3.1 Overview of registration dossiers

Table 4 : Overview of registrations (intermediate registrations versus article 10 full registration)

EC /List number	CAS Number	Substance name	REACH Annex	Article 10 Registrations (active)	Intermediate Registrations (active)	Not-updated NONS
228-250-8	6197-30-4	Octocrilene		11	-	-

3.2 Information on tonnage

The ECHA website indicates that the substance is registered under REACH regulation and is manufactured in and/or imported to the European Economic area at >1,000 to <10,000 tons per year.

The SPIN database, which is the database for substances in preparations in Nordic countries (Finland, Denmark, Norway, and Sweden) - based on data from the Product Registries in these countries- indicates that in 2020, 7.5 tons in Denmark; 4.7 tons in Sweden were used. As seen in the figure 1, the amount of octocrilene in the Nordic countries, is low and stable for years except for Denmark were the consumption dropped between 2018 and 2019. It is interesting to note that this drop is not found in the number of preparations containing octocrilene. In general, it is difficult to link the number of preparations and the tonnage reported.

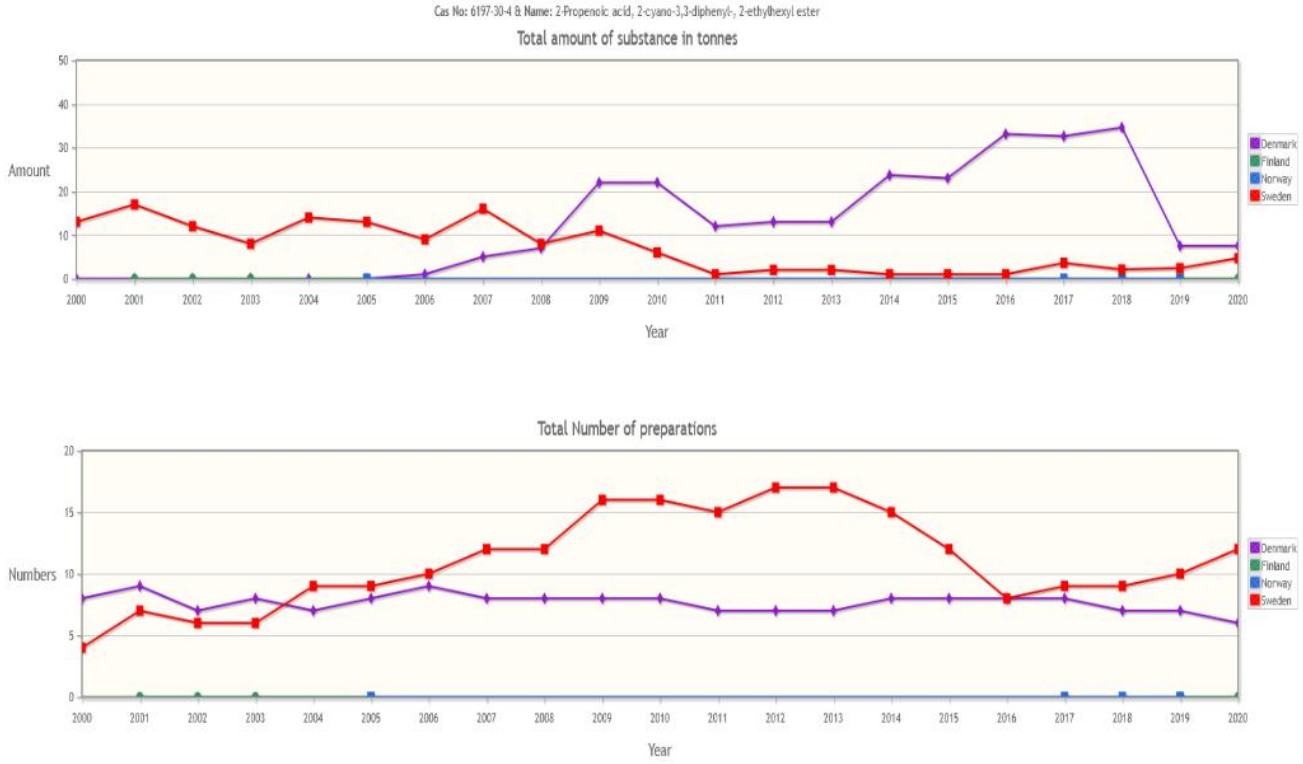


Figure 1 : Total amount in tons of octocrilene according the SPIN Database

The tons of octocrilene reported in the SPIN database are not coherent with those registered on the ECHA website. We can therefore hypothesis that Octocrilene is under-declared in the SPIN database or is more manufactured and/or imported in the EEA by countries other than the Nordic ones.

3.3 Overview of uses

In the following table, are gathered all the uses of octocrilene that have been retrieved from registration dossiers based on information available on ECHA website. They are classified according to the technical function and the product or article type.

Table 5 : Summary of the uses described in the ECHA website

Main types of applications structured by product or article types	Octocrilene	Technical function
PROC 1: Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions	M, F, I, P	Manufacture of the substance, chemical production (M, I, P), chemical production without exposure (F), formulation of non-liquid cream and cream for skin and high viscosity products (F), formulation of low viscosity liquid for spray application (F), formulation of cosmetic products, personal care products, fine fragrances, end products (F, I), storage (F)
PROC 2: Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions	M,F, I, P	Manufacture of the substance, Chemical production (M), chemical production with occasional exposure (F, I, P), formulation of non-liquid cream and cream for skin and high viscosity products (F), formulation of low viscosity liquid for spray application (F), formulation of cosmetic products ,personal care products, fine fragrances, end

Main types of applications structured by product or article types	Octocrilene	Technical function
		products (F, I)
PROC 3: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions	M, F, I, P	Synthesis or formulation (M), Manufacture or formulation (M), manufacture or formulation in closed batch processes with occasional exposure (F, I, P), formulation of non liquid cream and cream for skin and high viscosity products (F), formulation of low viscosity liquid for spray application (F), formulation of cosmetics and personal care products, fine fragrances, end products (F), mixing operations (F)
PROC 4: Chemical production where opportunity for exposure arises	M, F, I, P	Chemical production (M, I, P), formulation of preparations (F), formulation of cosmetics (F)
PROC 5: Mixing or blending in batch processes	M,F, I, P	Manufacture (M), Mixing or blending in batch processes (F, I, P), formulation of non-liquid cream and cream for skin and high viscosity products (F), formulation of preparation(F), formulation of low viscosity liquid for spray application (F), formulation of cosmetics and personal care products, fine fragrances, end products (F, I)
PROC 7: Industrial spraying	M, I, P	Manufacture (M), Industrial spraying (I, P), printing and reproduction of recorded media, manufacture or rubber products, plastic products including compounding and conversion(I)
PROC 8a: Transfer of substance or mixture (charging and discharging) at non-dedicated facilities	M,F, I, P	Transfer of substance or preparation (M), Transfer of substance or mixture (F, I, P), formulation of no- liquid cream and cream for skin and high viscosity products (F), formulation of low viscosity liquid for spray application (F), formulation of cosmetics and personal care products, fine fragrances, end products (F, I), equipment cleaning and maintenance (F), use as an additive (P)
PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities	M, F, I, P	Manufacture of the substance, Transfer of substance or preparation (M, I, P), Transfer of substance or mixture (F), formulation of non-liquid cream and cream for skin and high viscosity products (F), formulation of low viscosity liquid for spray application (F), formulation of cosmetics and personal care products, fine fragrances, end products (F, I), use as an additive (P)
PROC 9: Transfer of substance or mixture into small containers (dedicated filling line, including weighing)	M,F, I, P	Manufacture of the substance, Transfer of substance or preparation (M, I, P), Transfer of substance or mixture (F), formulation of non-liquid cream and cream for skin and high viscosity products (F), formulation of low viscosity liquid for spray application, preparations (F, I), formulation of cosmetics and personal care products, fine fragrances, end products (F, I)
PROC 10: Roller application or brushing	M, I, P	Manufacture of the substance (M), roller application or brushing (I, P)
PROC 11: Non industrial spraying	P	Use as an additive (P)
PROC 12 : Use of blowing agents in manufacture of foam	I	Industrial uses resulting in inclusion into a matrix (I)
PROC 14: Tabletting, compression, extrusion, pelletisation, granulation	M, F, I, P, A	Manufacture of the substance (M), Tabletting, compression, extrusion, granulation(F, I, P, A), formulation of cosmetics and personal care products, end products, end products (F)
PROC 15: Use as laboratory reagent	M, F, I, P	Manufacture of the substance, laboratory use (M, I, P), Perfumes, fragrances, cosmetic, personal care products (F, I) and cream for skin and high viscosity products (F), formulation of low viscosity liquid for spray application (F), formulation of cosmetics and personal care products (I)
PROC 21: Low energy manipulation	P	Use as an additive (P)

Main types of applications structured by product or article types	Octocrilene	Technical function
of substances bound in materials and/or articles		
PROC 24 : High (mechanical) energy work-up of substances bound in materials and/or articles	I, P	Manufacture of rubber products, plastic products including compounding and conversion(I,), use as an additive (P)
PROC 26: Handling of solid inorganic substances at ambient temperature	M, I	Manufacture of the substance (M), laboratory chemicals, perfumes, frangrances, pharmaceuticals, photo-chemicals, cosmetics, personal care products (I)
ERC 1 : Manufacture of the Substance	M	Manufacture (M)
ERC2: Formulation into mixture	F	Formulation (F)
ERC3: Formulation into solid matrix	F	Formulation of cosmetic products involving with organic solvents (F)
ERC4: Use of non-reactive processing aid at industrial site (no inclusion into or onto article)	I	Uses at industrial sites (I)
ERC5: Use at industrial site leading to inclusion into/onto article	I	Uses at industrial sites (I)
ERC6a: Use of intermediate	I	Uses at industrial sites (I)
ERC6b: Use of reactive processing aid at industrial site (no inclusion into or onto article)	I	Uses at industrial sites (I)
ERC6c: Use of monomer in polymerisation processes at industrial site (inclusion or not into/onto article)	I	Uses at industrial sites (I)
ERC6d: Use of reactive process regulators in polymerisation processes at industrial site (inclusion or not into/onto article)	I	Uses at industrial sites (I)
ERC8a: Widespread use of non-reactive processing aid (no inclusion into or onto article, indoor)	P, C	Use in cosmetic products, perfumes, and fragrances (C)
ERC8b: Widespread use of reactive processing aid (no inclusion into or onto article, indoor)	P, C	Consumer uses (C)
ERC8c: Widespread use leading to inclusion into/onto article (indoor)	I, C	Use as additive (C)
ERC8d: Widespread use of non-reactive processing aid (no inclusion into or onto article, outdoor)	I, P, C	Use in cosmetic ingredients (C), consumer products (C)
ERC8f: Widespread use leading to inclusion into/onto article (outdoor)	P	
ERC10a : Widespread use of articles with low release	A	Plastic articles (A), paper application(A)
ERC11a : Widespread use of articles with low release	A	Plastic articles (A)
PC 1 : Adhesives, sealants	C	Consumer application (C)
PC 39 : Cosmetics, personal care products	C, F, I	Use in cosmetics (C, I), formulation (F)
PC 21 : Laboratory chemicals	C, F	Consumer uses(C)
PC 28 : Perfumes, fragrances	C, F	Use in cosmetic ingredients (C) formulation (F)
PC 29 : pharmaceuticals	C	Consumer uses (C)
PC 30 : photo-chemicals	C	Consumer uses (C)

F: formulation, I: industrial use, P: professional use, C: consumer use, A: article service life

The ECHA website indicates that octocrilene is used in various **consumer products**: cosmetics and personal care products, perfumes and fragrances that can be also released in the environment.

Regarding the uses by **professional workers** and at industrial sites, the ECHA website mentions that octocrilene can be used in cosmetics and personal care products, laboratory chemicals, perfumes and fragrances, pharmaceuticals and photochemicals. Octocrilene is used in printing and recorded media reproduction and formulation of mixtures and/or re-packaging. It is used also in the manufacture of rubber products.

According to the SPIN Database, the uses categories reported between 2018 and 2020 are the following:

-surface treatment,

-paints, laquers and varnishes,

-cleaning/washing agents,

According to Senta et al (Senta et al, 2020) UV Filters (like octocrilene) are widely used in sunscreen lotions, but also in other cosmetics and a wide range of other products, including plastics, textile, food packages, adhesives, paints and rubbers.

Moreover, the PSC Ineris Database confirms that octocrilene is used as a UV filter in cosmetics (sun creams), personal care products, make-up (nail varnish and concealers). It also indicates that octocrilene is an anti-UV for plastics, adhesives and coatings. It is also reported to be released in the environment through indoor use (machine wash liquids/detergents, automotive care products, paints and coating or adhesives, fragrances and air fresheners) and outdoor use as processing aid.

As it can be seen in the upper table, octocrilene could be found in various uses mostly for consumers. Those consumer products are in cosmetics, personal care products and fragrances mostly for its UV absorber, UV filter and light stabilizer properties. It can also be used in laboratory chemicals, pharmaceuticals and photo-chemicals, processing aids, in plastics, adhesives, coatings, rubber products.

This chemical is also reported to be used at workplace (manufacture, formulation etc.) and by workers.

It can be released in the environment through various consumer uses (machine wash liquids/detergents, automotive care products, paints and coating adhesives, fragrances and air fresheners).

3.4 Release to the environment

Release to the environment of this substance can therefore occur when the products containing octocrilene are themselves released into the environment. It can also occur from industrial use: in the production of articles, in processing aids at industrial sites, as an intermediate step in further manufacturing of another

substance (use of intermediates), as processing aid, for thermoplastic manufacture and as processing aid.

Finally the ECHA website indicates that release to the environment of this substance is likely to occur from outdoor use in long-life materials with low release rate (e.g. metal, wooden and plastic construction and building materials) and indoor use in long-life materials with low release rate (e.g. flooring, furniture, toys, construction materials, curtains, foot-wear, leather products, paper and cardboard products, electronic equipment).

This substance can be found in products with material based on: plastic (e.g. food packaging and storage, toys, mobile phones) and paper (e.g. tissues, feminine hygiene products, nappies, books, magazines, wallpaper).

4 Hazard Information

4.1 Human Health

During the process of evaluation of octocrilene, concerns were identified for toxicity to reproduction, toxicity to thyroid and endocrine disruption properties. EOGRTS (OECD TG 443) in rats as well as a mechanistic subacute toxicity study in rats to investigate the potential underlying mode of action (MoA) of the thyroid effects were requested.

ANSES has considered the studies submitted in the registration dossier as well as experimental and human data from the open literature (up to August 2020) regarding toxicity to reproduction, toxicity to thyroid and endocrine disruption properties. The conclusions of these studies are briefly exposed here under.

