CRITICAL REVIEWS IN TOXICOLOGY
https://doi.org/10.1080/10408444.2025.2535394

REVIEW ARTICLE

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Comprehensive review of avobenzone (butyl methoxydibenzoylmethane) toxicology data and human exposure assessment for personal care products

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ABSTRACT

A comprehensive review of existing toxicity and human exposure data for the ultraviolet filter avobenzone (butyl methoxydibenzoylmethane) was conducted to assess its safety as currently used in over-the-counter sunscreen formulations. Avobenzone has a suitable safety profile without any clear markers of toxicity or endpoints of concern. There are sufficient clinical studies and *in vitro* and *in vivo* toxicity studies in animal models to assess avobenzone's pharmacokinetics, pharmacodynamics, and potential toxicological properties, supportive of its long history of safe use. No harmonized dermal absorption value was available, but the clinical data indicate low percutaneous absorption of avobenzone in humans (≤0.59% of the applied dose). There were no data to characterize the distribution of avobenzone; however, four tentative metabolites of avobenzone have been identified, and limited excretion in urine was demonstrated in human biomonitoring studies. Avobenzone generally did not cause dermal irritation or sensitization, but indications of photoallergy have been reported in clinical case studies. The acute toxicity profile indicated that avobenzone has minimal toxicity. The no-observed-adverse-effect level (NOAEL) for general toxicity from a rat dietary subchronic toxicity study was 450 mg/kg/day. There was no evidence of avobenzone effects on immune tissues or the estrogen, androgen, or thyroid systems. Although there were no formal 2-year carcinogenicity studies for avobenzone, a 90-day dietary exposure study in rats did not show any increase in hyperplasia of any tissue or evidence of cytotoxicity, and avobenzone has not shown any indication of genotoxicity either *in vitro* or *in vivo*. Together, this indicates that key events for modes of action for avobenzone are absent and carcinogenicity in humans is unlikely. Based on the selected rat subchronic NOAEL and conservative assumptions for estimating the systemic exposure dose (SED) from the application of sunscreen products, margins of exposure (defined as the ratio of NOAEL to SED) greater than 100 were obtained for avobenzone. Therefore, the available data show that avobenzone is unlikely to pose a risk to human health when used in sunscreen products at concentrations up to the permitted maximum usage levels in the United States and Canada, which is 3%.

ARTICLE HISTORY
Received 13 May 2025
Revised 9 July 2025
Accepted 10 July 2025

KEYWORDS
Avobenzone; butyl methoxydibenzoylmethane; 70356-09-1; toxicology; exposure assessment; sunscreen; UV filter; personal care products; cosmetics

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Introduction

Avobenzone (butyl methoxydibenzoylmethane, BMDBM, BMDM; CAS no. 70356-09-1) is an oil-soluble dibenzoyl methane derivative (Figure 1) used in many commercially available sunscreens as a topical long wavelength ultraviolet (UV) filter (see Table 1 for identifiers and properties). Avobenzone is one of the most effective absorbers in the UVA range of the electromagnetic spectrum, blocking both UVA-I (340-400 nm) and UVA-II (320-340 nm) wavelengths (NCBI 2025). Importantly, avobenzone is currently the only dedicated UVA absorber listed in the Over-the-Counter (OTC) Sunscreen Drug Monograph (USFDA 2022b); thus, it is an essential UV filter for the formulation of effective, broad-spectrum sunscreen products. Such products help protect consumers from sunlight-associated skin damage and disease, such as skin cancers, premature aging, and abnormal pigmentation that result from UV-induced damage to DNA and other macromolecules, and production of reactive oxygen species (Schuch et al. 2017).

Figure 1. Chemical structure of avobenzone (butyl methoxydibenzoylmethane). https://pubchem.ncbi.nlm.nih.gov/compound/Avobenzone

Avobenzone is prone to degradation upon exposure to sunlight; therefore, to increase its stability and duration of action, photostabilizers are often added to sunscreen products that contain avobenzone (NCBI 2025). To help stabilize avobenzone, antioxidants generally regarded as safe and effective, such as ascorbic acid, are used to complement the photoprotection offered by avobenzone. Octocrylene, another UV filter, is used frequently to stabilize avobenzone in sunscreen formulations (Gabros et al. 2025).

Avobenzone has a long history of safe use in sunscreen products in the United States (US) and elsewhere. Since publication of the U.S. Food and Drug Administration (FDA) 1999 Final Monograph, avobenzone has been classified as a category I UV filter (USFDA 1999). Following OTC reform legislation in 2020 (USFDA 2019), avobenzone's classification has been under review by the FDA. In its current classification, the allowable maximum concentration of avobenzone in sunscreen products is limited to 3% in the United States and Canada; 5% in Europe, the Southern Common Market (MERCOSUR), Australia, China, Korea, and the Association of Southeast Asian Nations (ASEAN) countries; and 10% in Japan (DSM 2007; EP 2009; Jansen et al. 2013; Kockler et al. 2013; TGA 2021). These permitted levels are based on review of avobenzone safety, efficacy, and postmarket surveillance data by numerous regulatory bodies and safety experts around the world. From 1992 to 2009, the FDA reviewed and approved five OTC New Drug Applications (NDAs) containing avobenzone at concentrations ranging from 2% to 3% (USFDA 2022a). As part of the approval process, the FDA reviewed the safety of avobenzone (together with other active sunscreen ingredients) at levels of 2% to 3% in each NDA formulation and various dosage forms. Table 2 provides a summary of the FDA-approved OTC sunscreen NDA products that contain avobenzone. None of the global regulatory bodies that have approved avobenzone for use in sunscreen products have reported any health or safety concerns related to the use of this material.

Although the FDA's review of avobenzone's classification implies that there might be safety concerns that have not been adequately addressed, this opinion is not shared by other regulatory authorities. To assist this review process, the purpose of this assessment seeks to (1) develop a comprehensive summary of the pharmacokinetic (PK) and toxicological data that exists for avobenzone; (2) estimate the systemic exposure dose from the application of sunscreen products employing conservative assumptions; and (3) provide an estimate of the derived margin of exposure (MoE) for avobenzone when used in sunscreen products at concentrations up to 3%.

Materials and methods

A literature review was conducted to identify clinical and nonclinical studies that evaluated avobenzone PK and toxicity. Studies were identified through expert organizational

Table 1. Avobenzone identifiers and physicochemical properties.

Identifier/property	Attribute
INCI	Avobenzone
IUPAC	1-(4-*tert*-Butylphenyl)-3-(4-methoxyphenyl)propane-1,3-dione
CAS registry	70356-09-1 (active)
	112725-59-4; 185160-18-3; 87075-14-7 (deprecated)
EINECS (EC)	274-581-6
COLIPA	S666
Synonyms	Avobenzonum
	Butyl methoxydibenzoylmethane
	4-*tert*-Butyl-4′-methoxydibenzoylmethane
	1,3-Propanedione, 1-(4-(1,1-dimethylethyl)phenyl)-3-(4-methoxyphenyl)-
	1-(4-(1,1-Dimethylethyl)phenyl)-3-(4-methoxyphenyl)-1,3-propanedione
	1-(p-*tert*-Butylphenyl)-3-(p-methoxyphenyl)-1,3-propanedione
Trade names	Parsol 1789®
	Neo Heliopan® 357
	Eusolex 9020®
Molecular formula	$C_{20}H_{22}O_3$
Molecular weight (g/mol)	310.39
Physical description	Off-white to yellowish, crystalline powder (HSDB)
Vapor pressure (Pa) at 25 °C	$<1.0 \times 10^{-5}$ (experimental)
Melting point (°C)	81-86 (experimental)
Boiling point (°C)	>400 (experimental)
Solubility in water (mg/L) at 20 °C	0.027 (experimental)
Octanol/water partition (log K_{ow}) at 40 °C	4.51 (predicted)
Henry's law constant (H_{cc}) (unitless)	Not reported
Henry's law constant (H_{pc}) (atm-m^3/mol)	2×10^{-10} (predicted)
Density (relative)	1.221 (experimental)
Type of sunscreen ultraviolet (UV) ray filter	UV-A I
Wavelength absorption (Abs.) range (nm)	310-340 (experimental)
Maximum wavelength absorption (nm); UV absorption (E 1%/1 cm)	357

CAS: Chemical Abstracts Service; COLIPA: The European Cosmetic and Perfumery Association; EC: European Commission; EINECS: European Inventory of Existing Commercial Chemical Substances; HSDB: Hazardous Substances Data Bank; INCI: International Nomenclature Cosmetic Ingredient; IUPAC: International Union of Pure and Applied Chemistry.
Sources: (EC 2000; ECHA 2022; NCBI 2025).

Table 2. NDAs containing avobenzone (2% to 3%) 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	Avobenzone (2%) Ecamsule (2%) Octocrylene (10%) Titanium dioxide (2%)	Cream (topical)	OTC
ANTHELIOS 40 (L'Oréal USA Products Inc)	N022009	2 approvals: 31 Mar 2008, 29 Oct 2009	Avobenzone (2%) Ecamsule (3%) Octocrylene (10%) Titanium dioxide (5%)	Cream (topical)	OTC
ANTHELIOS SX (L'Oréal USA Products Inc)	N021502	21 Jul 2006	Avobenzone (2%) Ecamsule (2%) Octocrylene (10%)	Cream (topical)	OTC
CAPITAL SOLEIL 15 (L'Oréal USA Products Inc)	N021501	2 Oct 2006	Avobenzone (2%) Ecamsule (3%) Octocrylene (10%)	Cream (topical)	OTC
SHADE UVAGUARD (Bayer Healthcare LLC)	N020045	7 Dec 1992	Avobenzone (3%) Octinoxate (7.5%) Oxybenzone (3%)	Lotion (topical)	DISC

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

and state, federal, and international regulatory electronic databases to locate substance-specific information and data. These results were supplemented with additional published literature retrieved from the PubMed database. Relevant unpublished toxicity information generated by manufacturers, mostly obtained from the European Chemicals Agency (ECHA) database, was included. Citation of the ECHA database was based on the last known update to the file. Additional literature was identified 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), the Scientific Committee on Consumer Products (SCCP), the Scientific Committee on Cosmetic and Non-food Products (SCC-NFP), and the Scientific Committee on Cosmetology (SCC). Any relevant unpublished reports of toxicity studies performed by a manufacturer, mostly obtained from the ECHA database, were included.

The information 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:

> (avobenzone OR butyl methoxydibenzoylmethane OR Parsol 1789 OR 70356-09-1 OR 112725-59-4 OR 185160-18-3 OR 4-tert-butyl-4-methoxydibenzoylmethane) 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 retrieved 194 papers, from which titles and abstracts were screened by two independent reviewers to identify potentially relevant articles. Those that addressed avobenzone 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 test guideline (TG) issued 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 noted when applicable for studies described in this avobenzone profile. Although priority was given to such studies, other studies that were not GLP and/or OECD compliant were considered in the overall weight-of-evidence evaluation taking into account an assessment of the quality of the study. In the overall weight-of-evidence evaluation, quality of studies was considered, and *in vivo* evaluations were given stronger consideration than *in vitro* assessments, and the strongest consideration was given for studies performed in humans (much less weight given for individual case reports compared to carefully performed controlled investigations).

