

REVIEW ARTICLE

Review of the safety of octocrylene used as an ultraviolet filter in cosmetics

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Abstract

Octocrylene or octocrilene is an organic ultraviolet (UV) filter which absorbs mainly UVB radiation and short UVA wavelengths. It is used in various cosmetic products to either provide an appropriate sun protection factor in sunscreen products or to protect cosmetic formulations from UV radiation. There is no discussion that UV filters are beneficial ingredients in cosmetics since they protect from skin cancer, but octocrylene has been recently incriminated to potentially induce adverse effects on the endocrine system in addition to having allergic and/or photoallergic potential. However, the substance has the advantage to work synergistically with other filters allowing a beneficial broad photoprotection, e.g. it stabilizes the UVA filter avobenzone (i.e. butylmethoxydibenzoylmethane). Like all chemicals used in cosmetics, the safety profile of octocrylene is constantly under assessment by the European Chemical Agency (ECHA) since it has been registered according to the European regulation Registration, Evaluation, Authorisation and Restriction of Chemicals. Summaries of safety data of octocrylene are publicly available on the ECHA website. This review aims to present the main safety data from the ECHA website, as well as those reported in scientific articles from peer-reviewed journals. The available data show that octocrylene does not have any endocrine disruption potential. It is a rare sensitizer, photocontact allergy is more frequent and it is considered consecutive to photosensitization to ketoprofen. Based on these results, octocrylene can be considered as safe when used as a UV filter in cosmetic products at a concentration up to 10%.

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Conflict of interest

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Introduction

Octocrylene or octocrilene (CAS n. 6197-30-4) is an organic compound with an aromatic structure which is also known as 2-ethylhexyl 2-cyano-3,3-diphenyl-2-propenoate; 2-ethylhexyl 2-cyano-3,3-diphenylacrylate or the 2-ethylhexyl ester of 2-cyano-3,3-diphenyl acrylic acid.

It is an organic ultraviolet (UV) filter, which absorbs mainly UVB radiation and short UVA wavelengths.¹ Due to its UV radiation absorption properties, it is used in sunscreens with other UV filters to provide an adequate sun protection factor (SPF). It is also used to stabilize other UV filters such as avobenzone, a filter particularly effective against UVA²; this association thus provides an optimal UV protection. Various cosmetic products

such as facial creams or lip care products contain octocrylene to either provide an adequate SPF or to protect the cosmetic formulation from UV radiation.³

In Europe, UV filters allowed in cosmetic products are regulated in Annex VI of Cosmetics Regulation (EC) No. 1223/2009. According to this regulation, octocrylene is authorized as a UV filter in cosmetic formulations at a maximum concentration of 10.0% as acid form in Europe (Annex VI/10). Of note, octocrylene is also authorized as a UV filter in sunscreen products in the same conditions in the USA.

Octocrylene may cause allergies and/or (photo)allergies and has been suspected to have an endocrine disrupting activity. Indeed, in 2013, the Danish Centre on Endocrine Disruptors

assessed the endocrine disrupting potential of all UV filters used in Europe, including octocrylene.⁴ In addition, on 16 May 2019, the European Commission called for data on a list of 14 ingredients – including octocrylene – with potential disrupting properties used in cosmetic products (https://ec.europa.eu/growth/content/call-data-ingredients-potential-endocrine-disrupting-properties-used-cosmetic-products_en). The objective of the present document is therefore to evaluate the safety of octocrylene on the basis of the publicly available safety data from scientific literature and safety agencies. It is worth noting that the risk assessment of a chemical substance performed by European safety agencies such as the European Chemical Agency (ECHA) is based on the appraisal of all relevant publicly available information on this ingredient, including results from *in vitro* and *in vivo* studies published in peer-reviewed journals and from unpublished studies carried out by the manufacturers at the request of safety agencies. Both kinds of results are summarized below.

Method of data search

Octocrylene has been recently registered at the European level in Regulation (EC) No. 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals. It is under assessment by the ECHA. Although the assessment has not been finalized because additional data were requested by the ECHA from the product manufacturers, summaries of safety data are available since 2014 and were recently updated with additional data on ECHA website.⁵ In addition, published safety data on octocrylene were updated by searching publications in peer-reviewed journals available on PubMed at the end of January 2019. The following search terms were used: ‘octocrylene’ OR ‘octocrilene’. No limits for publication dates were set. The articles were screened by two reviewers based on titles and abstracts, only those dealing with the safety of octocrylene were selected. Of note, all articles dealing with environmental effects of octocrylene were excluded. Finally, a manual search of data available in grey literature was conducted.