4.1.1 Toxicity to reproduction

Table 6 : Studies on toxicity to reproduction.
All reported changes are statistically significant, unless otherwise specified *(in italic)*

Method	Results	Reference and Remarks

Extended one-generation reproductive toxicity - with F2 generation and developmental neurotoxicity (Cohorts 1A, 1B with extension, 2A and 2B) OECD 443 (2011) rat (Wistar - Crl:WI(Han)) F0: 28 animals/dose/sex Cohort 1A primary assessment of effects upon reproductive systems and of general toxicity. Cohort 1B follow-up assessment of reproductive performance by mating F1-animals and for obtaining additional histopathological data in case of suspected reproductive or endocrine toxicants, or when results from cohort 1A are equivocal. Cohort 2A neurobehavioral testing followed by neuro-histopathology assessment as adults. Cohort 2B neuro-histopathology assessment at weaning Oral: feed 0, 750, 2100 and 7000 ppm reduced to 50% in dams during lactating periods. (Eq. to : 0, 46/56, 127/155, 425/498 mg/kg bw/d in M/F during F0 premating period) Exposure: F0: males 10-week premating period, during mating up to sacrifice (20 weeks) Females: 10-week premating period, during mating, gestation and lactation up to the day of sacrifice after lactation day 21 (23 weeks) F1: from weaning up to sacrifice (approx. 13 weeks in Cohort 1A, approx. 17 weeks (males) and approx. 21 weeks (females) in Cohort 1B; approx. 11	**At 750 ppm:** No treatment-related findings **At 2100 ppm:** <u>*General toxicity:*</u> ↑ hyperplasia of follicular epithelial cells (mild-moderate) and loss of colloid in F0 M (14/28) *non-statistically significant ↑ hyperplasia of follicular epithelial cells (mild-moderate) and loss of colloid in F1A M (7/20)* <u>*Fertility:*</u> No treatment-related findings <u>*General and sexual development:*</u> No treatment-related findings <u>*Neurodevelopmental toxicity:*</u> No effect <u>*Hormones levels:*</u> No effects on TSH or T4 **At 7000 ppm:** <u>*General toxicity*</u>*:* ↓ Final BW (5 to 10%) in M & F and correlated ↓ food consumption ↑ GGT ↑ rel liver weight (21%/31% in M/F) ↑ rel thyroid weight (25% to 30%) in M & F ↑ hyperplasia of follicular epithelial cells (mild to moderate) and loss of colloid 18/28 and 17/28 in F0 M & F, 16/20 and 13/20 in F1A M & F <u>*Fertility:*</u> ↓mean number of implantation sites *non stat* (F0: 10.7 vs 12.3; F1B 9.3 vs 10.7) *Non-statistically significant but biologically relevant.* ↓ number of pups delivered (F0: 9.6 vs 11.4; F1B 9.3 vs 10.3) ↓mean number of live pups on PND0 <u>*General and sexual development:*</u> ↓ BW (10%) on PND21 Delay in preputial separation (46.3 d vs 43.0 d) Delay in vaginal opening (33.9 d vs 31.4 d) and ↑ in first estrus stage (35.5 d vs 32.8 d) <u>*Neurodevelopmental toxicity*</u>*:* *Non-statistically significant effects but considered as biologically relevant without additional statistical analyses and submission of raw data (ASR), historical control data and positive controls.* <u>*ASR:*</u> *over 20%↓ of the maximum auditory startle response amplitude in M & F in several blocks ↓12% If all trials averaged and average across both sexes.* <u>*Motor Activity:*</u> *↓ 20% total distance moved in F* <u>FOB:</u> ↓12% (stat sign) forelimb grip strength in M <u>*Morphometric changes*</u> *in M* <u>*Hormones levels:*</u> No effects on TSH and T4 analysis in F0 and F1A adults and in F1 and F2 pups sacrificed on PND21. *Non-statistically significant ↓of T4 level in high dose PND4 pups (25% and 33% ↓in F1 and F2 pups). However, low number of high dose pups due to low litter size.* **NOAEL parental toxicity = 750 ppm** based on increased incidence of follicular epithelial cells hyperplasia and loss of colloid (mild, moderate) statistically significant in F0 males and not statistically significant in F1A males.	Unpublished study report (2019a) 1 (reliable without restrictions) **3 (Not reliable for DNT)*** **Key study** **GLP: GLP compliance is claimed. However, raw data for ASR, not submitted while requested.** Test material: Batch 51324997VO Purity : 99.3%

weeks in cohort 2A). F2: indirectly exposed until weaning. (continuous via feed)	**NOAEL reproductive = 2100 ppm** based decreased mean number implantation sites and correlated decreased mean number of fetuses per litter. **NOAEL offspring = 2100 ppm based** on statistically significant lower BW at weaning and associated delayed puberty onset in M and F **NOAEL DNT = 2100 ppm based** on effects on ASR, motor activity and morphometrics.	
Dose-range-finding study for EOGRTS **EOGRTS** rat (Wistar - Crl:WI(Han)) 12 animal/dose/sex oral: feed 0, 5000 and 15000 ppm reduced to 50% in dams during lactating periods. (Eq. to : 0, 279-399/351-392, 812-1271/919-1335 mg/kg bw/d in M/F during premating period) Exposure: Males: 4-week premating period, during mating (1 week) up to sacrifice (D42) Females: 4-week premating period, during mating, gestation and lactation up to the day of sacrifice after lactation day 21.	**At 5000 ppm** *General toxicity:* ↓ BW (5%) in F ↑ urea in females ↑ rel liver weight (21%/17% in M/F) ↑ thyroid weight (27%/6% in M/F) ↑ hyperplasia of follicular epithelial cells and loss of colloid (18/24 animals) **At 15000 ppm** *General toxicity:* ↓ terminal BW (13% /10% in M/F) ↓ Hb and eosinophils in F ↑ GGT and urea in females ↑ albumin in M ↑ rel liver weight (44%/45% in M/F) ↑ rel thyroid weight (44%/25% in M/F) ↓ rel pituitary weight in F (26%) ↑ hyperplasia of follicular epithelial cells and loss of colloid (21/24 animals) *Fertility:* ↓mean number of implantation sites (9.7 vs. 12.7 in controls ↓ number of pups delivered (8.9 vs 12.1) related to ↓mean number of implantation sites *General and sexual development:* ↓ birth BW and postnatal BWG (↓30% on PND21)	Unpublished study report (2018e) 1 (reliable without restrictions) Range-finding study GLP: Yes Test material: Batch 51324997VO Purity : 99.3%
Prenatal Developmental Toxicity Study OECD 414 (1981) rat (Wistar - Crl:WI(Han)) 25 dams /dose/sex Doses: 100, 400, 1000 mg/kg bw/d oral: gavage Vehicle: olive oil Exposure: day 6 through day 15 of gestation (daily)	**Maternal toxicity:** At 400 mkd: ↑ (6%) abs and rel liver weight At 1000 mkd: ↑(9%) abs and rel liver weight + clinical signs (salivation) **Developmental toxicity:** No signs of embryo-/ fetotoxicity at any dose level **NOAEL (maternal toxicity): 400 mg/kg bw/day** **NOAEL (developmental toxicity): 1000** mg/kg bw/day	Unpublished study report (1993a) 1 (reliable without restrictions) Key study GLP: Yes Test material: Batch: 505396 - 70182 Purity : 98.3%

Percutaneous developmental toxicity study in rabbits (New Zealand White) 17dams/group Dermal: 0, 7.5% and 30% in petrolatum/Finsolv Eq; to: 0, 65, 267 mg/kg bw/d (nominal conc.) Exposure: days 6 through 18 of gestation (daily)	No effect on dams or fetuses at any dose level NOAEL (maternal toxicity): > 267 mg/kg bw/day (nominal) NOAEL (developmental toxicity): > 267 mg/kg bw/day (nominal)	Odio, 1994 2 (reliable with restrictions) supporting study experimental result Test material: Octocrilene obtained from BASF Purity : Not mentioned
Oral developmental toxicity study in mice (CD-1) oral: gavage 100, 300, 1000 mg/kg bw/d Exposure: days 8 through 12 of gestation (daily) Chernoff-Kavlock developmental toxicity assay [Chernoff N and Kavlock RJ (1982).	No effect on dams or fetuses at any dose level NOAEL (maternal toxicity): > 1000 mg/kg bw/day (actual dose received) NOAEL (developmental toxicity): > 1000 mg/kg bw/day (actual dose received)	Odio, 1994 2 (reliable with restrictions) supporting study experimental result Test material: Octocrilene obtained from BASF Purity : Not mentioned

*: Due to the numerous major limitations and the insufficient documentation for assessment, the DNT part of the study is not considered as reliable (Klimish score 3). For numerous end-points, historical control data and positive control are missing, methods description is often incomplete and the statistical analyses are not appropriate. Furthermore, raw data are not available for auditory startle response which is not in line with GLP.

Sexual function and fertility

An Extended One Generation Reproductive Toxicity Study (EOGRTS) (Unpublished study report, 2019a), according to OECD 443 and GLP-compliant (except for the DNT part) represents the key study in the Evaluation dossier. Animals were treated by diet with 4 different doses: 0, 750, 2100 and 7000 ppm (Eq. to: 0, 46/56, 127/155, 425/498 mg/kg bw/d in males/females). Cohorts 1A (assessing reproductive endpoints on the F1 generation) and 1B (assessing reproductive endpoints, maintained and bred to obtain F2 generation) and Cohorts 2A and 2B focused on neurodevelopmental endpoints.

- No treatment-related effects were observed in animals of the F0-generation and F1-generation on estrous cyclicity, sperm parameters, fertility and reproductive indices of male and female animals or weight and histopathology of the reproductive organs.

- **A 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 (13% decrease); and consequently, a lower mean number of delivered pups: 9.6 versus 11.4 in controls (16% decrease)) and of Cohort 1B of the F1-generation (implantation sites: 9.3 versus 10.7 in controls (13% decrease); pups: 9.3 versus 10.3 in controls (14% decrease)) were considered treatment-related and adverse**.

These findings were also observed in the high dose (15000 ppm) females of the range finding study (Unpublished study report, 2018e), (implantation sites: 9.7 versus 12.7 in controls (24% decrease); pups: 8.9 versus 12.4 in controls (28% decrease)) (Unpublished study report, 2018).

Table 7 : Mean number of implantation sites and mean number of pups/litter

Parameter	F0-generation (ppm)				F1-generation Cohort 1B (ppm)				DRF study (ppm)		
	0	750	2100	7000	0	750	2100	7000	0	5000	15000
Mean number of implantation sites	12.3	12	11.6	10.7	10.7	11.6	11.1	9.3	12.7	12.1	9.7
Mean number of pups delivered	11.4	11.3	10.6	9.6*	10.3	10.8	10.2	9.3*	12.1	11.6	8.9**
Mean number of live pups/litter day 0	11.4	11.3	10.3	9.6*	10.2	10.8	9.9	9.3*	12.1	11.6	8.9**

* : statistically significantly different from control $p < 0.05$,
**: statistically significantly different from control $p < 0.01$

The registrants mentioned that maternal stress exposure may explain effects on the developing embryo during the preimplantation period. Indeed, since the octocrilene dependent changes in these reproductive parameters occurred at a maternally toxic dose level, a dependency between these effects cannot be excluded. However, no effect on stress marker organs (i.e.: thymus, spleen, adrenals) were noted in top dose females of both generations which could support the claim that stress occurred. Furthermore, while some systemic toxicity was observed at the high dose level consisting in significant decreased body weight of F0 females (-9%) and F1 females (-6%) at the end of the premating period as well as increased liver and thyroid weight and thyroid histopathological findings, **no marked general systemic toxicity (e.g. lethality, dramatic reduction in absolute body weight, coma) was noted.**

The registrants proposed to carry out an additional mechanistic reproductive toxicity study in Wistar rats with a comparable octocrilene application 10 weeks before mating until completion of the implantation phase (i.e. gestational day 7) in order to elucidate, if the events leading to the decrease in implantation sites occur before fertilization or during early development including impairment of implantation. However, no additional study has been submitted.

- Delay of puberty onset was noted in high dose F1 animals. Balano-preputial separation (control: 43.0 days, high dose 46.4 days), vaginal opening (control: 31.4 days, high dose: 33.9 days), and first estrous stage in Cohort 1A occurred later. However, the weight at puberty onset was not affected by treatment. The delayed balano-preputial separation and vaginal opening were therefore considered as a consequence of the delayed general development (10% lower pup weights at weaning).

There was no effect on reproductive organs in a GLP-compliant 90-day dietary study (Unpublished study report, 1993b), according to OECD TG 408 (1981) in Wistar rats (tested doses: 0, 750, 2250, 4500 and 15000 ppm equivalent to 53/63, 163/187, 315/365, 1027/1143 mg/kg bw/day in males/females).

In a Chinese epidemiological study from the open literature, no association between octocrilene urinary levels and Polycystic ovary syndrome (PCOS) was observed either in an unadjusted binary logistic regression model or in a model adjusted for potential confounders (cases n = 40, control n = 83). With stratification according to body mass index (cases n = 25, control n = 27), a positive association between octocrilene and PCOS risk was observed in obese and overweight women (BMI>24). This single case-control study with a far too limited number of cases does not allow drawing any conclusion (Gu, 2014).

No effects on human sperm (sperm acrosome reaction, sperm penetration, proportion of hyperactivated sperm cells or sperm viability) exposed to 10 µM octocrilene were observed (Rehfeld, 2018).

Conclusion on the classification of octocrilene under CLP regarding sexual function and fertility

The critical effect identified is the lower number of implantation sites in high dose dams as compared to control animals, with subsequently smaller litter sizes. Those effects are consistently observed across the two generations in the EOGRTS as well as in the range finding study. Considering that those effects are of moderate magnitude and are observed only in the high dose groups together with mild systemic toxicity in dams, **classification of the substance with Category 2 for effects on fertility (H361f), is considered warranted according to the criteria of Regulation (EC) 1272/2008 (CLP).**

Developmental toxicity

In the key prenatal toxicity study in rats performed according to OECD TG 414 and GLP-compliant (Unpublished study report, 1993a), there was no indication of any substance-induced embryo-/fetotoxicity or signs of any teratogenicity up to the dose of 1000 mg/kg bw/day (unpublished study report, 1993). Octorilene caused some slight effects in the dams at 1000 mg/kg bw/day, and a marginal increase of the relative liver weight at 400 mg/kg bw/day.

Two supportive prenatal developmental toxicity studies one after dermal application of octocrilene in rabbits and the other one after oral application in mice did not show developmental toxicity in other species than the rat (Odio, 1994).

In the EOGRTS, no treatment-related effects were observed on post-implantation loss, stillborn pups, dead, missing and/or cannibalized pups, pup viability indices, sex ratio, clinical signs of pups nor on macroscopic observations at sacrifice in F1 and F2 pups. In the high-dose group, the body weight of F1 and F2 pups was lower (-10% on postnatal day 21). Decreased body weight in F1 pups weight was observed from PND 14 (mainly when starting eating diet) BW in F2 pups it was observed from PND4 (only suckling). At this dose level F0 and F1 females' body weights were 11% and 9% lower compared to controls at the start of lactation.

The numerous limitations of the DNT part of the EOGRTS (not appropriate statistical analysis, absence of historical controls and positive control, poor reporting of the methods and lack of raw data for the auditory startle response) hamper to draw any final conclusion on developmental neurotoxicity (DNT). **The DNT of the EOGRTS is therefore considered of poor reliability.** While not considered by the study author and the registrant, it cannot be excluded that the following parameters have been impacted by treatment. Statistically significant decrease of the forelimb grip strength in high dose males were noted as well as some effects on the auditory startle response (ASR), the motor activity (MA) and morphometric. The effects observed on ASR and MA (decreased max startle amplitude in high dose

animals, decreased motor activity in high dose females) did not reach statistical significance. However, they are considered biologically relevant (10% to 20% change) and adverse in the absence of appropriate statistical analyses and submission of historical control data (allowing the assessment of the biological relevance of the variation observed) and positive control data (allowing assessment of the tests sensitivity). Regards to morphometrics, the effects in the measurements on hippocampus gyrus, corpus callosum and striatum measurements observed in high dose animals are considered adverse without additional statistical analyses (multivariate analysis of measurements in conjunction with other factors (age, sex, treatment)), submission of historical control and positive control data and more details on how and when low dose and mid dose tissues were processed to the block stage (Unpublished study report, 2019).

Conclusion on the classification of octocrilene under CLP regarding developmental toxicity

Octocrilene did not exhibit foetotoxic or teratogenic effects in the available studies. Altered growth (lower body weight at PND 21) was observed in F1 and F2 pups at dose level where effect on body weight of the same magnitude was observed in lactating dams.
Regarding DNT cohort, at the high dose level, effects on ASR, motor activity and on morphometrics cannot be excluded. **However, if the data raise a concern, the fact that the finding are not contextualized and found only at the high dose level, does not allow to demonstrate an hazard with the confidence necessary to fulfil CLP criteria. Their low reliability hampers a final conclusion.**

Lactation

There were no indications of impaired nursing behavior or decreased pup viability during lactation in the EOGRTS. This study does not provide indications that Octocrilene could alter quality of the breast milk. While octocrilene has been measured in the milk of lactating women in limited biomonitoring studies (Schlumpf, 2010), the extent of pup exposure to octocrilene during lactation in the EOGRTS is unknown (concentration of octocrilene in milk was not investigated).

Overall, based on the available data no classification for effects on or via lactation seems warranted according to the criteria of Regulation (EC) 1272/2008 (CLP).