Results

Photodegradation and photostability

Avobenzone may be susceptible to photodegradation due to its ability to undergo keto-enol tautomerism (Kockler et al. 2013). Specifically, the enol form of avobenzone absorbs in the UVA range, and exposure to UV light may cause an equilibrium shift to the diketo form, which absorbs in the UVC range, thereby reducing its long wavelength UV protection (Kockler et al. 2013). Therefore, in order to provide maximum efficacy, avobenzone is typically combined with other UV filters, such as octocrylene, or excited state quenchers, such as diethylhexyl 2,6-naphthalate and ethylhexyl methoxycrylene, which photostabilize it during exposure to UV (Nash and Tanner 2014, Sohn 2016). The photostability of avobenzone has been an area of research in the past 3 decades to ensure that the formulation can deliver UV absorbance as intended. When properly photostabilized, avobenzone is much less likely to undergo photodecay to products without established toxicity profiles. Several studies have identified photodegradation products of avobenzone under certain conditions (see details in Table 3). As previously noted, avobenzone is photostabilized in end-user products; therefore, these data on photodegradants are presented only for reference and do not imply any health risk concerns for consumers under typical usage scenarios.

In addition to the studies described in Table 3, the transformation of avobenzone in conditions of aquatic chlorination and UV irradiation has been studied (Trebse et al. 2016). Avobenzone was stable under UV irradiation but degraded in water and reported to form two pairs of substituted benzoic aldehydes and acids; there was a positive correlation in which higher levels of these products were observed during longer irradiations (Trebse et al. 2016).

Pharmacokinetics

The following sections discuss the absorption, distribution, metabolism, and excretion of avobenzone based on its physicochemical properties and from basic *in vitro* and *in vivo* PK studies. Available human biomonitoring studies on avobenzone were reviewed for each PK endpoint; some evaluated avobenzone levels in plasma and/or urine, whereas others monitored analytes after intentional oral or dermal exposure to avobenzone. Clinical studies were given priority when characterizing avobenzone PK endpoints; however, nonclinical/animal data were relied upon when clinical data were limited or not available. The PK of avobenzone are well characterized in clinical and nonclinical studies. In general, it has been noted that the dermal absorption of avobenzone is limited; however, clinical studies have reported measurable plasma concentrations (>0.5 ng/L) after single or repeated applications in Maximal Usage Trials (MUsT) (Matta et al. 2019; 2020). There are no studies in which information on the organ-specific distribution of avobenzone has been reported, although four tentative metabolites for avobenzone have been identified. Human biomonitoring studies have noted urinary excretion of avobenzone with a mean systemic terminal half-life of 33 to 112 h (Matta et al. 2019, 2020).

Absorption

Several clinical and nonclinical studies that investigated the dermal absorption of avobenzone alone or in combination with other UV filters and in different formulations are summarized in Table 4. Studies that investigated the measured plasma or receptor fluid concentrations of avobenzone following application and studies that reported epidermis/dermis levels, which could then act as a reservoir and release avobenzone over time, were considered relevant for this

Table 3. Summary of photostabilization/photodegradation studies of avobenzone.

Study methodology	Results	Reference
The photostabilizing ability of 11 compounds was tested by dissolving avobenzone at 4% and the test compound with and without 3.6% octocrylene in 70% ethanol/30% mixture (1:1) caprylic/capric triglyceride and C12-15 alkyl benzoate ester solvent, then applying the solution to roughened glass plates at 2 mg/cm^2. After drying, the glass plates were exposed in an Atlas Suntester XLS to 25 MED and analyzed by HPLC to determine amount of avobenzone remaining.	Octocrylene was the most effective individual stabilizer; at 3.6% it preserved 90% of the avobenzone. The combination of 3.6% octocrylene and 4% 4-MBC or 4% BEMT preserved 100% of the avobenzone.	(Mendrok-Edinger et al. 2009)
Similar to the above study, the selected photostabilizers were tested alone and in combination with 3.6% octocrylene in model SPF 30 sunscreen formulations containing 4% avobenzone, using the COLIPA method (Matts et al. 2010) to determine each sunscreen's UVA protection factor (UVAPF). The UVAPF before and after irradiation with 25 MED in an Atlas Suntester XLS was compared, then the labeled SPF/UVAPF ratio was calculated.	The 9 formulations tested were similar in composition, differing only by the photostabilizing system. Octocrylene (3.6%) alone preserved 92% of the sunscreen's UVAPF. The authors concluded that octocrylene, 4-MBC, and BEMT all could photostabilize avobenzone sufficiently to meet the COLIPA 3:1 requirement.	(Mendrok-Edinger et al. 2009)
This study compared 3% ethylhexyl methoxycrylene with 3% octocrylene to photostabilize 3% avobenzone dissolved in ethyl acetate, a non-photoactive diluent, and 2% octadecene/MA copolymer. The resulting solutions were applied to roughened PMMA plates and, after drying, were exposed to 25 MED by a solar simulator.	The plate containing 3% ethylhexyl methoxycrylene retained 90.4% of its UVA absorbance and 97.7% of its UVB absorbance. The plate containing 3% octocrylene retained 85% of its UVA absorbance and 92.9% of its UVB absorbance.	(Bonda et al. 2010)
In a study that investigated the photodegradation of avobenzone in cyclohexane, avobenzone was irradiated for 100 h in a quartz immersion well photoreactor.	3 photodegradation products of avobenzone (2 benzoic acid derivatives and t-butylbenzene) were identified by nuclear magnetic resonance spectrometry	(Roscher et al. 1994)
The degradation products of avobenzone were isolated and identified by HPLC and GC-MS in a study in which avobenzone was irradiated with UV light for 8 h in several solvents, including isopropanol, methanol, cyclohexane, and isooctane.	Avobenzone reportedly degraded exponentially in the nonpolar solvents (cyclohexane and isooctane) but was stable in polar solvents. The first stage of the avobenzone degradation process resulted in benzoyl and phenacyl radicals, followed by several recombination and/or oxidation reactions. Overall, 14 photoproducts were identified that can be classified into several groups, including benzaldehydes, benzoic acids, phenylglyoxals, acetophenones, benzils, dibenzoyl methanes, and dibenzoyl ethanes.	(Schwack and Rudolph 1995; Karlsson et al. 2009)
The photodegradation of avobenzone in water was evaluated using LC-MS following UV irradiation (250 W/m^2 every 4 min for a total dose of 60 kJ/m^2).	In addition to 3 products previously identified by Schwack and Rudolph (1995), 22 additional degradation products (a hydroxypropenone and a 1,4-diketone) were detected.	(Huong et al. 2008)
The photostability of 15 commercial sunscreen emulsions, some containing avobenzone, were investigated. Each tested sunscreen formulation contained multiple UV filters.	All 15 sunscreens were photostable in the UVB range; however, photoinstability was observed in 7 products in the UVA range, all of which contained a combination of EHMC and avobenzone, together with other UV filters. No photodegradation products for any of the UV filters were assessed in the study. Given the study design (multiple UV filters in each sunscreen), there is limited information to determine the extent of avobenzone's contribution to increasing the photoinstability of the 7 sunscreens in the UVA range. Therefore, no conclusions regarding the photostability could be made from this study.	(Hojerova et al. 2011)

4-MBC: 4-methylbenzylidene camphor; BEMT: Bis-ethylhexyloxyphenol methoxyphenol triazine; COLIPA: The European Cosmetic, Toiletry and Perfumery Association; EHMC: ethylhexyl methoxycinnamate; GC-MS: gas chromatography–mass spectrometry; HPLC: high performance liquid chromatography; LC-MS: liquid chromatography–mass spectrometry; MED: minimal erythema dose; PMMA: Poly(methyl methacrylate); SPF: sun protection factor; UV: ultraviolet; UVAPF: UVA Protection Factor.

endpoint. The clinical and *in vitro* human skin data demonstrate that the dermal absorption of avobenzone is low (≤0.59% of the applied dose in a clinical study), closely matching the dermal absorption of approximately 0.39% reported using *in vitro* porcine skin. Given that there are reliable dermal bioavailability studies in humans, the maximum dermal absorption of 0.59% of the applied dose of avobenzone reported by the SCC (EC 2000) was used for limit derivation and risk assessment purposes for avobenzone.

Encapsulation technology is being investigated to improve the efficacy of sunscreen UV filters, specifically avobenzone. Generally, this strategy involves encapsulating an active ingredient (e.g. avobenzone) into a "shell," either permanently or temporarily. Although encapsulation technology is not used in currently marketed sunscreen products, several *in vitro* studies evaluating its effectiveness have been reported and are summarized in Table 5. The collective evidence of these studies show that several materials have been successfully used to entrap avobenzone in order to decrease

Table 4. Summary of dermal absorption/penetration studies of non-encapsulated avobenzone.