Absorption and bioavailability data

Transdermal/percutaneous absorption

Four studies on the transdermal absorption of octocrylene are available in the scientific literature,^{6–9} and an additional study is available in ECHA summaries of safety data (unpublished study as cited by ECHA, 2019⁵). All of these studies were performed *in vitro* on human skin samples maintained alive. The article of Potard *et al.*⁹ also included an *in vivo* absorption study of octocrylene in the *stratum corneum* of humans.

The results of these studies showed that 16–24 h after application of octocrylene (8–10%) on the surface of skin samples, most of the octocrylene remained on the surface of the skin as non-

penetrated material (>95%) and detectable amounts of the applied dose were found in the *stratum corneum*, and in low amounts or below the detection limit in other skin layers (epidermis, dermis or receptor medium). None of the authors determined a percentage of dermal absorption. Hayden’s study showed that only 0.4% of octocrylene was found in the epidermis and approximately 0.05% in the fluid receptor.⁷ Therefore, it can be concluded that transdermal absorption of octocrylene is very low.

Bioavailability

No specific animal data on octocrylene kinetics are available in the scientific literature as well as in the grey literature (e.g. data available on ECHA website). In an oral 90-day toxicity study conducted in rats, octocrylene was shown to be bioavailable in the gastro-intestinal tract.⁵ Data in humans available in the scientific literature contain assessment of exposure to octocrylene and show that octocrylene was found in human milk after dermal exposure at very low amounts – i.e. 27.50 ± 22.15 ng/g of lipids.¹⁰ Human metabolism is under investigation by a research team (publication in preparation as mentioned by Bury *et al.*²), who recently identified three metabolites, 2-cyano-3,3-diphenylacrylic acid (CPAA), 2-ethyl-5-hydroxyhexyl 2-cyano-3,3-diphenyl acrylate (5OH–OC) and 2-(carboxymethyl)butyl 2-cyano-3,3-diphenyl acrylate (‘dinor OC carboxylic acid’, DOCCA) in a pilot biomonitoring study in the urine of 35 volunteers not occupationally exposed to octocrylene. Results of this pilot study showed that metabolites of octocrylene were primarily found at low concentrations – i.e. 59.0 (38.4–95.5) µg/L for CPAA; 0.663 (0.651–0.805) µg/L for DOCCA; 0.044 (0.030–0.093) µg/L 5 OH–C – in urine of volunteers using sunscreen products. However, those results need to be confirmed in a larger population.

A study published in May 2019 also assessed the systemic availability in human of some UV filters including octocrylene.¹¹ This randomized clinical trial included 24 healthy participants who were allocated to four treatments groups receiving a different sunscreen formulation (spray, lotion and cream), four times per day for 4 days, in indoor conditions, at a rate of 2 mg/cm² on 75% of body surface area. All the four formulations applied contained octocrylene at various concentrations: 2.35%, 6% or 10%. The overall maximum plasma concentrations (C_{max}) of octocrylene observed over the study duration, ranged from 2.9 to 7.8 ng/mL. Furthermore, the AUC increased from day 1 to day 4 of application and terminal half-life was relatively long (mean range: 42–84 h), suggesting a possible accumulation of octocrylene over time. However, given the conditions of this study, further studies are needed to determine the clinical significance of these findings. Although these data have been published after our cut-off date (January 31, 2019), we considered this study important to be included in our review because this is the first one to assess the systemic availability of octocrylene in humans.

Conclusion Available *in vitro* dermal absorption studies of octocrylene showed that most octocrylene concentrations are found in the *stratum corneum* and that very few quantities are found in the epidermis (0.4%) and in the receptor fluid (<0.05%). *In vivo*, a very recent study in human volunteers showed systemic exposure to octocrylene with maximal concentrations ranging from 2.9 to 7.8 ng/mL under indoor maximal use conditions. Octocrylene has been found at very low amounts in human milk, and some metabolites of octocrylene were primarily detected in urine of volunteers using sunscreen products. The clinical significance of systemic availability and the metabolism of octocrylene in humans both need further investigation.

Repeated dose toxicity

Two repeated dose toxicity studies are available: one study was carried out in rabbits via dermal route¹² and the other was conducted in rats via oral route (unpublished study as cited by ECHA, 2019⁵) (Table 1).

Topical route In the dermal 13-week repeated dose toxicity study in rabbits (five animals per sex per dose), no significant toxic effects were observed up to the maximum tested dose of 534 mg/kg bw/day.