4.1.2 Thyroid toxicity

Table 8 : Repeated dose toxicity studies

Method	Results	Reference & Remarks
90-day rat study **Wistar male/female** **10 animals/dose/sex** sub-chronic toxicity: oral (feed) 0, 750, 2250, 4500 and 15000 ppm	**At 750 and 2250 ppm:** No treatment-related findings **At 4500 ppm:** In both sexes: ↓ bilirubine Hypertrophy of periacinar (=centrilobular) hepatocytes	Unpublished study report (1993b) 1 (reliable without restriction) key study experimental study

Eq to.: 53/63, 163/187, 315/365, 1027/1143 mg/kg bw/day in M/F Vehicle: none Exposure: 3 months (continuously in the diet) OECD Guideline 408 (1981) EU Method B.26 (1988)	Thyroid: follicular hypertrophy associated pale staining colloid In females: ↑ platelets, total protein and globulins, ↓ ALT and AST ↑ absolute and relative liver weight **At 15000 ppm:** In both sexes: ↓ food consumption (13%/10% in M/F), ↓ BW (10%/8% in M/F) ↓ BWG (16%/15% in M/F) ↑ γGT ↑ absolute and relative liver weight Hypertrophy of periacinar and centriacinar hepatocytes Thyroid: follicular hypertrophy associated pale staining colloid In females: ↑ platelets. ↓PTT, Hb, MCV, and MCHC ↑cholesterol, total protein and globulins, ↓ ALT and AST. In males: ↑ nb of hypertrophic cells in the pituitary gland. **NOAEL: 2250 ppm (163/187 mg/kg bw/day in M/F)** **LOAEL: 4500 ppm (315/365 mg/kg bw/day in M/F)**	GLP: Yes Test material: octocrilene Batch: 505396-70182 Purity : 98.3% Test material 2-ethylhexyl 2-cyano-3,3-dipheny lacrylate / 6197-30-4 / 228-250-8, (full information in Annex II).
Mechanistic study in Wistar rats on thyroid toxicity via enzyme induction in the liver Rat Wistar - Crl:WI(Han)) 5 animals/dose/sexe short-term repeated dose toxicity: oral (feed) 0,1000, 3000 and 10000ppm Eq to: Subset A: 65/72, 188/215, 650/720 mg/kg bw/day in M/F Subset B: 63/69, 193/207, 630/690 mg/kg bw/day in M/F Vehicle: None Exposure: Subset A: 28 days Subset B: 14 days	**At 1000 ppm:** No treatment-related findings **At 3000 ppm:** Bioanalytical examinations (subset B) In both sexes: ↑ BROD-activity (2-fold) ↑ PROD activity (2-fold) In females ↑T4- UDPGT-activity (1.5-fold) In males: and induction of Thyroxin 5'-deiodinase type D3 (2-fold) **At 10000 ppm:** ↓ BW (7.3% to 9.3%) and ↓BWG in males subset B and in both sexes subset A Clinical pathology (subset A) ↑ Urea in both sexes ↑ γGT, Cholesterol, trygliceride, P, WBC and lymphocyte in females Hormone levels ↑ TSH (2-fold) in females (subset B) and in both sexes (subset A) ↓T4 (10-25%) non statically significant (in both sexes subsets A and B)	Unpublished study report (2019b) 1 (reliable without restriction) supporting study experimental study GLP: Yes Test material: octocrilene Batch: 51324997V0 Purity : 99.5% Test material 2-ethylhexyl 2-cyano-3,3-dipheny

Similar to OECD TG 407 (2008)	Pathology ↑ liver weight in females (subset B) and both sexes (subset A). Liver diffuse hypertrophy in females (subset A) and both sexes (subset B). Hypertrophy/hyperplasia of follicular cells accompanied by altered colloid in both sexes (subset A and B). Bioanalytical examinations (subset B) In both sexes ↑ PROD activity (10/6-fold in M/F) ↑ BROD-activity (>6-fold) ↑ MUF-GT and Hobi-GT activities (1.5- to 2-fold) ↑ T4- UDPGT-activity (1.9/3.1-fold in M/F) In males: ↑ total CYP 450 (1.5-fold) ↑ EROD activity (1.3-fold) Induction of Thyroxin 5'-deiodinase type D3 (2-fold) ↓Thyroxin 5'-deiodinase type D1 (1.5-fold)	lacrylate / 6197-30-4 / 228-250-8, (full information in Annex II).

In a GLP-compliant 90-day dietary study, according to OECD TG 408 (Unpublished study report, 1993b), in Wistar rats (tested doses: 0, 750, 2250, 4500 and 15000 ppm equivalent to 53/63, 163/187, 315/365, 1027/1143 mg/kg bw/day in males/females), follicular hypertrophy associated with pale staining colloid were observed from 4500 ppm onwards in both sexes (7/10 and 4/10 in males and females at 4500 ppm and 10/10 in males and females at 15000 ppm). Increased absolute and relative liver weight were noted from 4500 ppm in females and at 15000 ppm in males. At the high dose level, general toxicity was substantiated by a decreased of the final body weight - 10% and - 8% in males and females respectively (Unpublished study report, 1993).

In a mechanistic subacute toxicity study in Wistar rats similar to OECD TG 407 and GLP-compliant (Unpublished study report, 2019b), at concentrations of 0, 1000 ppm, 3000 ppm and 10000 ppm over a period of 14 days (Subset B) and 28 days (Subset A), corresponding to 63-72, 188-215 and 630-720 mg/kg bw/day, hypertrophy/ hyperplasia of follicular cells (5/10 animals) accompanied by altered colloid were observed in both sexes of both subsets at 10000 ppm. After a treatment period of 14 days (subset B), high dose group females showed also absolute and relative weight increases of the liver, while after a treatment period of 28 days (subset A) and an increase of the absolute relative liver weights of males and females were noted as well as a decrease of the final body weight in males (10.8%) (Unpublished study report, 2019).

In the EOGRTS (tested concentrations: 0, 750, 2100 and 7000 ppm equivalent to: 0, 46/56, 127/155, 425/498 in males/females during F0 premating period), a statistically significant increase of hyperplasia of follicular epithelial cells and loss of colloid were observed in 14/28 F0 males and a non-statistically significant increased incidence of activated thyroids in F1A males (7/20 vs 2/20 in controls) in the absence of any general or liver toxicity [a slight statistical increase of relative liver weight (7% and 10% in F0 and F1A males respectively)] was noted but not considered adverse in the absence of correlated histopathological or clinical findings. At 7000 ppm, hyperplasia of follicular epithelial cells and loss of colloid (18/28 and 17/28 in males and females respectively) associated with increased thyroid weights (25% to 30%) were noted in both sexes. At this dose level, increased absolute and relative liver weights were reported in both sexes of any

generation as well as decreased final bodyweight (5% to - 10% according sex and generation) (Unpublished study report, 2019).

In the dose-range-finding study, related to EOGRTS (tested concentrations: 0, 5000 and 15000 ppm equivalent to: 0, 279-399/351-392, 812-1271/919-1335 in males/females during premating period) increased hyperplasia of follicular epithelial cells and loss of colloid were observed in 18/24 and 21/24 animals at 5000 and 15000 ppm respectively correlated by a dose-related increase of thyroid weight. Increased relative liver weight was observed in both sexes from 5000 ppm while final bodyweight was impacted from 5000 ppm females (- 5%) and at 15000 ppm in males (-13%) (Unpublished study report, 2018).

The potential mode of action (MoA) Phenobarbital-like, underpinning thyroid effects was investigated in the mechanistic subacute toxicity study and is further discussed in chapter 4.1.3 dedicated to endocrine disruption properties. Hepatic enzymatic induction indicative of nuclear receptors activation was supported by:

- An increase of T4-UDPGT-activity (main phase II enzyme involved in T4 clearance) from 3000 ppm in female (1.5 fold) and at 10000 ppm in males (1.9 fold) and females (3.1 fold).
- An increase of other phase II enzymes MUF-GT and HOBI-GT at 10000 ppm in both sexes.
- A dose-dependent increase of BROD and PROD activity (marker for Cyp2b activity linked to CAR nuclear receptor activation) in both sexes from 3000 ppm (2 folds and >6 folds at 3000 and 10000 ppm respectively). This phase I enzymes are not involved in T4 clearance but support enzymatic induction via CAR activation.

An alternative molecular initiating event (MIE) related to deiodinases activities (D1 and D3) has been investigated. D1 activity was significantly reduced in high dose males (-32% compared to controls) whereas D3 activity was significantly induced (2 folds compared to controls) in mid and high dose males. Therefore, the contribution of changes in deiodinases activity may also contribute to alteration of thyroid hormones levels in males.
In high dose group males and females, hypertrophy/hyperplasia of follicular cells accompanied by altered colloid was observed as well as a 2-fold increase in TSH levels (statistically significant in females). While not statistically significant, a 10% to 25% decrease of T4 levels was also noted.

Based on the MoA analysis performed during the evaluation, while some uncertainties remain, the available data seem to support the postulated MoA. No substance-specific data that provide proof of the non-relevance for humans has been submitted. Nevertheless, while phenobarbital-l like liver induction is known to act also in human, it is acknowledged that its consequences may differ: elevated TSH in rodents leading to thyroid hypertrophy and potential thyroid tumors may have limited relevance to human thyroid cancer due to species quantitative differences in sensitivity (mainly, but not exclusively due to the differences in plasma transporters of THs).

Conclusion on the classification of octocrilene under CLP regarding thyroid toxicity

Thyroid is a target organ. Follicular hypertrophy/ hyperplasia and pale staining colloid were consistently observed in the available repeated dose oral toxicity studies in rats **but at dose levels exceeding the guidance values for Category 2 (i.e.: 100 mg/kg bw/d for a 90-day study and 300 mg/kg bw/d for a 28-day study). Therefore, according to the criteria laid down under CLP**

Regulation and based on the available information, no classification of octocrilene seems warranted for STOT RE.

4.1.3 Endocrine disrupting properties

During the evaluation, the assessment of endocrine disrupting properties of octocrilene has been carried out according to ECHA/EFSA ED guidance (2018).

4.1.3.1 Estrogenic, androgenic, and steroidogenic (EAS) modalities

Table 9 : Studies on EAS activity

Method	Results	Reference & Remarks
***In vivo* data**		
Hershberger Assay screening for potential antiandrogenic activity Rat Wistar castrated males (6/dose) oral: gavage Doses / Concentrations: 300, 1000 mg/kg bw/d Vehicle: corn oil Exposure: 10 days (daily) Testosterone propionate (0.4 mg/kg) according to OECD Protocol and Guidance for the Conduct of the Rodent Hershberger Assay ; Phase 2 of the Validation of the Rodent Hershberger Assay (#OECD TG 441)	**At 300 mg/kg bw/d** ↑ Abs (23%) and rel (28%) liver weights **At 1000 mg/kg bw/d** ↑ Abs (42%) and rel (41%) liver weights ↓ (~20%) Abs and rel weights of ventral prostate and levator ani plus bulbocavernosus muscles. Weight of the other 3 sensitive tissues (SV, GP and CWG) decreased but not statistically significant (~10%) No effect on hormone level (T, LH and DHT) **Positive**	Unpublished study report (2003) 2 (reliable with restrictions) Supporting study Mechanistic study GLP: Yes Test material: Batch: 90-3634 Purity : 98.8%
Uterotrophic assay rat Wistar female 10 sexually immature females/goup oral: gavage Doses: 0, 250,1000 mg/kg bw/d Vehicle: olive oil Exposure: 3 days (daily) The aim of the present study was to investigate a possible influence of the test substance octocrilene on the uterus	**At 250 mg/kg bw/d** No treatment related effect **At 1000 mg/kg bw/d** ↓BWG and BW No effect on uterus weight and no histopathological findings. **Negative**	Unpublished study report (2001a) 2 (reliable with restrictions) supporting study mechanistisc study GLP: No Test material: Batch: 133635 Purity : 98%

weight and uterus morphology of juvenile rats after repeated oral administration (#OECD TG 440)		
***In vitro* data**		
***In vitro* estrogenic activity filters** YES assay Saccharomyces cerevisae hERα/ ß-galactosidase activity	Octocrilene: ER antagonist (AC50 = 2.570 µM), AR agonist (AC50 = 0.63 mM), AR antagonist (AC50 = 25 µM)	Kunz, 2006 2 (reliable with restrictions) weight of evidence experimental result Test material: octocrilene
Hormonal activity, cytotoxicity and developmental toxicity of UV filters Test systems Saccharomyces cerevisae BLYES and BLYAS strains served to detect estrogenic and androgenic activity, respectively hERα/bioluminescence hAR/bioluminescence BLYR strain to explore cytotoxicity	Octocrilene not cytotoxic Not estrogenic or androgenic ER antagonist (AC50 = 18.7 mM), biphasic concentration-response curve AR antagonist (AC50 = 7.29 mM) biphasic concentration-response curve	Balazs, 2016 2 (reliable with restrictions) weight of evidence experimental result Test material: octocrilene
Steroid profiling in H295R cells to identify chemicals potentially disrupting the production of adrenal steroids Test system H295R cells	Octocrilene at 10 µM enhanced progesterone but slightly decreased corticosteroids and adrenal androgens was observed, suggesting further mechanistic studies on whether octocrylene might inhibit and/or down regulate the expression of CYP17A1 and 3b-HSD2.	Strajhar, 2016 2 (reliable with restrictions) weight of evidence experimental result Test material: octocrilene

<u>Lines of evidence for activity related to EAS-modalities</u>

- E-modality

Level 2 of OECD Conceptual Framework:
Octocrilene had no estrogenic activity in two yeast transactivation assays (Kunz, 2006 and Balazs 2016). I was also negative in 5 out of the 5 assays investing E–agonism in TOX21 battery.
Octocrilene had slight antiestrogenic activity in two yeast transactivation assays (Kunz, 2006 (AC_{50} = 2.57 mM) and Balazs 2016 (AC_{50} = 18.7 mM)). Octocrilene

was also slightly positive (AC_{50} values exceeding the cytotoxicity lower bound threshold and less than 50% activity) in 5 out of the 6 investing E–antagonism in TOX21 battery.
Level 3 of OECD Conceptual Framework:
In an uterotrophic assay in immature female Wistar rats (Unpublished study report, 2001), Octocrilene did not induce histopathological and weight changes in the uterus up to 1000 mg/kg bw/d.

- A-modality

Level 2 of OECD Conceptual Framework:
Octocrilene had slight androgenic activity in one yeast transactivation assay (Kunz, 2006 (AC_{50} = 0.63 mM) and was negative in another one (Balazs 2016). Octocrilene was also negative in 3 out of the 3 assays investing A–agonism in TOX21 battery.
Octocrilene had antiestrogenic activity in two yeast transactivation assays (Kunz, 2006 (AC_{50} = 24.5 µM) and Balazs 2016 (AC_{50} = 7.29 mM)). Octocrilene was also positive in in 2 out of the 3 assays investing A–antagonism in TOX21 battery.
Level 3 of OECD Conceptual Framework:
A GLP-compliant 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), octocrilene was administered in corn oil via gavage to groups of 6 castrated but Testosterone propionate (0.4 mg/kg) substituted male Wistar rats for 10 days at dose levels of 300 and 1000 mg/kg bw/day (Unpublished study report, 2003). At the top dose, octocrilene induced a significant decrease (~20%) of absolute and relative weights of ventral prostate and levator ani plus bulbocavernosus muscles. Weight of the other 3 sensitive tissues (SV, GP and CWG) also decreased but without reaching statistical significance (~10%). Based on those results, antiandrogenic activity of octocrilene was confirmed *in vivo*.

- S-modality

Level 2 of OECD Conceptual Framework
In an *in vitro* test using H295R cells for steroid profiling, octocrilene at 10 µM enhanced progesterone but slightly decreased corticosteroids and adrenal androgens was observed, suggesting further mechanistic studies on whether octocrilene might inhibit and/or down regulate the expression of CYP17A1 and 3b-HSD2 (Strajhar, 2016). Octocrilene slightly inhibited aromatase (AC_{50} = 23.1 µM, 43% activity) in TOX21 battery.

Based on the open literature and TOXCAST/TOX21 data, **octocrilene exhibits antiandrogenic activity** *in vitro* consistently across assays, corroborated *in vivo* by a positive result in a Hershberger Assay. Based on the available data there is poor evidence that octocrilene has E or S activity.

<u>Lines of evidence for adverse effects related to EAS-modality:</u>

<u>EAS-mediated parameters</u>

- **EAS-mediated parameters have been sufficiently investigated according to ECHA/EFSA ED guidance (2018) as a guidelined EOGRTS in rats (level 5 of OECD Conceptual Framework for Testing and Assessment of Endocrine Disrupting Chemicals) is available** (level 5 of OECD Conceptual Framework for Testing and Assessment of Endocrine Disrupting Chemicals**) and EAS-mediated parameters were not affected by treatment in any of the available regulatory studies**. In the EOGRTS, octocrilene administration did not alter weight and histopathology of the male reproductive organs (testis, epididymis, prostate, seminal vesicles and coagulating glands), sperm parameters,

weight and histopathology of the female reproductive organs (ovary, uterus vagina), follicles and corpora lutea counts, estrous cyclicity, anogenital-distance or nipple development. The delay observed in sexual maturation in both high-dose males and high-dose females was linked to delayed general development.

- In a Chinese epidemiological study from the open literature, no association between octocrilene urinary levels and Polycystic ovary syndrome (PCOS) was observed either in an unadjusted binary logistic regression model or in a model adjusted for potential confounders (cases n = 40, control n = 83). With stratification according to body mass index (cases n = 25, control n = 27), a positive association between octocrilene and PCOS risk was observed in obese and overweight women (BMI>24). This single case-control study with a far too limited number of cases does not allow drawing any conclusion (Gu, 2014).
- No effects were observed on human sperm (sperm acrosome reaction, sperm penetration, proportion of hyperactivated sperm cells or sperm viability) exposed *in vitro* to 10 µM octocrilene (Rehfeld, 2018).

Parameters sensitive to but not diagnostic of EAS-modality

A decreased number of implantation sites was observed in high dose females of the two generations in the EOGRTS study as well as in high dose females of the EORGRT range finding study. The decrease in the number of uterine implantation sites can result from a decrease in the number and / or quality of gametes/embryos or from an alteration of the implantation process itself. From the EOGRTS results, follicles and corpora lutea counts performed in cohort 1A were not affected by treatment. It is noteworthy that the measurement conditions are not optimal since corpora lutea of gestating females F0 and F1 cohort 1B were not counted. Estrous cycle length and normality were not modified. Epididymal and testicular sperm parameters were also not impacted by treatment. Those results do not suggest an alteration in the number and / or quality of gametes/embryos and an alteration of the implantation process could be suspected. Therefore, considering the existing knowledge as described in OECD GD 150, decreased number of implantation sites taken in isolation (in the absence of any other effects related to EAS modality) does not support on its own adversity via any one of the EAS modalities.