Test system	Treatment regimen	Results	Reference
Human (*in vivo*)	4 subjects each administered ^{14}C-avobenzone in diethylene glycol monoethyl ether at 25 μCi (10% avobenzone) via 10-cm^2 gauze square taped to the skin for 8 h with or without occlusion	Applied dose recovery was 0.08%-0.28% (non-occluded) and 0.48% (occluded) from skin stripping and 0.012%-0.016% (non-occluded) and 0.08% (occluded) from urine; no radioactivity noted in plasma/feces.	(ECHA 2022)
Human (*in vivo*)	Follow-up to above study, with unlabeled Parsol MCX (OMC) added to avobenzone (no other details provided).	Applied dose recovery was 0.32% and 0.04% (occluded) and 0.56% and 0.03% (total 0.59% of the applied dose) (without occlusion) from skin stripping and urine, respectively; no radioactivity noted in blood/feces.	(EC 2000)
Human (*in vivo*)	24 subjects each administered 1 of 4 sunscreens containing 2%-3% avobenzone (2 sprays, 1 lotion, or 1 cream) at 2 mg/cm^2 to 75% of the total body surface area 4 times per day for 4 days	Geometric mean maximum plasma concentration of avobenzone ranged from 1.6 ng/mL for the cream to 4.0 ng/mL for the spray sunscreens, greater than FDA threshold value of 0.5 ng/mL for systemic absorption of sunscreen UV filters (USFDA 2019).	(Matta et al. 2019)
Human (*in vivo*)	12 subjects each administered 1 of 4 sunscreens containing 3% avobenzone (1 lotion, 3 sprays) at 0 h on day 1 and 4 times each day on days 2-4 at 2-h intervals for a total of 13 applications	For avobenzone, the geometric mean C_{max} was 7.1 ng/mL (2.9-28 ng/mL) for the lotion and approximately 3.5 ng/mL for other formulations, average AUC ranges for days 1 and 4 were 10.3-23.1 and 42.7-93.4 ng*h/mL, respectively (highest AUC was for the lotion), serum concentration decreased over time to approximately 0.8-1.61 ng/mL by day 7 and 0.1-0.4 ng/mL by day 14, and mean systemic terminal half-life was 73.7-112 h.	(Matta et al. 2020)
Human (*in vivo*)	Two different oil-in-water emulsions containing 3.72% avobenzone (74.4 μg avobenzone in a 2-mg emulsion) were applied to a 4 x 5 cm area of the flexor forearm for 1 h and 20 tape strips were removed from the skin (1 emulsion also contained 10% octocrylene).	Results showed that 50%-55% of the applied dose was found within 10% of the stratum corneum, and smaller concentrations were found up to a relative depth of approximately 50% of the stratum corneum.	(Jacobi et al. 2005)
Human (*in vivo*)	Following application of a 2 mg/cm^2 dose of either an oil-in-water emulsion or an oil containing 1.5% avobenzone for 1 h to the forearms of volunteers (7 males and females), 10-30 tape strippings were taken.	For the oil formulation, avobenzone was localized on the skin surface and in the uppermost part of the stratum corneum, whereas deeper penetration of avobenzone was found for the oil-in-water emulsion.	(Lindemann et al. 2003)
Human (*in vivo*)	6 subjects each administered 3.7% avobenzone emulsion at 2 mg/cm^2 to a 5 x 6 cm skin area, followed by tape stripping 1 h after application.	The highest amounts of avobenzone were detected on the surface of the skin, and the concentration decreased with increasing stratum corneum depth. For lateral spreading, mean values of 72 ± 11% inside and 6 ± 3% outside the application area for forearms (no vertical axis data), 80 ± 6% inside and 9 ± 6% outside on the parallel axis, and 1 ± 1% outside on the vertical axis were noted, indicating that the preferred direction of lateral spreading was parallel to the body axis on the back.	(Jacobi et al. 2011)
Human (*in vivo*)	Sunscreen oil-in-water emulsions containing 1.5% avobenzone and 4% 4-methylbenzylidene camphor were applied to a skin area of 8 x 10 cm^2 at a dose of 2 mg/cm^2, and tape strips were taken 1 h after application.	The majority of applied avobenzone was recovered on the first strip (25 μg/cm^2), and only a fraction of applied avobenzone dose (0.07 μg/cm^2) was recovered from the deepest penetrated horny layer (approximately at 35% of the full thickness of the horny layer), indicating that avobenzone applied to skin remains in the upper part of the horny layer and is unlikely to contact any living cells of the skin after a short-term exposure.	(Weigmann et al. 2001)
Human (*in vivo*)	Oil-in-water emulsions containing avobenzone or its complex with HP-β-CD (nonencapsulated or loaded into lipid microparticles) were applied to subjects for 60 min.	Results showed that 9.7% of the applied avobenzone dose in cream containing nonencapsulated avobenzone penetrated the stratum corneum, whereas 17.1% or 15.1% of the applied dose penetrated the stratum corneum for the formulations containing the avobenzone/HP-β-CD complex and the microparticles loaded with avobenzone, respectively; only 6% of the applied dose penetrated the stratum corneum for the cream containing the microencapsulated avobenzone/HP-β-CD complex.	(Scalia, Coppi, et al. 2011)
Human (*in vivo*)	Emulsions (lipid microparticles loaded with EHMC and avobenzone) were applied to upper and lower forearms of 6 females (aged 20-25 years) free of dermatologic disorders, for 60 min.	Results showed that 30.3 ± 3.3% of the avobenzone dose diffused into the stratum corneum for the cream containing the nonencapsulated sunscreen agents, whereas a significantly reduced percentage (22.7 ± 5.4%) of the applied avobenzone dose diffused into the stratum corneum for the cream containing the microencapsulated filters.	(Scalia, Mezzena, et al. 2011)

(*continued*)

Table 4. Continued.

Test system	Treatment regimen	Results	Reference
Human (*in vivo*)	Sunscreen formulations containing EHT free or encapsulated in lipid microparticles in conjunction with the EHMC and avobenzone applied at 2 mg/cm^2 to forearms of 16 females for 60 min, followed by tape stripping.	For nonencapsulated EHT-containing formulation, 61.3% of applied avobenzone dose did not penetrate the stratum corneum, and 20.5% of the applied dose was recovered from skin strips (almost identical values noted for the encapsulated EHT-containing formulation).	(Scalia et al. 2019)
Human (*in vivo*)	The suction blister technique was used to assess penetration of UV filters, including avobenzone, across the epidermis of 5 subjects after 3 h of application of 2 mg avobenzone onto a 3.5 cm^2 blister roof.	The total amount of avobenzone detected in the blister fluid was 0.0031 ± 0.0001 mg (0.15% of the applied avobenzone dose penetrated across the human epidermis).	(Klinubol et al. 2008)
Human (*in vivo* and *in vitro*)	*In vivo*: An oil-in-water emulsion containing free avobenzone or lipospheres loaded with 2% avobenzone was applied to a 2 x 5 cm area of forearms of 3 subjects at 2 mg/cm^2 for 30 min followed by 10 tape strippings. *In vitro*: 50 mg of the same oil-in-water emulsion, as the donor phase, was applied on the membrane at a formulation finite dose of 2.88 mg/cm^2 for 4 h.	*In vivo*: Unabsorbed avobenzone recovered was 81.3% and 85.27% of the applied dose for avobenzone alone and avobenzone in lipospheres, respectively; total avobenzone recovered in stratum corneum was 9.68% and 16.65% of the applied dose for avobenzone alone and avobenzone in lipospheres, respectively, and the majority of the penetrated avobenzone was recovered in upper layers of the stratum corneum, and only 1.63% (avobenzone alone) and 3.7% (avobenzone in lipospheres) of the avobenzone was recovered from the stratum corneum in the deeper layers (tapes 8-10). *In vitro*: Avobenzone skin permeation of 50%-80% of the applied dose using lipophilic receptor medium, and poor avobenzone skin permeation (<1% of the applied dose) using a hydrophilic receptor.	(Iannuccelli et al. 2008)
Rat (*in vivo*)	1% avobenzone in Carbitol™ (diethylene glycol monoethyl ether) was applied dermally at 120 mg/cm^2 for 6 h	1.4% and 2.3% avobenzone was recovered in the stratum corneum and deeper skin layers, respectively	(EC 2000)
Rat (*in vivo*)	2 sunscreen formulations (each 234 mg/kg of formulation resulting in 11.7 mg/kg avobenzone) containing either a 5% avobenzone emulsion or 5% avobenzone lotion were applied to male Sprague-Dawley rats (OECD guidelines)	Applied avobenzone dose recovery was 16.3%-17.8% in the stratum corneum, 2.0%-3.4% in the epidermis, and 0.11%-0.15% in the dermis.	(Kim et al. 2015)
Human skin (*in vitro*)	A 2% formulation in a water-in-oil cream containing radiolabeled avobenzone was applied at a dose equivalent to 50 µg/cm^2 to isolated human abdominal cadaver skin samples for 16 h (chamber experiment).	Total radioactivity was 4.5%, 7%, and 16% of the applied dose after 1, 6, and 16 h, respectively (lower dermis contained only 0.35% of the applied dose at 16 h and no radioactivity was found in the receptor chamber at any time).	(EC 2000)
Minipig skin (*in vitro*)	Radiolabeled avobenzone (either ^{14}C 2% or ^{14}C 7.5%) from 3 different vehicle preparations (oil-in-water lotion, oil-in-water cream, and water-in-oil cream) was applied to 5-cm^2 skin samples (equivalent to doses of 120 and 450 µg/cm^2 or absolute amounts of 600 and 2250 µg, respectively) for 6 h (OECD TG 428).	Total penetration rate of avobenzone from all vehicles was generally very low, between 0.9% and 3.9% (1.0%-1.7% from the horny layer of the skin, 0.9%-3.4% from the stripped skin, i.e., stratum corneum, and 0.5% in receptor chamber).	(ECHA 2022)
Human skin (*in vitro*)	Water-in-oil cream containing 2% radiolabeled avobenzone was applied to a 2-cm^2 area of human cadaver abdominal skin (100 µg avobenzone exposure) mounted in an exposure chamber for 1, 6, and 18 h.	Avobenzone recovery increased with exposure time from 0.3% (1 h) to over 0.7% (6 h) to 10.14% (18h) with the majority penetrating into the upper part of the dermis (no radioactivity detected in penetration chamber water at any time).	(ECHA 2022)
Human skin (*in vitro*)	Skin permeation of avobenzone in various formulations was assessed in Franz-type diffusion cells using either a single application or daily repeated application of 20 mg/cm^2 applied to adult human skin stratum corneum and epidermis with the subcutaneous fat removed (OECD Guidance 156).	Avobenzone skin permeation (percentage of applied dose) ranged from not detectable to 0.53% in the receiving compartment (single application) or from not detectable to 0.36% (repeated-dose application), depending on vehicle.	(Montenegro et al. 2018)
Naked rat skin (*in vitro*)	1.5% of a solution containing ^{14}C-labeled avobenzone in acetone or deltyl was applied to a 180-µg/cm^2 area of isolated skin for 1 or 6 h.	For acetone formulations, the amounts recovered in the stratum corneum were about 10% of the applied dose at 1 and 6 h, whereas the amount in the skin was 4% at 1 h and 11% at 6 h. For deltyl vehicle formulations, avobenzone was recovered at 4% and 5% and 4% and 7% for stratum corneum and skin penetration, for 1 h and 6 h, respectively (no radioactivity found in chamber fluid).	(EC 2000)
Naked rat skin (*in vitro*)	Avobenzone was applied to skin samples at concentrations of 120, 360, and 1200 µg/cm^2 for 1, 6, 16, and 24 h.	Applied dose recovery was 7%, 17%, 28%, and 44% from the stratum corneum by stripping and in the	(EC 2000)

(*continued*)

Table 4. Continued.