Oral route

In the oral 13-week repeated dose toxicity study in rats (10 animals per sex per dose), rats were treated with octocrylene at ingested doses of about 58, 175, 340 and 1085 mg/kg bw/day. Effects on liver, thyroid and pituitary gland were observed in animals receiving octocrylene at doses of 340 and 1085 mg/kg bw/day. These changes were probably due to hepatic enzyme induction reported with octocrylene in rats.

An additional study was conducted in rats to investigate mechanisms related to potential thyroid effects of octocrylene via enzyme induction in the liver. This study was divided into two subsets with rats treated with octocrylene at doses of 63/72, 188/215 and 630/720 mg/kg bw/day in males/females, respectively, via oral route for 14 or 28 days (Table 1). Effects on liver and thyroid such as increased TSH serum levels (ranges of T3 and T4 levels were still physiological) were observed and these were investigated. The conclusion states that octocrylene has the potential to induce liver enzyme activity in rats at high doses (340 and 1085 mg/kg bw/day) which in turn may induce indirect effects on the thyroid.⁵ Indeed, the induction of hepatic enzymes increased the clearance of thyroid hormones (T3 and T4) and thus resulted in an increased TSH levels through a positive hormonal feedback mechanism. This mechanism of action, i.e. impact on thyroid hormones by increasing the peripheral metabolism of thyroid hormones through an induction of hepatic microsomal enzymes, is well described.¹³ In addition, rats are far more sensitive to those thyroid effects than humans due to the shorter plasma half-life of thyroxine (T4) and the

considerable differences in the transport proteins for thyroid hormones compared to humans.^{5,14}

Conclusion No systemic effects were reported after dermal exposure to octocrylene in rabbits at very high dose (534 mg/kg bw/day) compared with those used in cosmetic products. After oral exposure, effects on liver and thyroid were reported in a study conducted in rats at high doses (340 and 1085 mg/kg bw/day in males). These effects were investigated in an additional mechanistic study which showed that effects on thyroid were indirect and due to hepatic enzyme induction potential of octocrylene in rats at very high oral doses.

Reproductive effects in animals

Overall, five studies assessing the reproductive effects of octocrylene in animals are available (Table 2). Two studies were conducted via topical route¹²: a 13-week repeated dose toxicity study in rabbits (see section Repeated dose toxicity) which specifically investigated male genital organs and a developmental toxicity study in rabbits. Three studies were carried out via oral route: a developmental toxicity study in mice¹² and two additional reproductive toxicity studies carried out in rats and reported in summaries of safety data available on ECHA website (unpublished studies as cited by the ECHA, 2019⁵).

Topical route In the 13-week repeated dose toxicity, rabbits (five animals per sex per dose) received topical applications of octocrylene. No significant toxic effects were observed at doses tested up to 534 mg/kg bw/day (see section Repeated dose toxicity). Specific investigation on male genital organs was performed, and no effects were reported on testicular and epididymal morphology as well as on sperm count and motility.

In the developmental study conducted in rabbits (17 females per dose), doses of octocrylene up to 267 mg/kg bw/day were administered via dermal route. No effects on maternal, reproductive and offspring parameters were reported.

Oral route

In the developmental study conducted in mice (12 females per dose) treated orally with octocrylene at doses up to 1000 mg/kg bw/day, no effects on implantations, resorptions, number of live, dead fetuses or bodyweight and pup size were observed.¹²

In the first developmental study available on ECHA's website,⁵ rats (25 females per dose) were treated with octocrylene via oral route at doses of 100, 400 or 1000 mg/kg bw/day from day 6 to day 15 of gestation. Maternal effects were transient salivation at the highest dose and relative increased liver weights at the middle and high dose compared with control. No effects were observed in pups.

The second key study available on ECHA's website is an extended one-generation reproductive toxicity study carried out in rats (P: 28 animals per sex per dose (28 males and 27 females);