Weight of Evidence for EAS-mediated adversity and activity

Based on the available data, some EAS activity (antiandrogenic activity) has been observed, but while EAS-mediated parameters for Human health have been sufficiently investigated according to ECHA/EFSA ED guidance (2018), there is no indication of adversity based on EAS-mediated parameters. In the absence of EAS-mediated pattern of effects, the first condition of the ED criteria is not met; **therefore, based on the current knowledge and according to ECHA/EFSA ED guidance, the substance does not meet the ED criteria for Human health regarding EAS-modalities (scenario 1a of ECHA/EFSA ED Guidance**).

4.1.3.2 Thyroidal modality

Lines of evidence for activity related to T-modality:

In vitro data

No specific *in vitro* data have been submitted. From Toxcast/Tox21 data, octocrilene was negative in TOX21_TSHR assays for both agonist and antagonist ways. Octocrilene was positive in TOX21_TR_LUC_GH3_Antagonist assay but at

high concentration AC50 = 26 µM while the TOXCAST cytotoxicity thresholds were set at 5.463 µM and 30.742 µM for the lower bound and the mean respectively.
Regarding hepatic xenobiotic nuclear receptors, octocrilene was positive in TOX21_CAR_Agonist assay with an AC50 of 2.72 µM but also positive in TOX21_CAR_Antagonist assay with an AC50 of 8.34 µM (borderline activity). The Substance was positive in TOX21_PXR_Agonist assay with an AC50 of 12.9 µM and was negative in TOX21_AhR_LUC_Agonist assay.
No information is available on other relevant molecular initiating events such as inhibition of Sodium-iodide symporter (NIS) or Thyroid peroxidase (TPO).

In vivo data

- Hormonal changes

In the 14-d/28-d mechanistic study in rat (Unpublished study report, 2019a), an increase of TSH levels was observed in high dose (10000 ppm) males (97-99% not statistically significant) and females (105-112% statistically significant) at different time points. Not statistically significant decrease of T4 (10-25%) was observed at different time points of the same dose level. These hormonal changes were not corroborated by the hormone analysis performed in the EOGRTS (Unpublished study report, 2019) in which hormonal levels were not impacted by treatment. It is noteworthy that in the EOGRTS, a high inter-individual variability was noted (the coefficients of variation of TSH measurements in untreated controls of the EOGRTS were higher than 25% value recommended in appendix B of ECHA/EFSA ED Guidance); the tested doses were lower (high dose of 7000 ppm versus 10000 ppm in the mechanistic study) and the analyses in adults F0 and F1 were only performed at sacrifice contrary to the mechanistic study where thyroid hormones were measured at different time points. Critical windows of potential hypo-thyroxinaemia were investigated (PND4 and PND21) compliantly to EOGRTS guideline. A non-statistically significant, decrease of T4 level in high dose PND4 pups compared to controls was observed in both generations (25% and 33% decrease in F1 and F2 respectively). However, the low number of high dose culled pups (pooled pup from 5 and 4 litters for F1 and F2 respectively) due to the pre-implantation loss observed at this dose level compromises the reliability of the result. TH levels during late pregnancy in dams (another crucial period for the development of the offspring nervous system) was not investigated since not required according to EOGRTS guideline.

- Changes in enzymes' activity relevant to T-modality

  - (CAR/PXR-mediated) induction of endocrine-relevant enzymes:

In the rat mechanistic study (Unpublished study report, 2019b), induction of liver T4-UDPGT was substantiated by 1.5-fold increased activity in mid-dose females (3000 ppm) and 2-3 fold increased activity in high-dose males and females (10000 ppm). 2-fold increase of BROD (marker of CAR/PXR activation and induction CYP2B/3A subfamily enzymes) in both sexes and PROD (marker of CAR and marker of induction CYP2B subfamily enzymes) activities in males of the mid-dose group and a more extensive induction (>6-fold) of BROD/PROD activities in both sexes in the high dose group.

  - Deiodinases activity

In the rat mechanistic study (Unpublished study report, 2019), liver type III deiodinase (D3) was induced (2-fold increased activity) in mid and high-dose males while liver type I deiodinase (D1) was inhibited (1.5-fold reduced activity) in high-dose males. It should be highlighted that D3 induction decreases the biological activity of thyroid hormones via inner ring deiodination of T4 (thyroxine) and T3 (triiodothyronine) leading to rT3 (reverse T3, an inactive form of T3) and T2

(diiodothyronine), respectively. Therefore, this MIE may partly contribute to the observed decrease of T4 levels in males.

The available information in rats shows that the substance have endocrine disruption activity (decreased T4 and increased TSH) indicating a chemical capable of perturbing TH-signaling.

Lines of evidence for activity related to T-modality

T-mediated parameters

Thyroid follicular hypertrophy/hyperplasia and pale staining colloid were consistently observed in the available toxicity studies in rats as reported in chapter 4.1.2. These thyroid effects are summarised in the table below together with potential liver effects and/or general toxicity observed at the same dose levels.

Table 10 : Dose and time concordance for T-mediated adversity, general toxicity including liver toxicity based on available empirical data for the rat

Dose ppm	14 days mechanistic study	28 days mechanistic study	5-11 weeks range-finding study for EOGRTS	13 weeks 90-d study	13-21 weeks EOGRTS
750				**Thyroid:** No effect **Liver:** No effect	**Thyroid:** No effect **Liver:** No effect
1000	**Thyroid:** No effect **Liver:** No effect	**Thyroid:** No effect **Liver:** No effect			
2100					**Thyroid:** Follicular hyperplasia and loss of colloid in F0 males (14/28)- Non stat ↑ in F1C1A males (7/20) **Liver:** ↑ 7% wt-rel-BW (F0 M) -↑ 10% wt-rel-BW (F1C1A M) No histopathological finding
2250				**Thyroid:** No effect **Liver:** No effect	
3000	**Thyroid:** No effect **Liver:** No effect	**Thyroid:** No effect **Liver:** No effect			
4500				**Thyroid:** Follicular cell hypertrophy pale staining	

Dose ppm	14 days mechanistic study	28 days mechanistic study	5-11 weeks range-finding study for EOGRTS	13 weeks 90-d study	13-21 weeks EOGRTS
				colloid (7/10 M, 4/10 F) **Liver:** centrilobular hypertrophy (4/10 M, 8/10 F), centracinar hypertrophy in M (7/10) ↑ *19% wt-rel-BW (F)*	
5000			**Thyroid:** Follicular hyperplasia and loss of colloid. ↑ wt-to-BW (27%/6% in M/F) **Liver:** ↑ *wt-rel-BW (21%/17% in M/F) -No histopathological finding* ↓ BW (5%) in F		
7000					**Thyroid:** Follicular hyperplasia and loss of colloid M & F. ↑ wt-rel-BW (25% to 30%) in F0 M & F and F1 M **Liver:** ↑ wt-rel-BW 23%/31% (M/F) -No histopathological finding. ↑ GGT ↓ Final BW (5 to 10%) in M & F
10000	**Thyroid:** Follicular cell hypertrophy (2/5 M & 3/5 F). **Liver:** diffuse hypertrophy in females (1/5 M & 3/5 F) ↑ wt-rel-BW 23%/27% (M/F) ↓ BW (8% M)	**Thyroid:** Follicular cell hypertrophy altered colloid (2/5 M & 3/5 F). **Liver:** diffuse hypertrophy (3/5F) ↑ wt-rel-BW 23%/27% (M/F) ↓ BW (8%/6% in M/F)			

Dose ppm	14 days mechanistic study	28 days mechanistic study	5-11 weeks range-finding study for EOGRTS	13 weeks 90-d study	13-21 weeks EOGRTS
15000			**Thyroid:** Follicular hyperplasia and loss of colloid. ↑ *wt-rel-BW* (44%/25% in M/F) **Liver:** ↑ wt-rel-BW (44%/45% in M/F)-No histopathological finding ↓ terminal BW (13% /10% in M/F) MTD	**Thyroid:** Follicular cell hypertrophy pale staining colloid (10/10 M and F) **Liver** centrilobular hypertrophy (9/10 M, 10/10 F), ↑ wt-rel-BW 27%/76% (M/F) ↓ BW (10%/8% in M/F) MTD	

Parameters sensitive to but not diagnostic of T-modality

Decreased number of implantation sites in high dose groups of the EOGRTS and the EOGRTS-range finding studies and hypertrophic cells in the pituitary gland of high dose males of the 90-d study were observed in the presence of general toxicity.
The numerous limitations of the DNT part of the EOGRTS (not appropriate statistical analysis, absence of historical controls and positive control, poor reporting of the methods and lack of raw data for the auditory startle response) hamper to draw any final conclusion on developmental neurotoxicity which if being conclusive should be considered as an adverse effect sensitive but not diagnostic of the T modality.

Weight of evidence for T-mediated adversity and activity

The overall WoE indicates that thyroid effects were consistently observed in rats. While it is acknowledged that thyroid mediated adverse effects may be driven by liver enzymatic induction (further discussed in the below reported MoA analysis for T-modality), **they cannot be considered as secondary to overt general or liver toxicity.**

Since adversity is observed based on T-mediated parameters the biological plausibility of the link between the T-mediated adversity and endocrine activity should be documented through a MoA (scenario 2b of EFSA/ECHA ED GD).

MoA analysis for T-modality

The registrant proposed that thyroid histopathological findings result from increased thyroid hormones clearance due to liver enzymes induction by activation of hepatic xenobiotic nuclear receptors (phenobarbital-like MoA). This MoA was investigated in the 28-d mechanistic study.

1- MoA: Nuclear receptors activation to the adverse outcome "thyroid tumors"

The eMSCA performed a WoE analysis of the proposed mode of action in line with ECHA/EFSA ED guidance which is summarised in Table 11.

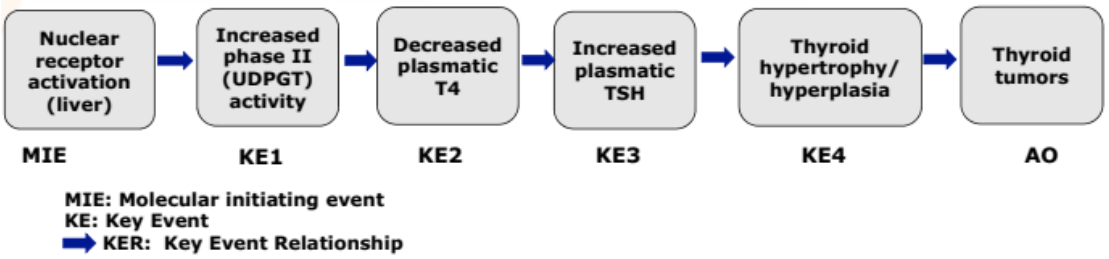


Figure 2 : Postulated mode of action

Table 11: Summary of the MoA analysis

	MIE to KE1	KE1 to KE2	KE2 to KE3	KE3 to KE4	KE4 to AO
Biological plausibility for the KER	Strong, well-documented	Strong, well-documented	Strong, well-documented	Strong well documented	Strong well documented
Empirical support for the KER	Not measured	Weak to moderate Not stat decreased of T4 in the mechanistic study, KER not evaluated in other studies	Moderate Decreased T4 and increased TSH at the same dose in the mechanistic study No effect on T4 and TSH in the EOGRTS adults and PND21 pups. TSH not measured in PND4 pups.	Moderate Strong in the mechanistic study No effect on TSH in the OEGRTS	- No carcinogenicity study available
Essentiality of the KE	No specifically designed experimental studies but based on well-established biological knowledge				
Consistency	All KEs (except MIE from TOXCAST data) were measured only in the mechanistic study in rats. While KE 4 was consistently observed across studies, hormonal changes (KE2 and KE3) were only observed in the mechanistic study at (10000 ppm). No hormonal effects were noted in the EOGRTS up to 7000 ppm while thyroid hyperplasia was observed from 2100 ppm in males and at 7000 ppm in females. No data with other species are available.				
Analogy	The MoA has been observed in rodents with multiple substances and this is well documented.				
Specificity This MoA as such is specific; however, the AO could be a consequence of activation of different MIE (TPO inhibition, NIS inhibition) which were not investigated.					

Uncertainties:

- MIE data only from Tox-21, Nuclear receptors activation not investigated
- Alternative MIE poorly investigated
- Coefficients of variation of TSH (PND21 pups) and T4 (PND4 and PND21 pups) measurements in untreated controls of the EOGRTS far above than 25%.
- Analysis of the response/response and dose concordance limited by the design and dose spacing in the available studies
- No chronic study available

2- Other putative MoAs

In Noyes et al., 2019, in view of the highly conserved vertebrate thyroid system, an adverse outcome pathways (AOP) network for chemically induced thyroid activity has been set for both human and wildlife in order to organize and assess available thyroid data and evaluate the evidence of the causality. From the AOPs network of Noyes et al., **cognitive impairments and auditory impairments are two other major outcomes of interest for mammals that can result from decreased in T4 and/or T3 levels.**

From the available data, two MIE could be identified:

- Nuclear receptor activation (CAR/PXR)
- Inhibition deiodinase D1/Induction of deiodinase D3

Regarding the alternative MIE "Inhibition deiodinase D1/Induction of deiodinase D3". This MIE was only investigated in the mechanistic study. Effects were only observed in males. This MIE may therefore contribute to decrease T4 levels in males in conjunction with nuclear receptor activation. However, it cannot explain the decrease of T4 observed in females.

A throughout WoE of the two putative MoAs is not possible based on the available data since no conclusion can be drawn on developmental neurotoxicity (adverse outcome).

Conclusion for T-modality

Based on the MoA analysis performed by the eMCA, while some uncertainties remain the available data seem to support the MoA postulated by the registrant (i.e.: nuclear receptors activation leading to thyroid hyperplasia).

The provided data do not investigate the relevance of the observed thyroid effects of octocrilene for humans following current testing strategies as recommended and described by the EFSA/ECHA Guidance (2018) Appendix A. Indeed no substance-specific data have been submitted that provide proof of the non-relevance as recommended in Annex A. Nevertheless, while phenobarbital-like liver induction is known to act also in human, it is acknowledged that elevated TSH in rodents leading to thyroid hypertrophy and potential thyroid tumors may have limited relevance to human thyroid cancer due to species quantitative differences in sensitivity (mainly, but not exclusively due to the differences in plasma transporters of THs).

Elevated TSH may not be a reliable biomarker for thyroid cancer in humans; however, increased TSH in rodents does indicate a chemical capable of perturbing TH signaling in other species including human and potentially inducing relevant other adverse outcomes than thyroid cancers.

Impaired pre- and postnatal- neurological development, a crucial adverse outcome potentially linked to a drop in T4 (due to liver induction or other MIEs) during critical

periods has not been adequately investigated due to severe limitations in the DNT part of the EOGRTS.

Considering the remaining uncertainties, no final conclusion could be set on ED-potential of octocrilene regarding T-modality for Human health.

4.1.4 Conclusion on human health

Toxicity for reproduction

- Sexual function and fertility

The critical effect identified was the lower number of implantation sites in high dose dams as compared to control animals, with subsequently smaller litter sizes. Those effects were consistently observed across the two generations in the EOGRTS as well as in the range finding study. Considering that the effect was of moderate magnitude and was observed only in the high dose groups together with mild systemic toxicity in dams, **classification of the substance with Category 2 for effects on fertility (H361f), is considered warranted according to the criteria of Regulation (EC) 1272/2008 (CLP).**

- Developmental toxicity

Octocrilene did not exhibit foetotoxic or teratogenic effects in the available studies. Altered growth (lower body weight at PND 21) was observed in F1 and F2 pups. However, at this dose level, effects of BW of the same magnitude was observed in adults. Regarding DNT cohort, at the high dose level, effects on ASR, motor activity (functional deficiency) and on morphometrics (structural abnormality) cannot be excluded. **However, the low reliability of the data hampers a final conclusion.**

- Effect on or via lactation

Based on the available data **no classification for effects on or via lactation seems warranted** according to the criteria of Regulation (EC) 1272/2008 (CLP).

For the suspected toxicity to reproduction, after evaluation of the data obtained through the evaluation, the eMSCA considers that **a classification for sexual function and fertility is warranted**.

Toxicity to thyroid

Thyroid is a target organ. Follicular hypertrophy/ hyperplasia and pale staining colloid were consistently observed in the available repeated dose oral toxicity studies in rats **but at dose levels exceeding the guidance values for Category 2 (i.e.: 100 mg/kg bw/d for a 90-day study and 300 mg/kg bw/d for a 28-day study).** Therefore, according to the criteria laid down under CLP Regulation and based on the available information, **no classification of octocrilene seems warranted for STOT RE.**

Endocrine disruption properties

- Estrogenic, androgenic, and steroidogenic (EAS) modalities

Based on the current knowledge and according to ECHA/EFSA ED guidance**, and in the absence of adverse pattern of effects mediated by EAS modalities, the substance does not meet the ED criteria for Human health regarding EAS-modalities** (scenario 1a of ECHA/EFSA ED Guidance).