Test system	Treatment regimen	Results	Reference
		remainder of the skin at the 1-, 6-, 16-, and 24-h timepoints, respectively.	
Minipig skin (*in vitro*)	2% avobenzone in 3 different vehicles (oil-in-water lotion, oil-in-water cream, and water-in-oil cream) was applied to skin preparations at a dose of 120 μg/cm^2 for 6 h.	Avobenzone recovery in the skin for each vehicle was 2.6%, 3.7%, and 2.9%, respectively.	(EC 2000)
Human (*in vivo* and *in vitro*)	*In vivo*: Avobenzone in either an oil-in-water emulsion gel or petrolatum jelly was applied at 2 mg/cm^2 to 2 x 2 cm areas on the volar side of the forearm of 6 subjects for 30 min. *In vitro*: Franz cells (∼3 mg/cm^2 of same sunscreen products applied to human full-thickness skin for 0.5 or 6 h).	*In vivo*: Avobenzone recovery was 12.9 ± 3.5 μg/cm^2 (29.2% of the applied dose), and 3.9 ± 1.7 μg/cm^2 (10.6% of the applied dose) in strips 2-16, reflecting measurements taken from the upper to deeper parts of the stratum corneum, for samples to which the emulsion gel and petrolatum were applied, respectively. *In vitro*: Avobenzone was not detectable in the dermis after 0.5 and 6 h for either vehicle, indicating no dermal penetration.	(Chatelain et al. 2003)
Human skin (*in vitro*)	Penetration and retention of avobenzone in female abdominal skin was evaluated in Franz-type diffusion cells.	Results indicated 95%-98% of avobenzone was recovered on the surface of the epidermis as nonpenetrated material, and concentrations of avobenzone found in viable human epidermis after application, once adjusted for skin partitioning and binding effects, was at least 5-fold lower than those appearing to cause toxicity in cultured human keratinocytes.	(Hayden et al. 2005)
Pig ear skin (*in vitro*)	Sunscreens containing 5% avobenzone in either water-in-oil emulsion or oil-in-water emulsion were applied at 2.0 mg/cm^2 or 0.5 mg/cm^2 to full-thickness pig-ear skin using static glass diffusion cells based on the Franz design (similar to OECD TG 428).	Avobenzone recovery in the receptor fluid 24 h after the application of 2 mg/cm^2 dose (100 μg/cm^2 avobenzone) was 1.1 ± 0.3 μg/cm^2 (1.1% of the applied dose) and 0.5 ± 0.009 μg/cm^2 (0.5% of the applied dose) for water-in-oil emulsion and oil-in-water emulsion, respectively, whereas following the 0.5 mg/cm^2 dose (25 μg/cm^2 of the applied dose), the corresponding values were less than the LLOQ for both emulsions.	(Klimova et al. 2015)
Mouse skin (*in vitro*)	Avobenzone was applied at 4.4 mg/cm^2 to baby mouse skin (epidermis and dermis) using Franz diffusion cells and monitored for up to 24 h.	Avobenzone recovery in the receptor fluid was 0.8 ± 0.28% of the applied dose.	(Klinubol et al. 2008)
Human skin (*in vitro*)	Human epidermis samples stripped of subcutaneous fat collected during abdominoplasty surgery mounted on Franz diffusion cells were exposed to sunscreen products containing five UV filters, including 20 g/L avobenzone, for 8 h.	All sunscreen agents, including avobenzone, were found within the epidermis (up to 0.25 g/m^2 or 14% of the applied dose) at the 8 h timepoint.	(Jiang et al. 1999)
Mouse skin (*in vitro*)	Sunscreen ingredient permeation through young (8-week-old) and senescent (24-week-old) mouse skin was assessed in Franz cells irradiated by UVA (10 J/cm^2) and/or UVB (175 mJ/cm^2) light.	Photoaging did not augment skin absorption of avobenzone, no avobenzone was detected in the receptor fluid after 24 h, and skin deposition of avobenzone in aged skin was 2x less than in young skin.	(Hung et al. 2014)

AUC: Area under the curve; EHMC: Ethylhexyl methoxycinnamate; EHT: Ethylhexyl triazone; HP-β-CD: Hydroxypropyl-β-cyclodextrin; LLOQ: Lower limit of quantitation; NOAEL: No-observed-adverse-effect level; OECD: Organization for Economic Co-operation and Development; TG: Test guideline; UV: ultraviolet.

its skin penetration and improve its photostability and efficacy.

Distribution

Specific information on the systemic or organ/tissue distribution of avobenzone was not available. However, in a study using multiple spectroscopic techniques and supported by molecular docking tools, avobenzone was found to interact with bovine serum albumin (BSA) with a binding affinity greater than four other sunscreens (oxybenzone, octinoxate, enzacamene, and homosalate) (Ao et al. 2018). Avobenzone had a binding constant of 2.60×10^5 M^{-1} at 37 °C at a pH of 7.4. The positive values obtained for the thermodynamic endpoints indicated that the binding process between avobenzone and BSA examined in this study was driven predominantly by the hydrophobic force. There was one hydrogen bond between avobenzone and BSA, specifically at Lys-437, and the formation of a hydrogen bond may decrease the hydrophilicity and increase the hydrophobicity to stabilize the avobenzone-BSA system. Although clinical effects of this interaction (avobenzone-BSA) are unknown, this binding is likely to affect the distribution of avobenzone and contribute to its reported half-life (Matta et al. 2019, 2020).

Metabolism (in vitro)

Limited information on the metabolism or metabolic product generation of avobenzone was identified. In rat and human liver microsomal incubations with 10 μM avobenzone *in vitro*, several oxidative metabolites and glutathione (GSH) adducts

Table 5. Summary of dermal absorption/penetration studies of encapsulated avobenzone.

Test system	Treatment regimen	Results	Reference
Porcine skin (*in vitro*)	Sunscreens containing avobenzone and octocrylene in free form or encapsulated in a sol-gel silica capsule were applied at 2 mg/cm^2 to jacketed Franz cell-mounted porcine skin for 2 h for penetration measurements, after which the skin was tape-stripped.	Avobenzone penetrated deep into the stratum corneum (detected up to layer 6) under the free formulation, whereas when encapsulated almost no penetration was detected inside the stratum corneum. No information regarding the penetrance of avobenzone from the Franz cell study was reported.	(Cozzi et al. 2018)
Porcine ear skin (*in vitro*)	The epidermal penetration of encapsulated versus nonencapsulated sunscreens was investigated in pig ear skin using Franz diffusion cells using a 24-h exposure. Encapsulated sunscreens used oil-containing polyamide nanocapsules with avobenzone in the presence of α-tocopherol as an antioxidant agent.	For nonencapsulated avobenzone, 5.61% of the applied dose penetrated the skin, whereas similar, yet slightly lower penetrant values were observed for the encapsulated avobenzone. In all cases, the epidermal penetration of encapsulated and nonencapsulated avobenzone was low, while the release values for nonencapsulated avobenzone were higher.	(Hanno et al. 2012)
Human skin (*in vitro*)	Avobenzone in different silicone emulsifiers was applied to separated stratum corneum and epidermis from samples of healthy adult human skin obtained from abdominal reduction surgery and mounted in Franz-type diffusion cells with receptors filled with water/ethanol (50:50 v:v).	The percentage of the avobenzone dose applied that permeated through excised skin from the different emulsions for up to 22 h ranged from 0.15%-0.34%; no significant emulsion-specific effect on skin permeation of avobenzone was noted.	(Montenegro et al. 2004)
Human skin (*in vitro*)	In a follow-up to the previous study, the release and permeation of the UV filters EHMC and avobenzone from 6 commercial oil-in-water emulsions was assessed (performed according to OECD TG 428, with minor changes). Each formulation (20 mg/cm^2) was applied to the skin surface, which was prepared with stratum corneum and epidermis from adult human skin and mounted on Franz-type diffusion cells with receiving chamber solutions of water/ethanol (50:50 v:v) for 24 h.	For avobenzone, the amount that permeated after 24 h ranged from 0.42%-3.15% of the applied dose.	(Montenegro and Puglisi 2013)
Human skin (*in vitro*)	This study assessed the penetration and photostability of UV filters, including avobenzone in nanostructured lipid carriers (NLC) and nanoemulsions (NE). NLC or NE formulations containing 1.12% (w/w) avobenzone were applied to excised human breast skin (isolated stratum corneum/epidermis [SCE] only) mounted on Franz-type diffusion cells with receptor compartments filled with a water-ethanol solution (50:50 v:v) for 24 h. For photostability testing, 2 mg/cm^2 of each formulation was spread onto a 5 x 5 cm glass plate and subsequently irradiated for 10 min corresponding to an incident UVA dose of 270 kJ/m2 (equivalent to 90 min of sunshine at noon during the summer).	The penetration study results indicated that permeation was reduced for avobenzone in NLC compared to NE. Additionally, a comparison between the penetration of SCE for avobenzone-NLC and avobenzone + OMC-NLC indicated no significant increase, suggesting that concurrent application of these UV filters has little effect on penetration *in vitro*. Based on the photostability results, the authors noted that avobenzone was less photostable than other UV filters, and no significant differences in the photostability were observed between NLC and NE formulations.	(Puglia et al. 2014)
Porcine ear skin (*in vitro*)	The transdermal diffusion of 4 PMMA-encapsulated UV filters, including avobenzone, was evaluated in porcine ear skin using Franz diffusion cells.	Avobenzone had a drug flux of 5.02 μg/cm^2 at 3 h and a calculated lag time of 0.03 h (shortest lag time for the UV filters tested). No detectable concentration of UV filters was found in the receiver solution for all encapsulated UV filters except for encapsulated avobenzone. Avobenzone was detected in the receiver solution 2 h after exposure, and the calculated lag time was about 0.66 h, indicating that avobenzone was released from encapsulation. However, the concentration of avobenzone in the receiver fluid at both 2 and 3 h following application of encapsulated avobenzone was lower than what was reported for avobenzone alone, suggesting that PMMA attenuated the skin permeability of avobenzone.	(Wu et al. 2014)
Human skin (*in vitro*)	Solutions containing avobenzone (15 μg/mL) free or complexed with cyclodextrins (HP-β-CD and SBE7-β-CD) were applied for a 6-h period to excised full-thickness human female breast and abdomen skin in Franz diffusion cells to assess human skin penetration and retention of avobenzone.	Results indicated that 70.3%-77.2% of the applied avobenzone dose remained on the skin surface, and that 14.1%-16.78% of the applied avobenzone dose penetrated within the skin; however, avobenzone was not detected in the dermis or in the receptor fluid. Additionally, 84.6%-95.5% of the absorbed avobenzone was localized to the stratum corneum, with no	(Simeoni et al. 2004)

(*continued*)

Table 5. Continued.