Table 1 Summary of the repeated dose toxicity studies on octocrylene

References	Species, strain and number of animals	Route of exposure	Doses	Duration of exposure	Main findings	Dose descriptor (mg/kg bw/day)
Odio <i>et al.</i> , 1994 ¹²	Rabbit New Zealand White 5 animals per sex per dose	Dermal	0, 130, 264 and 534 mg/kg bw/day	5 days per week for 13 weeks (total of 65 applications)	At all doses, slight to moderate skin irritation (erythema and desquamation) at the site of compound application correlated to decreased bodyweight gain No evidence for haematological or macroscopic and histopathological abnormalities	NOAEL: 534
Unpublished study as cited by ECHA, 2019 ⁵	Rat Wistar 10 animals per sex per dose	Oral	0, 750, 2250, 4500 and 15 000 ppm in diet corresponding to 53, 163, 315 and 1027 mg/kg bw/day in males and 63, 187, 365 and 1143 mg/kg bw/day in females Mean doses in all animals 0, 58, 175, 340 and 1085 mg/kg bw/day	13 weeks	Decreased food consumption bodyweight gain and bodyweight at 1085 mg/kg bw/day Hepatic effects such as increased absolute and relative liver weights, hypertrophy of periacinar and centriacinar hepatocytes at 340 and 1085 mg/kg bw/day Hematological effects such as decrease in MCV, MCH, MCHC at 1085 mg/kg bw/day and decreased and increase in platelets at 340 and 1085 mg/kg bw/day Slight or moderate hypertrophy of the thyroid, follicular epithelium and associated pale staining colloid at 340 and 1085 mg/kg bw/day	NOAEL: 175
Unpublished study as cited by ECHA, 2019 ⁵ (Supportive mechanistic study)	Rat Wistar 5 animals per sex per dose	Oral	0, 1000 ppm, 3000 ppm and 10 000 ppm in diet corresponding to 63, 188 and 630 mg/kg bw/day for 14 day-treatment group and 72, 215 and 720 mg/kg bw/day for 28 day-treatment group	14 days (Subset B) and 28 days (Subset A)	Decreased mean bodyweights and bodyweight at the highest dose in both subsets Subset B (14 days): <ul style="list-style-type: none"> increased absolute and relative weight of liver at the highest dose in both sexes increased serum levels of TSH at the highest dose in females minimal follicular cell hypertrophy/hyperplasia of the thyroid gland at the highest dose in both sexes 	No NOAEL determined as mechanical study

Table 1 Continued

References	Species, strain and number of animals	Route of exposure	Doses	Duration of exposure	Main findings	Dose descriptor (mg/kg bw/day)
					<p>Subset A (28 days):</p> <ul style="list-style-type: none"> • decreased bodyweight at the highest dose in males • increased absolute and relative weight of liver at the highest dose in both sexes • increased serum levels of TSH at the highest dose in both sexes • minimal follicular cell hypertrophy/hyperplasia of the thyroid gland at the highest dose in both sexes 	

Bw, bodyweight; MCH, Mean Corpuscular Haemoglobin; MCHC, Mean Corpuscular Haemoglobin Concentration; MCV, Mean Corpuscular Volume.

F1 generation: Cohort 1A: 19 animals per sex per dose/Cohort 1B: 25 animals per sex per dose/Cohort 2A: 10 animals per sex per dose/Cohort 2B: 10 animals per sex per dose).⁵ No final conclusion is available, and it was not yet assessed by ECHA. In this study, rats were treated with octocrylene at oral (diet) doses (males/females, respectively) of 55/58, 153/163 and 534/550 mg/kg bw/day. A decreased number of implantation sites and consequently a lower number of pups delivered was observed in animals treated at the highest dose. No other effects on male and female fertility and reproductive parameters such as oestrus cycle, epididymal and testicular sperm parameters were observed in all groups tested. Regarding pups, no effects on sexual and neurodevelopmental were observed. Only low bodyweight was observed in pups at the highest dose tested but this was considered due to relatively high compound intake via initiating food uptake.

No data in humans are available.

Conclusion Based on available animal data, octocrylene does not induce developmental or teratogenic effects. In an extended one-generation reproductive toxicity study, only rats treated with the highest dose of octocrylene via oral route showed a decrease in the number of implantation sites and consequently a low number of pups. This very high dose of 550 mg/kg bw/day cannot be considered to be relevant to the dermal use of octocrylene as a cosmetic ingredient. Moreover, no other effects on male and female fertility and reproductive parameters such as oestrus cycle, epididymal and testicular sperm parameters were observed in all groups tested. Regarding pups, no effects on sexual and neurodevelopmental parameters were observed.

Endocrine disruption potential

According to commission regulation 2018/605 amending the Plant Protection Regulation No. 1107/2009, a substance shall be considered as having endocrine disrupting activity in humans if: it shows an adverse effect in an intact organism or its progeny leading to functional changes; it has an endocrine mode of action (anti-oestrogenic, androgenic or anti-androgenic activity, steroidogenesis alteration and thyroid and anti-thyroid hormone activity); the adverse effect is a consequence of the endocrine mode of action.