- Thyroidal modality

Based on the MoA analysis performed, while some uncertainties remain the available data seem to support the postulated MoA via liver enzyme induction. However, considering the deficiencies of the DNT part of the EOGRTS**, no final conclusion could be set on ED-potential of octocrilene regarding T-modality for Human health.**

Since the available information in rats showed that the substance has endocrine disruption activity (decreased T4 and increased TSH) also relevant for the environment (in view of the highly conserved vertebrate thyroid system), **an additional test (LAGDA) has been requested by the eMSCA in order to clear the potential concern related to Endocrine disruption for the Environment.**

The evaluation of the reliability of the available DNEL was not performed. Nevertheless, the eMSCA recommends that the Registrant(s):

- update the registration dossier, taking into account the NOAEL of 750 ppm (Eq. to 46 mg/kg bw/d) in the EOGRTS based on increased incidence of follicular epithelial cells hyperplasia and loss of colloid (mild, moderate) statistically significant in F0 males and not statistically significant in F1A males would justify a lower DNEL.

- make a reassessment of the appropriateness of the relevant risk management measures (RMM) to ensure that the RMMs currently in place adequately control worker exposure to octocrilene and for uses not covered by a specific regulation (e.g. the cosmetic uses).

4.2 Environment

4.2.1 Environmental hazard assessment

4.2.1.1 Aquatic compartment (including sediment)

Fish

✓ *Short-term toxicity to fish*

Table 12 : Short-term effects on fish

Method	Results	Remarks	Reference
Danio rerio freshwater static equivalent or similar to EU Method C.1 (Acute Toxicity for Fish)	EC50 (96 h) >0.5 mg.L^{-1} (nominal)	2 (reliable with restrictions) supporting study experimental result	Unpublished study report (1995a)

Method	Results	Remarks	Reference
		Test material (EC name): octocrilenele	
Leuciscus idus freshwater static German standard DIN 38412, part 15	LC50 (96 h) >10000 mg.L^{-1} (nominal) based on mortality	2 (reliable with restrictions) supporting study experimental result Test material (EC name): octocrilene	Unpublished study report (1990)

In the first study (1995a) conducted according to EU Method C.1, no analytical measurements have been performed throughout this test. Therefore, no information about the exact measured value of the saturated concentration determined in a preliminary experiment is known. Only an approximated value is given. In addition, the concentrations tested exceed the water solubility.

In a second test (1990) *Leuciscus idus* was exposed for 96 hours to test substance concentrations of 5000 mg.L^{-1} and 10000 mg.L^{-1}. At termination, a LC_{50} of > 10000 mg.L^{-1} was determined (Unpublished study report (1990)). But the study protocol did not follow the guidance document on aquatic toxicity testing of poorly water-soluble substances. In addition, the concentrations tested exceed the water solubility.

The acute toxicity of octocrilene to fish was tested in two guideline studies. Considering the methodological limitations in these two studies, **acute fish toxicity endpoints are considered as supportive data.**

✓ *Long-term toxicity to fish*

Table 13 : Long-term effects on fish

Method	Results	Remarks	Reference
Gasterosteus aculeatus freshwater OECD guidance document No 148: Androgenised female stickleback screen (AFSS)	NOEC (21d) >8.64 µg.L^{-1} (total fraction) (meas. (geom. mean)) based on Spigging protein inhibition/induction	1 (reliable without restriction) supporting study experimental study Test material octocrilene	Unpublished study report (2018b)

No androgenic or anti-androgenic effects were observed up to the total fraction of octocrilene (8.64 µg.L^{-1}).

Aquatic invertebrates

✓ *Short-term toxicity to aquatic invertebrates*

Table 14 : Short-term effects on aquatic invertebrates

Method	Results	Remarks	Reference
Daphnia magna freshwater static OECD Guideline 202 (Daphnia sp. Acute Immobilisation Test)	EC50 (48 h) >0.023 $mg.L^{-1}$ (meas. (arithm. mean)) based on behavior, mobility	2 (reliable with restriction) supporting study experimental result Test material (EC name): octocrilene	Unpublished study report (2001b)

The saturated octocrilene concentration of 0.023 $mg.L^{-1}$ is a calculated value by extrapolation of measured concentrations instead of a direct measured concentration. **Consequently, acute endpoint value is considered as supportive data.**

✓ *Long-term toxicity to aquatic invertebrates*

Table 15 : Long-term effects on aquatic invertebrates

Method	Results	Remarks	Reference
Daphnia magna freshwater OECD Guideline 211 (Daphnia magna Reproduction Test))	NOEC (21d): 2.66 $\mu g.L^{-1}$ (meas. (TWA)) based on reproduction	1 (reliable without restriction) key study experimental study Test material (EC name): octocrilene	Unpublished study report (2018c)

Algae and aquatic plants

Table 16 : Effects on algae and aquatic plants

Method	Results	Remarks	Reference
Desmodesmus subspicatus (algae) freshwater static OECD Guideline 201 (Alga, Growth Inhibition Test)	EC50 (72 h) >220 $mg.L^{-1}$ test mat. based on growth rate (nominal) NOEC (72 h): 100 $mg.L^{-1}$ based on growth rate (nominal)	2 (reliable without restriction) supportive study experimental result Test material (EC name): octocrilene	Unpublished study report (2010)

The study protocol did not include analytical measurements performed throughout the test to determine the measured value of the saturated concentration. According to guideline OECD no 23 (on aquatic toxicity testing of difficult substances and mixtures), the effect concentration can be expressed based on the nominal concentrations for tests with chemicals that cannot be quantified by analytical methods at the concentrations causing slight effects as in the present case.

Consequently this endpoint should be considered as supportive endpoint. It can be concluded that algae is not the most sensitive trophic level. This endpoint is used to reduce the assessment factor in the determination of a PNEC.

Other aquatic organisms

Table 17: Effects on other aquatic organisms

Method	Results	Remarks	Reference
Isochrysis galbana *Mytilus galloprovincialis* *Paracentrotus lividus* saltwater not specified no guideline followed	NOEC (72h): 40 µg.L^{-1} test mat. (nominal) based on: cell density (*Isochrysis galbana*) NOEC (48h): 20 µg.L^{-1} test mat. (nominal) based on: development stage (*Mytilus galloprovincialis*) NOEC (48h): 20 µg.L^{-1} test mat. (nominal) based on: growth rate (*Paracentrotus lividus*) EC10 (72h) >103 µg.L^{-1} test mat. (nominal) based on: cell density (*Isochrysis galbana*) EC10 (48h): 511 µg.L^{-1} test mat. (nominal) based on: development stage (*Mytilus galloprovincialis*) EC10 (48h): 162 µg.L^{-1} test mat. (nominal) based on: growth rate (*Paracentrotus lividus*) EC50 (72h) >150 µg.L^{-1} test mat. (meas. (not specified)) based on: cell density (*Isochrysis galbana*) EC50 (48h) >650 µg.L^{-1} test mat. (nominal) based on: development stage (*Mytilus galloprovincialis*) EC50 (48h) >737 µg.L^{-1} test mat. (nominal) based on: growth rate (*Paracentrotus lividus*)	2 (reliable with restrictions) supporting study experimental study	Giraldo A et al., (2017)
Pocillopora damicornis	*P. damicornisis* significantly impacted at 50 µg.L^{-1}.	2 (reliable with restrictions)	Stien D et al., (2019)

Method	Results	Remarks	Reference
seawater tested concentrations: 1000, 300, 50, and 5 µg.L^{-1} 7 days of exposure No guideline followed	The highest non-toxic OC concentration in our assay was 5 µg.L^{-1}.	supporting study experimental result Test material (EC name): octocrilene	
Seriatopora. caliendrum *Pocillopora. damicornis* Tested concentration: 5, 30 and 100 µg/L – singly or in combination with EHMC 3.6% w/w as active ingredient in sunscreen water (with 7% w/w of EHMC) 7 days of exposure No guideline followed	***S. caliendrum*** Total polyp retraction: LOEC = 1000 µg.L^{-1} (Single OC) LOEC = 5 µg.L^{-1} (combined EHMC and OC) LOEC = 5 µg.L^{-1} (sunscreen water) Mortality, Visual bleaching, Zooxanthellae density: LOEC = 100 µg.L^{-1} (combined EHMC and OC) LOEC = 30 µg.L^{-1} (sunscreen water) ***P. damicornis*** Total polyp retraction: LOEC = 1000 µg.L^{-1} (Single OC) LOEC = 100 µg.L^{-1} (combined EHMC and OC) LOEC = 5 µg.L^{-1} (sunscreen water) Mortality, Visual bleaching, Zooxanthellae density: LOEC = 100 µg.L^{-1} (combined EHMC and OC) Mortality, Visual bleaching: LOEC = 30 µg.L^{-1} (sunscreen water) Zooxanthellae density: LOEC = 100 µg.L^{-1} (sunscreen water)	2 (reliable with restrictions) supporting study experimental result Test material (EC name): octocrilene single octocrilene in combination with EHMC octocrilene in sunscreen water	He T et al., (2019)

In the scientific literature, the acute toxicity of octocrilene towards various marine organisms (i.e. *Isochrysis galbana*, *Mytilus galloprovincialis* and *Paracentrotus lividus*) was investigated (Giraldo et al. 2017). All tests were carried out as non-GLP using non-standardised protocols. The resulting effect concentrations were as follow:

1. *Isochrysis galbana* (cell density): EC50 > 150 $\mu g.L^{-1}$, NOEC 40 $\mu g.L^{-1}$
2. *Mytilus galloprovincialis* (development stage): EC50 > 650 $\mu g.L^{-1}$, EC10: 511 $\mu g.L^{-1}$; NOEC 20 $\mu g.L^{-1}$
3. *Paracentrotus lividus* (growth rate): EC50 737 $\mu g.L^{-1}$, EC10: 162 $\mu g.L^{-1}$; NOEC 20 $\mu g.L^{-1}$.

However toxicity parameters were calculated based on nominal concentrations. The study protocol included analytical measurement performed at the beginning of the exposures and after 48h. **The chemical analyses showed that octocrilene has a low stability in seawater, because after 48 h the dissolved concentration was below nominal concentrations** (83% lower for octocrilene). The measured concentrations at 48h were 0.90, 1.25, 42.38 $\mu g.L^{-1}$ for the tested nominal concentration 5, 20, 150 $\mu g.L^{-1}$ respectively.

In a study (Stien et al. 2019), the accumulation and the toxicity of octocrilene in corals was evaluated. Adult *Pocillopora damicornis* coral was treated at concentrations of 5, 50, 300, and 1000 $\mu g.L^{-1}$ (nominal concentration). Most polyps were closed at concentrations of 300 $\mu g.L^{-1}$ and higher. Octocrilene was transformed into fatty acid conjugates via oxidation of the ethylhexyl chain, yielding very lipophilic octocrilene analogues that accumulate in coral tissues. Second, the differential analysis of coral profiles revealed higher levels of 15 acylcarnitines. Acylcarnitines are common biomarkers of cell toxicity, and, in many models including human pathologies, elevated acylcarnitine concentration has been correlated with mitochondrial dysfunction in which mitochondrial fatty acid β-oxidation and cell bioenergetics are affected. The coral reef builder species *P. damicornisis* was significantly impacted by octocrilene after only 7 days of exposure to 50 $\mu g.L^{-1}$ based on the level of acylcarnitine. The highest non-toxic octocrilene concentration in the assay was 5 $\mu g.L^{-1}$(nominal concentration).

In another study (He et al. 2019), two hard coral species, *Seriatopora caliendrum* and *Pocillopora damicornis* were exposed during 7-day at adult life stage to two organic UV filters, ethylhexylmethoxy-cinnamate (EHMC; octinoxate) and octocrilene (single- and combined-chemical tests), and diluted sunscreen wash-off water containing both active ingredients. Toxicity and bioaccumulation was evaluated. In the sunscreen product exposures, 5% sunscreen water (containing EHMC and octocrilene) caused high mortality in *S. caliendrum* (66.7–83.3%) and *P. damicornis* (33.3–50%), and tissue concentrations were up to 10 times greater than in the single-chemical exposures; co-exposure to EHMC and octocrilene at similar levels to those in the sunscreen products resulted in bioaccumulation similar to the single-chemical tests. These results confirm the bioaccumulation potential of EHMC and octocrilene and show that other ingredients in sunscreen products may increase the bioavailability of active ingredients to corals and exacerbate the toxicity of sunscreen products.

Sediment organisms

Table 18 : Effects on sediment-dwelling organisms.

Method	Results	Remarks	Reference
Chironomus riparius Freshwater-sediment system static 2.5, 5, 10 mg/kg sediment dw (nominal) 0.53 (21% nominal), 1.27 (25% nominal), 2.33 (23% nominal) mg/kg sediment dw (measured at the start of the test, s 5 days after spiking) 28 days of exposure equivalent or similar to OECD Guideline 218 (Sediment-Water Chironomid Toxicity Test Using Spiked Sediment)	NOEC (28d): 1.27 $mg/kg_{sediment\ dw}$ (meas. (not specified)) based on growth NOEC (28d): >2.33 $mg/kg_{sediment\ dw}$ (meas. (not specified)) based on development time	2 (reliable with restriction) supporting study experimental result Test material (EC name): octocrilene	Campos D et al., (2017)
Chironomus riparius Freshwater-sediment system 0.08, 0.4, 2, 10 and 50 mg/kg sediment dw (nominal) 28 days of exposure static OECD Guideline 218 (Sediment-Water Chironomid Toxicity Test Using Spiked Sediment)	NOEC (28 d) > 50 $mg/kg_{sediment\ dw}$. (nominal) based on mortality NOEC (28 d) > 50 $mg/kg_{sediment\ dw}$ (nominal) based on emergence rate (males) NOEC (28 d) > 50 $mg/kg_{sediment\ dw}$ (nominal) based on emergence rate (females)	2 (reliable with restrictions) supporting study experimental result Test material (EC name): octocrilene	Kaiser et al., (2012)
Potamopyrgus antipodarum Freshwater-sediment system 0.08, 0.4, 2, 10 and 50 mg/kg sediment dw (nominal) 56 days of exposure static	No effect on the embryo numbers (reproduction)		

Method	Results	Remarks	Reference
Lumbriculus variegates Freshwater-sediment system 0.08, 0.4, 2, 10 and 50 mg/kg sediment dw (nominal) 28 days of exposure static OECD Guideline 225 (Sediment-Water Lumbriculus Toxicity Test Using Spiked Sediment)	No effect on the biomass and the number of worms (reproduction)		

C. riparius larval growth was significantly reduced after 28-days exposure to 1.27 mg/$kg_{d.w.}$ of octocrilene (Campos et al. 2017). Octocrilene did not significantly affect development time (days until emergence) of female nor male.

A study (Kaiser, et al. 2012) aimed to evaluate toxic effects and endocrine disruption of three common UV filters including octocrilene on aquatic organisms, focusing particularly on infaunal and epibentic invertebrates. Tests were performed according to OECD guidelines with minor changes on the following species (not exhaustive):

- *Potamopyrgus antipodarum*, sensitive for endocrine active substances,
- Aquatic oligochaete *Lumbriculus variegates* extensively used as a standard test organism for sediment toxicity and bioaccumulation tests (OECD 225),
- *Chironomus riparius* widely distributed in a broad range of water bodies with an important ecological role (OECD 218).

Study results showed that octocrilene did not affect any of the test organisms in the tested concentrations, up to 50 $mg.kg^{-1}_{d.w.}$

However, studies report nominal concentrations only and that can be misleading given octocrilene high lipophilicity that might reduce its bioavailability.

Based on all available data on sediment organism, all coming from the scientific literature, a $NOEC_{larval\ growth}$ of 1.27 $mg.kg_{dw}^{-1}$ (measured) was observed in a *Chironomus riparius* chronic toxicity test according to OECD 218 (Campos et al. 2017). Nevertheless, as concentrations measurement at the end of the test are not specified, the equilibrium partitioning method will be used to derive the $PNEC_{sediment}$ as first screening approach.

4.2.1.2 Terrestrial compartment

Table 19 : Effects on soil macro-organisms

Method	Results	Remarks	Reference
Eisenia fetida freshwater Long-term Substrate: artificial soil according to OECD Guideline 222 (Earthworm Reproduction Test (Eisenia fetida/Eisenia andrei))	NOEC (8wk): 125 $mg/kg_{soil\ dw}$ (nominal) based on reproduction NOEC (8wk) >500 $mg/kg_{soil\ dw}$ (nominal) based on mortality NOEC (8wk) >500 $mg/kg_{soil\ dw}$ (nominal) based on biomass	1 (reliable without restriction) key study experimental result Test material (EC name): octocrilene	Unpublished study report (2017)

4.2.1.3 Microbiological activity in sewage treatment systems

Table 20 : Effects on micro-organisms

Method	Results	Remarks	Reference
activated sludge of a predominantly domestic sewage freshwater static ISO 8192 (Test for Inhibition of Oxygen Consumption by Activated Sludge) equivalent or similar to OECD Guideline 209 (Activated Sludge, Respiration Inhibition Test)	IC_{50} (30 min) > 10000 $mg.l^{-1}$ (nominal) based on respiration rate	1 (reliable without restriction) key study experimental result Test material (EC name): octocrilene	Unpublished study report (1995b)
activated sludge, domestic freshwater static OECD Guideline 209 (Activated Sludge, Respiration Inhibition Test)	EC_{50} (30 min) > 1000 $mg.L^{-1}$ (nominal) based on respiration rate	2 (reliable with restrictions) supporting study experimental result Test material (EC name): octocrilene	Unpublished study report (1991b)

The toxicity of octocrilene to microorganisms was tested in three studies investigating the respiration inhibition by the substance in activated sludge and Pseudomonas putida respectively. Two tests on respiration inhibition in activated

sludge were performed. In a study following guideline ISO 8192, an IC50 > 10000 $mg.L^{-1}$ was determined. A guideline study according to OECD 209 detected no respiration inhibition up to a substance concentration of 1000 $mg.L^{-1}$. The results are comparable to a test on P. putida conducted in compliance with DIN 38412, part 27 and reporting an EC50 > 10000 $mg.L^{-1}$. However, a solubiliser was used in this study.