Test system	Treatment regimen	Results	Reference
		significant differences between complexed or free avobenzone. However, a small (but significant) effect of complexation of avobenzone with SBE7-β-CD was noted in the epidermis, where the total penetration of avobenzone was reduced when avobenzone was complexed with SBE7-β-CD (2.29 ± 1.1% vs. 0.66 ± 0.52 for free and complexed avobenzone, respectively).	
SKH-1 hairless mouse skin (*in vitro*)	The effects of avobenzone complexation with HP-β-CD on the transdermal penetration and photostability of avobenzone were investigated using formulations containing 0.12 mg/mL avobenzone and up to 30% (w/w) HP-β-CD applied to SKH-1 hairless mouse skin samples mounted on modified Franz diffusion cells.	The dermal penetration of avobenzone increased as a function of avobenzone dose applied, whereas the transdermal penetration was inversely associated with HP-β-CD concentration in the applied solution. The cyclodextrin provided avobenzone photostability up to 500 kJ/m^2 UVA irradiation for up to 80 min.	(Yang J et al. 2008)
Porcine skin (*in vitro*)	Cutaneous deposition and permeation of avobenzone was assessed using stick formulations containing either free avobenzone or avobenzone incorporated in mesoporous silica (SBA-15) that were applied to porcine skin mounted in Franz diffusion cells for 6, 12, or 24 h.	Reduced percutaneous permeation of avobenzone was reported when avobenzone was incorporated in mesoporous silica (SBA-15). The permeation of avobenzone in free formulation versus SBA-15 encapsulation was 0.15 ± 0.13% versus 0.05 ± 0.03%, respectively, of the applied avobenzone dose	(Daneluti et al. 2019)

EHMC: Ethylhexyl methoxycinnamate; HP-β-CD: hydroxypropyl-β-cyclodextrin; NLC: nanostructured lipid carriers; NE: nanoemulsions; OECD: Organization for Economic Co-operation and Development; OMC: Octyl methoxycinnamate; PMMA: Poly(methyl methacrylate); SBE7-β-CD: Sulfobutylether-β-CD; SCE: Stratum corneum/epidermis; TG: Test guideline; UV: ultraviolet.

were detected (Guesmi et al. 2020). In general, the metabolism of sunscreen compounds, including avobenzone, was higher in rat liver microsomes than in human liver microsomes, although the same oxidative metabolites were observed in both study systems. The microsomal incubation of avobenzone yielded a single oxidation product (avobenzone + O), a demethylated product (BDMBM-CH_2), and an avobenzone-CH_2+O metabolite; one avobenzone-derived GSH adduct corresponding to the AVB-CH_2+O-2H + GSH molecule was also noted (Guesmi et al. 2020). Others have noted specific metabolites for avobenzone; however, little is known about the four tentative urinary metabolites of avobenzone: desmethylhydroxy avobenzone, hydroxyl avobenzone, desmethylavobenzone carboxylic acid, and dehydrated dihydrohydroxy avobenzone, identified in a volunteer in the study described below (Klotz et al. 2019).

Specific *in vivo* metabolism studies of avobenzone were not available.

Excretion

In clinical trials reported by Matta et al. (see Table 4), the mean systemic terminal half-life for avobenzone was 33 to 112 h (Matta et al. 2019, 2020).

In a dermal absorption and excretion study of avobenzone in healthy volunteers (summarized in Table 4), only a small fraction of the applied dose (0.012% to 0.016%) was detected in the urine (ECHA 2022).

In a human biomonitoring study, the urinary toxicokinetics and metabolite profile were assessed for real-life sunscreen application conditions (initial application and re-applications after 2 and 4 h) (Hiller et al. 2019). In this study, 20 healthy volunteers (both sexes, but unspecified subtotals) who sunbathed for 1 day outside during the summer were subsequently exposed to a commercial sunscreen containing octisalate, avobenzone (2.3%), octocrylene, and titanium dioxide for 9 h via the dermal route mimicking theoretical real-life application conditions (2 mg/cm^2 body surface area; double reapplication). Following dermal application, the highest median plasma avobenzone concentration was 4.0 μg/L, with a maximum reaching 11.3 μg/L; while the median concentration at 72 h after exposure was below the limit of detection (1.1 μg/L). Excretion kinetics for avobenzone indicated that the urinary excretion of avobenzone was low, with a median urine concentration of 3.4 μg/g creatinine (range: below the limit of detection to 25.2 μg/g creatine). Avobenzone was detected in $<$20% of the samples, and the concentrations were close to the limit of detection with high intra-individual variability between the sampling time points. Therefore, descriptive kinetic data for avobenzone were not available.

In a method development study, human biomonitoring of plasma and urine was performed following application of a sunscreen formulation containing octocrylene, avobenzone, and octisalate (Klotz et al. 2019). The sunscreen was applied to the whole body of a volunteer at a dose of 2 mg sunscreen per cm^2 skin. The volunteer also received a second and third dose of the sunscreen (as half the initial dose) at 2- and 4-h time points after the first application; urine and plasma samples were collected for up to 24 h after the first application. The maximum avobenzone concentrations reported were 25 and 2 μg/L in the urine and plasma samples, respectively.

Toxicology

The following sections discuss the potential toxicological effects of avobenzone exposure based on evidence from *in vitro* assays, *in vivo* studies with laboratory models, and

clinical studies. Clinical studies were identified for irritation and sensitization endpoints, but few clinical studies were identified that investigated other adverse health effects after avobenzone exposure.

Acute toxicity

A summary of the available acute toxicity data for avobenzone is found in Table 6. Based on the presented data, and EPA's hazard determination guidelines (see Supplemental Table 1), acute exposure to avobenzone is considered to result in low toxicity to mammals.

In an acute dermal toxicity study in rats (OECD TG 402), the median lethal dose (LD_{50}) for avobenzone following dermal exposure was determined to be >1000 mg/kg (ECHA 2022). Groups of five male and five female Füllinsdorf albino rats were administered avobenzone at doses of 0, 500, and 1000 mg/kg applied dermally with occlusion for 24 h and then were observed for 14 days. No mortality was observed at any of the doses. Erythema was observed for all animals (including controls), but no dose-response pattern was observed. In this study, avobenzone was tested up to a maximum dose of only 1000 mg/kg, and therefore did not meet the European regulatory cutoff for classification, which is 2000 mg/kg (EP 2021).

In an acute oral toxicity study in rats (OECD TG 401), the oral LD_{50} for avobenzone was >16,000 mg/kg (ECHA 2022). Groups of 10 male and 10 female Sprague-Dawley rats were administered avobenzone at a limit dose of 16,000 mg/kg via oral gavage. There were no deaths, no signs of systemic toxicity or irritation, and no toxicologically significant effects on body weight gain. Necropsy revealed a marked decrease of sperm and accumulation of cellular debris in the epididymal tubules of the males and vacuolation of hepatocytes in some males and females, which may have been related to treatment. The ECHA registrant noted that, based on the lack of mortality at this high dose, avobenzone may be classified as practically nontoxic according to the OECD Globally Harmonized System.

No acute inhalation studies for avobenzone were identified.

Repeated-dose toxicity

A summary of the available repeated-dose toxicity data for avobenzone, based on the duration of avobenzone exposure (i.e. subacute [≤1 month], subchronic [≤3 months], or chronic [>3 months]) (Aleksunes and Eaton 2019), is found in Table 7.

In a subacute dermal toxicity study, avobenzone was applied to four groups of five male and five female rats at doses of 0, 120, and 200 mg/kg/day (abraded skin) and 230 mg/kg/day (intact skin) for 5 h per day with occlusion, followed by rinsing, for 4 weeks (EC 2000). Some skin irritation was observed in all groups, and some nonsignificant hematologic changes were also observed. No significant changes were reported at necropsy, with histological examination revealing no abnormalities in internal organs or the skin. Based on the lack of any treatment-related effects, the no-observed-adverse-effect level (NOAEL) for general toxicity endpoints was 230 mg/kg/day for intact skin and 200 mg/kg/day for abraded skin.

A subacute, dermal, repeated-dose toxicity study in rabbits conducted according to OECD TG 410 was available for avobenzone (ECHA 2022). In this study, avobenzone was applied at doses of 30, 100, and 360 mg/kg/day to the skin with occlusion on male and female New Zealand white rabbits (10 animals per sex per dose) for 6 h per day for 21 days. Half of the treated animals were tested with intact skin, and the other half were tested with abraded skin. No behavioral changes or signs of overt toxicity, excluding microscopic pathology of skin, were observed in surviving rabbits from treated and nontreated control groups. The severity of dermal reactions of rabbits receiving avobenzone was generally greater than in the controls and increased in a dose-related

Table 6. Summary of acute toxicity studies for avobenzone.

Species/strain	Route of exposure/test guideline	Endpoint	Dose (mg/kg)	U.S. EPA hazard ID	Reference
Rat/Füllinsdorf albino	Dermal/OECD TG 402	LD_{50}	>1000	NA	(ECHA 2022)
Rat/Sprague-Dawley	Oral/OECD TG 401	LD_{50}	>16,000	NA	(ECHA 2022)

ID: identification; LD_{50}: median lethal dose (the dose at which 50% of the animals died); NA: not applicable; TG: Test guideline; OECD: Organization for Economic Co-operation and Development.

Table 7. Summary of repeated dose toxicity studies for avobenzone.

Study type (testing guidelines)	Species *Strain* No. of animals/sex	Route	Doses (mg/kg/day) [NOAEL in bold]	Basis for NOAEL	Reference
Subacute studies					
4-week dermal toxicity study	Rat *Unspecified* 5 rats/dose/sex	Dermal with occlusion	0, 120, **200** (abraded skin); **230** (nonabraded skin)	Highest dose tested	(EC 2000)
21-day dermal toxicity study (OECD TG 410)	Rabbit *New Zealand white* 10 male rats/dose	Dermal with occlusion	0, 30, 100, **360**	Highest dose tested	(ECHA 2022)
Subchronic studies					
90-day dietary toxicity study (OECD TG 408)	Rat *Füllinsdorf albino* 12 rats/dose/sex	Oral (dietary)	0, 200, **450**, 1000	Hematologic effects	(ECHA 2022)

NOAEL: No-observed-adverse-effect level; OECD: Organization for Economic Co-operation and Development; TG: Test guideline.

manner. Well-defined to moderate dermal reactions were generally observed in rabbits treated with 360 mg/kg/day avobenzone, with slight to well-defined dermal reactions observed in rabbits treated with 30 or 100 mg/kg/day (ECHA 2022). Microscopic examination of the treated skin sites revealed an increased incidence of epidermal thickening in rabbits from the vehicle control and treatment groups when compared to the untreated control group. Therefore, it was difficult to conclude whether the dermal reactions observed were test substance-related or a reaction to the vehicle. The NOAEL for systemic toxicity was the highest applied dose of 360 mg/kg/day.

A GLP-compliant 90-day subchronic oral toxicity study (OECD TG 408) was conducted for avobenzone (ECHA 2022). Groups of 12 male and 12 female Füllinsdorf albino rats (6 to 8 weeks of age) were administered avobenzone via the diet at doses of 0, 200, 450, and 1000 mg/kg/day for 91 to 94 days. During the treatment period, and up to 30 days post-treatment, no treatment-related effects on clinical signs, mortality, body weight, or food consumption were noted. Treatment-related decreases in mean red blood cells and hemoglobin were noted in the 1000 mg/kg/day females at week 14 of treatment. Additionally, the mean relative liver weights of 1000 mg/kg/day male rats and the mean absolute and relative liver weights of 200 mg/kg/day female rats approached the upper limit of the normal physiological range for historical controls for this laboratory, whereas 450 and 1000 mg/kg/day females had liver weights above the physiological range. The liver weights were associated with a slight increase in hepatic parenchyma cell size in 1000 mg/kg/day females (the only dose level examined). The liver weights of 1000 mg/kg/day male and female rats were comparable to control animals after the 30-day recovery period (ECHA 2022). The increase in liver weights was interpreted by the ECHA registrant as a process of liver adaptation (Williams and Iatropoulos, 2002) to treatment (ECHA 2022). Based on this evidence, along with the general agreement with the ECHA registrant regarding liver physiology and considering the potential for hematologic effects in females at the highest dose, the middle dose of 450 mg/kg/day was considered the NOAEL for general toxicity.

