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REVIEW ARTICLE

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Comprehensive review of octocrylene toxicology data and human exposure assessment for personal care products

Kimberly G. Norman[a], Lewis E. Kaufman[b], Peter Griem[c], Carl D'Ruiz[d], Linda Loretz[a], Alexandra Kowcz[a], Samuel M. Cohen[e], Anthony R. Scialli[f], Alan R. Boobis[g], David Jacobson-Kram[h], Rita Schoeny[i], Thomas J. Rosol[j], Gary M. Williams[k], Norbert E. Kaminski[l], F. Peter Guengerich[m] and J. F. Nash[n]

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ABSTRACT

A comprehensive review was conducted of existing toxicity and consumer exposure data for the ultraviolet (UV) filter octocrylene (2-ethylhexyl-2-cyano-3,3-diphenylacrylate) as currently used in over-the-counter sunscreen formulations. Octocrylene has a long history of safe use, and there are sufficient *in vitro* studies, *in vivo* toxicity studies in animal models, and clinical data to characterize octocrylene's pharmacokinetics, pharmacodynamics, and potential toxicologic properties. Although no harmonized dermal absorption value was available, *in vitro* studies using human skin samples revealed very low percutaneous absorption (0.33% of the applied dose). There are no specific data on the distribution of octocrylene; however, there is some information on background levels of octocrylene and its metabolism, and it has limited presence in plasma and urine from human biomonitoring studies. Six tentative metabolites of octocrylene have been identified, although metabolite-specific toxicity profiles were not available. Octocrylene generally did not cause eye or skin irritation, skin sensitization, or phototoxicity, but dermal sensitization has been reported in some clinical case studies. Octocrylene is not acutely toxic. The no-observed-adverse-effect level (NOAEL) from a 90-day rat dietary toxicity study was 175 mg/kg/day, based on liver, thyroid, and pituitary effects at higher dose levels that produced hepatic enzyme induction. The NOAEL for parental systemic, reproductive, and developmental toxicity from an extended one-generation reproductive toxicity study in rats was 153/163 mg/kg/day (males/females). There was no evidence of octocrylene effects on neurodevelopment, immune tissues, or androgenic, estrogenic, or thyroid endpoints. Although there are no formal 2-year carcinogenicity studies for octocrylene, a 90-day subchronic dietary toxicity study in rats did not show an increase in hyperplasia of any tissue or evidence of cytotoxicity. Furthermore, octocrylene has not triggered any indications for genotoxicity either *in vitro* or *in vivo*. Together, these data indicate that carcinogenicity in humans is unlikely. In a mouse photocarcinogenicity study, octocrylene significantly reduced tumor number and tumor volume resulting from exposure to solar-simulated UV radiation. Based on the most health-protective rat NOAEL (153 mg/kg/day, for reproductive effects and general toxicity) and conservative assumptions for estimating the systemic exposure dose from the application of sunscreen products, margins of safety for octocrylene were greater than 100. Therefore, the available data show that octocrylene poses no human health risks when used in sunscreen products at concentrations up to 10%, which is consistent with existing global regulatory safety acceptance and approval of the ingredient.

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Octocrylene; 6197-30-4; toxicology; exposure assessment; sunscreen; UV filter; personal care products; cosmetics

Abbreviations: 5OH–OC: 2-ethyl-5-hydroxyhexyl 2-cyano-3,3-diphenyl acrylate; ADME: Absorption, distribution, metabolism, and excretion; AR: Androgen receptor; ATSDR: Agency for Toxic Substances and Disease Registry; AUC: Area under the curve; BROD: benzyloxyresorufin-O-debenzylase; CAR: Constitutive androstane receptor; CDAA: 2-cyano-3,3-diphenylacrylic acid; C_{max}: Maximum (peak) concentration; CYP: Cytochrome P450; DOCCA: 2-(carboxymethyl)butyl 2-cyano-3,3-diphenyl acrylate (dinor OC carboxylic acid); DPCA: 3,3-diphenyl-cyanoacrylate; E2: 17β-estradiol; EC: European Commission; EC_{50}: Half maximal effect concentration; ECHA: European Chemicals Agency; EOGRTS: Extended one-generation reproductive toxicity study; EPA: U.S. Environmental Protection Agency; ER: Estrogen receptor; EROD: ethoxyresorufin-O-deethylase; F_1: First filial; F_2: Second filial; FAO: Joint Food and Agriculture Organization; FDA: U.S. Food and Drug Administration; FOB: Functional observational battery; GLP:

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Good laboratory practice; GSH: Glutathione; hAR: Human androgen receptor; hERα: Human estrogen receptor α; hERβ: Human estrogen receptor β; HOBI-GT: HOBI-UDP-glucuronosyltransferase; IARC: International Agency for Research on Cancer; IC_{50}: Half maximal inhibitory concentration; IPCS: International Program on Chemical Safety; IRIS: EPA Integrated Risk Information System; iTTC: Internal threshold of toxicological concern; IVPT: *In vitro* permeation test; JECFA: FAO/WHO Expert Committee on Food Additives; LD_{50}: Median lethal dose; MoS: Margin of safety; MUF-GT: MUF-UDP-glucuronosyltransferase; MUsT: Maximal usage trial; NDA: New Drug Application; NOAEL: No-observed-adverse-effect level; OECD: Organization for Economic Co-operation and Development; OEHHA: California Office of Environmental Health Hazard Assessment; OPPTS: EPA Office of Prevention, Pesticides, and Toxic Substances; OTC: Over-the-counter; P: Parental; PB: Phenobarbital; PCB: Aroclor 1254; PK: Pharmacokinetic; PND: Postnatal day; PROD: pentoxyresorufin-O-dependentylase; RA: Relative activity; REC_{10}: Concentration showing 10% of the activity of E2; SCC: Scientific Committee on Cosmetology; SCCP: Scientific Committee on Consumer Products; SCCNFP: Scientific Committee on Cosmetic Products and Non-food Products; SCCS: Scientific Committee on Consumer Safety; SIDS: OECD Screening Information DataSet; SD: Standard deviation; SED: Systemic exposure dose; $t_{1/2}$: plasma half-life; T_3: Triiodothyronine; T_4: Thyroxine; TG: Test guideline; t_{max}: Time of maximum plasma concentration; TSH: Thyroid-stimulating hormone; TTC: Threshold of toxicological concern; UDP: Uridine 5′-diphospho; UGT: Uridine diphospho glucuronosyltransferase; U.S.: United States of America; UV: Ultraviolet; UVA: Ultraviolet A; UVB: Ultraviolet B; V_d: Volume of distribution; WHO: World Health Organization

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Introduction

Octocrylene (2-ethylhexyl-2-cyano-3,3-diphenylacrylate; CAS no. 6197-30-4; Figure 1) is a lipid-soluble acrylate ester derivative (NCBI 2023) and an effective liquid ultraviolet (UV) filter (see Table 1 for identifiers and properties). The conjugated acrylate portion absorbs UVB and short-wave UVA wavelengths in the range of 290 to 360 nm, which protects the skin from direct DNA damage. The ethylhexanol portion is a fatty alcohol, which functions as an emollient due to its hydrophobicity. Octocrylene is used in commercially available sunscreen products as a UV filter at concentrations up to 10% in combination with other UV filters (Drugbank 2022). Such products help protect consumers from UV-induced skin damage, including sunburn, premature skin aging, aging skin disorders, lowered immunity against infection (Poon et al. 2003), DNA damage, and skin cancer. In addition, octocrylene is known to stabilize the UV filter avobenzone in combination sunscreen formulations (Gabros et al. 2022).

Octocrylene has a long history of safe use in sunscreen products in the United States (U.S.) and globally. Since publication of the U.S. Food and Drug Administration (FDA) 1999 Final Monograph, octocrylene has been classified as a category I UV filter (USFDA 1999); however, it is currently under review following passage of over-the-counter (OTC) reform legislation in 2020 (USFDA 2019). The allowable maximum concentration of octocrylene in sunscreen products is 10% globally (EP 2009; Jansen et al. 2013; TGA 2021). This permitted level is based on review of octocrylene safety, efficacy, and postmarket surveillance data by numerous regulatory bodies and safety experts around the world. Currently, none of the global regulatory bodies that have approved octocrylene for use in sunscreen products have reported any associated health or safety concerns.

From a new drug approval perspective, it is notable that from 2006 to 2009, the FDA reviewed and approved four OTC New Drug Applications (NDAs) containing octocrylene at

a concentration of 10% (USFDA 2022). As part of the approval process, the FDA reviewed the safety of octocrylene (together with other active sunscreen ingredients) at a level of 10% in each NDA formulation and various dosage forms. Given the rigor of the NDA process, it is inferred that at this time octocrylene was considered safe for use in these sunscreen products. Table 2 provides a summary of the FDA-approved OTC sunscreen NDA products that contain octocrylene.

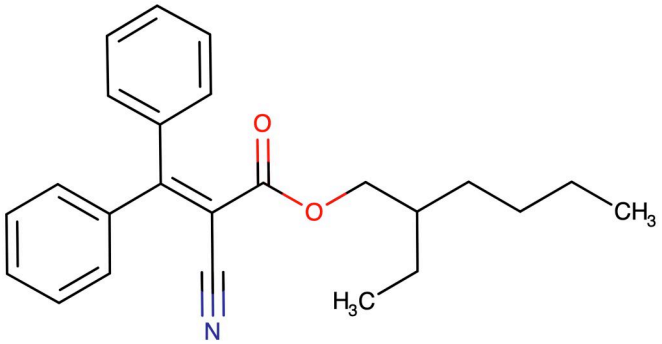

Figure 1. Chemical structure of octocrylene (2-ethylhexyl-2-cyano-3,3-diphenylacrylate) (Drugbank 2022).

The purpose of this assessment was to: (1) develop a comprehensive summary of the pharmacokinetic (PK) and toxicologic data that exist for octocrylene, (2) employ conservative assumptions for estimating the systemic exposure dose (SED) from the application of sunscreen products, and (3) provide an estimate of the derived margin of safety (MoS; which is the ratio of no-observed-adverse-effect level [NOAEL] to SED) for octocrylene when used in sunscreen products at concentrations up to 10%.

Table 1. Octocrylene identifiers and physicochemical properties.

Identifier/property	Attribute
INCI	Octocrylene
IUPAC	2-Ethylhexyl 2-cyano-3,3-diphenylprop-2-enoate
CAS registry	6197-30-4 (active) 149984-83-8; 80135-31-5; 194304-33-1 (deprecated)
EINECS (EC)	228-250-8
Synonyms	Octocrilene 2-Ethylhexyl 2-cyano-3,3-diphenylacrylate 2-Ethylhexyl -2-cyano-3,3-diphenyl acrylate 2-Ethylhexyl 2-cyano-3,3-diphenyl-2-propenoate 2-Ethylhexyl 2-cyano-3,3-diphenylprop-2-enoate 2-Cyano-3,3-diphenylacrylic acid 2-ethylhexyl ester 2-Propenoic acid, 2-cyano-3,3-diphenyl-, 2-ethylhexyl ester
Trade names	Parsol® 340 Neo Heliopan® 303 Eusolex® OCR UVINUL® N 539 T
Molecular formula	$C_{24}H_{27}NO_2$
Molecular weight (g/mol)	361.482
Physical description	Yellow, clear, viscous liquid
Vapor pressure (mmHg) at 25 °C	3.15 x 10^{-9} (experimental)
Melting point (°C)	−10 (experimental)
Boiling point (°C)	>300 (experimental) (substance decomposes before boiling)
Solubility in water (µg/L) at 20 °C ± 0.5 °C	Range: 9–153 (experimental)
Octanol/water partition (log K_{ow}) at 23 °C	6.1 (experimental)
Henry's law constant (H_{cc}) (unitless)	1.01 x 10^{-6} (predicted)
Henry's law constant (H_{pc}) (atm-m^3/mol)	2.46 x 10^{-8} (predicted)
Density (g/cm^3) at 25 °C	1.05 (experimental)

CAS: Chemical Abstracts Service; EC: European Commission; EINECS: European Inventory of Existing Commercial Chemical Substances; INCI: International Nomenclature Cosmetic Ingredient; IUPAC: International Union of Pure and Applied Chemistry.
Sources: (ECHA 2023; NCBI 2023; USEPA 2023).

Table 2. New Drug applications containing octocrylene (10%) approved by U.S. FDA.

Product name (applicant holder)	NDA number	Approval date	Active ingredients and levels approved	Dosage form (route of administration)	Marketing status
ANTHELIOS 20 (L'Oréal USA Products Inc)	N021471	5 Oct 2006	**Octocrylene (10%)** Avobenzone (2%) Ecamsule (2%) Titanium dioxide (2%)	Cream (topical)	OTC
ANTHELIOS 40 (L'Oréal USA Products Inc)	N022009	2 approvals: 31 Mar 2008, 29 Oct 2009	**Octocrylene (10%)** Avobenzone (2%) Ecamsule (3%) Titanium dioxide (5%)	Cream (topical)	OTC
ANTHELIOS SX (L'Oréal USA Products Inc)	N021502	21 Jul 2006	**Octocrylene (10%)** Avobenzone (2%) Ecamsule (2%)	Cream (topical)	OTC
CAPITAL SOLEIL 15 (L'Oréal USA Products Inc)	N021501	2 Oct 2006	**Octocrylene (10%)** Avobenzone (2%) Ecamsule (3%)	Cream (topical)	OTC

NDA: New Drug Application; OTC: over-the-counter.

Materials and methods

A literature search was conducted to identify clinical and nonclinical studies that evaluated octocrylene toxicity. Studies were primarily identified through expert organizational and state, federal, and international regulatory electronic databases to identify substance-specific information and data, and these results were supplemented with additional published literature retrieved from the PubMed database. Relevant unpublished toxicity information performed by a manufacturer, mostly obtained from the European Chemicals Agency (ECHA) database, was included. Additional literature was identified and manually obtained through references cited by published papers, reviews, and regulatory documents captured in the searches.

The following electronic databases were used to identify substance-specific information and data: the ECHA database, PubChem, the U.S. Environmental Protection Agency (EPA) CompTox Dashboard, the EPA Integrated Risk Information System (IRIS), ChemIDPlus, the Organization for Economic Co-operation and Development (OECD) eCHEM Portal, OECD Screening Information DataSet (SIDS), the International Program on Chemical Safety (IPCS) INCHEM catalog, the FDA databases, GESTIS Substance database, the Agency for Toxic Substances and Disease Registry (ATSDR), the International Agency for Research on Cancer (IARC) publications, the California Office of Environmental Health Hazard Assessment (OEHHA) chemical database, the database that provides chemical evaluations from the Joint Food and Agriculture Organization (FAO)/World Health Organization (WHO) Expert Committee on Food Additives (JECFA), and opinions from the European Commission (EC) scientific committees, especially the Scientific Committee on Consumer Safety (SCCS) and its predecessors the Scientific Committee on Consumer Products (SCCP), the Scientific Committee on Cosmetic Products and Non-food Products (SCCNFP), and the Scientific Committee on Cosmetology (SCC).