Moreover toxicity control of the manometric respirometry test to determine the "ready" biodegradability revealed that **octocrilene is not toxic for bacteria**. It should be noted that the initial biomass concentration recommended in the OECD 301F guideline is 1.6 $g.L^{-1}$ instead of 800 $mg.L^{-1}$. This argument justified that this data is reliable with restriction.

4.2.1.4 Endocrine disruption assessment.

Because uncertainty persists regarding the ED property of octocrilene, a LAGDA test has been requested after substance evaluation of octocrilene[2] . The results of the LAGDA test will be taken into account for further regulatory actions if necessary. The figure here under explains how the results of the LAGDA test would improve/re-inforce or confirm the need for restriction.

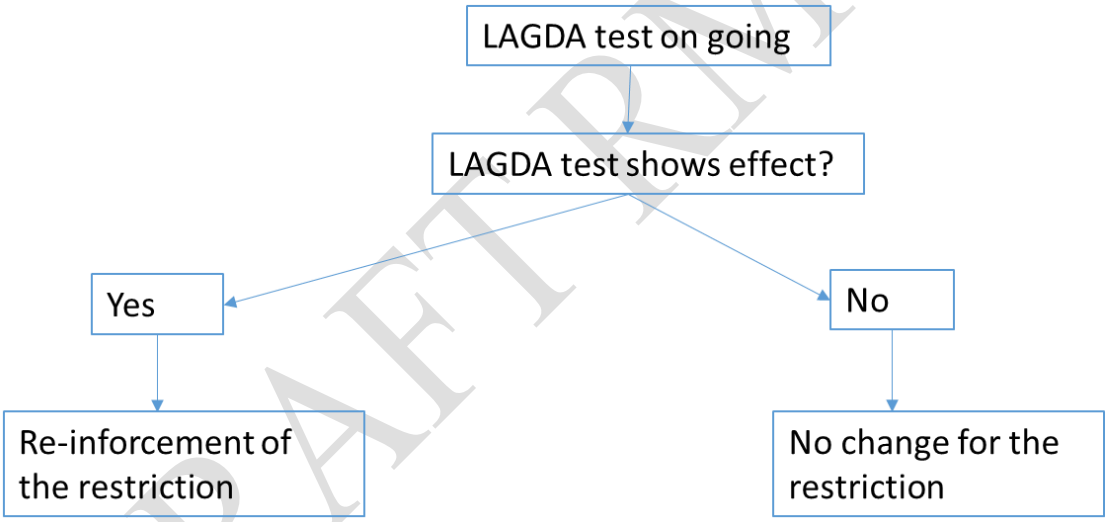


Figure 3 : Influence of the results of the LAGDA test in the building of a restriction dossier under REACH

[2] https://echa.europa.eu/documents/10162/a9fe9bc3-1dc3-03f2-b307-c25de6fbe6fb

4.2.2 PBT and vPvB assessment

4.2.2.1 Persistence assessment

The studies on biodegradation in water (screening tests) are summarized in the following table:

Table 21 Screening tests for biodegradation in water

Method	Results	Remarks	Reference
Test type: ready biodegradability activated sludge, non-adapted according to EU Method C.4-D (Determination of the "Ready" Biodegradability – Manometric Respirometry Test)	no biodegradation % Degradation of test substance: 0 after 28 d (O_2 consumption)	1 (reliable without restriction) key study experimental result Test material (EC name): octocrilene	Unpublished study report (1995a)
Test type: ready biodegradability activated sludge, domestic, non-adapted according to OECD Guideline 301 F (Ready Biodegradability: Manometric Respirometry Test)	Poorly biodegradable % Degradation of test substance: 0 - 10 after 28 d (O_2 consumption)	2 (reliable with restrictions) supporting study experimental result Test material (EC name): octocrilene	Unpublished study report (1991a)

Two guideline studies (screening tests) on the ready biodegradability of octocrilene are available. The biodegradation of the substance was tested in two Manometric Respirometry tests according to EU Method C.4 -D and OECD guideline 301F, respectively. Both tests used non-adapted activated sludge as inoculum. At termination of the test after 28 days of inoculation, the detected degradation rate was in the range of 0 - 10 % (Unpublished study report (1995a), Unpublished study report (1991a)). Thus, octocrilene is not readily biodegradable according to OECD criteria. The substance is considered as poorly biodegradable.

Based on the provided screening data (ready biodegradability tests), **octocrilene appears to be a potentially persistent substance (P)**. No further testing is required for the time being.

Conclusion on P / vP properties: **potentially P and vP**

4.2.2.2 Bioaccumulation assessment

Evidence of non-B / non-vB properties

Table 22: Studies on aquatic bioaccumulation

Method	Results	Remarks	Reference
Danio rerio aqueous (freshwater) flow-through Total uptake duration: 28 d Total depuration duration: 16 d OECD Guideline 305 (Bioconcentration: Flow-through Fish Test)	Bioaccumulation factor: BCF: 858 dimensionless (normalised lipid fraction) (kinetic, corrected for growth) Lipid content: 5.5 % (Lipid content was determined during each sampling occasion during the entire test duration (uptake and depuration))	2 (reliable with restriction) supporting study experimental result Test material (EC name): octocrilene	Unpublished study report (2008)
Oncorhynchus mykiss Feed flow-through Natural water: freshwater Uptake duration: 14 d Depuration duration: 7 d According to OECD Guideline 305: Dietary Exposure Bioaccumulation Fish Test	Bioaccumulation factor: BMF kgl: 0.034 dimensionless (whole body w.w.) Lipid content: 3.5 % (start of exposure) (- average from 3 fish) 3.6 % (end of exposure) (- average from 3 fish) 3.9 % (End of depuration period) (- average from 3 fish) Transformation products: Possible metabolites were not identified; however, as the BMF was based on total radioactivity, it has to be mentioned that the measured amount on fish represents both the parent molecule as well as any possible metabolite.	1 (reliable without restriction) key study experimental result Test material (EC name): octocrilene	Unpublished study report (2018d)

In the first study, the bioaccumulation of octocrilene in *Danio rerio* was investigated using a flow through system set up according to OECD 305. This study was conducted at low concentrations of radio-labelled octocrilene (0.1 µg.L^{-1}). Fish were exposed via the water phase to the ^{14}C-radiolabeled test substance for 28 days. After a depuration period of 15 days the test was terminated and a mean growth and lipid corrected BCF of 858 based on the whole body wet weight was determined. This BCF takes into account both parent and any possible metabolite. The BCF value was however calculated from octocrilene measurements in unfiltered water samples whereas concentrations are reported lower in filtered water samples (raw data are not shared in the full study report). A more reliable BCF value was expected to be calculated from octocrilene measurements in filtered samples in order to get rid of likely adsorption/absorption behavior to particles considering that fish are fed during the test. Moreover the real dissolved concentration of octocrilene in water is expected much lower than the available provided concentration. Thus the provided result by this study is considered unsatisfactory because underestimated.

A second fish bioaccumulation study using *Oncorhynchus mykiss* and dietary exposure was carried out with ^{14}C-radiolabeled test substance (1 µg/g feed) for 14 days. The resulting lipid and growth corrected kinetic BMF was 0.0334. This study is considered as relevant.

In another study, the bioaccumulation kinetics of octocrilene in wild Mytilus galloprovincialis mussels was investigated (Vidal-Liñán, 2018). 450 mussels were exposed for 30d to 1 $\mu g.l^{-1}$ of octocrilene with a water renewal every 48h, followed by a 20d depuration period. The uptake and accumulation of waterborne octocrilene was very rapid, and after only 24 h of exposure to 1 µg L^{-1}, the tissular concentration was 327 µg kg_{dw}^{-1}. The kinetics of bioaccumulation of octocrilene significantly fitted to an asymptotic model with BCF values of 2210 L kg_{dw}^{-1}, even if no plateau was reached. It is common for mussels data to be expressed in dry weight but the B criterion is based on a BCF value expressed in wet weight. Consequently, the BCF would be far below the B criterion.

Conclusion on aquatic bioaccumulation

Octocrilene is not bioaccumulative and not very bioaccumulative according to the REACH PBT/vPvB criteria and considering a BMF value in fish of 0.034 dimensionless.

Conclusion on B / vB properties: **not B/vB.**

Nevertheless, although octocrilene is not considered as a bioaccumulative substance, several studies in the scientific literature show accumulation of octocrilene in wildlife. Octocrilene in mussels (concentrations ranging from under 2 to 7112 ng g^{-1} $_{dw}$) was observed next to recreational bath waters during the summer (Bachelot et al. 2012). High concentration with a range 89-782 $ng \cdot g^{-1}$ $_{lipid\ weight}$ was observed in tissue liver of Franciscana dolphin (Gago-Ferrero et al. 2013). Octocrilene was found at high concentration, 1735 $ng \cdot g^{-1}$ $_{dw}$, in the sea hare *Aplysia dactylomela* (Caden-Aizaga et al. 2022).

4.2.2.3 Toxicity assessment

Evidence of T properties

Based on the results from a chronic daphnia toxicity (OECD 211, NOEC of 2.66 µg/L), **the substance is considered as toxic (T) for the environment**.

Conclusion on T properties: **T**

PBT status of the assessed substance: the substance is **not PBT / vPvB**.

5 Environmental exposure & risk assessment

5.1 Hazard information

Based on the data presented above in part 4.2, table 23 summarizes the PNEC available for each compartment.

Table 23 : 1 PNEC derivation and other hazard conclusions

PNEC DERIVATION AND OTHER HAZARD CONCLUSIONS		
Hazard assessment conclusion for the environment compartment	**Hazard conclusion as proposed by the eMS**	**Remarks/Justification**
Freshwater	PNEC aqua (freshwater): 0.266 µg.L^{-1}	Assessment factor: 10 (three chronic aquatic toxicity tests representing three trophic levels (algae, invertebrates and fish). Extrapolation method: assessment factor OECD 211 (Daphnia reproduction study; NOEC of 2.66 µg.L^{-1}, mean measured)
Marine water	PNEC aqua (marine water): 0.027 µg.L^{-1}	Assessment factor: 100 (three chronic aquatic toxicity tests representing three trophic levels (algae, invertebrates and fish) but no marine water data following OECD guidelines available. Extrapolation method: assessment factor OECD 211 (Daphnia reproduction study; NOEC of 2.66 µg.L^{-1}, mean measured)
Sediments (freshwater)	PNEC sediment (freshwater): 0.1302 mg/$kg_{sediment\ dw}$ = 0.0283 mg/$kg_{sediment\ ww}$	Extrapolation method: equilibrium partitioning method Additional safety factor of 10 (logPow > 5)
Sediments (marine water)	PNEC sediment (marine water): 0.013 mg/$kg_{sediment\ dw}$ = 0.00283 mg/$kg_{sediment\ ww}$	Extrapolation method: equilibrium partitioning method Additional safety factor of 10 (logPow > 5)
Sewage treatment plant	PNEC STP: 10 mg.L^{-1}	Assessment factor: 100 Extrapolation method: assessment factor Activated sludge (EC_{50} >1000 mg/l)
Soil	PNEC soil: 1.25 mg/$kg_{soil\ dw}$ = 1.11 mg/$kg_{soil\ ww}$	Assessment factor: 100 Extrapolation method: assessment factor

		OECD 222 (earthworm reproduction test) with a NOEC of 125 mg/kg dw
Air	No hazard identified	-
Secondary poisoning	Secondary poisoning is not considered relevant	Octocrilene is not bioaccumulative and not very bioaccumulative according to the REACH PBT/vPvB criteria. Therefore, according to the R.16 chapter of the guidance on the Information Requirements and CSR, no secondary poisoning assessment should be performed and therefore no $PNEC_{oral}$ needs to be defined.

5.2 Environmental exposure assessment

5.2.1 Physicochemical properties

Table 24 :Physicochemical properties used for exposure estimation

Input	Value	Unit	Reference
Molecular weight	361.47	$g.mol^{-1}$ [25°C]	EPI Suite v4.11
Vapour pressure	$3.15E^{-09}$	mmHg [25°C]	MPBPWIN v1.43
Henry's law constant	$1.52E^{-05}$	$Pa.m^3.mol^{-1}$ [25°C]	EUSES 2.1.2
Water solubility	40	$\mu g.L^{-1}$ [20°C]	Unpublished study report (2018b)
Partition coefficient n-octanol/water (Log Kow)	6.1	[log10]	Unpublished study report (2018d)

5.2.2 Environmental fate and distribution

Table 25 : Environmental fate and distribution properties used for exposure estimation

Input	Value	Unit	Reference
Organic carbon/water partition coefficient (Koc)	48 898	$L.kg^{-1}$ [20°C]	Unpublished study report (2018a)
Hydrolysis (DT_{50})	206	years [pH 7, 25°C]	HYDROWIN v2.00
Photo-transformation in air (DT_{50})	6.19	hours [25°C]	AOPWIN v1.92 model

Biodegradability	Not readily biodegradable	[-]	Unpublished study report (1995a) Unpublished study report (1991a)
Soil-water partition coefficient	$1.47E^{+03}$	[$m^3.m^{-3}$]	EUSES model 2.1.2
Total rate constant for removal from agricultural top soil	$2.54E^{-06}$	days [12°C]	EUSES model 2.1.2
Total rate constant for removal from grassland top soil	$4.39E^{-06}$	days [12°C]	EUSES model 2.1.2

The Environmental fate and distribution properties of octocrilene suggest that the substance will not evaporate from the water surface into the atmosphere but most probably adsorb to soil and suspended particles. Thus, the substance will mainly distribute into soil and sediment.

Table 26 : Distribution in STP used for exposure estimation

CALCULATED FATE AND DISTRIBUTION IN THE STP – SIMPLETREAT V4	
COMPARTMENT	**PERCENTAGE [%]**
Air	$4.24E^{-06}$
Water	18.66
Sludge	81.35
Degraded in STP	0

5.2.3 Emission scenario parameters: description

Table 27 : Description of the emission scenario parameters

ES n°	Exposure Scenario name
Tonnage approach	
Life Cycle Stage (LCS) M: Manufacture	
1	Manufacture of octocrilene
Life Cycle Stage (LCS) F: Formulation or re-packing	
2	Formulation of cosmetic preparations
3	Formulation of preparations (production of plastisol)

Life Cycle Stage (LCS) IS: Use at industrial sites	
4	Industrial use resulting in inclusion into or onto matrix, Production of plastic articles
5	Industrial use of additive resulting in inclusion into a matrix, including application in coatings, adhesives and plastics
Life Cycle Stage (LCS) C: Widespread use	
6	Wide dispersive use of cosmetic ingredients (indoor use) PC 28 Perfumes, fragrances PC 39 Cosmetics
7	Professional applications, (indoor use), Use as Additive - Wide dispersive indoor use resulting in inclusion into or onto a matrix
8	Professional applications, (outdoor use), Use as Additive - Wide dispersive outdoor use resulting in inclusion into or onto a matrix
Life Cycle Stage (LCS) C: Consumer use	
9	Indoor consumer use as additive - Wide dispersive indoor use resulting in inclusion into or onto a matrix
10	Outdoor consumer end-use of plastic articles
11	Indoor Consumer end-use of plastic articles
Consumption approach	
12	Exposure scenario for UV-filters used in sunscreen products applied on human skin. Emissions during swimming on both freshwater lakes and marine coastal waters
13	Exposure scenario for UV-filters used in sunscreen products applied on human skin. Removal through showering and bathing of humans

Tonnage approach

Please see confidential annex.

Consumption approach: Exposure of the environment via Human

For the emission scenario 12: Emissions during swimming on both freshwater lakes and marine coastal waters to UV-filters used in sunscreen products applied on human skin, a different approach of calculation is proposed. Indeed, the wide dispersive outdoor use of this substance in cosmetic applications (i.e. the use as UV filter in sunscreen products) leads to propose an environmental exposure assessment based on application (and thus, tonnage-independent): it therefore covers the direct release into lake and coastal areas including both water and sediment compartments.