Irritation, sensitization, phototoxicity, photoirritation, and photoallergenicity

Human studies. As part of comments submitted on 21 December 2007 to FDA's proposed amendment to the Final Tentative Sunscreen Monograph (DSM 2007), it was indicated that no cases of phototoxicity or photoallergenicity effects had been reported for 14 on-market sun care products containing 4% to 5% avobenzone, and 11 on-market products containing 4% to 4.5% avobenzone in combination with 1% to 6% titanium dioxide. These observations were based on consumer use trials, product patch test, stability, and photoallergy tests.

One study (de Oliveira et al. 2015) in 17 male and female volunteers (aged 24.5 ± 6.7 years) evaluated the effect of the patch application of six oil-in-water sunscreen emulsions (including 3.0% avobenzone and a combination of 0.1% rutin and 3.0% avobenzone) on various skin properties to determine skin tolerance. Epicutaneous patches (Finn Chambers®) were applied to the volar forearm for 24 h. Each patch had seven chambers, containing each of the formulations tested as well as water (negative control). There was no significant increase in skin redness for any of the emulsion formulations compared to water control. Stratum corneum hydration was not statistically different for any emulsion formulation compared to the water control. There was no significant effect of any of the emulsion formulations on transepidermal water loss compared to water control, indicating that none of the formulations perturbed skin barrier function. The authors concluded that all formulations were safe for human use due to their good cutaneous compatibility.

Three studies were performed in 2004 to evaluate the photoallergic potential of three avobenzone-containing formulations (at concentrations ranging from 4.5% to 5%) in a total of 71 healthy human volunteers following repeated skin contact and UV irradiation (DSM 2007). For each study, during the induction phase, the product was applied in duplicate for 24 h, after which test sites were irradiated with 2x the individual's predetermined minimal erythema dose (MED) (UVA and UVB). This process was repeated twice weekly for 3 weeks, for a total of six induction applications and irradiations. Evaluations were performed daily during the induction phase. Following the induction phase, the individuals received 2 weeks of rest prior to the challenge phase. For the challenge phase, the product was applied in duplicate on previously untreated areas for 24 h, after which one set was irradiated with UVA (7 to 10 J/cm^2). Evaluations were performed after 24, 48, and 72 h post-challenge. The three formulations were found to not induce irritant, photoirritant, allergic, or photoallergic contact dermatitis in any of the 71 subjects. Based on these observations, avobenzone at 4.5% to 5% does not have irritation, sensitization, photoirritation, or photoallergenic potential.

Three studies were performed in 1993 or 2004 to evaluate the photoallergic potential of formulations containing a combination of avobenzone and titanium dioxide (DSM 2007). Two studies (2004) were conducted using two formulations, each containing 4.5% avobenzone and 5% titanium dioxide, in a total of 55 healthy human volunteers (28 females and 17 males) following repeated skin contact and UV irradiation. For each study, during the induction phase, the product was applied in duplicate for 24 h, after which test sites were irradiated with 2x the individual's predetermined MED (UVA and UVB). This process was repeated twice weekly for 3 weeks, for a total of six induction applications and irradiations. Evaluations were performed daily during the induction phase. Following the induction phase, the individuals received 2 weeks of rest prior to the challenge phase. For the challenge phase, the product was applied in duplicate on previously untreated areas for 24 h, after which one set was irradiated with UVA (7 to 10 J/cm^2). Evaluations were performed after 24, 48, and 72 h post-challenge. Neither test product was found to induce irritant, photoirritant, allergic, or photoallergic contact dermatitis in any subject. The third study (1993) evaluated the photosensitization potential of a sunscreen cream (sun protection factor [SPF] 30) containing a

combination of 2% avobenzone and 5.5% titanium dioxide, as well as ethylhexyl methoxycinnamate (EHMC, percentage not specified) in 50 healthy human volunteers (31 females and 19 males; 22-59 years of age). On the first day of the study, the product was applied in duplicate to the healthy skin of the back in Finn Chambers®. On the second day, one of the sets was irradiated with UVA (10 J/cm^2). For the nonirradiated set, skin reactions were scored on the third day. For the irradiated set, skin reactions were scored on the fourth and fifth days. Neither the patch nor photopatch tests showed positive results, and it was concluded that the product was neither sensitizing nor photosensitizing. Based on the observation that in all subjects, none of the three formulations containing avobenzone and titanium dioxide (at a ratio of 4.5:5 or 2:5.5) induced irritant, photoirritant, allergic, or photoallergic contact dermatitis, it was concluded that a combination of avobenzone (4.5%) and titanium dioxide (5%) does not have irritation, sensitization, photoirritation, or photoallergenic potential.

Human patch test studies were performed in 1994 and 2004 to evaluate the primary skin irritation and allergic hypersensitivity potential of two sunscreen products (lotion SPF 20 and a lipstick SPF 20) containing a combination of avobenzone and titanium dioxide (DSM 2007). The sunscreen lotion (SPF 20) contained a combination of avobenzone (2.2%) and titanium dioxide (1.6%) as well as EHMC (octinoxate) and 4-methylbenzylidene camphor (percentages not specified). The patch test was performed on 50 male or female volunteers, all of whom had atopic dermatitis but were in an eczema-free interval. Based on no positive reactions at any time point, it was concluded that, under the conditions of this test, the sunscreen lotion produced no evidence of primary irritation or allergic hypersensitivity. Further, it was noted that the investigator (a physician specialist in dermatology and allergenicity) considered the sunscreen lotion to be safe for use, including for persons with very sensitive skin, based on the study population with atopic dermatitis. Another patch test was performed with the sunscreen lipstick (SPF 20), which contained a combination of avobenzone (4%), titanium dioxide (1%), and EHMC (percentage not specified). The patch test was performed on 50 volunteers (23 females and 27 males, 18–78 years of age). The volunteers were patch-tested with known allergens. No allergic reactions were observed in any of the 50 volunteers (DSM 2007). One volunteer had a nonpersistent irritation reaction, which resolved by the 96-h evaluation. Based on no evidence of primary irritation or allergic hypersensitivity in two human patch tests with a total of 100 subjects that had allergic or atopic skin, it was concluded that combination avobenzone and titanium dioxide sun care products do not induce an allergenic or hypersensitivity reaction, but on rare occasions may induce a primary irritation reaction.

A human repeated insult patch test was conducted in 50 volunteers (41 females and 9 males; 28-68 years old) with two avobenzone-containing formulations (either 10% in 1:1 ethanol/diethylphthalate [EtOH/DEP] or 3% in cosmetical emulsion) and their respective formulation controls (Symrise 2012). The test substances (100 mg each), including well-tolerated standards and controls, were applied under an occlusive test plaster to the back of each test subject. The test plasters were removed after 48 h or, if over the weekend, 72 h (Symrise 2012). Skin reactions were scored 30 min after test plaster removal. The test substances were then reapplied to the same test areas under occlusive test plasters. The process was repeated for 3 weeks (Symrise 2012). After the 3-week induction phase, the subjects had a 14-day break prior to the challenge phase. The challenge was carried out in 49/50 subjects. For the challenge phase, the test substances were applied contralaterally on previously unused skin areas on the back. The test plasters were removed after 48 h, and skin reactions were scored at this time, as well as 1 and 2 days later (48, 72, and 96 h post-application, respectively). The test product containing 10% avobenzone in 1:1 EtOH/DEP caused no reactions during the observation period and was described as very well tolerated by the skin in this investigation. The test product containing 3% avobenzone in a cosmetic emulsion caused four slight reactions, i.e. transient and reversible during the first week, five slight reactions during the second week, and one moderate, i.e. more intense but also reversible, and two slight reactions during the third week (no reaction was documented during the challenge phase). Due to these observations, the formulation was described to be well tolerated by the skin in this investigation. It was concluded that, based on the negative human repeated insult patch test results in 50 volunteers (no dermatologically relevant reactions), the avobenzone-containing formulations (10% in 1:1 EtOH/DEP and 3% in cosmetical emulsion) were not sensitizing.

In a clinical trial of 11 male and 40 female subjects, approximately 0.2 mL of a 10% avobenzone solution was applied to the skin with occlusion for 24 h and repeated 10 times with 24- or 48-h rest intervals (EC 2000). Following exposure and 10 days of rest, challenge applications were made to the original site of avobenzone application and to new sites. Overall, no adverse reactions were observed.

The photoallergy to sunscreen chemicals, including avobenzone, was investigated via photopatch testing in an epidemiology study of 1155 patients (Bryden et al. 2006). This study was performed in patients who had a known photosensitivity disease, a history of sunscreen reaction, exposed-site dermatitis during the summer months, and/or exposed-site skin problem. Duplicate allergen series were applied to mid-upper back skin and left for 24 or 48 h. Following removal of the patches, one set (the dark control) was covered with a light-impermeable occlusive dressing and the other set was irradiated with 5 J/cm^2 UVA. Skin readings were performed at 24, 48, and 72 h post-irradiation. Among the patients tested, 66 showed photoallergic contact reactions, and 22 patients had a photoallergic contact reaction to avobenzone. Further, 79 patients experienced a contact allergic reaction to sunscreen ingredients, and 10 of these patients experienced contact allergic reactions to avobenzone. In addition, two patients reported photoaugmentation to avobenzone, while photoinhibition was reported in one patient. Three patients also reported an irritant reaction to avobenzone. In summary, patients who are sensitive to skin diseases have the potential to experience photoallergy and contact allergy to avobenzone.

In another study on photoallergic contact dermatitis in 2715 patients, 4.1% of the study population had a positive reaction to UV filters in general, while only 0.1% of the study population had a positive reaction to 2% to 10% avobenzone (in petrolatum) (Darvay et al. 2001). Patients who had undergone photopatch testing for allergic contact and photoallergic reaction to UV filters were assessed. Similar to the previous study, this study was performed in people who had a presumed photosensitivity disorder, had a history of a worsening itchy rash on exposed sites, exhibited signs of chronic eczematous eruption on exposed sites, or were suspected of having chronic actinic dermatitis. Among patients who experienced a photoallergic reaction to photopatch testing, 52 were positive for UV filters, with avobenzone accounting for four individuals. Similarly, 51 patients had an allergic contact reaction to UV filters, with only three patients experiencing a positive reaction to avobenzone. These results indicate that photoallergic and allergic contact reactions to avobenzone are rare even in sensitive subpopulations.