The information and data obtained from databases was supplemented with additional published literature retrieved from the PubMed database from its inception date through 31 December 2023, using the following search construct:

> (octocrylene OR octocrilene OR 2-ethylhexyl 2-cyano-3,3-diphenylacrylate OR Parsol 340 OR 6197-30-4 OR 228-250-8 OR 2-ethylhexyl 2-cyano-3,3-diphenyl-2-propenoate) AND (human OR clinical OR nonclinical OR animal) AND (toxic* OR abnormal OR adverse OR develop* OR repro* OR endo* OR carc* OR geno* OR metabol* OR pharmaco* OR immuno*)

This search generated 186 papers, from which titles and abstracts were screened by two independent reviewers to identify potentially relevant articles. Articles that examined octocrylene and its physicochemical properties, PK, pharmacodynamics, and/or toxicity were included for the full-article review.

Many of the studies described herein were compliant with good laboratory practice (GLP) regulations and/or a particular testing guideline (TG) provided by the OECD, the European Union (EU), the EPA Office of Prevention, Pesticides, and Toxic Substances (OPPTS), and/or the FDA. This information, along with a specific method or OECD TG number, is acknowledged when applicable for studies described in this octocrylene profile.

Results

Pharmacokinetics

The following sections discuss the absorption, distribution, metabolism, and excretion (ADME) of octocrylene based on its physicochemical properties and from *in vitro* and preclinical *in vivo* PK studies. Available human clinical and biomonitoring studies on octocrylene were also reviewed; some evaluated background levels of octocrylene and occasionally of its metabolites in plasma and/or urine, whereas others monitored analytes after intentional oral or dermal exposure to octocrylene.

Absorption

Octocrylene is lipophilic, has low water solubility, a high octanol-water partition coefficient (Table 1), and therefore is presumed to be absorbed in the gastrointestinal tract by micellular solubilization (ECHA 2023). Absorption of octocrylene by the oral route is supported by systemic effects observed in oral repeated-dose studies (Table 4) and more recent human PK studies (see Human studies). Although no *in vivo* studies assessing the inhalation PK of octocrylene are available, it is presumed that exposure to this compound by this route is low due to its low vapor pressure, and that inhalation exposure to pump or propellant sprays is lower than dermal exposure (Table 1). According to the ECHA database, the dermal absorption of octocrylene is low, with a maximum of 0.2%, based on weight-of-evidence assessment of all available *in vitro* and *in vivo* data, as no key study was available (ECHA 2023). Low dermal absorption of octocrylene is supported by the lack of systemic effects observed in studies with dermally exposed animals (Table 4 and Table 9) and recent work that assessed the predictive utility of *in vitro* permeation test (IVPT) methods by comparing *in vitro* absorption (skin permeation and retention) with *in vivo* absorption (area under the curve [AUC] and skin retention) for several commercial sunscreen formulations (Yang et al. 2022). Although octocrylene has low skin permeation potential, this work found that a small amount of octocrylene in commercially available sunscreens was absorbed following a single-dose *in vitro* application to dermatomed human cadaver skin samples (Yang et al. 2022). Furthermore, systemic availability of octocrylene after dermal application is apparent from its presence in blood plasma as reported by Hiller et al. (2019) and Matta et al. (2019, 2020).

According to a 1993 *in vitro* percutaneous absorption study report, a formulation containing 10% octocrylene applied at 5 mg/cm^2 for a 16-h period to 12 samples of dermatomed human skin resulted in an average penetration through the skin of 0.33 $\mu g/cm^2$ (0.08% of the applied dose) for octocrylene (SCCS 2021; ECHA 2023). Mean (± standard deviation [SD]) recovered octocrylene was $0.17 \pm 0.24\ \mu g/cm^2$ in the receptor medium and $0.16 \pm 0.07\ \mu g/cm^2$ in the dermis; it was unclear from the ECHA entry whether octocrylene was

detected in the epidermis (ECHA 2023). The mean (+ 1 SD) of 0.64 μg/cm^2 (receptor medium plus dermis) would correspond to an absorption of approximately 0.14% of the applied dose.

In a GLP-compliant OECD TG 428 study, 10% w/w octocrylene (97.4% purity) was applied at 3 mg/cm^2 to dermatomed human skin preparations for a 24-h period (SCCS 2021). Split-thickness human skin samples from six female donors aged 22 to 63 years were mounted onto modified Franz cells. Following exposure, the upper layers of the stratum corneum were removed by tape stripping, and the epidermis, dermis, and receptor fluid were analyzed for the presence of octocrylene. Mean (± SD) recovered octocrylene by tape stripping was 2.06 ± 0.94 μg/cm^2 (0.69 ± 0.31% of the applied dose) from the stratum corneum and 0.45 ± 0.52 μg/cm^2 (0.15 ± 0.18% of the applied dose) in the epidermis and dermis. No detectable levels of octocrylene were found in the receptor fluid and/or receptor chamber wash. Therefore, the maximum mean (± SD) octocrylene absorbed (epidermis, dermis, and receptor fluid) was estimated to be 0.45 ± 0.52 μg/cm^2, corresponding to 0.15 ± 0.18% of the applied dose. This upper bound absorption value of 0.33% (mean + 1 SD) was used for risk characterization purposes. This study was found to be of superior scientific quality compared to other data. The fraction of absorbed dose is used in this assessment over the quantitative skin content because the applied amount of formulation *in vitro* is significantly higher than the target amount for consumers.

In a 1998 *in vitro* study report, a cosmetic formulation containing 8% octocrylene was applied at 3 mg/cm^2 for a 16-h period to dermatomed human skin (SCCS 2021; ECHA 2023). Although no detectable octocrylene was found in the receptor medium, 0.125% of the applied dose was found in each of the epidermis (mean ± SD of 0.3 ± 0.7 μg/cm^2) and dermis (mean ± SD of 0.3 ± 1.0 μg/cm^2), as well as 4.3% in the stratum corneum (SCCS 2021; ECHA 2023). Based on the amount detected in the epidermis and dermis, it was concluded that approximately 0.25% of the applied dermal dose of octocrylene was bioavailable (SCCS 2021; ECHA 2023).

Finally, recent studies have explored predictive modeling to describe the absorption of dermally applied octocrylene. One effort that developed a physiologically-based kinetic model successfully simulated the plasma concentration profiles of clinical PK data for octocrylene (Matta et al. 2020; Li et al. 2023). The model was built using *in vitro* and *in silico* data in a bottom-up approach and then was validated against the human dermal PK data (Li et al. 2023f). Another effort resulted in an integrated mechanistic dermal absorption model designed to simulate steady-state plasma concentrations of octocrylene and other UV filters. This model was trained using IVPT data integrated with previously published IVPT and clinical PK data *via* a Bayesian Markov chain Monte Carlo method and then validated using real-world *in vivo* datasets (Hamadeh et al. 2024).

Distribution

No specific information was available on the distribution of octocrylene upon absorption, except for the data discussed in the Human studies section below.

Metabolism

According to the ECHA database, pathways for the hepatic metabolism of octocrylene have been proposed (ECHA 2023). It has been suggested that octocrylene may undergo the following metabolism: hydrolysis of the ester bond by esterases to form 2-cyano-3,3-diphenyl-2-propenoic acid and 2-ethylhexanol, oxidation of both hydrolysis products by P450-dependent monooxygenases, P450-dependent decarboxylation of 2-cyano-3,3-diphenyl-2-propenoic acid, and glucurono-/sulfo- or glutathione (GSH)–conjugations of metabolic oxidation products (ECHA 2023). Recent studies have identified plasma and urinary metabolites in humans (see Human studies section below).

In a recent study, the oxidative metabolism of octocrylene was investigated *in vitro* (Guesmi et al. 2020). Octocrylene was incubated with human and rat liver microsomes in the presence of reduced β-nicotinamide adenine dinucleotide phosphate and GSH. The authors noted that the ester bond of octocrylene could be hydrolyzed to form 3,3-diphenylcyanoacrylate (DPCA) and 2-ethylhexanol. Peaks for DPCA, a single oxidation metabolite (octocrylene + O), and a GSH adduct of another (phenyl-) oxidation metabolite were detected. There were no qualitative differences between rat and human liver microsomes in the metabolism of octocrylene. Based on the findings, the authors proposed that the site of oxidation of octocrylene was the alkyl group, which is in agreement with the single hydroxylated metabolite of octocrylene, 5OH-octocrylene, previously reported in a pilot biomonitoring study (Bury et al. 2019) (see Human studies below).

Excretion

It is presumed that following metabolism of octocrylene into polar, low-molecular-weight metabolites, that these are excreted *via* the urine. At least one of these metabolites contains a chromophore structure, based on the observation of dark yellow discoloration of the urine from some animals in a subchronic repeated-dose toxicity study after consumption of a diet containing octocrylene at a high concentration (ECHA 2023) (see Repeated-dose toxicity). Recent literature has confirmed this pathway of elimination for octocrylene, with the detection of novel urinary metabolites in humans at background levels of exposure to the sunscreen (Bury et al. 2018) and after intentional oral exposure to octocrylene (Bury et al. 2019) (see Human studies).

Human studies

There are several human studies on octocrylene available in the literature that either evaluated background levels of octocrylene, and occasionally metabolites, in plasma and/or urine or monitored analytes after intentional oral or dermal exposure to octocrylene. In those studies that evaluated the PK following intentional exposure, various PK parameters of octocrylene and/or its metabolites were characterized.

Human PK parameters, including serum concentration, AUC plasma concentration-time curve, time of maximum plasma concentration (t_{max}), and plasma half-life ($t_{1/2}$), were

reported following dermal application of various sunscreen formulations containing varying concentrations of octocrylene (Matta et al. 2019, 2020). For example, Matta et al. (2019) randomized 24 individuals equally to application of one of four sunscreen products (two sprays, a lotion, and a cream). Sunscreen was applied to 75% of the body surface using 2 mg/cm^2 of product 4 times per day for 4 days. A total of 30 blood samples were collected over 7 days from each individual. Geometric mean maximum concentrations (C_{max}) of octocrylene (and t_{max}) were 2.9 ng/mL (74.5 h) for spray #1; 7.8 ng/mL (65 h) for spray #2; 5.7 ng/mL (54.5 h) for the lotion; and 5.7 ng/mL (72 h) for the cream. The terminal plasma elimination $t_{1/2}$ for octocrylene was 84.4, 43.3, 45.2, and 45.9 h, respectively, for the same formulations, which is likely a reflection of slow dermal absorption.

In another maximal usage trial (MUsT), individuals were randomized to application of one of four different sunscreen products including lotion ($n = 12$), aerosol spray ($n = 12$), nonaerosol spray ($n = 12$), and pump spray ($n = 12$) containing various UV filters, including octocrylene (Matta et al. 2020). The sunscreen product was applied to each individual covering 75% of their body surface area using 2 mg/cm^2 of product. The first application was at 0 h on day 1 and then 4 times on day 2 through day 4 at 2-h intervals. A total of 34 blood samples were collected over 21 days from each individual. Day 1 represented a single application exposure, whereas days 2 through 4 represented repeated exposure applications. The plasma concentration of all the tested ingredients in all products exceeded 0.5 ng/mL on single application and remained above the threshold until 23 h after application. For sunscreen products that contained octocrylene, the geometric mean C_{max} values across the entire period were 7.8, 6.6, and 6.6 ng/mL for lotion, aerosol spray, and nonaerosol spray, respectively. After a single application, the geometric mean C_{max} values of octocrylene on day 1 were 1.5, 1.3, and 1.4 ng/mL for lotion, aerosol spray, and nonaerosol spray, respectively. One individual that was administered octocrylene-containing sunscreen *via* aerosol spray had octocrylene levels below the lower limit of quantification (0.4 ng/mL). The terminal plasma elimination $t_{1/2}$ for octocrylene was 49.5, 48.4, and 79.1 h for lotion, aerosol spray, and nonaerosol spray, respectively, which is likely a reflection of slow dermal absorption. Tape stripping analysis demonstrated that greater amounts of octocrylene were detectable in the skin at day 7 than at day 14.

In another study, reported detection rates of octocrylene from a sample of the general population of China ($n = 75$) were approximately 95%, with mean urinary background concentrations of 0.59 μg/g creatinine (Ao et al. 2018). Although octocrylene was abundant in indoor dust samples (detection rate: 99.0% of 203 samples; mean concentration of 2240 ng/g), no significant correlations were found with paired urine samples; however, the concentrations in the indoor dust samples were positively correlated with family income and sunscreen use.

Recent literature has identified metabolites of octocrylene in humans at background exposure levels (Bury et al. 2018) and after intentional oral or dermal exposure to octocrylene (Bury et al. 2019). A pilot study detected the presence of three specific octocrylene metabolites in urine samples from the general population: 2-cyano-3,3-diphenylacrylic acid (CDAA); 2-(carboxymethyl)butyl 2-cyano-3,3-diphenyl acrylate (dinor OC carboxylic acid; DOCCA); and 2-ethyl-5-hydroxyhexyl 2-cyano-3,3-diphenyl acrylate (5OH-OC) (Bury et al. 2018). Overall, detectable urinary levels of CDAA, DOCCA, and 5OH-OC were found in 91%, 37%, and 17% of the 35 volunteers, respectively. Additionally, the highest concentrations of these metabolites were detected in the urine of three individuals who had used sunscreen within 5 days prior to sample collection.

In another study by this group, six urinary metabolites were tentatively identified after a single oral dose of octocrylene at approximately 5 mg, corresponding to 61.8 to 89.5 μg/kg in three healthy male volunteers (Bury et al. 2019). Elimination kinetics were determined for three of these metabolites, specifically CDAA, DOCCA, and 5OH-OC. CDAA was found to be the major urinary metabolite, accounting for 40% to 50% of the administered octocrylene dose, whereas DOCCA and 5OH-OC were minor metabolites, accounting for 0.11% to 0.16% and 0.005% to 0.011% of the administered octocrylene dose, respectively. Correspondingly, the average maximum creatinine-adjusted urinary concentrations (C_{max}) for CDAA, DOCCA, and 5OH-OC were 2450, 10.6, and 1.85 μg/g creatinine, respectively. Overall, the elimination kinetics in urine were biphasic and similar between volunteers for each metabolite with peak urinary concentrations between 1.4 and 5 h postdose; however, there were differences in elimination kinetics between the metabolites. There were considerably longer mean elimination half-lives for DOCCA (phase 1: 3 h; phase 2: 16 h) and CDAA (5.7 h; 16 h) relative to 5OH-OC (1.3 h; 6.4 h). Accordingly, more than 90% of all 5OH-OC excreted was recovered within 12 h post-dose compared to only 54% for DOCCA and 52% for CDAA. Regarding mass balance, approximately 50% of the oral dose was recovered in urine within 48 h. Given that minimal elimination continued after 48 h and the additional (minor) metabolites identified but not quantified were presumed not to add significantly to the fraction of the dose excreted *via* urine, the authors posited that a notable fraction of the oral dose is excreted *via* feces (Bury et al. 2019).