Several studies investigating the endocrine disruption potential are available since the assessment performed by the Danish Centre on Endocrine Disruptors⁴ (Table 3). In a recent *in vitro* study assessing the potential effects of chemical UV filters on human sperm, no effects on sperm acrosome reaction, sperm penetration, proportion of hyperactivated sperm cells or sperm viability were observed.¹⁵

The following studies are available on the ECHA website (unpublished studies as cited by ECHA, 2019⁵) in order to assess the potential of endocrine activity of octocrylene. A uterotrophic assay, which is a short-term screening test to evaluate the ability

Table 2 Summary of studies investigating reproductive toxicity of octocrylene

References	Species, strain and number of animals	Type of study	Route of exposure	Doses	Duration of exposure	Main findings
Odio et al., 1994 ¹²	Rabbit New Zealand White 5 animals per sex per dose	Subchronic repeated dose toxicity study	Dermal	0, 130, 264 and 534 mg/kg bw/day	5 days per week for 13 weeks (total of 65 applications)	No effects were reported on testicular and epididymal morphology as well as on sperm count and motility
	Rabbit New Zealand White 17 females per dose	Developmental toxicity study	Dermal	0, 65 and 267 mg/kg bw/day	Days 6 through 18 of gestation	No treatment related adverse effects
	Mouse CD-1 12 females per dose	Developmental toxicity study	Oral	0, 100, 300, and 1000 mg/kg bw/day	Days 8 through 12 of gestation	No treatment related adverse effects
Unpublished study as cited by ECHA, 2019 ⁵	Rat Wistar 25 females per dose	Developmental toxicity study	Oral	0, 100, 400 and 1000 mg/kg bw/day	Days 6 through 15 of gestation	Transient salivation in at 1000 mg/kg bw/day Increases in relative liver weights at 400 and 1000 mg/kg bw/day No treatment related adverse effects in pups
	Rat Wistar P: 28 animals per sex per dose (28 males and 27 females) F1 generation: Cohort 1A: 19 animals per sex per dose Cohort 1B: 25 animals per sex per dose Cohort 2A: 10 animals per sex per dose Cohort 2B: 10 animals per sex per dose	Extended one generation reproductive toxicity study	Oral	0, 750, 2100 and 7000 ppm in diet corresponding to 55, 153 and 534 mg/kg bw/day in males and 58, 163 and 550 mg/kg bw/day in females	<p><u>Males:</u> 10-week pre-mating period, during mating up to the day of sacrifice (approx. 13 weeks)</p> <p><u>Females:</u> P: 10-week pre-mating period, during mating, gestation and lactation up to the day of sacrifice after lactation day 21 F1 generation: from weaning up to sacrifice (approx. 10 weeks in Cohort 1A, approx. 13 weeks (males) and approx. 18 weeks (females) in Cohort 1B; approx. 8 weeks in cohort 2A) F2 generation: indirectly exposed until weaning</p>	Decreased number of implantation sites and consequently a lower number of pups at 550 mg/kg bw/day Decreases in bodyweight of pups at 550 mg/kg bw/day No effects on male fertility and male and female reproductive parameters such as oestrus cycle, epididymal and testicular sperm parameters at all doses No effects on sexual and neurodevelopmental parameters in pups

approx.: approximately; bw: bodyweight; P: parental.

Table 3 Summary of studies investigating endocrine disruption potential of octocrylene

References	Species, strain and number of animals or biological sample	Type of study	Route of exposure	Doses	Duration of exposure	Main findings
Rehfeld <i>et al.</i> , 2018 ¹⁵	Human sperm	<i>In vitro</i>	-	10 µmol/L	-	No effects on sperm acrosome reaction, sperm penetration, proportion of hyperactivated sperm cells or sperm viability
Unpublished study as cited by ECHA, 2019 ⁵	Rat Wistar 10 females per dose	Uterotrophic assay	Oral	0, 250 and 1000 mg/kg bw/day	3 consecutive days	Decreases in bodyweight gain at 1000 mg/kg bw/day No modification of uterus weight and histopathology
Unpublished study as cited by ECHA, 2019 ⁵	Rat Wistar 6 males per dose	Hershberger assay	Oral	0, 300 and 1000 mg/kg bw/day	10 consecutive days	Decreases in absolute and relative ventral prostate and muscle bulbocavernosus/levator ani weights at 1000 mg/kg bw/day No effects on hormone levels (testosterone, dihydrotestosterone and luteinizing hormone) and on histology of prostate, seminal vesicle and bulbo-urethral gland

bw: bodyweight.

of a chemical to elicit biological activities consistent with agonists or antagonists of natural oestrogens, was carried out in immature female rats (10 per dose) treated with octocrylene at doses of 250 and 1000 mg/kg bw/day via oral route. No effects on uterine weights or uterine histopathology were observed. Octocrylene has therefore no uterotrophic (oestrogenic) effects.