Emission scenario 12:

Exposure scenario for UV-filters used in sunscreen products applied on human skin **Emissions during swimming on both freshwater lakes and marine coastal waters**				
Inputs				
Input	**Symbol**	**Value**	**Unit**	**Reference**
Partition coefficient organic carbon-water	K_{oc}	48898	[l.kg^{-1}]	S
Concentration of UV-filter in sun screen product	$C_{product}$	10	[%]	Berardesca E et al., 2019
Quantity of sunscreen lotion applied per day by a consumer	$Q_{sunscreen\_appl}$	18	[g.d^{-1}]	SCCS Notes of Guidance for the testing of cosmetic ingredients and their safety evaluation 10TH revision (EC, 2018).
Daily number of swimmers	$N_{swimmer}$	1500	[-]	Emission scenario document for Product Type 19 – Repellents and attractants, 2015. ECHA. Appendix 6.3.
Amount of sunscreen product released into the environment	$C_{after\_swimming}$	0.5	[-]	Cosmetics Europe: Guidelines for evaluating sun product water resistance, 2005.
Fraction of swimmers sunscreen product with active substance	F_{swim}	0.7	[-]	S (registrant data)
Volume of water body	$V_{waterbody}$	435000	[m^3]	Emission scenario document for Product Type 19 – Repellents and attractants, 2015. ECHA. Appendix 6.3.
First order rate constant for biodegradation in surface water	$kdeg_{water}$	6.93E-07	[d^{-1}]	S – No degradation
Number of emission days (emission period of 1 day)	Temission,1d	1	[d]	Emission scenario document for Product Type 19 – Repellents and attractants, 2015. ECHA. Appendix 6.3.
Number of emission days (emission period of 91 days)	Temission,91d	91	[d]	Emission scenario document for Product Type 19 – Repellents and attractants, 2015. ECHA. Appendix 6.3.

OUTPUT				
Local emission rate to wastewater	$Elocal_{water}$	9.45E-01	[kg.d^{-1}]	$Elocal_{water}$ = * $C_{product}$ * $Q_{sunscreen\_appl}$ * $N_{swimmer}$ * F_{swim} * $C_{after\_swimming}$ * 10^{-3}
Local concentration in water body after one day	$Clocal_{water,1d}$	2.17E-03	[mg.L^{-1}]	$Clocal_{water,1d}$ = ($Elocal_{water}$ * 10^3 * $T_{emission,1d}$ /$V_{waterbody}$)/ (1+Kp_{susp} * $SUSP_{water}$ * 10-6)
Local concentration in water body over 91 days	$Clocal_{water,91d}$	1.98E-01	[mg.L^{-1}]	$Clocal_{water,91d}$ = $Elocal_{water}$ * 10^3 * $T_{emission,1d}$ / $V_{waterbody}$
Refined local concentration in water body over 91 days (including degradation)	$Clocal_{water,91d-ref}$	1.98E-01	[mg.L^{-1}]	$Clocal_{water,91d-ref}$ = $Clocal_{water,1d}$ * { [1-($e^{-kdegwater}$ * $Temission_{,1d}$)^$Nemission_{,91d}$] / [1-$e^{-kdegwater}$ * $T_{emission,1d}$] }
Refined local concentration in marine coastal waters (without lagoon area)				
INPUTS				
Tidal period (h)	T_{period}	12.41	[h]	Emission scenario document for Product Type 21: Antifouling products, 2004, Table 0.3
Dilution per tide (%)	DIL_{Tide}	50	[%]	According to ESD for PT 21 (p. 118), the average tidal hight in the OECD regions is 1.5 m. Taking into account that the majority of swimmers will be in the coastal area of maximum 2 m water depth, it can be concluded that at least 50 % of the water is replaced by fresh water during each tidal period. Therefore, 50 % water replacement is considered as a worst case.
rate constant for dilution in marine coastal water	$K_{dilution\ tide}$	1.34E+00	[d^{-1}]	$K_{dilution\ tide}$ = (ln(T_{period}) – ln($T_{period/2}$))/ (T_{period}/24)
OUTPUT				
Local concentration in water body after one day and Tidal period	$Clocal_{water,1d,\ Tidal}$	5.69E-04	[mg.L^{-1}]	$Clocal_{water,1d,\ Tidal}$ = $Clocal_{water,1d}$ * exp(- $K_{dilution\ tide}$ * 1)
Local concentration in water body over	$Clocal_{water,91d,\ Tidal}$	2.94E-03	[mg.L^{-1}]	$Clocal_{water,91d-ref}$ = $Clocal_{water,1d}$* { [1-($e^{-kdilution\ tide}$ *

91 days and tidal period				$T_{emission,1d})^{\wedge}N_{emission,91d}]$ / $[1-e^{-kdilution\ tide} * T_{emission,1d}]\}$

S: supplied by applicant

Emission scenario 13

Removal through showering and bathing of humans				
Inputs				
Partition coefficient organic carbon-water	K_{oc}	48898	[l.kg^{-1}]	S
Concentration of UV-filter in sun screen product	$C_{product}$	10	[%]	Berardesca E et al., 2019
Quantity of sunscreen lotion applied per day by a consumer	$Q_{sunscreen\_appl}$	18	[g.d^{-1}]	SCCS Notes of Guidance for the testing of cosmetic ingredients and their safety evaluation 10TH revision (EC, 2018).
Number of inhabitants feeding one sewage treatment plant	N_{local}	10000	[-]	Emission scenario document for Product Type 19 – Repellents and attractants, 2015.
Amount of sunscreen product released into the wastewater	$C_{waste\ water}$	0.5	[-]	Considering that 50% is removal during swimming event
Fraction of inhabitant using a sunscreen product with substance	F_{inh}	0.7	[-]	S
OUTPUT				
Local emission rate to wastewater	$Elocal_{water}$	6.30	[kg.d^{-1}]	

5.3 Environmental risk assessment

5.3.1 Local assessment

FR-MSCA's conclusion of the environmental risk assessment for each exposure scenario of octocrilene are shown in the table below.

Table 28 : Results of the environmental risk assessment

Exposure Scenario	STP	Water (including fresh and marine water)	Sediment (including fresh and marine sediment)	Agricultural soil	Groundwater
Life Cycle Stage (LCS) M: manufacture of octocrilene					
ES 1 - Manufacture of octocrilene	PEC: 1.11E-04 $mg.L^{-1}$ **RCR: < 0.001**	$PEC_{freshwater}$: 5.52E-07 $mg.L^{-1}$ **RCR: < 0.01**	$PEC_{freshsediment}$: 5.87E-04 $mg.kg_{wwt}^{-1}$ **RCR: < 0.1**	No application of the STP sludge on agricultural soil (incineration of sludge)*	NR
Life Cycle Stage (LCS) F: Formulation					
ES 2 - Formulation of cosmetic preparations	NR	NR	NR	NR	NR
ES 3 - Formulation of preparations (production of plastisol)	PEC: 8.48E-04 $mg.L^{-1}$ **RCR: <0.001**	$PEC_{freshwater}$: 7.90E-05 $mg.L^{-1}$ **RCR: <1**	$PEC_{freshsediment}$: 8.41E-02 $mg.kg_{wwt}^{-1}$ **RCR: 2.97**	PEC: 1.37E-01 $mg.kg_{wwt}^{-1}$ **RCR: <1**	0.16 $\mu g.L^{-1}$

Life Cycle Stage (LCS) IS: Use at industrial sites					
ES 4 - Industrial use resulting in inclusion into or onto matrix, Production of plastic articles	PEC: 1.78E-04 $mg.L^{-1}$ **RCR: <0.001**	$PEC_{freshwater}$: 1.66E-05 $mg.L^{-1}$ **RCR: <0.1**	$PEC_{freshsediment}$: 1.77E-02 $mg.kg_{wwt}^{-1}$ **RCR: < 1**	PEC: 2.88E-02 $mg.kg_{wwt}^{-1}$ **RCR: <0.1**	<0.1 $\mu g.L^{-1}$
ES 5 - Industrial use of additive resulting in inclusion into a matrix, including application in coatings, adhesives and plastics	NR	NR	NR	NR	NR
Life Cycle Stage (LCS) PW: Widespread use					
ES 6 - Wide dispersive use of cosmetic ingredients (indoor use) PC 28 Perfumes, fragrances / PC 39 Cosmetics	PEC: 4.01E-03 $mg.L^{-1}$ **RCR: <0.001**	$PEC_{freshwater}$: 3.74E-04 $mg.L^{-1}$ **RCR: 1.41**	$PEC_{freshsediment}$: 3.98E-01 $mg.kg_{wwt}^{-1}$ **RCR: 14.1**	PEC: 6.49E-01 $mg.kg_{wwt}^{-1}$ **RCR: <1**	0.75 $\mu g.L^{-1}$
ES 7 - Professional applications, (indoor use), Use as Additive - Wide dispersive indoor use resulting in inclusion into or onto a matrix	PEC: 9.20E-06 $mg.L^{-1}$ **RCR: <0.001**	$PEC_{freshwater}$: 8.57E-07 $mg.L^{-1}$ **RCR: <0.01**	$PEC_{freshsediment}$: 9.12E-04 $mg.kg_{wwt}^{-1}$ **RCR: < 0.1**	PEC: 1.49E-03 $mg.kg_{wwt}^{-1}$ **RCR: <0.01**	<0.1 $\mu g.L^{-1}$
ES 8 - Professional applications, (outdoor use), Use as Additive - Wide dispersive outdoor use resulting in inclusion into or onto a matrix	PEC: 1.02E-05 $mg.L^{-1}$ **RCR: <0.001**	$PEC_{freshwater}$: 9.53E-07 $mg.L^{-1}$ **RCR: <0.01**	$PEC_{freshsediment}$: 1.01E-03 $mg.kg_{wwt}^{-1}$ **RCR: < 0.1**	PEC: 1.65E-03 $mg.kg_{wwt}^{-1}$ **RCR: <0.01**	<0.1 $\mu g.L^{-1}$
Life Cycle Stage (LCS) C: Consumer use					

ES 9 - Indoor consumer use as additive - Wide dispersive indoor use resulting in inclusion into or onto a matrix	PEC: 2.56E-05 $mg.L^{-1}$ **RCR: <0.001**	$PEC_{freshwater}$: 2.38E-06 $mg.L^{-1}$ **RCR: <0.01**	$PEC_{freshsediment}$: 2.53E-03 $mg.kg_{wwt}^{-1}$ **RCR: < 0.1**	PEC: 4.13E-03 $mg.kg_{wwt}^{-1}$ **RCR: <0.01**	<0.1 $\mu g.L^{-1}$
ES 10 - Outdoor consumer end-use of plastic articles	PEC: 8.18E-05 $mg.L^{-1}$ **RCR: <0.001**	$PEC_{freshwater}$: 7.62E-06 $mg.L^{-1}$ **RCR: <0.1**	$PEC_{freshsediment}$: 8.11E-03 $mg.kg_{wwt}^{-1}$ **RCR: < 1**	PEC: 1.32E-02 $mg.kg_{wwt}^{-1}$ **RCR: <0.1**	<0.1 $\mu g.L^{-1}$
ES 11 - Indoor Consumer end-use of plastic articles	PEC: 1.28 E-06 $mg.L^{-1}$ **RCR: <0.001**	$PEC_{freshwater}$: 1.19E-07 $mg.L^{-1}$ **RCR: <0.001**	$PEC_{freshsediment}$: 1.27E-04$mg.kg_{wwt}^{-1}$ **RCR: < 0.01**	PEC: 2.07E-04 $mg.kg_{wwt}^{-1}$ **RCR: <0.1**	<0.1 $\mu g.L^{-1}$
ES 12 - Exposure scenario for UV-filters used in sunscreen products applied on human skin Emissions during swimming on both freshwater lakes and marine coastal waters	NR	$PEC_{freshwater}$: 1.98E-01 $mg.L^{-1}$ **RCR: 744**	$PEC_{freshsediment}$: 2.11E+02$mg.kg_{wwt}^{-1}$ **RCR: 7443**	NR	NR
ES 12 - Refined local concentration in marine coastal waters (without lagoon area)	NR	$PEC_{marinewater}$: 2.94E-03 $mg.L^{-1}$ **RCR: 109**	$PEC_{marinewater}$: 3.31E+00 $mg.L^{-1}$ **RCR: 1108**	NR	NR
ES 13 - Removal through showering and bathing of humans	PEC: 5.88E-01 $mg.L^{-1}$ **RCR: <0.1**	PEC: 5.48E-02 $mg.L^{-1}$ **RCR: 206**	PEC: 5.83E+01 $mg.kg_{wwt}^{-1}$ **RCR: 2058**	PEC: 9.50E+01 $mg.kg_{wwt}^{-1}$ **RCR: 86**	110 $\mu g.L^{-1}$

5.3.2 Combined assessment

In addition, the aggregated emissions from all wide dispersive uses at a local STP are considered as well.

Exposure Scenario	STP $mg.L^{-1}$	Water (including fresh and marine water) $mg.L^{-1}$	Sediment (including fresh and marine sediment) $mg.kg_{wwt}^{-1}$	Agricultural soil $mg.kg_{wwt}^{-1}$	Groundwater[1]
Life Cycle Stage (LCS) IS: Use at industrial sites					
ES 4 - Industrial use resulting in inclusion into or onto matrix, Production of plastic articles	PEC: 1.78E-04	$PEC_{freshwater}$: 1.66E-05	$PEC_{freshsediment}$: 1.77E-02	PEC: 2.88E-02	<0.1 $\mu g.L^{-1}$
Life Cycle Stage (LCS) PW: Widespread use					
ES 6 - Wide dispersive use of cosmetic ingredients (indoor use) PC 28 Perfumes, fragrances / PC 39 Cosmetics	PEC: 4.01E-03	$PEC_{freshwater}$: 3.74E-04	$PEC_{freshsediment}$: 3.98E-01	PEC: 6.49E-01	0.75 $\mu g.L^{-1}$
ES 7 - Professional applications, (indoor use), Use as Additive - Wide dispersive indoor use resulting in inclusion into or onto a matrix	PEC: 9.20E-06	$PEC_{freshwater}$: 8.57E-07	$PEC_{freshsediment}$: 9.12E-04	PEC: 1.49E-03	<0.1 $\mu g.L^{-1}$
ES 8 - Professional applications, (outdoor use), Use as Additive - Wide dispersive outdoor use resulting in inclusion into or onto a matrix	PEC: 1.02E-05	$PEC_{freshwater}$: 9.53E-07	$PEC_{freshsediment}$: 1.01E-03	PEC: 1.65E-03	<0.1 $\mu g.L^{-1}$

Life Cycle Stage (LCS) C: Consumer use					
ES 9 - Indoor consumer use as additive - Wide dispersive indoor use resulting in inclusion into or onto a matrix	PEC: 2.56E-05	$PEC_{freshwater}$: 2.38E-06	$PEC_{freshsediment}$: 2.53E-03	PEC: 4.13E-03	<0.1 µg.L^{-1}
ES 10 - Outdoor consumer end-use of plastic articles	PEC: 8.18E-05	$PEC_{freshwater}$: 7.62E-06	$PEC_{freshsediment}$: 8.11E-03	PEC: 1.32E-02	<0.1 µg.L^{-1}
AGGREGATED EVALUATION	∑PEC: 4.31E-03 RCR: 4.31E-04	∑PEC: 4.02E-04 RCR: 1.49E+01	∑PEC: 4.28E-01 RCR: 1.51E+01	∑PEC: 6.98E-01 RCR: 6.31E-01	∑PEC: 8.09E-01 > 0.1 µg.L^{-1}

[1] Threshold value of 0.1 µg.l^{-1}: maximum allowable concentration given for pesticides by the Drinking Water Directive 98/83/EC

If an aggregated exposure from tonnage approach scenarios is considered (aggregated exposure to octocrilene from wide dispersive uses, consumer uses and one industrial use), risks are also confirmed for aquatic compartment including sediment and for **groundwater**.

5.4 Monitoring data

A review of the scientific literature is described below about the occurrence of octocrilene in the aquatic compartment; note that the review is not exhaustive and does not permit to have a representativeness of the spatial and temporal variability. Moreover, no data about the occurrence of octocrilene in sediment compartment is carried out and the table below describes only occurrence in aquatic compartment. Nevertheless, this review confirms the occurrence of octocrilene in the aquatic compartment with several values above the hazard threshold values (PNEC values), confirming a risk for aquatic organisms by the use of octocrilene.

Table 29 : Occurrence of octocrilene in the aquatic compartment. Value above the PNEC value are highlighted in red –PNEC aqua (freshwater): 266 $ng.L^{-1}$ - PNEC aqua (marine water): 27 $ng.L^{-1}$.