In the same study, the same metabolites with similar ratios were detected, though at much lower concentrations and with a considerable delay, in the urine of one 33-year-old male volunteer dermally exposed (whole body) to 10.9 g of a commercially available sunscreen containing 2% octocrylene, corresponding to 217 mg (2.41 mg/kg) (Bury et al. 2019). To simulate swimming activity, the volunteer showered to rinse off the sunscreen 4.75 h after application. After the single dermal application, peak urinary creatinine-adjusted metabolite levels (71.4, 1.15, and 0.140 μg/g creatinine for CDAA, DOCCA, and 5OH-OC, respectively) were 2.5 to 5.4 times higher than pre-application background levels (29.0, 0.454, and 0.026 μg/g creatinine). Additionally, the metabolite background levels were comparable to background levels previously reported for 32 volunteers in the general population not knowingly exposed to octocrylene, whereas postapplication levels were comparable to levels previously reported for three individuals who had used sunscreen within

5 days prior to urine collection (Bury et al. 2018). Apart from considerable differences in the dose administered and the urinary metabolite concentrations between the oral and dermal exposure study, there were also differences in elimination kinetics (Bury et al. 2019). Although a clear excretion profile was not observed for DOCCA—likely due to its small renal conversion factor and long excretion half-life—peak urinary concentrations for 5OH-OC and CDAA were achieved approximately 24 h and between 24 and more than 48 h post-application, respectively. Additionally, 5OH-OC returned to baseline levels within 60 to 96 h, whereas CPAA levels were still elevated after 96 h. The authors concluded that an accumulation of octocrylene in the skin following repeated applications is expected due to slow dermal absorption.

In another study in one human volunteer intended to validate methods of quantification for octocrylene and its major metabolite, CDAA, after dermal application of 2 mg/cm^2 of an octocrylene-containing sunscreen (unspecified octocrylene concentration) followed by two additional applications after 2 and 4 h, each at 1 mg/cm^2, urine concentrations of octocrylene were low ($\leq$25 μg/L), while they were considerably higher for CDAA ($\leq$2500 μg/L). Maximum concentrations in plasma were 10 μg/L for octocrylene and 340 μg/L for CDAA (Klotz et al. 2019).

In a follow-up study by the same research group, plasma and urine samples from 28 healthy volunteers (14 per sex) were collected before, during, and after a real-life exposure scenario using a commercial sunscreen formulation containing 10.85% octocrylene (Hiller et al. 2019). Eight subjects were excluded prior to analysis of samples, resulting in a final study collective of 9 women and 11 men. The volunteers spent one day outside in swim clothes and applied a first dose of 2 mg of sunscreen per cm^2 of body surface area with two additional applications (i.e. 2 and 4 h later at doses of 1 mg/cm^2 each) followed by a shower 9 h after first application. Maximum plasma concentrations of 25.0 and 1351.7 μg/L were obtained for octocrylene and CDAA at 10.0 and 14.5 h, respectively, after the first dermal application. Plasma elimination rate constants (k_{el} in h^{-1}) of 0.016 and 0.019 were obtained for octocrylene and CDAA, respectively, with terminal plasma $t_{1/2}$ of 43.9 and 36.1 h for the first phase period between 24 and 72 h after first application. Additionally, comparison of the AUCs demonstrated an octocrylene-to-CDAA plasma concentration ratio of 1:62. This large difference in quantities of octocrylene and CDAA detected in plasma following dermal octocrylene exposure was also observed in urine. For instance, maximum urinary concentrations of 91.4 and 5210 μg/g creatinine were observed for octocrylene and CDAA, respectively. Additionally, considering 81% of urine samples were below the limits of detection for octocrylene, a consistent excretion profile over time or calculation of the cumulative excreted amount was not possible. However, for CDAA, urinary concentrations peaked 15.9 h after first dermal application and demonstrated an elimination rate constant (k_{el} in h^{-1}) of 0.018 and a terminal $t_{1/2}$ of 37.7 h. Additionally, 32.9% of the total 7-day urinary CDAA amount excreted was obtained within 24 h after first application and 63.3% within 48 h. The absolute cumulative CDAA amount excreted over 24 h was up to 4760 μg, corresponding to 6900 μg of octocrylene (about 0.09% of the applied dose) (Hiller et al. 2019).

Toxicology

Acute toxicity

Octocrylene was nontoxic in three GLP-compliant acute toxicity studies, two with a single oral gavage exposure (OECD TG 401) and another with a single dermal exposure (OECD TG 402) (see Table 3). The oral median lethal dose (LD_{50}) values for octocrylene were >2000 mg/kg in Sprague-Dawley rats (Symrise 1992c) and >5000 mg/kg in Wistar rats (ECHA 2023), and the dermal LD_{50} value was >2000 mg/kg in Sprague-Dawley rats (Symrise 1992d).

Repeated-dose toxicity

Although no chronic (>3 months) toxicity studies were identified for octocrylene, there were two subacute (<1 month) dietary toxicity studies in Wistar rats, one subacute inhalation toxicity study in Wistar rats, and two subchronic (1-3 months) toxicity studies, specifically a 13-week dermal study in New Zealand white rabbits and a 90-day dietary study in Wistar rats (Table 4).

In one subacute dietary palatability study reported in 2000, groups of three male and three female Wistar rats were administered octocrylene at 0, 4500, and 15,000 ppm in the diet (corresponding to 0, 456/449, and 1369/1393 mg/kg/day for males/females, respectively) for 14 days with no test substance-related effects noted (ECHA 2023).

In a subacute dietary toxicity study reported in 2019 (OECD TG 407-like) that investigated the mechanisms of effects on the liver and thyroid, groups of five male and five female Wistar rats were administered octocrylene at 0, 1000, 3000, and 10,000 ppm in feed, corresponding to doses of 0, 63 to 72, 188 to 215, and 630 to 720 mg/kg/day, respectively, for either 14 or 28 days (ECHA 2023). There were no

Table 3. Summary of acute toxicity studies for octocrylene.

Species/strain (no. of animals)	Route of exposure/test guideline	Endpoint	Dose (mg/kg)	Observed effect(s)	Reference
Rat/Sprague-Dawley (5/sex/dose)	Oral (GLP-compliant OECD TG 401)	LD_{50}	>2000	No mortality or treatment-related effects	(Symrise 1992c)
Rat/Wistar (5/sex/dose)	Oral (GLP-compliant OECD TG 401)	LD_{50}	>5000	No mortality or treatment-related effects	1993 study report (ECHA 2023)
Rat/Sprague-Dawley (5/sex/dose)	Dermal (GLP-compliant OECD TG 402)	LD_{50}	>2000	No mortality or treatment-related effects	(Symrise 1992d)

GLP: Good laboratory practices; LD_{50}: Median lethal dose (the dose at which 50% of the animals died); OECD: Organization for Economic Co-operation and Development; TG: Test guideline.

Table 4. Summary of repeated-dose toxicity studies for octocrylene.

Study type (test guideline)	Species/strain (no. of animals)	Route	Doses (mg/kg/day) [NOAEL in bold]	Basis for NOAEL	Reference
Subacute studies					
14-day palatability study	Rat/Wistar (3/sex/dose)	Oral (dietary)	Males: 0, 456, and **1369**[A,B] Females: 0, 449, and **1393**[A,B]	No treatment-related effects except minor effects on food intake, body weight, and body weight gain	2000 study report (ECHA 2023)
14- and 28-day mechanistic study (OECD TG 407-like)	Rat/Wistar (5/sex/dose)	Oral (dietary)	0, 63–72, **188**–**215**, and 630–720[C,D]	Supportive mechanistic study demonstrating organ effects in 90-day study as secondary to hepatic enzyme induction	2019 study report (ECHA 2023)
28-day inhalation toxicity study	Rat/Wistar (6/sex/dose)	Inhalation	0, 110, 330, **1000** mg/m^3	No treatment-related adverse effects except for minor effects on activity levels, transient body weight decreases, and food intake	(Creutzenberg 2007)
Subchronic studies					
13-week dermal toxicity study	Rabbit/New Zealand white (5/sex/dose)	Dermal	0, 93, 189, and **381**[E]	No treatment-related adverse effects except slight to moderate local skin irritation and decreased body weight gain	(Odio et al. 1994)
90-day dietary toxicity study (OECD TG 408)	Rat/Wistar (10/sex/dose)	Oral (dietary)	0, 58, **175**, 340, and 1085[F]	Effects on liver, thyroid, and pituitary secondary to hepatic enzyme induction	1993 study report (ECHA 2023)

NOAEL: No-observed-adverse-effect level; OECD: Organization for Economic Co-operation and Development; TG: Test guideline.
[A]Approximate corresponding doses based on a diet containing octocrylene at 0, 4500, and 15,000 ppm.
[B]No NOAEL reported, as this was a palatability study that showed no treatment-related effects up to approximately 1369 mg/kg/day in males and 1393 mg/kg/day in females.
[C]Approximate corresponding doses based on a diet containing octocrylene at 0, 1000, 3000, and 10,000 ppm.
[D]No NOAEL reported, as this was a mechanistic study showing no treatment-related effects at doses between 188–215 mg/kg/day. Treatment-related effects on liver and thyroid were observed at doses between 630–720 mg/kg/day.
[E]Extrapolated daily doses (7 days/week) from actual octocrylene doses of 0, 130, 264, and 534 mg/kg that were applied 5 days/week for 13 weeks.
[F]Approximate corresponding doses based on a diet containing octocrylene at 0, 750, 2250, 4500, and 15,000 ppm.

treatment-related deaths, clinical signs of toxicity, changes in food or water intake, or gross pathologic or neoplastic histopathologic findings. However, the following effects were noted in the highest dose group: body weight loss (<10%), increased blood urea nitrogen levels, increased (absolute and relative) liver weights, diffuse hepatocytic hypertrophy, hepatic enzyme induction, thyroid follicular cell hypertrophy and hyperplasia, a female-specific increase in cholesterol, triglyceride, and inorganic phosphate levels, and female-specific, though not statistically significant, increases in total white blood cells and absolute lymphocytes. Additionally, at various time points, thyroid-stimulating hormone (TSH) values in the high-dose group were significantly elevated in females relative to controls and were nearly 2-fold higher in males (not statistically significant). Also in the high-dose group, there was an induction of cytochrome (CYP) P450 2B-dependent liver enzyme activities (i.e. total CYP 450 and ethoxyresorufin-O-deethylase (EROD) in males, as well as pentoxyresorufin-O-dependentylase [PROD] and benzyloxyresorufin-O-debenzylase [BROD] in males and females) by up to 10-fold, and of T_4-specific uridine 5′-diphospho (UDP)-glucuronosyltransferase (UGT), MUF-UDP-glucuronosyltransferase (MUF-GT), and HOBI-UDP-glucuronosyltransferase (HOBI-GT) in males and females. In addition, high-dose group males showed reduced iodothyronine deiodinase type D1 activity and increased activity of type D3. The increase in UGT-accelerated thyroid hormone clearance in both sexes was interpreted as a compensatory feedback mechanism that led to high TSH levels and hypertrophy/hyperplasia of follicular thyroid gland cells. This might explain why circulating thyroid hormone levels (triiodothyronine [T_3] and thyroxine [T_4]) were within normal physiologic range at the specific time points investigated). This effect is not unique to octocrylene, as hepatic microsomal enzyme inducers acting *via* the constitutive androstane receptor (CAR; e.g. phenobarbital [PB], pregnenolone 16α-carbonitrile, and Aroclor 1254 [PCB]) can alter thyroid hormone homeostasis in the rat by increasing T_4 glucuronidation while not necessarily affecting T_3 levels, due to the compensatory increase in TSH levels (Hood and Klaassen 2000; ECHA 2023). CAR activation as the likely mode of action for these effects is supported by the findings of increased liver weights, hepatocellular hypertrophy, and characteristic CYP induction. This effect on TSH does not appear to be relevant to humans (Capen et al. 1999).

In another subacute toxicity study, Wistar rats were exposed to octocrylene *via* the inhalation route at concentrations of 0 (clean air), 110, 330, or 1000 mg octocrylene/m^3 for 6 h/day, 5 days/week for 28 days (Creutzenberg 2007). No treatment-related systemic toxicity was observed in any exposure group. The only notable clinical observation was reduced physical activity of the high-exposure animals (primarily males) for 1 to 2 h after the end of daily octocrylene exposure. Functional observational battery (FOB) and locomotor activity measurements were also taken during the last week of exposure. The FOB revealed no treatment-related effects. Locomotor activity measurements (15-min intervals

for 90 min) indicated possible interrelated effects with decreased overall time in movement and significantly increased overall time in rest for the mid- and high-exposure males, but not for females. However, a clear dose dependency was not observed for these effects. In addition, no non-adaptive, treatment-related hematology, clinical chemistry, organ weight, or histopathology effects were noted in any groups. Based on these findings, the maximum exposure concentration of 1000 mg/m^3 was considered the NOAEL for both males and females.

In a GLP-compliant dermal subchronic toxicity study, groups of five male and five female New Zealand white rabbits had 2 mL/kg of a 7.5%, 15%, or 30% octocrylene-containing mixture applied topically (uncovered) to their shaved back 5 days per week for 13 weeks (Odio et al. 1994). This regimen corresponded to an octocrylene dose of 130, 264, or 534 mg/kg/application (93, 189, or 381 mg/kg/day, respectively). No mortality was observed, and there were no treatment-related clinical signs (except for local findings at the application site) or effects on kidney weights, hematology, macroscopic and microscopic pathology, or morphology of testicles, epididymides, and sperm. All groups of octocrylene-treated rabbits exhibited dose-dependent hindlimb alopecia and slight-to-moderate skin irritation, as evidenced by erythema and desquamation. Additionally, octocrylene-treated rabbits demonstrated a greater incidence of histopathological skin abnormalities (acanthosis, hyperkeratosis, pleocellular infiltrates, and epidermal necrotic debris) relative to controls. Furthermore, in both sexes, mid- and high-dose treatment reduced body weight gain relative to controls while, at the low dose, this observation was statistically significant only in males. Male absolute liver weights were significantly reduced in all treatment groups; however, since body weight gain was also reduced with treatment, no differences were observed in relative liver weights for any of the treatment groups. In contrast, female absolute liver weights were not affected by treatment, but relative liver weights were significantly increased in the mid- and high-treatment groups due to treatment-related reductions in body weight gain at these exposure levels. SCCS (2021) concluded that "[o]verall, no signs of significant toxicity were noted in male or female rabbits after 13 weeks of topical treatment with various doses of octocrylene," and reported that the NOAEL was the highest dose tested (SCCS 2021). Accordingly, the NOAEL for systemic effects in this study was considered to be 381 mg/kg/day.

In a 90-day subchronic dietary toxicity study (OECD TG 408) reported in 1993, groups of 10 male and 10 female Wistar rats were fed diets containing octocrylene at 0, 750, 2250, 4500, and 15,000 ppm, corresponding to doses of approximately 0, 58, 175, 340, and 1085 mg/kg/day, respectively (ECHA 2023). There were no deaths or treatment-related clinical signs, ophthalmologic findings, testes or adrenal weight changes, or microscopic findings in adrenal glands, male reproductive organs (i.e. epididymides, prostate, and testes), or female reproductive organs (i.e. mammary gland, ovaries, uterus, and vagina). Treatment-related findings in the two highest dose groups included decreased total bilirubin in both sexes, increased total protein, platelets, and globulins, along with decreased alanine and aspartate aminotransferases in females (ECHA 2023). Treatment-related findings noted only in the highest dose group included decreases in body weight, body weight gain, and food intake in both sexes, decreased prothrombin time, hemoglobin mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration in females, increased alkaline phosphatase and total cholesterol in females, and dark yellow discoloration of the urine as well as an increase in platelets and gamma-glutamyl transferase activity in both sexes. Additionally, absolute and relative liver weights were increased in both sexes of the highest dose group and in females of the second highest dose group. Furthermore, treatment-related hepatocytic hypertrophy and hypertrophy of the thyroid follicular epithelium associated with pale-staining colloid were observed in both sexes of the two highest dose groups, as well as an increase in the number of hypertrophic cells in the pituitary gland of males in the highest dose group (ECHA 2023).