A retrospective analysis was conducted of 280 patients who had undergone patch and photopatch testing with sunscreen agents, including avobenzone, at a contact dermatitis clinic between February 1985 and March 1987 (English et al. 1987). The patients, who were selected based on known photosensitivity or suspected sunscreen dermatitis, were patch and photopatch tested with a pre-selected series of relevant contact allergens and photoallergens and with the International Contact Dermatitis Research Group (ICDRG) standard series of contact allergens. One patient had a contact allergic reaction to avobenzone and developed contact allergic reactions to hydroxyl methoxy methyl benzophenone and isopropyl dibenzoylmethane but did not develop any photoallergic reactions. One other patient had a photoallergic reaction to avobenzone and developed an allergic (but not photoallergic) reaction to isopropyl dibenzoylmethane. It was noted that, in the present study and from previous reports (Schauder and Ippen 1986; de Groot and Weyland 1987), all six patients who were either allergic (four patients) or photoallergic (two patients) to avobenzone were also allergic to isopropyl dibenzoylmethane. However, the authors acknowledged that without knowing whether these patients were exposed to both compounds, it was not possible to determine whether these allergens cross react (English et al. 1987).

A retrospective analysis was conducted in 355 patients (246 females and 109 males; average age of 43.9 years) who had undergone photopatch testing with seven sunscreen agents at two Swedish dermatology clinics (Stockholm and Uppsala) between 1990 and 1996 (Berne and Ros 1998). The patients were originally referred for photopatch testing due to diagnoses of polymorphic light eruption ($n = 133$) or atopic dermatitis or other eczemas ($n = 121$), or as part of an investigation of photosensitivity. Photopatch tests were carried out according to the Scandinavian standard photopatch test protocol. Skin reactions were scored on day 1, at which time one of the duplicate sets of test panels was irradiated with UVA at 5 J/cm^2 (Stockholm; 274) or 10 J/cm^2 (Uppsala (81). Both test panels were evaluated 1 day after irradiation (on day 2), and most were also evaluated on day 3. With respect to avobenzone, six photocontact reactions and no contact reactions were observed. Avobenzone was the third most common allergen, after benzophenone-3 (15 photocontact, 1 contact) and isopropyl dibenzoylmethane (8 photocontact, 4 contact).

The European Multicenter Photopatch Test Study (EMCPPTS) Taskforce evaluated the frequency of photoallergic contact dermatitis to common photoallergens, including 19 organic UV absorbers (including 10% avobenzone) and five topical nonsteroidal anti-inflammatory drugs (NSAIDs) commonly used in Europe, in a prospective analysis of 1031 patients (715 females and 316 males; median age 46 years) who were patch tested at 30 centers across 12 European countries (Kerr et al. 2012). The patients were originally referred for photopatch testing as part of investigations of suspected photoallergic contact dermatitis, including dermatitis of exposed sites during summer months, history of reaction to a sunscreen product, or history of reaction to a topical NSAID. Photopatch tests were carried out according to a standardized technique, the European consensus methodology. Specifically, the test agents were applied in duplicate to the skin of the back and removed at 24 or 48 h (66% and 34% of patients, respectively, depending on test center). One set was then irradiated with UVA (5 J/cm^2, or less if MED testing revealed objective photosensitivity). The other set was covered with a UV-impenetrable material. Skin reactions were graded using the ICDRG system and, whenever possible, relevance was assigned to positive reactions using the COADEX system (de Waard-van der Spek et al. 2015). Scoring was performed pre-irradiation and immediately post-irradiation, as well as 24, 48, and 72 h post-irradiation (or later); the 48-h postirradiation endpoint was considered the key endpoint for subsequent data analysis. With respect to photoallergic contact dermatitis reactions to UV filters, 148 reactions in 95 subjects (9.2%) were reported, including 18 reactions to avobenzone (10 weak reactions, 6 strong reactions, and 2 extreme positive allergic reactions). Allergic contact dermatitis reactions occurred in few patients, including three reactions to avobenzone.

Another study was conducted in 11 patients (10 females and 1 male; average age of 51 years; 9 of the 11 with some history of atopy) who self-identified as having an allergy or reaction to at least one sunscreen product. These subjects, most of whom reported the reaction worsening with sun exposure, were recruited for patch and photopatch testing to determine whether they had relevant photoallergy or allergic contact dermatitis to sunscreen active ingredients (Shaw et al. 2010). Patients were patch-tested using Finn Chambers® with the 65 allergens on the North American standard tray, 36 allergens on a supplemental tray, a 28-allergen sunscreen tray (including avobenzone 5% petrolatum), and any relevant personal sunscreens. For the sunscreen tray, the duplicate sets were applied to the patients' backs. After 24 h (day 2), the photopatches were removed, skin reactions were scored, and one set of photopatches was irradiated with UVA (10 J/cm^2; none of the patients had abnormal UVA MEDs). Skin reactions were scored immediately after UVA exposure, as well as on days 3, 5, and 7. None of the patients had positive patch test or photopatch test reactions to avobenzone.

A photopatch test was conducted in 25 volunteers (15 females and 10 males; mean ± SD age of 51.6 ± 13.2 years) (Symrise 2016a). Photopatch testing was performed with an avobenzone-containing formulation (6% in 1:1 EtOH/DEP), the formulation control (1:1 EtOH/DEP), and a negative control (Aqua demin). Photopatch testing was conducted according to the amended *proDERM* Standard Protocol-71. Specifically, the two formulations and negative control were applied in duplicate to the backs of the subjects using small Finn Chambers® backed on Scanpor®. The patches were removed after 24 h, at which time one set was irradiated with UVA (10 J/cm^2) and skin reactions were scored 1, 24, 48, and 72 h post-irradiation. No strong reactions were observed at any time. For the avobenzone-containing formulation, skin reactions were slightly higher for the unirradiated site than for the irradiated site. For the formulation control and negative control, skin reactions were higher for the irradiated site than the unirradiated site. For all time points, skin reactions evoked by the avobenzone-containing formulation and formulation control were below or in the range of the negative control, and the reactions decreased over time. It was concluded that, based on the negative photopatch test results in 25 volunteers, the avobenzone-containing formulation (6% in 1:1 EtOH/DEP) was not phototoxic.

A photopatch test was conducted in 25 volunteers (22 females and 3 males; mean ± SD age of 43.0 ± 15.7 years) (Symrise 2016b). Photopatch testing was performed with an avobenzone-containing formulation (6% in 1:1 EtOH/DEP), formulation control (1:1 EtOH/DEP), and a negative control (Aqua demin.). Photopatch testing was conducted according to the amended *proDERM* Standard Protocol 75.01. For the induction phase, the two formulations and negative control were applied under occlusive Finn Chambers® backed on Scanpor® tape on the backs of the subjects for 24 h twice weekly for 3 weeks (total of six occlusive 24-h induction patches during 3 weeks). For each of the six induction patches, the patch was removed after 24 h, at which time the treated site was irradiated with 1.5 times the individual's MED with sun-like UV light (i.e. UVA and UVB). Skin reactions were scored before reapplication of fresh test material. Following the induction phase, the subjects received 2 weeks rest prior to the challenge phase. For the challenge phase, the two formulations and negative control were applied in duplicate to previously unexposed skin areas for 24 h. When the patches were removed, one set of treated sites was irradiated with UVA (5 J/cm^2), and skin reactions were scored 1-, 24-, 48- and 72-h postirradiation. During the induction and challenge phases, skin reactions evoked by the avobenzone-containing formulation and formulation control were always in the range of the negative control. It was concluded that, based on the negative photopatch test results in 25 volunteers, the avobenzone-containing formulation (6% in 1:1 EtOH/DEP) was not photosensitizing.

According to a clinical study excerpt, 2% avobenzone in petrolatum was used for possible sensitization induction by its application to two distinct areas of the skin of the back of 25 volunteers with occlusion for 24 h (EC 2000). The test area was exposed to 3 MED 24 h post-induction (the MED for each subject was determined by finding the time taken to produce erythema using UVA and UVB irradiation). This procedure was carried out six times, on days 1, 4, 8, 11, 15, and 18. The challenge dose was administered 10 days after the completion of induction; specifically, avobenzone was applied to two fresh skin sites and occluded for 24 h. The skin sites were additionally exposed to 10 J/cm^2 UVA irradiation for an unspecified amount of time. No photosensitization was reported for this study.

In a retrospective analysis of 76 patients who were photopatch-tested with a range of substances, 39.5% had at least one positive photopatch test reaction (Victor et al. 2010). Specifically, 69 positive photopatch test reactions and 45 positive patch test reactions were detected in 30 and 23 patients, respectively. Of the positive photopatch test reactions, 23.2% were associated with sunscreens, and 4.3% were associated with exposure to 10% avobenzone in petrolatum.

Animal studies. In one study, avobenzone was applied to the skin of rabbits (10 per sex per dose) at doses of 30, 60, and 360 mg/kg/day with occlusion for 6 h each day for 21 consecutive days (EC 2000). Each treatment group consisted of five skin-abraded and five skin-intact animals. Dose-related erythema was observed in treated animals; however, some irritation was also found in vehicle control animals. Skin abrasion did not affect irritancy in the study, and no treatment-related effects on body weight, food or water consumption, or hematologic changes were observed.

In another study, two groups of six rabbits were administered 0.5 mL of an avobenzone solution over a 4-cm^2 abraded and non-abraded skin site on each animal for 4 h with occlusion; avobenzone was dissolved in ethanol/2-phenylethanol (50/50) to a final concentration of 10% (EC 2000). The resulting primary irritation indices for vehicles and avobenzone were 1.17 and 1.39, respectively. No additional details were provided.

A standard Draize eye irritation test in rabbits found no adverse effects of avobenzone at a maximum 20% concentration (limit of solubility) (EC 2000).

A Freund's complete adjuvant (FCA) test for avobenzone in guinea pigs was reported (EC 2000). The treatment group (n = 8-10) received three intradermal induction injections of 50% avobenzone in FCA on days 0, 4, and 9. On days 21 and 35, following induction, a challenge was made by epicutaneous application of 0.025 mL of avobenzone at the minimal irritant concentration and at three lower concentrations (each one-third of the preceding concentration). Overall, there was no evidence of sensitization at any time point.

In a guinea pig maximization test, no evidence of sensitization was observed at challenge doses of avobenzone up to 20% (EC 2000). For induction, groups of 20 to 25 guinea pigs were administered either FCA (control), 0.1 mL of 5% avobenzone in FCA, or 5% avobenzone in saline via the intracutaneous route. Seven days following exposure, a 20% suspension of avobenzone was administered via the epicutaneous route with occlusion for 2 days. Treatment with the challenge dose was carried out on day 21 with either 20% or 6% avobenzone solutions for 24 h; no sensitization was reported at either of the concentrations tested.

A toxicology excerpt for sensitization in guinea pigs noted that no evidence of sensitization was reported in an open epicutaneous test (EC 2000). The experimental groups of animals ($n = 20$) were administered solutions containing 20% or 6% avobenzone daily to one flank for 21 days. Following exposure, a challenge dose of either the maximal nonirritant dose, or one-third or one-ninth of the maximal nonirritant dose, was administered on day 21 and day 35 to the opposite flank. No sensitization was reported at any dose or time point. Further details regarding this study were not available.