VALUE (max)	UNIT	DETAILS	REFERENCE
71 (max)	ng.l^{-1}	Seawater – coastal area July to August 2017 Hong-Kong and South China Sea	Tsui et al., (2019)
79 (mean)		Seawater - Artificial beaches (recreational purposes) at the river and reef sites April to October 2011 Okinawa Island, Japan.	Tashiro et al., (2013)
8 (mean)		Seawater - Reef sites April to October 2011 Okinawa Island, Japan.	
1 324 (max)		Semi-enclosed Beaches 1-1.5 m depth. May to October 2011 Gran Canaria Island, Spain.	Rodriguez et al., (2015)
109 (max)		Mouth of River near Melbourne with mainly WWTP effluents. 29–30 August 2011 Melbourne, Australia	Allinson et al., (2018)
103 (median) 6 812 (max)		Surface water (reflect WWTPs, beaches and aquatic recreational activities) Victoria Harbor: major tidal channel with strong current flushing and has long been utilized for disposal of waste water effluent August 2012, February and June 2013 Hong Kong	Tsui et al., (2014)
87 (median) 108 (max)		Surface water in Tokyo Bay Semi-enclosed sea surrounded by three prefectures and a receiving body for industrial, domestic and agricultural wastewater 2012-2013	

		Tokyo	
117 (median) 128 (max)		Jamaica Bay, Upper New York Bay and the East River near WWTP discharge points 2012-2013 New York	
145 (median) 377 (max)		Surface water - beaches and near WWTP discharge points 2012-2013 Los Angeles	
75 (median) 107 (max)		Surface water - beaches and near WWTP discharge points 2012-2013 Shantou	
36 (median) 102 (max)		Surface water - beaches and near WWTP discharge points 2012-2013 Chaozhou	
153 (median) 205 (max)		River water receiving municipal wastewater 2012-2013 Bangkok	
26 (median) 31 (max)		Arctic Ocean and Chukchi Sea between 65 and 75 °N 2012-2013 Artic	
32 (max)		Shallow estuary with semi-diurnal tide Freshwater from Jiulong River which flowed through the area of animal husbandry, industry, and large cities April to December 2014 China	Sun Q, et al., (2016)
13 (max)		Effluent wastewater samples in WWTPs, La Spezia Spring – summer 2011 Italy	Magi E, et al., (2012)
112 (max)		Surface riverwater, Genoa Spring – summer 2011 Italy	
32 (max)		Surface seawater, Beach in Genoa Spring – summer 2011 Italy	
119 (annual average) 382 (max) 261 (summer		Surface seawater Popular beach resort lined with hotel and other typical vacation amenities, tourist driven economy; multiple public beach access points (Myrtle Beach, SC)	Bratkovics S, et al., (2015)

average)		September 2010–October2011 South Carolina, USA	
8.58 (annual average) 77 (max) 26 (summer average)		Surface seawater Located in North Inlet National Estuarine Research Reserve (NERR); served as the environmental reference site (Georgetown, SC) September 2010–October2011 South Carolina, USA	
41.1 (annual average) 311 (max) 162 (summer average)		Surface seawater Northeastern most point on Folly Island, abandoned Coast Guard station with limited access (Folly Beach, SC) September 2010–October2011 South Carolina, USA	
194 (annual average) 1375 (max) 745 (summer average)		Surface seawater Mostly residential, popular local beach with significant surfing/watersports use (Folly Beach, SC) September 2010–October2011 South Carolina, USA	
711 (annual average) 3730 (max) 2016 (summer average)		Surface seawater Local government run park with family amenities and adjacent hotel(Folly Beach, SC) September 2010–October2011 South Carolina, USA	
290 (annual average) 1060 (max) 878 (summer average)		Surface seawater Southwestern most point on Folly Island, local government run park with access for up to 200 vehicles; includes amenities for daily beach use (Folly Beach, SC) September 2010–October2011 South Carolina, USA	
420 (max, top surface layer) 148 (max, water column)		Lave Beach, Marseille, recreational bathing area 15 July 2017 France	Labille et al., (2020)
142 (max, top surface layer) 31 (max, water column)		Pointe Rouge Beach, Marseille, recreational waterfront (high attendance and an urban environment) 15 July 2017 France	

150 (max, water column)		Prophète Beach, Marseille, Urban beach intensely frequented 15 July 2017 France	
259 (max) 68 (mean)	ng.l^{-1}	Yangtze River Delta (YRD) tributaries to the lower reach of Yangtze River, from the Qinhuai River and tributaries of Tai Lake April and May 2016 China	Peng et al., (2018)
31 (max) 7.9 (median)	ng.l^{-1}	Surface water of the Oder and Vistula (influenced by the cities Szczecin and Gdańsk). May 2015 Warnow river and the Mühlenfließ river in the Rostock region draining into the Baltic Sea. July 2015 Germany	Fisch et al., (2017)
369 (max)	ng.l^{-1}	Sea water, Gulf of Lion Subject to the highest touristic pressure July 2014, 3:00 pm France	Picot-Groz et al., (2018)
312 (min) 13 000 (max) 7 360 (mean)	ng.l^{-1}	Municipal wastewater, area around the Alna valley (Oslo East), which is an area with dense population and is home to a variety of industries, trade, and transport. 2018 Norway	NILU (2019)
< 30 (min) 800 (max) 126 (mean)	ng.l^{-1}	Surface water, area around the Alna valley (Oslo East) which is an area with dense population and is home to a variety of industries, trade, and transport. 2018 Norway	NILU (2019)

5.5 Conclusion for environment

Several environmental exposure scenarios show unacceptable risks (i.e. PEC/PNEC ratio above 1) for non-target organisms being in the aquatic compartment (freshwater, seawater) including sediment and groundwater contamination. Based on the data available in the registration dossier, the uses involved are the following:

From tonnage approach:

- Formulation of plastisol production for sediment compartment and groundwater;
- Wide dispersive use of cosmetic ingredients (perfumes, fragrances, cosmetics);

From consumption approach:

- Exposure scenario for UV-filters used in sunscreen products applied on human skin. Emissions during swimming on both freshwater lakes and marine coastal waters;

Risks are mainly observed for the specific use of octocrilene as UV filter in cosmetic ingredients. Risks are largely unacceptable using tonnage approach or consumption approach covering releases from bathing and washing of people wearing suncreams.

To note, lagoons are not specifically addressed in this dossier. Nevertheless and considering unacceptable risk for marine coastal waters, it should be noted, specific work has been carried out on coral reefs (to be published – Risk asessment of chemicals substances on coral reefs). A scientific study showed that octocrilene induced coral stress response, while triggering mitochondrial dysfunction at 50 µg/L (Stien et al. 2020). This value is well above the hazard threshold values but many uncertainties have been identified in this report.
Finally, it should be noted that octocrilene is a persistent substance in aquatic compartment. Several values of monitoring data for freshwater and seawater are above the hazard threshold values (PNEC values), confirming unacceptable risks identified via estimated exposure calculation.

6 Justification for the (no) need for regulatory risk management action at EU level

As a reminder, the objectives of this RMOA are to decide if there is a need for regulatory risk management action at an EU level. CLP's measures and those proposed under REACH are the core of this analysis. They are briefly compared with RMM regarding water protection as this is the compartment where risks are identified. This comparison could be enriched during the public consultation.

Indeed, as shown at the beginning of this RMOA, one of the conclusion of the SEv was the need to pursue investigation through a RMOA for environmental risks. Despite the impossibility to conclude on endocrine properties, waiting for the LAGDA test in the evaluation process, unacceptable environmental risks have been demonstrated:

- The specific use of formulation of plastisol for sediment compartment and groundwater.

- The specific use of octocrilene as filter UV in cosmetic ingredients. Risks are largely unacceptable using tonnage approach or consumption approach covering releases from bathing and washing of people wearing suncreams.

Taking into account all the concerns raised above, a need for further regulatory action is identified. Five RMOs have been assessed by ANSES in order to cover all the concerns raised above: classification, SVHC identification, restriction and water framework directive/ industrial emission directive.

6.1 Harmonised classification of substances under CLP (EC) No 1272/2008

Harmonized classification of substances according to the CLP regulation entails requirements, such as labelling. However it should be noted the CLP regulation does not apply to substances or mixtures used as cosmetic products in their finished state ie ready to use to consumers (art.1.5.c of the CLP regulation). On the contrary, cosmetic ingredients as raw materials or cosmetic mixtures (bulk) fall under the remit of the CLP regulation.

Nowadays, the Cosmetic regulation allows the use of octocrilene with a concentration of 9 or 10% according to the cosmetic uses[3]. As explained in this RMOA, a classification for sexual function and fertility is warranted (Repr. Category 2 (H361f)). The consequences of the classification for the reproductive endpoint as a category 2 may not be sufficient to protect the consumer. Indeed, if octocrilene is classified as Reprotoxic category 2, it shall be forbidden in the cosmetic regulation. Indeed, CLP regulation impact cosmetic uses as art.15 of the cosmetic regulation prohibits substances classified as CMR under the CLP regulation from use in cosmetic products, unless a specific exemption is granted. The exemption process ensures that the substance is safe when used under specific and controlled conditions. More precisely, according Article 15 of this regulation a substance

[3] https://health.ec.europa.eu/system/files/2022-08/sccs_o_249.pdf

classified in category 2 may be used in cosmetic products where the substance has been evaluated by the SCCS and found safe for use in cosmetic products. To these ends the Commission shall adopt the necessary measures in accordance with the regulatory procedure with scrutiny referred to in Article 32(3) of this Regulation. SCCS has already evaluated octocrilene, in 2021, and found it safe for use in cosmetic products. It is therefore difficult to forecast the impact on this use of the repro 2 classification. It might be low, depending on the statement done by SCCS about reproduction toxicity at the time of it's assessment.

On the other hand, no final conclusion could be set for the potential endocrine disruption of octocrilene regarding the T modality for human health. Nevertheless, an additional test has been requested by the eMSCA in order to clarify the potential risk related to endocrine disruption for the environment.

Octocrilene is considered to be persistent, but not bioaccumulable and toxic. So, even if the hazard endpoints endocrine disruption and PBT/PMT are now included into CLP[4], octocrilene cannot be classified for these endpoints based on the data available.

Therefore, this regulatory management option is not the most appropriate way to deal with the issue of octocrilene.

6.2 Identification as SVHC/Candidate Listing Inclusion in Annex XIV

First, octocrilene is persistent (P) and toxic (T) in the environment but not bioaccumulable (B). The M criteria has not been evaluated (log Koc>3). Since octocrilene is only identified as persistent and toxic, it cannot fulfill the SVHC criteria regarding PBT concerns.

Then, a substance that is classified as carcinogenic, reprotoxic or mutagenic can fulfill the criteria to be identified as SVHC. However, as the classification foreseen for the reprotoxic endpoint is only a category 2, it will not fulfill the 57(c) SVHC criteria.

Moreover, ANSES notes that environmental ED identification is still pending on the results obtained from the LAGDA test currently being performed. If octocrilene is identified as an endocrine disruptor for the environment, it may be further considered in the light on other data as discussed in section 4.2.2.

If octocrilene was once to be identified under SVHC and prioritized for annex XIV inclusion, it should be noted that the requirements for authorization only apply to articles produced in the EU. It cannot be ruled out that articles containing octocrilene are imported from outside the EU.

So far, octocrilene cannot be identified SVHC for the properties identified in art. 57 of REACH.

[4] Commission delegated regulation (EU) 2023/707 of 19 December 2022 amending Regulation (EC) No 1272/2008 as regards hazard classes and criteria for the classification, labelling and packaging of substances and mixtures : EUR-Lex - 32023R0707 - EN - EUR-Lex (europa.eu)

6.3 Restriction

As described in section 5, after performing an environmental risks assessment and comparing these results with monitoring data, it can be concluded that unacceptable risks for the environment were identified ahead of the study requested.

Consequently, further regulatory action is necessary to control this risk at the EU level. Octocrilene could, thus, be restricted and included in Annex XVII of REACH. In section 5, risks for the environment were proven for cosmetic uses but also for aggregated uses, including cosmetic uses. A restriction may apply to a substance, as such, or to one included in a mixture or an article. The restriction may also apply to substances in imported goods, which is not the case with an authorization process**.**

Restriction under REACH may be designed in different ways in order to reach the highest possible risk reducing effect without having a disproportionate economic impact on the EU market.

Regarding the substance covered by the scope of this RMOA, **the aim of a restriction would be to limit the discharge of octocrilene into the environment through its uses for which risks have been identified.**

The scope of the restriction would need to be defined precisely to ensure the effectiveness, the enforceability and the monitorability of the restriction but also its consistency with other existing pieces of legislations which may cover the same or close field. This capacity to target specifically the uses associated with risks highly depends on the quality of the information provided in the registration dossiers and that will be provided in the different phases prior to the restriction submission. The analysis of the available alternatives and the socio-economic analysis would also be required.

6.4 Other risk management measures: Water Framework Directive (2000/60/EC) and Industrial Emissions Directive (2010/75/EU)

6.4.1 Water Framework Directive (2000/60/EC)

Considering, on one hand, the unacceptable risks for the aquatic environment linked to octocrilene and, on the other hand, its potential vP property which can lead to a lasting and worrying contamination of water resources, octocrilene could be considered in the Water Framework Directive (WFD) for community action in the field of water policy (2000/60/EC.
The integration of octocrilene in the appendix X of this directive would allow to:

- introduce monitoring of octocrilene in waters,
- limit the contamination of environments by setting a limit value that takes into account the risks for the aquatic environment,
- protect water resources for the production of water intended for human consumption,
- provide means of action to limit emissions at the local level.

However, for this regulation to be applicable to all Member States, octocrilene would have to be on the list of priority substances in the field of water (appendix X of the WFD), which is not the current case.

For a substance to be included in the list of priority substances of the WFD, it is necessary that:
-It is taken into account as a candidate substance in the prioritization carried out by the JRC. For this, sufficient data must be available, covering almost all Member States.
- It is prioritized.
- It is retained by the Member States and the Commission.

Since the entry into force of the directive, a watch list has been set up in France[5] and Europe[6]: To date, octocrilene is not on any of these watch-lists. The substances appearing on this watch list must be selected from among those for which the available information indicates that they may present a significant risk, at European Union level, for or via the aquatic environment, but for which the monitoring are insufficient to reach a conclusion on the actual risk posed.

Finally, this directive would make it possible to establish an environmental limit value making it possible to regulate the discharges from the installations (of industries formulating and producing plastisol for example). In the case of octocrilene, risks are mainly observed for its use by consumers as UV filter in cosmetic ingredients, which cannot be covered by this directive. This directive would, on the other hand, be a good way to follow the application of concentration limit that could be set through a restriction, if octocrilene becomes a prioritized chemical (Which could be the case if octocrilene is identified as an endocrine disruptor depending on the outcome of the LAGDA test).

6.4.2 Industrial Emissions Directive (2010/75/EU)

Concerning the risks for environment, releases of octocrilene through industrial emissions during the formulation of plastisol could be regulated by defining more stringent tolerable release concentrations. By applying such an approach, two important risk management principles would be followed: the upstream limitation of releases, the principle "the polluter pays". Defining stringent release concentrations of octocrilene could be of added value to control environmental emission of octocrilene. It could be considered a complementary risk management option to the restriction proposed based on consumer use.

However, IED is a directive. Therefore, its implementation may differ across Europe. In addition, up to date, octocrilene is not integrated in the Annex II of this directive which lists the pollutant chemicals. This directive is therefore not applicable at the time being.

5 https://www.ineris.fr/sites/ineris.fr/files/contribution/Documents/Substances%20Pertinentes%20%C3%A0%20Surveiller%20%28SPAS%29%20v3.pdf

6 https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2020.257.01.0032.01.ENG&toc=OJ:L:2020:257:TOC

Regulations outside of REACH do not appear to be effective in managing the identified risks.

6.5 Conclusion

The objective of this RMOA is to identify the RMMs with regard to the conclusion that several environmental exposure scenarios to octocrilene show unacceptable risks.

From tonnage approach:

- Formulation of plastisol production for sediment compartment and groundwater;
- Wide dispersive use of cosmetic ingredients (perfumes, fragrances, cosmetics);

From consumption approach:

- Exposure scenario for UV-filters used in sunscreen products applied on human skin. Emissions during swimming on both freshwater lakes and marine coastal waters;

Unacceptable risks are observed for non-target organisms being in the aquatic compartment (freshwater, sweater) including sediment. These risks are confirmed with the concentration data of octocrilene in the environment.

It is also important to take into account that the ongoing LAGDA test will be taken into consideration but should not prevent any regulatory action considering the existing environmental risks identified for octocrilene. Additional RMM can already be proposed that are described in this document.

As shown in the sections 6, five risk management options were considered. While considering all the advantages, the drawbacks, the uses, the results of the exposure and risk assessment and the hazards, **ANSES considers that the most appropriate risk management option for octocrilene is a REACH restriction dossier (Article 68.1), in order to cover the environmental risks that have been demonstrated.**

7 Conclusions and actions

Subgroup name, EC number, substance name	Human Health Hazard	Environmental Hazard	Relevant use(s) & exposure potential	Last foreseen action	Action
Octocrilene (EC : **228-250-8)**	According to the available data and the literature, **no final conclusion could be set on ED-potential of octocrilene regarding T-modality for Human health.** A classification for sexual function and fertility is warranted (Repr. Category 2 (H361f)).	According to the available data and the literature, **Octocrilene is considered as potentially P/vP and T.**	Octocrilene is reported to be mainly used as an UV filter, UV absorber, light stabilizer in cosmetics, plastics, adhesives, coatings, rubber products.	Need for EU RRM Justification : Environmental risks cannot be excluded for various compartments in relation to industrial and consumer uses	Restriction

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9 Confidential Annex : Emission scenario parameters : Tonnage approach