At the highest dose, periacinar hepatocytes were found to be hypertrophic and, in addition to being larger, the affected cells had a more eosinophilic and homogenous cytoplasm than surrounding hepatocytes, an appearance consistent with induction of mixed function oxidases (ECHA 2023). Furthermore, hypertrophy of centrilobular hepatocytes was observed. The cytoplasm of these cells often contained variable numbers of fine vacuoles or microvesicles. These findings are indicative of microsomal enzyme induction and are interpreted as an adaptive metabolic response. Among the induced enzymes, UGTs are responsible for metabolizing thyroid hormones, thereby resulting in lowered levels of predominantly circulating T_4 with possible subsequent elevation of TSH secretion. The observed changes in the thyroid (hypertrophy of the follicular epithelium associated with pale staining colloid) are a reflection of this secondary effect. A higher incidence of hypertrophic cells in the pars distalis of the pituitary gland was observed. The cells had abundant pale eosinophilic cytoplasm and often contained large vacuoles. They tended to occur in the middle of the pars distalis rather than in the lateral regions, suggesting that they may be so-called thyrotropin cells, affected by the interference in the homeostatic feedback mechanism resulting from the decreased plasma levels of thyroxine. The moderate changes in the thyroid and the pituitary gland effects were found only at doses above the limit dose (1085 mg/kg/day); these effects were absent in the pituitary gland and predominantly classified as minimal in the thyroid at the next lower dose level (340 mg/kg/day). Animals in these dose groups showed corresponding liver-specific clinical chemistry and histopathologic changes.

The registrants concluded that the effects on the thyroid observed in the 90-day dietary toxicity study with octocrylene were secondary to the major treatment-related effect on the liver (ECHA 2023), although this conclusion was disputed during ECHA review (ECHA 2022). Nevertheless, it is well accepted that some substances (e.g. some pharmaceuticals or industrial chemicals, such as phenytoin, which shows structural similarities to octocrylene, carbamazepine, and rifampicin) can influence the thyroid-pituitary axis by

Table 5. Comparison of the thyroid system in humans and rodents.

Parameter	Human	Rat
Half-life of T_4	5–9 days	0.5–1 day
Half-life of T_3	1 day	0.25 days
High-affinity thyroxine binding globulin	Present	Absent
Primary serum-binding protein	Thyroxin-binding globulin	Albumin
T_4 production (rate/kg bw)	1x	10x
Serum T_3	147 ng/dL	25–100 ng/dL
Serum T_4	7.2 µg/dL	3–7 µg/dL
Serum TSH	0.05–0.5 ng/mL	0.6–3.4 ng/mL
Sex difference in serum TSH levels	No difference	Adult males > adult females
Follicular cell morphology	Follicular height is equal in males and females	Follicular height in males is greater than in females

T_3: Triiodothyronine; T_4: Thyroxine; TSH: Thyroid-stimulating hormone.
Sources: Choksi et al. (Choksi et al. 2003) and Lewandowski et al. (Lewandowski et al. 2004).

increasing thyroid hormone metabolism in the liver (Zoeller et al. 2007). The prime example for this group of substances is PB, a widely used barbiturate, which is a classical inducer of hepatic xenobiotic metabolizing enzymes with well-studied effects on homeostasis of the thyroid-pituitary axis by an extrathyroidal mechanism. (Meek et al. 2003). Further evidence for this mode of action comes from the mechanistic study described above (ECHA, 2023).

The sensitivity of the thyroid-pituitary axis to increased hepatic clearance of thyroxine is much higher in rats than in humans due to widely accepted species-specific differences in thyroid hormone regulation (McClain 1989, 1995; Choksi et al. 2003; Meek et al. 2003; Lewandowski et al. 2004). These differences include, for example, the $t_{1/2}$ of T_4 and T_3, the lack of the thyroxine-binding protein in the adult rat, and the structure of the thyroid colloid (see Table 5 for additional details). This effect on TSH does not appear to be relevant to humans (Capen et al. 1999).

Based on the liver, thyroid, and pituitary effects at higher dose levels that produced hepatic enzyme induction, a NOAEL of 175 mg/kg/day was identified for the 90-day dietary toxicity study of octocrylene in Wistar rats.

Irritation, skin sensitization, phototoxicity, and photosensitization

Octocrylene has previously been recognized as a nonirritant, a non-sensitizer, and non-phototoxic (SCC 1994; Nash 2006; ECHA 2023). An updated evaluation on the sensitization potential of octocrylene by SCCP indicated that, based on local lymph node assay results and reported human sensitization cases, octocrylene should be considered as a moderate skin sensitizer and skin photosensitizer (SCCS 2021). However, the SCCP noted that the number of reported cases of allergic contact dermatitis was small, with photoallergy mainly observed in individuals previously exposed to products containing the nonsteroidal anti-inflammatory drug ketoprofen (SCCS 2021).

In a GLP-compliant *in vivo* skin irritation study (OECD TG 404), no skin reactions were observed following application of octocrylene (Symrise 1992g). Octocrylene was applied at concentrations of 1, 10, 25, 50, and 100% (w/w) to the skin of four female albino New Zealand white rabbits. The skin of the rabbits was observed for indications of erythema and edema at 24, 48, and 72 h after test-article application. No erythema or edema was observed in any animals at octocrylene concentrations up to 100%.

In a GLP-compliant *in vivo* eye irritation study (OECD TG 405) in specific pathogen-free albino rabbits, octocrylene (98.5% purity) was applied to one eye, which was observed for irritation at 24, 48, and 72 h after application (Symrise 1992h). The only test compound-related effect was a very slight reaction of the conjunctiva (redness and discharge) in one rabbit 1 h after application. No test compound-related reactions of the conjunctive, iris, or cornea were observed in any rabbit at the 48- and 72-h observations. Based on this evidence, octocrylene was not classified as an eye irritant.

Clinical patch testing studies have shown positive reactions to octocrylene in 0.7% to 5% of the study population (SCCS 2021). In the largest study (a European multicenter photopatch test study), 1031 patients were patch-tested with 10% octocrylene for suspected photoallergic contact dermatitis (Kerr et al. 2012). Although positive reactions to photoallergenicity were reported in 0.7% of the population tested, the occurrence of photoallergy to octocrylene was strongly correlated with previous photoallergy to topical ketoprofen. Therefore, photoallergy to octocrylene alone is considered to be rare in the general population.

In a case study involving a 75-year-old woman who presented with diagnosed allergic contact dermatitis (eczematous-desquamative patches on the face, neck, and forearms), subsequent patch testing was positive for sunscreen that contained 10% octocrylene (Fidanzi et al. 2023). However, the authors noted that despite its widespread use in the cosmetics industry, allergic reactions to octocrylene are considered rare (Kerr et al. 2012; Fidanzi et al. 2023).

In a GLP-compliant guinea pig maximization test (OECD TG 406), octocrylene did not produce any evidence of delayed contact hypersensitivity (Symrise 1992a). Octocrylene (98% purity) at a concentration of 5% (w/w) was selected for the intradermal induction, whereas a 100% (w/w) test concentration was selected for the dermal induction and challenge application. The guinea pigs were challenged topically 3 weeks after the intradermal induction, and the challenge site was observed for signs of sensitization at 24, 48, and 72 h after the patch removal. No reactions or treatment-related effects were observed. Based on the results, according to the contemporaneous version of OECD TG 406 (OECD 1981), octocrylene was classified as a non-sensitizer (Symrise 1992a).

In a separate study, the sensitizing potential of octocrylene was investigated in a local lymph node assay study in female CBA/CA mice (three/group) (SCCS 2021). Mice were administered 25 μL of solution containing octocrylene at 1.0%, 2.5%, 5.0%, 15%, or 30% (w/v) dissolved in acetone/olive oil (4:1 v/v) to the dorsum of the ears daily for 3 consecutive days. Five days after the first injection, 20 μCi of [^{3}H]thymidine was injected *via* the intravenous route to mice, and the mice were subsequently euthanized to determine thymidine incorporation in lymph nodes. Based on thymidine incorporation results, octocrylene was considered to be a moderate sensitizer (SCCS 2021). However, the SCCS noted that this study was not performed according to any OECD and/or GLP quality assurance guidelines and several key deviations from OECD guidelines were identified, including the following: small animal numbers/groups, lack of information on variability within the groups, test concentrations not evenly spaced 2-fold, and the lack of controls for possible UV irradiation from windows or laboratory lighting. These deviations individually or together may have contributed to the effects noted in this study.

The phototoxicity/photoallergenicity potential of octocrylene was evaluated in guinea pigs (SCC 1994). Undiluted octocrylene was applied (induction dose = 0.2 mL) to the shaved shoulder region of 15 male guinea pigs with subsequent irradiation 30 min later (UVA = 9 J/cm^2 plus UVB = 0.3 J/cm^2) for 8 consecutive days. Following a 20-day rest period, a challenge dose (same as induction dose) was applied to the shaved area on both flanks of each animal. Phototoxicity was examined 1, 6, and 24 h after the first induction dose, as well as following the challenge application. No cutaneous reaction was observed after the first application and/or irradiation. A very slight erythema was noted in two treated animals 1 h after treatment, but not at the 6-, 24-, or even 48-h post-application timepoints. Based on these results, octocrylene was not considered to be phototoxic or photoallergenic at the dose levels tested.

Recent reports have identified benzophenone as a degradant of octocrylene (Downs et al. 2021; Foubert et al. 2021). Although benzophenone has been known to present in octocrylene as a starting material, its presence as a degradant whose presence is increased when exposed to high temperatures has renewed interest in its potential toxicity. Specifically, there have been reports of photocontact allergy to octocrylene, mainly in patients who used topical products containing ketoprofen, an anti-inflammatory drug (de Groot and Roberts 2014). Foubert et al. has made the important connection that photocontact allergy from octocrylene in patients photosensitized to ketoprofen may be due to the presence of benzophenone. The number of cases of photocontact allergy to octocrylene will need to be monitored and suppliers of this important UV filter will need to take steps to reduce the presence of benzophenone in products.

Genotoxicity, carcinogenicity, and photocarcinogenicity

Octocrylene is considered to be non-genotoxic based on results for all available genotoxicity studies (Table 6). These studies included bacterial reverse mutation tests (i.e. Ames tests), *in vitro* mouse lymphoma cell assays, mammalian chromosomal aberration tests, and a micronucleus assay in mice (Zeiger et al. 1987; Symrise 1992b; Odio et al. 1994; ECHA 2023).

Although no long-term rodent carcinogenicity study has been performed with octocrylene, there are no indications of a human-relevant carcinogenic hazard based on the empirical evidence from the previously described repeated-dose toxicity studies because all of the data are unremarkable for possible pre-neoplastic effects (see Repeated-dose toxicity). In the subchronic dermal toxicity study, none of the octocrylene-treated rabbits showed any evidence of macroscopic or histopathologic abnormalities in any organs examined (Odio et al. 1994). Additionally, in the 90-day rat dietary toxicity study, there was no evidence of treatment-related hyperplasia or gross lesions (ECHA 2023). Although that study did report increased thyroid hypertrophy, these effects were considered secondary to effects on the liver and species-specific with no relevance in humans (Capen et al. 1999), although this reasoning was disputed by ECHA (2022). Furthermore, CAR activation leading to increased hepatocellular proliferation has been shown not to be relevant to humans (Elcombe et al. 2014; Yamada et al. 2021, 2025). Finally, Cohen et al. (2025) examined carcinogenic modes of action, i.e. genotoxicity, estrogen activity, immunotoxicity, and cell proliferation/death, for octocrylene and found that any bioactivity in animal models was well above concentrations reported in humans following maximal usage (Matta et al. 2019, 2020; Cohen et al. 2025).

Octocrylene has been evaluated in a mouse model of photocarcinogenicity (Bode and Roh 2020). Female SKH-1 hairless mice ($N = 15$) were treated topically with a lotion containing 10% octocrylene alone or in combination with other UV filters: 7% octocrylene plus 6.9% zinc oxide and 7% octocrylene plus 3% avobenzone plus 6% titanium dioxide. Octocrylene-containing products were applied on the back of each mouse prior to a 1-h exposure to solar-simulated UV. Treatments were performed three times a week for 15 weeks. At week 15, UV exposure was discontinued while topical application of formulations containing octocrylene was continued until week 29. Total number and volume of tumors were measured and compared to vehicle-treated mice. Octocrylene alone and in combination with other UV filters significantly decreased the number of tumors and tumor volume as well as molecular markers of cell proliferation, for example, Ki-67.

Hormone-related effects

Studies on specific hormone-related pathways and adverse effects on developmental and reproductive toxicity were evaluated according to the OECD conceptual framework of weighted levels of data (OECD 2018). Although certain assays can inform on mechanistic pathways, others are more informative on adverse responses and useful for quantitative risk assessment. For example, the OECD describes data from Levels 1 to 2 (*in silico* and *in vitro*) as providing information on select mechanistic pathways, whereas Levels 3 to 5 entail *in vivo* assays that may also provide information on adverse effects for hormone-related endpoints (Supplemental Table 1)

Table 6. Genotoxicity/mutagenicity studies of octocrylene.

Testing guidelines	Assay	Test organism	Doses or concentrations	Results	References
In vitro studies					
OECD TG 471	Gene mutation	*S. typhimurium* TA98, TA100, TA1535, and TA1537, and *E. coli* strain WP2 uvr A	20–5000 μg/plate[c]; 4–2500 μg/plate[d]	Negative ±S9[a]	2001 study report (ECHA 2023)
OECD TG 471	Gene mutation	*S. typhimurium* TA98, TA100, TA1535, and TA1537	20, 100, 500, 2500, and 5000 μg/plate	Negative ±S9[a]	1993 study report (ECHA 2023)
OECD TG 471 (GLP)	Gene mutation	*S. typhimurium,* TA98, TA100, TA1535, TA1537, and TA1538	50, 150, 500, 1500, and 5000 μg/plate	Negative ±S9	Symrise Test No. 1992033 (Symrise 1992b)
Not specified	Gene mutation	*S. typhimurium* TA98, TA100, TA1535, and TA1537	100, 333, 1000, 3333, and 10,000 μg/plate	Negative ±S9	(Zeiger et al. 1987)
OECD TG 476	Gene mutation	Mouse lymphoma L5178Y cells	12.5, 25, 50, 100, and 200 μg/mL	Negative ±S9	1993 study report (ECHA 2023)
OECD TG 476	Gene mutation	Mouse lymphoma L5178Y cells	28–380 μg/mL (-S9)[e]; 6.7–89 μg/mL (+S9)[e]	Negative ±S9	(San and Sigler 1990; Odio et al. 1994)
OECD TG 473	Chromosomal aberration	Chinese hamster lung fibroblasts (V79)	3.75, 7.5, 15.0, 30.0, 60.0, and 90.0 μg/mL	Negative ±S9	2001 study report (ECHA 2023)
OECD TG 473	Chromosomal aberration	Chinese hamster ovary cells	up to 100 μg/mL	Negative ±S9	1993 study report (ECHA 2023)
Not specified	Chromosomal aberration	Chinese hamster ovary cells	0.02, 0.03, and 0.04 μg/mL[f]	Negative ±S9	(Putman and Morris 1990; Odio et al. 1994)
In vivo studies					
OECD TG 474	Micronucleus assay	NMRI mice	500, 1000, and 2000 mg/kg[b]	Negative	1993 study report (ECHA 2023)

±S9: With and without metabolic activation; +S9: With metabolic activation; -S9: Without metabolic activation; GLP: Good laboratory practice; NMRI: Naval Medical Research Institute; OECD: Organization for Economic Co-operation and Development; S9: Supernatant fraction containing cytosol and microsomes, usually obtained *via* centrifugation from liver homogenate; TG: Test guideline.