The second study was a Hershberger assay which is an *in vivo* short-term screening test to evaluate the ability of a chemical to elicit biological activities consistent with androgen agonists or antagonists. Castrate-peripubertal male rats (six per dose) received oral (gavage) octocrylene doses of 300 and 1000 mg/kg bw/day. Decreases in absolute and relative ventral prostate and muscle bulbocavernosus/levator ani weights were observed at the highest dose but these results were not considered relevant and can be explained by an enzyme induction. In addition, no octocrylene-related effects in clinical examinations, on hormone levels (testosterone, dihydrotestosterone and luteinizing hormone) and the histology of the prostate, seminal vesicle and the bulbo-urethral gland were reported. Therefore, it was concluded that octocrylene showed neither androgen nor antiandrogen effects.

Conclusion

Octocrylene did not induce any adverse effects on human sperm *in vitro*. In addition, in animal studies, neither oestrogenic nor androgen/antiandrogen effects were reported. This was confirmed in an extended one-generation reproductive toxicity study conducted in rats (see above, section Reproductive effects in animals) that did not show any significant effects of octocrylene on female and male fertility and reproductive parameters.

Therefore, based on the current available data, mainly short-term animal data, octocrylene does not show any endocrine disruption potential regarding reproductive and developmental parameters.

Cutaneous effects

Skin irritation

Undiluted octocrylene did not induce dermal or eye irritation in animal studies conducted in rabbits.⁵ In humans, irritant reactions with octocrylene are rare¹⁵; in a multicentre study conducted in 30 centres across 12 European countries, only seven irritant reactions were observed in six of 1031 patients (0.6%) patch-tested using 10% octocrylene in petrolatum for suspected photoallergic contact dermatitis.¹⁶

Sensitization and photosensitization

In a sensitization animal study conducted in Guinea pigs, no sensitization reactions following skin exposure to octocrylene was observed.⁵

In humans, two main types of sensitization reactions are reported in the scientific literature: contact allergy and photo-contact allergy/photoallergy (after UV radiation).

Regarding contact allergy attributed to octocrylene, some case reports and positive patch test studies in both adults and children can be found in the scientific literature.^{16–22}

In particular, a recent study conducted in Germany showed that among 2577 patients who were patch-tested with octocrylene at 10% in petrolatum, only two weak positive reactions were reported – i.e. 0.08%.²² The authors concluded that contact allergy attributed to octocrylene was ‘exceedingly rare’ although it is used in many cosmetic products (in Germany, from 2006 to 2009, about 60% of 462 cosmetic products contained octocrylene).²² The same conclusion has been made in a European multicentre photopatch test study where contact allergy attributed to octocrylene was reported in only 0.7% of 1031 patients patch-tested with 10% octocrylene in petrolatum for suspected photoallergic contact dermatitis.¹⁶ As shown in a study including both adult and paediatric patients patch-tested because of adverse skin reactions from sunscreen products, contact allergy to octocrylene appears to be more frequent and severe in children than in adults,²³ probably because of the immaturity of the skin epidermal barrier and the prevalence of atopic dermatitis in young children.²⁴ Based on these data, it can be concluded that contact allergy attributed to octocrylene is rare in the general population although this UV filter is commonly used in cosmetic products.

Scientific literature also includes several case reports, positive photopatch test studies and reviews on photoallergic reactions attributed to octocrylene.^{16,23–34}

Contrary to contact allergy, photoallergic contact dermatitis to octocrylene is much more frequent in adults than in children, in whom very few cases have been reported.²³ For instance, in the European photopatch test cited above, photocontact allergy to octocrylene was reported in 4% of 1031 adult patients patch-tested for suspected photoallergic contact dermatitis.¹⁶ The occurrence of photoallergy to octocrylene is strongly related to a previous photoallergy to topical ketoprofen.^{27,34} As a matter of fact, patients with photoallergic contact dermatitis caused by sunscreens and positive photopatch tests to octocrylene are mainly reported in France, Belgium, Italy and Spain,²⁷ countries in which topical ketoprofen is popular. This was confirmed in a recent study conducted in Italy where concomitant photocontact allergy to ketoprofen was reported in 61.5% of 156 patients.³¹ Many authors indicated that photocontact allergy cases reported with octocrylene are due to co-reactivity – i.e. are the result in the majority of cases to a previous photocontact allergy to ketoprofen.^{22,27,34} Although the mechanism for the co-reactivity of octocrylene and ketoprofen is not yet elucidated, de Groot *et al.*²⁷ ventured several hypotheses: (i) the benzophenone moiety in the chemical structure of ketoprofen may be responsible for photoallergy attributed to ketoprofen. Although the benzophenone moiety is not part of the octocrylene structure, aminolysis and hydrolysis of octocrylene in the skin may result in the formation of benzophenone which then can lead to cross-reactivity.