[a]In the standard plate test as well as in the preincubation test.

[b]*Via* oral gavage, with euthanasia occurring 16, 24, and 48 h after dose administration.

[c]Standard plate test.

[d]Preincubation test.

[e]Data on test concentrations are inconsistent, as values herein are congruent with concentrations in methods description; however, tabular presentation of results provide concentrations that are lower by 1000-fold.

[f]Though test concentrations of 0.008, 0.011, 0.015, 0.02, 0.03, 0.04, and 0.05 μg octocrylene/mL were used, chromosomal aberrations were evaluated from the three highest doses that yielded scorable metaphases (i.e. 0.02, 0.03, 0.04 μg/mL).

(OECD 2018). Although Level 4 assays provide data on adverse effects for hormone-related endpoints, Level 5 studies provide more comprehensive data over more extensive periods of the lifecycle (Manibusan and Touart 2017).

There are sufficient empirical data available for octocrylene to assess possible effects on thyroid hormone, androgenic, and estrogenic endpoints according to the OECD conceptual framework (presented in Table 7 and summarized below). Overall, despite octocrylene having some activity on specific hormones observed in *in vitro* assays, octocrylene exposure does not result in adverse endocrine-related responses based on the 11 available *in vivo* studies. According to the EPA, *in vitro* hormone activity is not always predictive of a potential hormone-related adverse outcome *in vivo*, in part because the *in vitro* assays do not fully account for toxicokinetic and toxicodynamic contributions to the toxicologic profile of a chemical (USEPA 2013). In addition, the chemical concentration necessary to cause receptor binding and activation in an *in vitro* system may not be present in the intact organism through environmental exposure. Therefore, *in vitro* hormone assays are best used to provide supporting data for hazard characterization in combination with *in vivo* toxicity data (USEPA 2013).

An evaluation of the ToxCast/Tox21 database determined that octocrylene was active in five *in vitro* endocrine-related assays (1/6 estrogen receptor [ER], 2/8 androgen receptor [AR], 1/6 thyroid hormone, and 1/2 steroidogenesis) (Onyango et al. 2023). These results represent curated data, excluding other assays with results that had multiple flags (e.g. borderline activity, low efficacy, curve overfitting, noise) or did not have a clear concentration-response curve for the octocrylene results. The effective concentrations in these *in vitro* assays (i.e. all active assays) were well above the cytotoxic limit, indicating general cell toxicity rather than specific endocrine pathway activity, and significantly higher than the plasma C_{max} of 0.0216 μM noted by Matta et al. (2019, 2020).

Although (anti)estrogenic and (anti)androgenic activities of octocrylene have been observed in some *in vitro* assays, these pathways and responses were not observed *in vivo*, as no related effects were reported in the rodent Hershberger and uterotrophic assays (Table 7) or in other high-tier developmental and reproductive toxicity studies (Level 4-5 data) discussed below.

In a competitive binding assay, the relative binding affinity of octocrylene for ERα and ERβ was 0.08 (half maximal inhibitory concentration [IC_{50}], 4.8×10^{-4} M) and 0.32 (IC_{50}, 6.0×10^{-5} M), respectively, of that of 17β-estradiol (E2) (Matsumoto et al. 2005). Matsumoto et al. also demonstrated estrogenic activity of octocrylene in the MCF-7 cell proliferation and CHOOSER assays (Matsumoto et al. 2005). The MCF-7 assay measures the proliferation response of human breast cancer cells to estrogens. At a concentration of 10^{-4} M, octocrylene increased cellular proliferation by almost 300% compared to the negative control (0.1% DMSO). The REC_{10} value (concentration of the chemical showing 10% of the activity of the positive control E2) was 1.7×10^{-5} M. The relative activity (RA) value, which represents the ratio of the REC_{10} value of octocrylene compared to that of E2 (which was arbitrarily set

Table 7. Assessment of octocrylene hormonal, developmental, and reproductive data according to OECD conceptual framework.

Assay/data	Results	References
Level 1 - Existing data and non-test information		
• Physicochemical properties • Available (eco)toxicological data • Read-across, chemical categories, QSARs, and other *in silico* predictions, and ADME model predictions	Available (not discussed here)	
Level 2 - In vitro (mammalian and non-mammalian) assays: select hormonal mechanism(s)/pathways(s)		
ER binding affinity	Octocrylene was positive for ER activity.	(Matsumoto et al. 2005)
ER binding assay (rat uterine cytosol) (OPPTS 890.1250, GLP-compliant)	Octocrylene was classified as "non-interacting" with the ER at soluble concentrations ranging from 10^{-10} to 10^{-4} M (precipitation occurred at 10^{-3} M).	(CeeTox 2012c; NTP 2024)*
AR binding assay (rat prostate cytosol) (OPPTS 890.1150, GLP-compliant)	Octocrylene was classified as "equivocal" (mean specific binding $\geq$50.4% relative to the AR at soluble concentrations of 10^{-10} to 10^{-4} M).	(CeeTox 2012a; NTP 2024)*
Human recombinant aromatase assay (OPPTS 890.1200, GLP-compliant)	Octocrylene was classified as a non-inhibitor (mean aromatase activity of 94% ± 1% SD) at the highest soluble concentration of 10^{-4} M.	(CeeTox 2012f; NTP 2024)*
Androgen or thyroid transactivation	Octocrylene was positive for (anti)androgenic activity.	(Kunz and Fent 2006)
AR transactivation activity assay (MDA-kb2 cells) (GLP-compliant)	Octocrylene did not show agonism or antagonism of AR-mediated transactivation in the test system.	(CeeTox 2012b; NTP 2024)*
ER transcriptional activation assay (human cell line [HeLa-9903]) (OECD 455, OPPTS 890.1300, GLP-compliant)	Octocrylene was not an agonist of hERα in the test system.	(CeeTox 2012d; NTP 2024)*
MCF-7 cell proliferation assays	Octocrylene was positive for ER agonism.	(Matsumoto et al. 2005)
H295R steroidogenesis assay (OPPTS 890.1550, GLP-compliant)	After normalization based on cell viability, statistically significant inhibition of testosterone and estradiol was noted at an octocrylene concentration of 100 μM in 1 run, but statistically significantly higher estradiol or induction of estradiol was noted at 1 μM in 2 different runs.	(CeeTox 2012e; NTP 2024)*
Other assays as appropriate	Octocrylene was positive for ER activity (in the CHOOSER assay).	(Matsumoto et al. 2005)
Level 3 - In vivo (mammalian) assays: select hormonal mechanism(s)/pathway(s)		
Uterotrophic assay (OECD TG 440)	No uterotrophic effect was noted.	(ECHA 2023)
Uterotrophic assay (OPPTS 890.1600, GLP-compliant)	Ovariectomized adult female Sprague-Dawley Crl:CD®(SD) IGS rats were orally administered octocrylene at 0 (vehicle control), 320, or 1000 mg/kg/day in corn oil or 0.1 mg/kg/day 17α-ethinyl estradiol (positive control) for 3 consecutive days. No body weight or estrogenic (uterotrophic) effects were noted at either dose level.	(ILS 2011; NTP 2024)*
Hershberger assay (OECD TG 441)	No androgenic or anti-androgenic effects were noted.	(ECHA 2023)
Hershberger assay (OPPTS 890.1400, GLP-compliant)	Groups of 8 castrated male Sprague-Dawley Crl:CD®(SD) IGS rats were orally dosed for 10 consecutive days with octocrylene at 0 (vehicle control), 320, or 1000 mg/kg/day in corn oil or with 0.4 mg/kg/day of testosterone propionate (agonist positive control). In the same study, separate groups of castrated male rats received 0.4 mg/kg/day testosterone propionate and either octocrylene in corn oil at 0, 100, 320, or 1000 mg/kg/day or 3 mg/kg/day of flutamide (antagonist positive control). No body weight, androgenic, or anti-androgenic effects were noted at either dose level.	(ILS 2012; NTP 2024)*
Level 4 - In vivo (mammalian) assays: adverse effects on specific hormone-relevant endpoints		
Repeated-dose 28-day toxicity study (OECD TG 407)	In a 28-day dietary (OECD TG 407-like) study in rats, a NOAEL of 202 mg/kg/day can be identified based on liver and thyroid effects as a secondary consequence of hepatic enzyme induction as well as female-specific hematological effects; however, the ECHA registrant did not identify a NOAEL, as this was a supportive mechanistic study.	(ECHA 2023)
Repeated-dose 90-day toxicity study (OECD TG 408)	In a 90-day dietary (OECD TG 408) study in rats, a NOAEL of 175 mg/kg/day was identified based on liver, thyroid, and pituitary effects as a secondary consequence of hepatic enzyme induction.	(ECHA 2023)
Prenatal developmental toxicity study (OECD TG 414)	In a teratogenicity (OECD TG 414) study of rats exposed *via* gastric intubation to 100, 400, and 1000 mg octocrylene/kg/day during GD 6-15, there were no signs of embryo or fetal toxicity observed, but the 2 highest doses induced signs of maternal toxicity as evidenced by increased liver weights.	(ECHA 2023)

(*continued*)

Table 7. Continued.

Assay/data	Results	References
Level 5 - In vivo (mammalian) assays: more comprehensive data over more extensive parts of an organism's lifecycle		
Three separate *in vivo* mammalian DART studies	There was no developmental or reproductive toxicity from octocrylene exposure (dermal/oral) in 3 *in vivo* mammalian toxicity studies: • Rabbit dermal NOAEL of >381 mg/kg/day; • Mouse oral NOAEL of >1000 mg/kg/day; no effects in a teratology study with mice orally exposed to 100, 300, and 1000 mg/kg/day during GD 8-12; • Rabbit dermal NOAEL of >267 mg/kg/day; no effects in a teratology study with rabbits dermally exposed to 65 and 267 mg/kg/day during GD 6-18.	(Odio et al. 1994)

ADME: Absorption, distribution, metabolism, and excretion; AR: Androgen receptor; DART: Developmental and reproductive toxicity; ECHA: European Chemicals Agency; ER: Estrogen receptor; GD: Gestation day; NOAEL: No-observed-adverse-effect level; OECD: Organization for Economic Co-operation and Development; OPPTS: Office of Prevention, Pesticides, and Toxic Substances (U.S. EPA); SD: Standard deviation; QSAR: Quantitative structure-activity relationship; TG: Test guideline.

at 10^6 M), was determined to be 0.29. Notably, co-exposure of MCF-7 cells to either octocrylene or E2 along with an ER antagonist, ICI 1827860 (10^{-6} M), reduced cellular proliferation to negative control levels, suggesting that cellular proliferation was mediated through the ER. The CHOOSER assay measures estrogenic activity using Chinese hamster ovary cells transformed with *ESR1* (human gene for ERα) and an estrogen-responsive promoter linked to a reporter gene. At 3×10^{-6} M, octocrylene significantly increased estrogenic activity compared to the negative control (0.1% DMSO); however, octocrylene-induced activity was only slightly above 100% (negative control) and there was no effect at higher or lower concentrations. The REC_{10} and RA values were $>1.0 \times 10^{-5}$ M and <0.52, respectively (Matsumoto et al. 2005).

In contrast to the positive responses in estrogenic activity testing reported by Matsumoto et al. (2005), Kunz and Fent found no estrogenic (human [h] ERα) activity in a yeast-based assay, but did demonstrate antiestrogenic (hERα) activity with an IC_{50} of 2.57 mM (Kunz and Fent 2006). Octocrylene was approximately 2250 times less potent (based on the ratio of the IC_{50} values) than the agonist standard, 4-hydroxytamoxifen. The efficacy of octocrylene was 118% relative to 4-hydroxytamoxifen (100%).

In an Ishikawa cell alkaline phosphatase assay, which reflects estrogenic activity, the threshold for alkaline phosphatase induction of octocrylene was 10^{-6} M (Meschi et al. 2002). At 10^{-5} M, a 1.9-fold increase in alkaline phosphatase activity was seen with octocrylene. For comparison, in the same culture conditions, E2 induced alkaline phosphatase activity in a concentration-related fashion between 10^{-11} and 10^{-9} M, with maximal effect (5.8-fold increase over controls) reached at 10^{-9} M. The EC_{50} for E2 was 0.017 nM; however, due to its low potency, the EC_{50} could not be determined for octocrylene at concentrations up to 10,000 nM. Based on this evidence, the authors concluded that octocrylene was completely devoid of estrogenic potential in this model system (Meschi et al. 2002).

When octocrylene (in corn oil) was administered orally at 250 and 1000 mg/kg/day for 3 consecutive days to immature female rats in a uterotrophic assay, it did not result in any uterotrophic (estrogenic) effects (ECHA 2023).

In another study, octocrylene was devoid of any estrogenic potential up to the maximum dose tested of 1000 mg/kg in rats (Eygonnet et al. 2002). In this study, ovariectomized rats were administered octocrylene once with 4 mL/kg at doses of 30, 100, 300, and 1000 mg/kg *via* the subcutaneous route. Three vaginal smears were taken 48, 56, and 72 h after treatment, and the presence of nucleated or squamous cornified cells (indicative of an estrogenic response) was recorded. No vaginal keratinization up to the maximum dose of 1000 mg/kg was observed in any dosed animals.

In a yeast-based human androgen receptor (hAR) transactivation assay, Kunz and Fent demonstrated both androgenic (EC_{50} of 6.27×10^{-4} M) and anti-androgenic (IC_{50} of 2.45×10^{-5} M) activity (Kunz and Fent 2006). In terms of the androgenic response, octocrylene was approximately 290,000 times less potent (based on the ratio of the EC_{50} values) than 4,5-dihydrotestosterone, and the potency of octocrylene was 21% relative to flutamide (100%). In terms of the anti-androgenic response, octocrylene was approximately 11 times less potent (based on the ratio of the IC_{50} values) than flutamide, and the efficacy of octocrylene was 86% relative to FT (100%).

In a Hershberger assay, octocrylene was administered in corn oil *via* oral gavage to groups of six castrated but testosterone propionate (0.4 mg/kg)–substituted male Wistar rats for 10 days at dose levels of 300 and 1000 mg/kg/day (ECHA 2023). Treatment-related effects included increased absolute and relative liver weights (at 300 and 1000 mg/kg/day), decreased absolute and relative ventral prostate weights (at 1000 mg/kg/day), and decreased weights of the bulbocavernosus/levator ani complex. No treatment-related clinical findings or effects on hormone concentrations (testosterone, dihydrotestosterone, and luteinizing hormones) or histology (prostate, seminal vesicle, and bulbo-urethral gland) were observed. With respect to the observed decreases in absolute and relative ventral prostate and bulbocavernosus/levator ani weights, the ECHA registrant stated:

> "[this finding] may have been fortuitous or is to be explained by an enzyme induction, indicated by the observed increased liver weights connected with a higher metabolism rate of the substituted androgen testosterone propionate. In contrast, absolute and relative weights of the other accessory sex organs were not significantly reduced. Moreover, the histology of prostate, seminal vesicle and the bulbo-urethral gland was comparable to the control. Therefore, under the conditions of the present study, regarding clinical examinations, hormone

investigations as well as pathological evaluations, no indication for an antiandrogen efficacy of octocrylene was determined" (ECHA 2023).

In a battery of unpublished studies (Table 7) sponsored by the National Toxicology Program, including six *in vitro* endocrine-related assays conducted by CeeTox, Inc., and uterotrophic and Hershberger assays conducted by Integrated Laboratory Systems, Inc., there were no indications of octocrylene-related estrogenic or androgenic activity or inhibition of aromatase activity (CeeTox 2012c, 2012a, 2012f, 2012b, 2012d). Variable results were noted in the four runs of the H295R steroidogenesis assay. After normalization of results based on cell viability, statistically significant inhibition of testosterone and E2 was noted at an octocrylene concentration of 100 μM in one run. However, statistically significantly higher E2 or induction of E2 was noted at 1 μM in two different runs (CeeTox 2012e; NTP 2024). There were no estrogenic (uterotrophic) effects noted in the uterotrophic assay with octocrylene oral gavage doses up to 1000 mg/kg/day (ILS 2011; NTP 2024). There were no androgen agonist/antagonist-related effects or properties reflective of 5α-reductase inhibition noted in the Hershberger assay at octocrylene oral gavage doses up to 1000 mg/kg/day (ILS 2012; NTP 2024).

As previously described (Repeated-dose toxicity), in a mechanistic subacute dietary toxicity study (OECD TG 407-like), male and female Wistar rats were fed a diet containing octocrylene (99.5% purity) up to 10,000 ppm, corresponding to 630 to 720 mg/kg/day for 14 or 28 days to evaluate any indirect thyroid effects of octocrylene exposure (Symrise 2019; ECHA 2023). The highest dose group demonstrated significantly elevated TSH values in females (days 14, 21, and 29) but not males (ECHA 2023). No effects on T_3 or T_4 levels were noted at any time point. Because there was a treatment-related induction of liver enzymes (PROD, BROD, and T_4-specific UGTs) accelerating the thyroid hormone clearance in both sexes, the ECHA registrant attributed the effect to a compensatory feedback mechanism that led to high TSH levels and hypertrophy/hyperplasia of follicular thyroid gland cells, although this reasoning was challenged by ECHA (2022). The registrant further noted that this effect is not unique to octocrylene, as some hepatic microsomal enzyme inducers (e.g. PB, pregnenolone-16α-carbonitrile, 3-methylcholanthrene, and PCB) can alter thyroid hormone homeostasis by increasing T_4 glucuronidation while maintaining T_3 levels *via* compensatory mechanisms such as increasing TSH levels (Hood and Klaassen 2000; ECHA 2023).

As previously described (Repeated-dose toxicity), in a 90-day dietary toxicity study (OECD TG 408), rats were administered octocrylene in the diet at 0, 750, 2250, 4500, or 15,000 ppm (0, 58, 175, 340, and 1085 mg/kg/day, respectively) (SCC 1994; ECHA 2023). Although there were no treatment-related testis or adrenal weight changes or microscopic changes in adrenal glands or reproductive organs, a NOAEL of 175 mg/kg/day was identified based on liver, thyroid, and pituitary changes as a secondary consequence of hepatic enzyme induction (SCC 1994; ECHA 2023). It is important to note, and is generally accepted, that thyroid hypertrophy resulting from hepatic enzyme induction in rats is of little relevance for humans (see additional discussion in Repeated-dose toxicity).

Additional evidence that octocrylene is not an anti-androgen was demonstrated by the lack of adverse effects seen with octocrylene exposure on testicular and epididymal morphology and on sperm quality in the 90-day rabbit study (Odio et al. 1994; Axelstad et al. 2013). Although *in vitro* yeast assays have shown positive androgenic and anti-androgenic activities, results from other *in vivo* mammalian testing have been negative (Kunz and Fent 2006; ECHA 2023).

Developmental and reproductive toxicity

None of the studies evaluating developmental and/or reproductive parameters following octocrylene exposure

Table 8. Summary of effects of octocrylene on specific hormones.

Study type (route)	Species/strain (no. of animals)	Doses (mg/kg/day)	Exposure duration	Main findings	Reference
Uterotrophic assay (oral)	Rat/Wistar (10 females/dose)	0, 250, 1000	3 days	• Decreases in body weight gain at highest dose • No modification of uterus weight and histopathology	2001 study report (ECHA 2023)
Uterotrophic assay (oral)	Rat/Sprague-Dawley (8 females/dose)	0, 320, 1000	3 days	• No estrogenic (agonist) effects	(ILS 2011)
Uterotrophic assay (subcutaneous)	Rat/Wistar (7 females/dose)	0, 300, 1000	1 dose	• No estrogenic (agonist) effects	(Eygonnet et al. 2002)
Hershberger assay (oral)	Rat/Wistar (6 males/dose)	0, 300, 1000	10 days	• No clear anti-androgenic (antagonist) effects[c] • No effects on hormone levels (testosterone, dihydrotestosterone and luteinizing hormone) or histology of prostate, seminal vesicle, and bulbo-urethral gland	2003 study report (ECHA 2023)
Hershberger assay (oral)	Rat/Sprague-Dawley (8 males/dose)	0, 320, 1000[a] or 0, 100, 320, 1000[b]	10 days	• No androgenic (agonist) effects • No anti-androgenic (antagonist) effects	(ILS 2012)

[a]To evaluate agonist properties (reference substance: testosterone propionate at 0.4 mg/kg).
[b]To evaluate antagonist properties (reference substance: flutamide at 3 mg/kg).
[c]Although at the highest dose decreases in absolute and relative ventral prostate and bulbocavernosus/levator ani weights were observed, the ECHA database states that this observation was not considered a result of an anti-androgenic effect of octocrylene but rather a spurious effect or explained by hepatic enzyme induction.

demonstrated adverse treatment-related effects on reproduction or development in the absence of maternal toxicity. In the one developmental toxicity study that did show treatment-related effects (decreased number of implantation sites, a lower number of pups, and a decrease in pup body weight), these effects occurred at a dose higher than that which elicited maternal toxicity (Table 9).

In a teratogenicity study (OECD TG 414) reported in 1993, groups of 25 female Wistar rats were exposed *via* gastric intubation to octocrylene at 0, 100, 400, and 1000 mg/kg/day on gestation days 6 to 15 (ECHA 2023). No signs of embryo or fetal toxicity were observed; however, the two highest doses induced maternal toxicity as evidenced by increased liver weights. Additionally, transient salivation was observed in the dams at the highest dose (SCC 1994; ECHA 2023).

In a GLP-compliant, dose range-finding study for an extended one-generation reproductive toxicity study (EOGRTS; OECD TG 443), 12 rats/sex/dose were fed diets containing octocrylene (99.4% pure) at doses of 0, 5000, and 15,000 ppm, resulting in total octocrylene intake of 279 to 399 and 812 to 1271 mg/kg for males and 323 to 618 and 796 to 1740 mg/kg for females, respectively, from 4 weeks prior to mating until postnatal day (PND) 21 for females or until termination for males (Symrise 1992e). The octocrylene doses were halved during the lactational phase to account for considerable increase in food consumption of the dams. Body weight decreases of 11% (males) or 21% (females) and corresponding decreased body weight gains and food intake were noted in the high-dose group animals in both sexes and statistically significant effects on body weight were also noted at the lower dose group, indicating that both doses exceeded the maximum tolerated dose for octocrylene. Hematology, clinical chemistry, and organ weight (e.g. liver and thyroid) changes consistent with overt toxicity were noted in the high dose group. Lower mean numbers of implantation sites and pups per litter, decreased birth weight, and lower postnatal body weights were also observed at the high dose. Based on the results of this dose-range finding study, octocrylene doses of 1271 and 1740 mg/kg/day for males and females, respectively, were considered too high for the pivotal EOGRTS (described below).

In the GLP-compliant definitive EOGRTS (OECD TG 443 study), Wistar rats were administered octocrylene (99.4% pure) in the diet at 0, 750, 2100, and 7000 ppm, corresponding to mean doses of 0, 55, 153, and 534 mg/kg/day in males and 0, 58, 163, and 550 mg/kg/day in females, respectively, starting 10 weeks prior to mating and until the end of mating for males and to PND 21 for females (Symrise 1992e, 1992f; ECHA 2023). Animals in the initial parental (P) generation (27-28 rats/sex/dose) were assessed for reproductive performance, and first filial (F_1) litters born to these animals were kept on their respective diets for up to 18 weeks. Pups (second filial [F_2]) born to F_1 animals were indirectly exposed to octocrylene through F_1 dams, evaluated for developmental neurotoxic effects, and euthanized at PND 21. At the high-dose level, there were treatment-related lower body weights and food consumption in the P generation and lower body weights in the F_1 generation. In mid- and high-dose group P generation animals and high-dose group F_1 animals, there was an increased prevalence of activated appearance of the thyroid gland (loss of colloid from the follicles, hypertrophy, and hyperplasia of follicular epithelial cells), which was considered to be adaptive changes in rats by the registrants but challenged by ECHA (2022). No other histopathologic changes, TSH or T_4 changes in P or F_1 generation adults, T_4 effects in PND 4 pups, or altered T_4 and TSH levels in PND 21 pups were reported. Lower mean numbers of implantation sites and pups delivered were noted for high-dose group P and F_1 females. No effects on sexual developmental parameters, implantation loss, stillborn pups, dead, missing and/or cannibalized pups, litter loss, pup viability indices, or sex ratio effects were reported. No neurotoxic or neurodevelopmental effects in F_2 pups were reported following dietary exposure to octocrylene. Overall study results indicated that there were differences in developmental and reproductive endpoints only at the highest dose level, which was a maternally toxic dose (Symrise 1992e; ECHA 2023). Based on these results, the NOAEL for parental toxicity, reproductive performance, and developmental toxicity was 2100 ppm (corresponding to 153 and 163 mg/kg/day for males and females, respectively).

Additional developmental and reproductive toxicity data

There were three additional studies conducted by Odio et al. that investigated reproductive or developmental endpoints (Odio et al. 1994). Although they did not comply with an OECD test guideline or fit within the OECD conceptual framework for assessing hormone responses, the standards and/or requirements of the FDA and OECD were used as the basis for study design and the studies were GLP-compliant. These studies demonstrated no evidence of octocrylene-induced developmental and/or reproductive effects: a previously described 13-week dermal study in rabbits, a percutaneous developmental toxicity study in rabbits, and an oral developmental toxicity study in mice.

As previously described (Repeated-dose toxicity), groups of five male and five female New Zealand white rabbits had 2 mL/kg (2.1 g/kg) of a 7.5%, 15%, or 30% octocrylene-containing mixture applied topically (uncovered) to the shaved back 5 days per week for 13 weeks (Odio et al. 1994). This treatment corresponded to an octocrylene dose of 130, 265, or 534 mg/kg/application, which approximates 93, 189, or 381 mg/kg/day (Odio et al. 1994). Overall, there were no treatment-related adverse effects on the male reproductive system, after a morphological examination of the testes, epididymis, and sperm (Odio et al. 1994).

In the percutaneous developmental toxicity study, groups of 17 female New Zealand white rabbits were treated topically with octocrylene at 0, 65, or 267 mg/kg/day on gestation days 6 to 18 (Kraus 1991; Odio et al. 1994). A NOAEL in the absence of any observed effects was identified as 267 mg/kg/day (ECHA 2023), as there were no treatment-related effects on survival, body weight gain, food intake, gross observations at necropsy, or any of the maternal, reproductive, and offspring endpoints examined (fetal survival rates, sex ratios, litter sizes, fetal weights, or fetal soft tissue alterations). Although one doe in each of the octocrylene-treated groups

Table 9. *In vivo* developmental and reproductive toxicity studies of octocrylene.

Study type (OECD TG)	Species/strain (no. of animals)	Route of exposure	Doses (mg/kg/day) [NOAEL in bold]	Duration of exposure	Main findings	Reference
Subchronic repeated-dose toxicity study	Rabbit/New Zealand white (5/sex/dose)	Dermal	0, 93, 189, **381**[a]	13 weeks	• No effects on testicular and epididymal morphology or sperm count and motility	(Odio et al. 1994)
Developmental toxicity study	Rabbit/New Zealand white (17 females/dose)	Percutaneous	0, 65, **267**	GD 6-18	• No treatment-related adverse effects	(Odio et al. 1994)
Developmental toxicity study	Mouse/CD-1 (12 females/dose)	Oral	0, 100, 300, **1000**	GD 8-12	• No treatment-related adverse effects	(Odio et al. 1994)
14- and 28-day mechanistic study (OECD TG 407-like)	Rat/Wistar (5/sex/dose)	Oral (dietary)	0, 63–72, **188–215**, 630–720[b]	14 or 28 days	• Supportive study that demonstrated the organ effects in the 90-day study were secondary to hepatic enzyme induction	2019 unnamed study report (ECHA 2023)
90-day toxicity study (OECD TG 408)	Rat/Wistar (10/sex/dose)	Oral (dietary)	0, 58, **175**, 340, 1085[b]	90 days	• Effects on liver, thyroid, and pituitary secondary to hepatic enzyme induction	1993 unnamed study report (ECHA 2023)
Developmental toxicity study (OECD TG 414)	Rat/Wistar (25 females/dose)	Oral	0, 100, 400, **1000**[e]	GD 6-15	• No treatment-related adverse effects in pups • Maternal effects of transient salivation at highest dose and increases in relative liver weights at 2 highest doses	1993 unnamed study report (ECHA 2023)
Extended one-generation reproductive toxicity study (OECD TG 443)	Rat/Wistar P: 28/sex/dose[c] F_1 Cohort 1A: 20/sex/group[d] F_1 Cohort 1B: 25/sex/group F_1 Cohort 2A: 10/sex/group F_1 Cohort 2B: 10/sex/group	Oral (dietary)	Males: 0, 55, **153**, 534[b] Females: 0, 58, **163**, 550[b]	P males: 10-week premating period through end of mating (~13 weeks) P females: 10-week premating period through mating, gestation, and termination after LD 21 F_1: from weaning to termination • Cohort 1A: ~10 weeks • Cohort 1B: ~13/18 weeks (males/females) • Cohort 2A: ~ 8 weeks F_2: indirectly exposed until weaning	• Decreased number of implantation sites and consequently lower number of pups at highest dose • Decreases in pup body weight at highest dose • No effects on male fertility, male and female reproductive parameters (e.g. estrous cycle or epididymal and testicular sperm endpoints) • No effects on sexual and neurodevelopmental endpoints in pups	(Symrise 1992e; ECHA 2023)

F_1: First filial generation; F_2: Second filial generation; GD: Gestation days; LD; Lactation day; NOAEL: No-observed-adverse-effect level; OECD: Organization for Economic Co-operation and Development; P: Parental generation; TG: Test guideline.

[a]Extrapolated daily doses (7 days/week) from actual octocrylene doses of 0, 130, 264, and 534 mg/kg that were applied 5 days/week for 13 weeks.

[b]Approximate corresponding doses based on a diet containing octocrylene at designated concentrations (in ppm).

[c]28 males and 27 females in the control group.

[d]19 females instead of 20 in the mid-dose group, as 1 animal appeared to be a male pup instead of a female pup and was euthanized without further examination.