However, at present, it cannot be definitively stated whether or not the reactions are attributable to cross-sensitization; (ii) some people may be hyper-photosusceptible to substances that are non-relevant allergens; (iii) co-reactivity – i.e. concomitant sensitization or prior or subsequent *de novo* photosensitization – may be involved in place of cross-reaction. The recent study of Romita *et al.*³¹ showed a decreasing trend in photocontact allergy attributed to octocrylene from 2014 to 2017, which could not be explained by a restricted use of topical ketoprofen at a European level, as allergy to ketoprofen is still high in their study. Aerts *et al.*²⁵ hypothesized that the presence of sensitizing impurities in some commercial batches of octocrylene could be the real allergen. The authors also suggested that recent commercial patch tests, more purified than before, might produce false negative reactions and underestimate the prevalence of photoallergy cases.²⁵

Conclusion The sensitizing potential of octocrylene has been extensively reviewed in the scientific literature and contact allergy to octocrylene is very rare in the general population. Photocontact allergy cases to octocrylene have been reported but are rare in the general population, and previous photosensitization to topical ketoprofen is apparently a prerequisite. Topical ketoprofen use is now discouraged by dermatologists and photocontact allergy cases to octocrylene hopefully will be less of a problem in the future.

Overall conclusion

Based on the current available safety data, octocrylene used as a UV filter in cosmetic products at a concentration of 10% can be considered as safe. There was no evidence of any endocrine disruption potential from experimental studies which demonstrated no adverse effects on reproductive (e.g. oestrus cycle, epididymal and testicular sperm parameters) and developmental parameters. Effects on thyroid reported in repeated toxicity studies conducted in rats at very high doses are species-specific and not relevant considering the doses at which octocrylene is used in human. The frequency of contact allergy and photocontact allergy in non-sensitized subjects is very rare with regards to its wide use in cosmetic products, particularly in sunscreen products.

However, it should be pointed out that most data dealing with the safety of octocrylene – except for cutaneous effects – are *in vitro* or animal data. The clinical significance of systemic availability and the metabolism of octocrylene in humans also need further investigation.