[e]NOAEL for developmental effects (maternal effects on liver weight were observed at ≥400 mg/kg/day).

aborted, this event was not statistically different from the control group or from historical control data in this strain of rabbit. Although the number of pregnant does was somewhat reduced in the low octocrylene-treated group, the authors suggested that this observation was not treatment-related, as treatment began 6 days post-insemination. One of the high-dose does produced a litter with a "high incidence" (not otherwise specified, data not shown) of short ribs among the fetuses, but no evidence of this or any other types of skeletal alterations were observed among fetuses from any other litter in the study (Odio et al. 1994).

In the oral developmental toxicity study, groups of 12 female CD-1 mice received octocrylene at 0, 100, 300, or 1000 mg/kg/day in corn oil *via* oral gavage on gestation days 8 to 12 (Odio et al. 1994). A NOAEL in the absence of any effects was identified at 1000 mg/kg/day (ECHA 2023), as there was no evidence of maternal or developmental toxicity observed at any dose tested. Although the pregnancy rate was lower in the high-dose group, this observation was not attributed to treatment, as treatment began after mating and there were no treatment-related effects on number of abortions, implantations, resorptions, or any other parameter that would suggest octocrylene had an effect on early embryo loss. Although pup mortality through the day after birth ranged between 4% and 7% within each treatment group and no pup mortality was observed in controls, the differences were not statistically significant (Odio et al. 1994).

Immunotoxicity

Some immunotoxicity data for octocrylene are available from the repeated-dose toxicity studies that evaluated immune-related endpoints (see details in the Repeated-dose toxicity section). There were no treatment-related adverse hematology or immune system-related organ changes (macroscopic or microscopic) in a 13-week dermal toxicity study in rabbits (Odio et al. 1994). Additionally, in the previously mentioned 90-day dietary toxicity study in rats (OECD TG 408), there was a female-specific increase in total protein, platelets, and globulins at the two highest doses, with an increase in platelets also observed in males at the highest dose (ECHA 2023). However, no additional immune system-related findings in hematology (i.e. leukocytes), gross pathology, or histopathology were reported (ECHA 2023).

Apart from these studies, only one other study evaluating immune-related endpoints was identified. In the freshwater insect *Chironomus riparius*, exposure to octocrylene up to 10 mg/L for 24 h did not affect immune-related gene expression (Muniz-Gonzalez and Martinez-Guitarte 2018). The relevance of this study to human risk assessment is unclear.

Neurotoxicity

The available data from *in vivo* studies demonstrate that octocrylene is not neurotoxic.

In the most robust study available (EOGRTS [OECD TG 443]), in which rats were administered octocrylene in the diet, there were no effects on neurodevelopment up to the highest dose tested, which was a mean intake of 534 mg/kg/day for males and 540 mg/kg/day for females (ECHA 2023) (see Developmental and reproductive toxicity section). Potential neurodevelopmental effects in this study were assessed *via* FOB and spontaneous motor activity (ECHA 2023). However, in its opinion on octocrylene, the ECHA considered the DNT portion of this study to have numerous limitations hampering any final conclusion on developmental neurotoxicity (ECHA 2022).

In the previously described 28-day inhalation toxicity study of rats exposed to octocrylene at concentrations of 0, 110, 330, or 1000 mg/m^3 for 6 h/day, 5 days/week for 28 days, the NOAEL was 1000 mg/m^3, the highest exposure level tested (Creutzenberg 2007). The only notable clinical observation was reduced activity of the high-dose animals (primarily males) for 1 to 2 h after the end of daily octocrylene exposure. The FOB assessment revealed no test material-related effects, except for possible locomotor activity effects, including decreased overall time in movement and significantly increased overall time in rest (which are interrelated) with the effects observed for several 15-min intervals in the mid- and high-dose group males. However, no effects were observed in the fourth 15-min interval, a clear dose dependency was not observed for locomotor activity effects in males, and no locomotor activity effects were observed for females.

Aside from the mammalian toxicology studies, there were non-mammalian toxicology studies that were identified on the potential neurotoxicity of octocrylene. In one study with the freshwater insect *Chironomus riparius*, there was no evidence of neurotoxicity, based on a lack of a monotonic or dose-dependent response from varying octocrylene exposure concentrations on acetylcholinesterase activity (Campos et al. 2017). Again, the human relevance of this study is unclear.

Risk characterization

To characterize the risk associated with the use of an octocrylene-containing sunscreen product, a MoS approach was used. A MoS was evaluated using the most health-protective NOAEL (153 mg/kg/day) from a reliable guideline study (OECD TG 443), which was determined to be protective of both reproductive/developmental effects and general toxicity. The MoS is a well-established risk assessment approach in which a selected reference or benchmark dose is divided by the measured or estimated exposure to quantify how many times lower the exposure is relative to the reference or benchmark dose. To calculate the MoS, we used the ratio of the NOAEL obtained from an animal toxicology study to the estimated human SED as shown in Equation (1). Although an MoS is not a probabilistic statement of risk, the concern for the exposure evaluated decreases as the value of the MoS increases. Accordingly, MoS values greater than 100 are interpreted to be acceptable and protective for non-genotoxic and non-carcinogenic assessments, whereas values lower than 100 suggest that the chemical exposure risk is not likely to be acceptable (SCCS 2023).

$$MoS = \frac{NOAEL}{SED} \quad (1)$$

Estimation of SED

The expected exposure to octocrylene *via* use of an octocrylene-containing sunscreen product was calculated using Equation (2) to derive the estimated SED from the product of the daily sunscreen applied (A) with an appropriate unit conversion factor (UC), the octocrylene concentration in the sunscreen (C), and the dermal absorption of octocrylene (D) divided by the individual's body weight (BW). Conservative assumptions were applied to the various terms of the equation (see Table 10).

$$SED\ (\mathrm{mg/kg/day}) = A\left(\frac{g}{day}\right) \times UC\left(1000\frac{mg}{g}\right) \times C\ (\%) \times \left(\frac{D(\%)}{BW}\right) \quad (2)$$

Sunscreen product exposure from applying formulations containing octocrylene were calculated for three separate scenarios: 1) 97.2 g/day maximum amount based on the MUsT, 2) 28 g/day based on the approximate amount to cover an adult body adequately in a single daily application per the American Academy of Dermatology, and 3) 3.46 g/day based on estimates for facial application of a sunscreen product.

Scenario 1. A 60-kg individual applies 97.2 g of a 10% octocrylene-containing sunscreen product per day with 0.33% dermal absorption of octocrylene; the SED of octocrylene was calculated to be 0.535 mg/kg/day.

$$SED = \left(97.2\frac{g}{day}\right) \times \left(1000\frac{mg}{g}\right) \times 0.1 \times \left(\frac{0.0033}{60\ kg}\right) = 0.535\ mg/kg/day$$

Scenario 2. A 60-kg individual applies 28 g of a 10% octocrylene-containing sunscreen product per day with 0.33% dermal absorption of octocrylene; the SED of octocrylene was calculated to be 0.154 mg/kg/day. This exposure represents a high-end estimate of consumer use based on authoritative assessments and published consumer usage data. The SCCS (2023) uses 18 g/day for two daily applications and cites clinical studies reporting a 95th percentile use of 13 g/day. The EPA cites an average of 3.18 g/day and a 90th percentile frequency of 0.005–0.14 applications/day, reflecting real-world behavior (USEPA 2011). Thus, using 28 g per day likely represents an upper bound of realistic exposure.

$$SED = \left(28\frac{g}{day}\right) \times \left(1000\frac{mg}{g}\right) \times 0.1 \times \left(\frac{0.0033}{60\ kg}\right) = 0.154\ mg/kg/day$$

Scenario 3. A 60-kg individual applies 3.46 g (facial application only) of a 10% octocrylene-containing sunscreen product per day with 0.33% dermal absorption of octocrylene; the SED of octocrylene was calculated to be 0.019 mg/kg/day.

$$SED = \left(3.46\frac{g}{day}\right) \times \left(1000\frac{mg}{g}\right) \times 0.1 \times \left(\frac{0.0033}{60\ kg}\right) = 0.019\ mg/kg/day$$

Octocrylene-specific MoS calculations

For octocrylene MoS calculations, two NOAELs (Table 11) were considered from the available reliable guideline animal toxicology studies; 153 mg/kg/day for male rats from the EOGRTS (OECD TG 443) (Symrise 1992e; ECHA 2023) and 175 mg/kg/day from the 90-day dietary toxicity study in rats (OECD TG 408) (ECHA 2023). This is consistent with SCCS guidelines, which state that "the NOAEL is mainly derived from a 90-day repeated-dose animal study or from a reproductive toxicity animal study" (SCCS 2023). Because no key dermal absorption study was available for octocrylene, in accordance with SCCS guidelines, the NOAEL value from an oral repeated-dose toxicity study was considered with an applicable conservative oral bioavailability assumption. Overall, the NOAEL of 153 mg/kg/day for male rats from the EOGRTS (OECD TG 443) (Symrise 1992e; ECHA 2023) was determined to be the most health protective, and thus was used for the MoS calculation. This NOAEL was determined to be protective of both reproductive/developmental effects and general toxicity.

The following section provides calculations for the obtained MoS values of >143 using three different exposure scenarios. These MoS values would be applicable to non-adult populations as well. According to the SCCS, although

Table 10. Assumptions for octocrylene systemic exposure dose calculations.

Term	Assumed value	Rationale
A (sunscreen applied)	97.2 g/day	Maximum amount based on FDA guidance for industry (i.e., assumed body surface area of 16,200 cm^2, sunscreen applied to 75% of body area, applied amount of 2 mg/cm^2, and 4 applications/day)
	28 g/day	Approximate amount to cover an adult body in a single daily application (American Academy of Dermatology, 2018)
	3.46 g/day	The value used for safety evaluations of facial application products (1.73 g/application x 2 applications/day)
UC (unit conversion factor)	1000 mg/g	
C (octocrylene concentration within product)	0.10	10% is the maximum concentration of octocrylene allowed in product formulations in the United States (Drugbank 2022)
D (dermal absorption of octocrylene)	0.0033	0.33% of the applied dermal dose of octocrylene was bioavailable in an *in vitro* study with human skin (see Absorption section)
BW (body weight)	60 kg	Typical body weight of an adult human female
	70 kg	Typical body weight of an adult human male

Table 11. NOAELs From key animal toxicology studies on octocrylene.

Study	NOAEL (basis) [detailed basis]	Reference
Extended one-generation reproductive toxicity study in rats (OECD TG 443)	153 mg/kg/day[a] (developmental and reproductive toxicity, parental systemic toxicity) [based on decreased number of implantation sites, number of pups, pup body weight, and decreased parental body weight]	2019 study report (ECHA 2023)
90-day dietary toxicity study in rats (OECD TG 408)	175 mg/kg/day (general toxicity) [based on liver, thyroid, and pituitary effects secondary to hepatic enzyme induction]	1993 study report (ECHA 2023)

NOAEL: No-observed-adverse-effect level; OECD: Organization for Economic Co-operation and Development; TG: Test guideline.
[a]NOAEL was determined to be the most health protective, and was selected for use in the margin of safety calculations.

the surface area/body weight ratio is 2.3-fold higher in newborns than in adults, changing to 1.8- and 1.6-fold higher at 6 and 12 months, respectively, this difference is generally covered by the intraspecies factor of 10 (3.2×3.2) that is already considered in the assessment of the MoS (SCCS 2023).

Based on the male rat NOAEL of 153 mg/kg/day from the EOGRTS (Symrise 1992e; ECHA 2023) and an oral bioavailability of 50% for rats based on the SCCS guidelines for when empirical data are missing (SCCS 2023), and supported by kinetic data in humans, the following calculations were used to obtain MoS values of >143 for adverse potential overt toxicity effects for the three previously described exposure scenarios.

Scenario 1.

$$MoS = \frac{153\ mg/kg/day\ (NOAEL) \times 0.50(bioavailability)}{0.535\ mg/kg/day(SED)} = 143$$

Scenario 2.

$$MoS = \frac{153\ mg/kg/day\ (NOAEL) \times 0.50(bioavailability)}{0.154\ mg/kg/day(SED)} = 497$$

Scenario 3.

$$MoS = \frac{153\ mg/kg/day\ (NOAEL) \times 0.50(bioavailability)}{0.019\ mg/kg/day(SED)} = 4026$$

Although oral bioavailability was conservatively assumed to be 50%, other risk evaluations of octocrylene, such as the one performed by the Danish EPA, have assumed 100% (DEPA 2015); therefore, adjusted MoS values could be up to 2x the values estimated above (i.e. 286, 994, or 8052 for Scenarios 1, 2, and 3, respectively).

The risk characterization of octocrylene based on a reported dermal penetration of 0.33% in an *in vitro* percutaneous absorption study is likely conservative considering it represents an upper bound absorption (mean + 1 SD). Furthermore, an alternative risk characterization of octocrylene based on FDA's clinical MUsT study data was also conducted.

Based on the NOAEL of 175 mg/kg/day from the 90-day dietary toxicity study in rats (ECHA 2023) and an oral bioavailability of 50% for rats based on the SCCS guidelines for when empirical data is missing (SCCS 2018), the following calculations were used to obtain MoS values of >164 for adverse potential overt toxicity effects for the three previously described exposure scenarios.

Scenario 1.

$$MoS = \frac{175\ mg/kg/day\ (NOAEL) \times 0.50(bioavailability)}{0.535\ mg/kg/day(SED)} = 164$$

Scenario 2.

$$MoS = \frac{175\ mg/kg/day\ (NOAEL) \times 0.50(bioavailability)}{0.154\ mg/kg/day(SED)} = 568$$

Scenario 3.

$$MoS = \frac{175\ mg/kg/day\ (NOAEL) \times 0.50(bioavailability)}{0.019\ mg/kg/day(SED)} = 4605$$

Estimation of maximum amount of octocrylene in the body from FDA's MUsT studies

The highest geometric mean C_{max} value reported for octocrylene in the MUsT studies was 7.8 ng/mL (Matta et al. 2020). The volume of distribution was calculated using GastroPlus® v9.7 PBPK software (Simulations Plus, Inc., Lancaster, CA) with the Lukacova method (Lukacova et al. 2008), as reviewed by Mathew et al. (Mathew et al. 2021). Assuming a volume of distribution (V_d) of 941 L (Lukacova et al. 2008), the total internal (systemic) dose of octocrylene is the product of the C_{max} and V_d as follows:

$$Amount\ of\ octocrylene\ in\ the\ body = 7.8\ ng/mL \times 10^{-6}\ mg/ng \times 941,000\ mL = 7.34\ mg$$

Therefore, this is the estimated amount of octocrylene in the body, i.e. 0.00734 g, at a fixed moment (C_{max}) in time following topical application of 9.72 g/day of this sunscreen active ingredient over 4 days.

The total applied dose in the MUsT study was 9.72 g (97.2 g x 0.01) (Matta et al. 2020). Therefore, the dermal penetration percentage for octocrylene is calculated as 0.076% (0.00734 g total internal dose divided by 9.72 g applied dose) according to Equation (3).

$$Dermal\ Penetration(\%) = \frac{Total\ Internal\ (Systemic) Dose(g)}{Total\ Dermally\ Applied\ Dose(g)} \times 100 \quad (3)$$

This calculation has numerous uncertainties, including lack of consideration for metabolite formation, elimination rate, and AUC analysis. However, this estimate of the dermal absorption based on the C_{max} in FDA's clinical MuST study

and estimated volume of distribution crudely supports a conservative value of 0.33% derived from *in vitro* skin penetration studies that was used in the MoS calculations.