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References

- Manová E, von Goetz N, Hungerbühler K. Ultraviolet filter contact and photocontact allergy: consumer exposure and risk assessment for octocrylene from personal care products and sunscreens. *Br J Dermatol* 2014; **171**: 1368–1374.
- Bury D, Belov VN, Qi Y *et al.* Determination of urinary metabolites of the emerging UV filter octocrylene by online-SPE-LC-MS/MS. *Anal Chem* 2018; **90**: 944–951.
- Danish Environmental Protection Agency. Survey and health assessment of UV filters. Danish Environmental Protection Agency, 2015.
- Axelstad M, Hass U, Kinnberg K, Bjerregaard P. Assessment of the endocrine disrupting potential of 23 UV-filters (j.no. MST-656-00150). Danish Center on Endocrine Disruptors, 2013.
- ECHA. Octocrylene - Registration Dossier - ECHA, 2019.
- Freitas JV, Praça FSG, Bentley MVLB, Gaspar LR. Trans-resveratrol and beta-carotene from sunscreens penetrate viable skin layers and reduce cutaneous penetration of UV-filters. *Int J Pharm* 2015; **484**: 131–137.
- Hayden CGJ, Cross SE, Anderson C, Saunders NA, Roberts MS. Sunscreen penetration of human skin and related keratinocyte toxicity after topical application. *Skin Pharmacol Physiol* 2005; **18**: 170–174.
- Potard G, Laugel C, Baillet A, Schaefer H, Marty JP. Quantitative HPLC analysis of sunscreens and caffeine during *in vitro* percutaneous penetration studies. *Int J Pharm* 1999; **189**: 249–260.
- Potard G, Laugel C, Schaefer H, Marty JP. The stripping technique: *in vitro* absorption and penetration of five UV filters on excised fresh human skin. *Skin Pharmacol Appl Skin Physiol* 2000; **13**: 336–344.
- Schlumpf M, Kypke K, Wittassek M *et al.* Exposure patterns of UV filters, fragrances, parabens, phthalates, organochlor pesticides, PBDEs, and PCBs in human milk: correlation of UV filters with use of cosmetics. *Chemosphere* 2010; **81**: 1171–1183.
- Matta MK, Zusterzeel R, Pilli NR *et al.* Effect of sunscreen application under maximal use conditions on plasma concentration of sunscreen active ingredients: a randomized clinical trial. *JAMA* 2019; **321**: 2082–2091.
- Odio M, Azri-Meehan S, Robinson S, Kraus A. Evaluation of subchronic (13 week), reproductive, and *in vitro* genetic toxicity potential of 2-ethylhexyl-2-cyano-3,3-diphenyl acrylate (Octocrylene). *Fundam Appl Toxicol* 1994; **22**: 355–368.
- Capen CC. Mechanistic data and risk assessment of selected toxic end points of the thyroid gland. *Toxicol Pathol* 1997; **25**: 39–48.
- Choksi NY, Jahnke GD, St Hilaire C, Shelby M. Role of thyroid hormones in human and laboratory animal reproductive health. *Birth Defects Res B Dev Reprod Toxicol* 2003; **68**: 479–491.
- Rehfeld A, Egeberg DL, Almstrup K *et al.* EDC IMPACT: chemical UV filters can affect human sperm function in a progesterone-like manner. *Endocr Connect* 2018; **7**: 16–25.
- EMCPTSA. European multicentre photopatch test study. *Br J Dermatol* 2012; **166**: 1002–1009.
- Agustí-Mejías A, Messeguer F, de la Cuadra J, Martorell-Aragonés A. Contact allergy to octocrylene in children: a report of 2 cases. *Actas Dermosifiliogr* 2014; **105**: 92–93.
- Boonchai W, Sathaworawong A, Wongpraparut C, Wanitphakdeedecha R. The sensitization potential of sunscreen after ablative fractional skin resurfacing using modified human repeated insult patch test. *J Dermatolog Treat* 2015; **26**: 485–488.
- Farquharson AA, Stoopler ET, Houston AM, Brown RS. Erythema multiforme major secondary to a cosmetic facial cream: first case report. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2016; **121**: e10–e15.
- Haisma MS, Schuttelaar ML. Contact urticaria caused by the ultraviolet absorber octocrylene in sunscreens. *Contact Derm* 2017; **77**: 254–256.
- Madan V, Beck MH. Contact allergy to octocrylene in sunscreen with recurrence from passive transfer of a cosmetic. *Contact Derm* 2005; **53**: 241–242.
- Uter W, Lessmann H, Geier J, IVDK. Is octocrylene a frequent contact allergen? *Contact Derm* 2017; **77**: 127–128.
- Avenel-Audran M, Dutartre H, Goossens A *et al.* Octocrylene, an emerging photoallergen. *Arch Dermatol* 2010; **146**: 753–757.
- Gilaberte Y, Carrascosa JM. Sun protection in children: realities and challenges. *Actas Dermosifiliogr (English Edition)* 2014; **105**: 253–262.
- Aerts O, Goossens A, Bervoets A, Lambert J. Almost missed it! Photo-contact allergy to octocrylene in a ketoprofen-sensitized subject. *Dermatitis* 2016; **27**: 33–34.
- Bennàssar A, Grimalt R, Romaguera C, Vilaplana J. Two cases of photo-contact allergy to the new sun filter octocrylene. *Dermatol Online J* 2009; **15**: 14.
- de Groot AC, Roberts DW. Contact and photocontact allergy to octocrylene: a review. *Contact Derm* 2014; **70**: 193–204.
- Heurung AR, Raju SI, Warshaw EM. Adverse reactions to sunscreen agents: epidemiology, responsible irritants and allergens, clinical characteristics, and management. *Dermatitis* 2014; **25**: 289–326.
- Karlsson I, Vanden Broecke K, Mårtensson J, Goossens A, Börje A. Clinical and experimental studies of octocrylene's allergenic potency. *Contact Derm* 2011; **64**: 343–352.
- Martina E, Rosa L, Postacchini V *et al.* Photoprotection and photodermatitis: a case. *Contact Derm* 2017; **76**: 54–55.
- Romita P, Foti C, Hansel K, Stingeni L. Photo-contact allergy to octocrylene: a decreasing trend? *Contact Derm* 2018; **78**: 224–225.
- Saraswat A. Contact allergy to topical corticosteroids and sunscreens. *Indian J Dermatol Venereol Leprol* 2012; **78**: 552–559.
- Travassos AR, Claes L, Boey L, Drieghe J, Goossens A. Non-fragrance allergens in specific cosmetic products. *Contact Derm* 2011; **65**: 276–285.
- Loh TY, Cohen PR. Ketoprofen-induced photoallergic dermatitis. *Indian J Med Res* 2016; **144**: 803–806.