Octocrylene safety conclusion

In conclusion, octocrylene can be considered to pose no human health risks when used as a sunscreen UV filter at concentrations up to 10%. Furthermore, based on the results of subchronic rodent toxicity studies, genotoxicity and mutagenicity studies, and evidence against immunotoxic or specific hormonal effects (Cohen et al. 2025), octocrylene is not expected to represent a cancer risk in humans.

Discussion

Based on the available nonclinical and human clinical safety test results, octocrylene shows a favorable safety profile without clear indications of toxicity or endpoints of concern. This conclusion has been reached and considered to be supported by global regulatory authorities as indicated by their registering this substance for use at up to 10% in consumer end-use products. Given its prevalence and long history of use as a UV filter, there are sufficient data from clinical use and nonclinical safety studies on octocrylene to assess its safety as a UV filter in OTC topical sunscreen products. Specifically, there are clinical studies as well as various *in vitro* and *in vivo* toxicity studies in animal models to facilitate the characterization of this chemical with respect to its pharmacokinetics, pharmacodynamics, and potential toxicological properties (see Table 12 for a summary of the available data).

Estimates of the dermal absorption of octocrylene have varied based on the model and dose concentrations used. Although no harmonized dermal absorption value is available, data from a GLP-compliant OECD 428 *in vitro* dermal absorption study using human skin samples indicate very low percutaneous absorption ($\leq$0.33% of the applied dose). Data from a human clinical trial using dermal administration are consistent with this absorption estimate. There are no clinical or nonclinical data with which to assess the distribution of octocrylene; however, there is some information regarding background levels of octocrylene and its metabolism and excretion in plasma and urine from human biomonitoring and clinical studies. Six tentative metabolites of octocrylene have been identified, although metabolite-specific toxicity profiles were not available. However, as the same metabolites were produced with rat and human liver microsomes, it is likely that the toxicity of the metabolites would have been covered, at least in part, by the studies with octocrylene, due to their *in situ* formation.

Indirect assessment of the bioaccumulation potential of octocrylene has been conducted in a case study of UV filters relative to the practical application of the interim internal threshold of toxicological concern (iTTC), which is used to refine the threshold of toxicological concern (TTC)–based assessment of human dermal exposure to consumer products (Najjar et al. 2023). Human dermal PK data from the FDA's MUsT studies (Matta et al. 2019, 2020) showed that the experimentally determined internal exposure to octocrylene was an order of magnitude lower than the 1 μM interim iTTC threshold, in contrast to the external exposure to octocrylene, which exceeded the external dose limits of the standard TTC

Table 12. Summary of octocrylene toxicological endpoints and risk characterization.

Property	Key octocrylene-related results
Pharmacokinetics	• Dermal absorption is low (0.33%). • Several recent human biomonitoring studies on octocrylene have characterized exposure levels based on analytes in plasma and/or urine. • In human maximal usage trials, the terminal half-life ranged from 43.5 to 84.4 h.
Acute toxicity	• Rat oral LD_{50} >5000 mg/kg • Rat dermal LD_{50} >2000 mg/kg
Repeated-dose toxicity	• A 14-day dietary (palatability) study in rats demonstrated no treatment-related adverse effects. • A 14-/28-day mechanistic dietary toxicity study (OECD TG 407-like) in rats characterized the compensatory mechanisms resulting from hepatic enzyme induction. • A 13-week dermal study in rabbits (approximately 93, 189, or 381 mg/kg/day) demonstrated no treatment-related adverse effects, except for slight to moderate local skin irritation and decreased body weight gain. • A 90-day dietary toxicity study (OECD TG 408) in rats demonstrated a NOAEL of 175 mg/kg/day based on liver, thyroid, and pituitary effects secondary to hepatic enzyme induction unlikely to be of toxicological relevance to humans.
Skin irritation, skin sensitization, phototoxicity, and photosensitization	• Non-irritant, a non-sensitizer, and non-phototoxic
Genotoxicity	• All existing *in vitro* and *in vivo* genotoxicity results are negative. • Although no long-term carcinogenicity study on octocrylene has been performed, repeated-dose studies (up to 90 days) demonstrated no evidence for induction of hyperplasia and/or pre-neoplastic lesions, immunotoxicity, or hormonal effects, suggesting long-term carcinogenicity studies are not warranted.
Hormonal, developmental, and reproductive toxicity	• Although hormonal effects have been observed in some *in vitro* assays, these pathways and responses were not observed *in vivo*, as no related effects were reported in the rodent Hershberger and uterotrophic assays and in other high-tier *in vivo* toxicity studies.
Neurotoxicity	• No effects on neurodevelopment were noted in an extended one-generation reproductive toxicity study (EOGRTS) (OECD TG 443) in rats.
Risk characterization	• Based on the NOAEL of 153 mg/kg/day from the EOGRTS, an adjusted MoS of 143 for adverse endocrine-related and DART effects was calculated.

DART: Developmental and reproductive toxicity; EOGRTS: Extended one-generation reproductive toxicity study; LD_{50}: Median lethal dose (the dose at which 50% of the animals died); NOAEL: No-observed-adverse-effect level; MoS: Margin of safety; OECD: Organization for Economic Co-operation and Development; TG: Test guideline.

approach (Najjar et al. 2023). The first step of this assessment verified that the case study chemicals, including octocrylene, were in the iTTC applicability domain (e.g. type of substance, mutagenicity/genotoxicity, concern for bioaccumulation, and concern for endocrine activity) (Blackburn et al. 2020). As previously discussed in the current paper, octocrylene has not demonstrated mutagenicity/genotoxicity nor is it expected to be a potent ER or AR agonist/antagonist (Browne et al. 2015; SCCS 2021; Najjar et al. 2023). Furthermore, octocrylene does not resemble known bioaccumulating chemicals such as the toxic industrial byproduct TCDD or its structural analogues, does not contain metabolic blocking groups, has a low bioconcentration factor when using a toxicokinetic approach to estimation of human bioaccumulation potential (Tonnelier et al. 2012), and is readily excreted from the body within days based on human PK data (Matta et al. 2019; 2020).

The acute toxicity profile indicates that octocrylene is nontoxic. Octocrylene generally did not cause eye or skin irritation, skin sensitization, or phototoxicity, but some indications of dermal sensitization have been reported in clinical case studies. The NOAEL for general toxicity from a 90-day rat dietary toxicity study was 175 mg/kg/day, based on liver, thyroid, and pituitary effects at higher dose levels that were secondary to hepatic enzyme induction. The NOAEL for parental systemic, reproductive, and developmental toxicity from an extended one-generation reproductive toxicity study in rats was 153/163 mg/kg/day (males/females). There was no evidence of effects of octocrylene on immune tissues or androgenic, estrogenic, or thyroid endpoints. However, in its final opinion on octocrylene, the SCCS noted that although available data suggest that there are potential endocrine effects, the current level of evidence is not sufficient to support a human health risk assessment based on endocrine effects (SCCS 2021).

There was no evidence of octocrylene-induced neurotoxicity, based on the most robust study available (EOGRTS [OECD TG 443]), in which potential neurodevelopmental effects were assessed in rats (ECHA 2023). However, in its opinion on octocrylene, the ECHA considered the DNT portion of this study to have numerous limitations hampering any final conclusion on developmental neurotoxicity, including inappropriate statistical analysis, absence of historical controls and positive control, poor reporting of the methods, and lack of raw data for the auditory startle response (ECHA 2022).

Although there are no formal 2-year carcinogenicity studies for octocrylene, a 90-day subchronic dietary toxicity study in rats did not show an increase in hyperplasia of any tissue or evidence of cytotoxicity, and octocrylene has not shown any indications for genotoxicity either *in vitro* or *in vivo*, or an effect on immunotoxicity or hormonal effects, together indicating that carcinogenicity in humans is unlikely (see Cohen et al. 2025). In support of this conclusion, Woutersen et al. evaluated whether preneoplastic lesions in subchronic toxicity studies could predict outcomes in chronic carcinogenicity studies for 163 non-genotoxic chemicals (Woutersen et al. 2016). Though 75% of the 148 compounds that were negative for preneoplastic lesions in subchronic studies were also negative in the carcinogenicity studies, the predictivity was improved to 97% when relevance of animal tumors was considered (Woutersen et al. 2016). The authors concluded their results indicated that chemicals showing no histopathologic risk factors for neoplasia in a subchronic rat study may be considered non-carcinogenic and do not require further testing in a carcinogenicity study (Woutersen et al. 2016). Similar conclusions have been drawn by other researchers (Cohen 2010; Cohen et al. 2019). Taken together, although no long-term carcinogenicity study on octocrylene has been performed, repeated-dose studies (up to 90 days) have demonstrated no evidence for induction of hyperplasia and/or pre-neoplastic lesions, suggesting long-term carcinogenicity studies are not warranted.

Overall, based on the NOAEL selected from the available animal toxicity studies and the conservative assumptions used for estimating the SED from the dermal application of sunscreen products, MoS values greater than 100 were obtained for octocrylene. Therefore, the available data on octocrylene is supportive of a determination that it poses no human health risks when used in sunscreen products at concentrations up to 10%. This conclusion is also consistent with the safety acceptance and global approval of octocrylene (EP 2009; Jansen et al. 2013; TGA 2021).

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Declaration of interests

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Appendix

Appendix Table 1. OECD conceptual framework for assessment of hormonal responses.

Level	Toxicological assessment[1]
Level 1: Existing data and non-test information	Physical and chemical properties (e.g. MW, reactivity, volatility, biodegradability)
	All available (eco)toxicological data from standardized or non-standardized tests
	Read across, chemical categories, QSARs and other *in silico* predictions, and ADME model predictions
Level 2: *In vitro* assays providing data about selected endocrine mechanism(s)/ pathways(s) (mammalian and non-mammalian methods)	Estrogen (OECD TG 493) or androgen receptor binding affinity (US EPA TG OPPTS 890.1150)
	ER transactivation (OECD TG 455 ISO 19040-3), yeast estrogen screen (ISO 19040-1 and 2)
	Androgen receptor transactivation (OECD TG 458)
	Steroidogenesis *in vitro* (OECD TG 456)
	Aromatase assay (US EPA TG OPPTS 890.1200)
	Thyroid assays (e.g. thyroperoxidase inhibition, transthyretin binding)
	Retinoid receptor transactivation assays
	Other hormone receptor assays as appropriate
	High-throughput screens
Level 3: *In vivo* assays providing data about selected endocrine mechanism(s)/ pathway(s); some assays may also provide evidence of adverse effects[2,6]	**Uterotrophic assay (OECD TG 440)**
	Hershberger assay (OECD TG 441)
	Amphibian metamorphosis assay (AMA) (OECD TG 231)
	Fish short-term reproductive screening assay (FSTRA) (OECD TG 229)[3]
	Androgenized female stickleback screen (AFSS) (OECD GD 148)
	EASZY Assay. Detection of Substances Acting through Estrogen Receptors using Transgenic cyp19a1b GFP Zebrafish Embryos (draft OECD TG)
	Xenopus embryonic thyroid signaling assay (XETA) (draft OECD TG)
	Juvenile medaka anti-androgen screening assay (JMASA) (draft OECD GD)
	Short-term juvenile hormone activity screening assay using *Daphnia magna* (draft OECD TG)
	Rapid androgen disruption adverse outcome reporter (RADAR) assay (draft OECD TG)
Level 4: *In vivo* assays providing data on adverse effects on endocrine relevant endpoints[3,6]	**Repeated dose 28-day study (OECD TG 407)**
	Repeated dose 90-day study (OECD TG 408)
	Pubertal development and thyroid function assay in peripubertal male rats (PP male assay) (US EPA TG OPPTS 890.1500)
	Pubertal development and thyroid function assay in peripubertal female rats (PP female assay) (US EPA TG OPPTS 890.1450)
	Prenatal developmental toxicity study (OECD TG 414)
	Combined chronic toxicity and carcinogenicity studies (OECD TG 451-453)
	Reproduction/developmental toxicity screening test (OECD TG 421)
	Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422)
	Developmental neurotoxicity study (OECD TG 426)
	Repeated dose dermal toxicity: 21/28-day study (OECD TG 410)
	Subchronic dermal toxicity: 90-day study (OECD TG 411)
	28-day (subacute) inhalation toxicity study (OECD TG 412)
	Subchronic inhalation toxicity: 90-day study (OECD TG 413)
	Repeated dose 90-day oral toxicity study in non-rodents (OECD TG 409)
	Fish sexual development test (FSDT) (OECD TG 234)
	Larval amphibian growth and development assay (LAGDA) (OECD TG 241)
	Avian reproduction assay (OECD TG 206)
	Fish early life stage (FELS) toxicity test (OECD TG 210)
	New guidance document on harpacticoid copepod development and reproduction test with *Amphiascus* (OECD GD 201)[3]
	Potamopyrgus antipodarum reproduction test (OECD TG 242)[4]
	Lymnaea stagnalis reproduction test (OECD TG 243)[4]
	Chironomid toxicity test (OECD TG 218-219)[4]
	Daphnia magna reproduction test (with male induction) (OECD TG 211)[4]
	Earthworm reproduction test (OECD TG 222)[4]
	Enchytraeid reproduction test (OECD TG 220)[4]
	Sediment water *Lumbriculus* toxicity test using spiked sediment (OECD TG 225)[4]
	Predatory mite reproduction test in soil (OECD TG 226)[4]
	Collembolan reproduction test in soil (TG OECD 232)[4]
Level 5: *In vivo* assays providing more comprehensive data on adverse effects on endocrine relevant endpoints over more extensive parts of the lifecycle of the organism[3,6]	**Extended one-generation reproductive toxicity study (EOGRTS) (OECD TG 443)[5]**
	Two-generation reproduction toxicity study (OECD TG 416, most recent update)
	Fish life cycle toxicity test (FLCTT) (US EPA TG OPPTS 850.1500)
	Medaka extended one-generation reproduction test (MEOGRT) (OECD TG 240)
	Avian two-generation toxicity test in the Japanese quail (ATGT) (US EPA TG OCSPP 890.2100/740-C-15-003)
	Sediment water chironomid life cycle toxicity test (OECD TG 233)[4]
	Daphnia multigeneration test for assessment of EDCs (draft OECD TG)[4]
	Zebrafish extended one-generation reproduction test (ZEOGRT) (draft OECD TG)

Notes: Adapted from the 2017 OECD revised conceptual framework (OECD 2018).

1. Assays with **bold text** designate *in vivo* mammalian assays.
2. Some assays may also provide some evidence for adverse effects.
3. Some endpoints can be sensitive to more than one mechanism and may be due to non-endocrine mechanisms.
4. At present, these invertebrate assays solely involve apical endpoints which can respond to some endocrine active substances and some non-endocrine active substances. Those in Level 4 are generally partial life cycle tests, whereas those in Level 5 are full or multiple life cycle tests.
5. The EOGRTS (OECD TG 443) is preferable for detecting endocrine disruption because it provides an evaluation of several endocrine endpoints in the juvenile and adult F1, which are not included in the two-generation study (OECD TG 416) adopted in 2001.
6. Depending on the guideline/protocol used, the fact that a substance may interact with a hormone system in these assays does not necessarily mean that when the substance is used it will cause adverse effects in humans or ecological systems.