The photoallergenic potential of avobenzone has been investigated in guinea pigs. In a study excerpt reported by the SCC, four groups of 10 guinea pigs (two test groups, a negative control, and a positive control) were induced with two concentrations of avobenzone (EC 2000). One group received 0.1 mL of 10% avobenzone in acetone to an 8-cm^2 area and was subjected to 10 J/cm^2 UVA irradiation 30 min later. The second treatment group received 1% avobenzone; whether these animals were also subject to UVA irradiation was not noted. This induction procedure was repeated five times over a 2-week period. On test days 21 and 35, a challenge dose of 0.025 mL of a 10% avobenzone solution was applied to both flanks over a 2-cm^2 area. After challenge dose application, the left flank of each animal was also irradiated as described above. There was no avobenzone-related photoallergenicity in the guinea pigs.

A study by Karlsson et al. investigated the allergenic potential of several photodegradants of avobenzone (Karlsson et al. 2009). Of the photodegradants identified, two dibenzoylmethanes, four arylglyoxals, and four benzils were screened for contact allergenicity/sensitization potential using the murine local lymph node assay (LLNA). Specifically, each degradation product was tested at five different concentrations using female CBA/CA mice in groups of three animals. Mice received 25 μL of a solution of test compound, dissolved in acetone/olive oil (4:1 v/v), on the dorsum of the ears daily for 3 consecutive days, and were injected intravenously 5 days after the first treatment with phosphate-buffered saline containing 20 μCi of [^{3}H]-thymidine. The draining lymph nodes were excised 5 h later and pooled for each group, and a single cell suspension of lymph node cells was prepared. The arylglyoxals were strong sensitizers in the LLNA and were highly reactive toward the nucleophile arginine, which indicated that immunogenic hapten-protein complexes could be formed with this compound. In contrast, benzils were not sensitizers in the LLNA but were cytotoxic in a cell proliferation assay. The authors concluded that it was very likely that the photocontact allergy of dibenzoylmethanes was caused by arylglyoxals (Karlsson et al. 2009).

In a mouse ear swelling model study, mice were photosensitized and photochallenged with avobenzone (Atarashi et al. 2012). During the photosensitization phase of the study, the clipped dorsal skin of the mice was painted with 50 μL of 10% avobenzone in acetone/olive oil (4:1) and subsequently irradiated with UVA (40 J/cm^2). This procedure was completed once daily for 3 consecutive days (days 0, 1, and 2). Prior to the photochallenge, a dial thickness gauge was used to measure the basal line thickness of both ears of all mice. For the photochallenge on day 5, both sides of each earlobe of the mice were painted with 25 μL of 10% avobenzone in acetone/olive oil (4:1) and subsequently irradiated with UVA (40 J/cm^2). Ear thickness was measured 24 h after irradiation and expressed as the mean increment in thickness above the basal line control value. Avobenzone did not induce significant ear swelling (i.e. no significant levels of photosensitivity) compared to the vehicle sensitization.

The effects of mangiferin and naringenin (a xanthone glucoside and flavone, respectively, that are found in certain fruit trees), as possible natural co-formulants to improve the efficacy of existing sunscreens on the photostability and phototoxicity of sunscreens containing avobenzone, were evaluated. It was noted that by itself, avobenzone was phototoxic *in vitro* according to OECD TG 432 (Kawakami and Gaspar 2015). Sunscreen formulations containing octocrylene, octyl methoxycinnamate (OMC), and avobenzone (4% w/w) were prepared and supplemented with or without mangiferin, naringenin, or both compounds. For photostability studies, samples of the formulations were spread onto glass plates, exposed to UVA radiation, and then analyzed by high-performance liquid chromatography. For phototoxicity studies, UV filters and antioxidants were evaluated using 3T3 fibroblast cultures that were or were not subjected to irradiation, according to OECD TG 432. Avobenzone and naringenin showed the highest photodegradation in formulation, whereas the addition of mangiferin promoted photostabilization of both avobenzone and/or naringenin. The *in vitro* results showed that avobenzone without either naringenin or mangiferin was phototoxic, avobenzone with naringenin showed phototoxic potential, and avobenzone with mangiferin was not phototoxic. The high antioxidant activity of mangiferin was considered to improve the photoprotective effects of the tested sunscreen formulations.

The toxicity of sunscreen formulations with or without UV radiation and after photodegradation was evaluated in an *in vitro* 3-dimensional human keratinocyte and fibroblast-based skin model using de-epidermized dermal culture substrate (Uco et al. 2018). A basic oil-in-water formulation was prepared with various ingredients commonly used in commercial sunscreens. Simple formulations were prepared by adding either avobenzone (4%) or OMC (10%) to the basic oil-in-water formulation, and more complex formulations were prepared by adding both UV filters (at concentrations ranging from 0.05% to 10%) in addition to other sunscreen components. Photodegradation of formulations was evaluated in a photostability chamber with UVA (320 to 400 nm; >200 $w{\cdot}h/m^2$) at 24.5 °C for 60 h. Formulations were either maintained untreated, placed in a photostability chamber uncovered (treated; photodegraded), or covered with aluminum foil to block UVA (treated; protected control). UV-vis spectrophotometry analyses showed a change in the absorption spectra of uncovered and protected avobenzone formulations, indicative of photodegradation. The avobenzone untreated and treated (protected control and photodegraded) formulations were then tested in the skin model in the presence or absence of UVA (340 nm; 1.7 mW/cm^2). Viability was evaluated in cells exposed to each formulation (not treated [NT], photodegraded [P], protected control [PC]) and condition (irradiated [I] or not irradiated [NI]). There was

a decrease in cell viability with all formulations/conditions tested, including the vehicle control formulation, compared to NI phosphate buffer solution, indicating epidermal toxicity of the basic formulation, irrespective of the UV filters and condition, in this model. With respect to avobenzone treatment groups, mean cell viability was highest in the not treated, not irradiated formulation (NT/NI: 83%; i.e. the parent formulation) and lowest in the not treated, irradiated group (NT/I: 59%), indicative of the phototoxic effects of irradiation. Cell viabilities in the other treatment groups were the following: photodegraded, not irradiated (P/NI: 73%); protected control, irradiated (PC/I: 65%); photodegraded, irradiated (P/I: 63%); and protected control, not irradiated (PC/NI: 62%).

The phototoxic potential of a sunscreen lipstick (SPF 20) containing 4% avobenzone and 1% titanium dioxide, as well as EHMC (percentage not specified), was evaluated in an *in vitro Saccharomyces cerevisiae* yeast test (DSM 2007). The study was conducted according to a variant of the Bagley and Coll method, which is based on observed growth inhibition of the yeast in an agar gel in response to the concomitant action of the tested xenobiotic and of the UVA radiation (delivered at an energy of 20 J/cm^2). The sunscreen lipstick was concluded to be non-phototoxic under the conditions of the study.

The *in vitro* cytotoxicity of avobenzone in mouse lymphoma L5178Y-R cells was investigated under dark and UV irradiation conditions to evaluate the baseline cytotoxicity of avobenzone, as well as any changes in toxicity following irradiation with simulated sunlight (Butt and Christensen 2000). For irradiation, solutions of avobenzone were exposed to simulated sunlight in an Oriel solar simulator for 2 or 20 h prior to the addition to cells. Cells were incubated with unexposed or sunlight-exposed solutions for 20 h, and cell survival was determined by trypan blue staining. Avobenzone was not toxic in the dark. At concentrations up to 5 ppm, a survival rate of about 95% was observed, which decreased to about 30% at a concentration of 10 ppm; however, no additional toxicity was induced with UV irradiation of the avobenzone solutions for 2 or 20 h. Notably, avobenzone was found to be stable, with very little loss to photo breakdown products after 2 or 20 h of irradiation compared to unirradiated solutions. Stability was determined from the shape of the absorbance spectrum as a function of wavelength for solutions of unexposed avobenzone and solutions irradiated for 2or 20 h. It was concluded that the sunlight-exposed avobenzone showed no significant increase in cytotoxicity compared to the unexposed UV filter.

Photomutagenicity, photogenotoxicity, and photocarcinogenicity

Bode and Roh (2020) reported avobenzone alone and in combination with other UV filters significantly reduced the appearance of tumors in a mouse model of UV-induced keratinocyte carcinoma. These findings in an animal model are consistent with the absence of photogenotoxicity investigated and summarized below.

In a study summary provided by the SCCS, the photomutagenicity potential of avobenzone was investigated in *S. cerevisiae* D7 (EC 2000). This organism allows for testing of multiple endpoints, including gene crossover, gene conversion, and reverse mutations. Although specific details regarding the avobenzone doses/concentrations used in these experiments were not available, photomutagenicity testing with avobenzone was performed under both UVA and UVB wavelengths, with intensities generally up to 500,000 J/cm^2 for UVA and up to 10,000 J/cm^2 for UVB, which are meant to represent the maximum likely UV exposures experienced by individuals applying sunscreens. Avobenzone alone was not photogenotoxic in this system, while UV radiation alone was mutagenic. The degree of radiation-induced mutagenesis was inversely correlated to the administered avobenzone concentration, i.e. mutagenicity decreased with increasing avobenzone.

In another study summary provided by the SCC, the photomutagenic activity of avobenzone was investigated in Chinese hamster ovary cells incubated *in vitro* with avobenzone concentrations of 15 to 90 μg/mL and subsequently exposed to 4000 J/m^2 UVA and 130 J/m^2 UVB for an unspecified duration (EC 2000). Avobenzone was devoid of photomutagenicity at the concentration levels tested. Additional details were not available for this study.

In a study designed to determine photogenotoxicity, Chinese hamster ovary cells were treated with the photomutagenic compounds 8-methoxypsoralem or chlorpromazine and irradiated with UV light with or without sunscreen UV filters (Chetelat et al. 1993). The potential for clastogenicity of two sunscreen ingredients, 2-phenylbenzimidazole sulfonic acid and avobenzone, was investigated using two distinct protocols in this study design. In the first design, cells attached to the culture dish were treated in the presence of the sunscreens in the medium, whereas in the second study design, cells were irradiated through a layer of sunscreen solution as a filter. For 2-phenylbenzimidazole sulfonic acid, a clear UVB-absorbing effect and a decreased frequency of UVB-induced chromosome aberrations was noted, whereas no such effect was noted for the UVA-absorbing avobenzone. Neither UV filter in the irradiated cell, including avobenzone concentrations up to 90 μg/mL, caused a significant increase in UV-induced chromosome aberrations, indicating that avobenzone was non-photomutagenic *in vitro*.

Finally, Bode and Roh (2020) found that avobenzone, alone or in combination with other UV filters, significantly reduced markers of cell proliferation and activation of oncoproteins as well as the formation of cutaneous papillomas and squamous cell carcinomas in the SKH-1 hairless mouse model. In this study, mice were exposed to solar-simulated UV three times a week for 15 weeks using a progressive (step-wise) increase influence. At the end of 15 weeks, solar-simulated UV was stopped but treatment with the sunscreen formulations continued until 29 weeks. The number and volume of tumors were measured once a week. Avobenzone (3%) significantly ($p < 0.001$) reduced tumor number and volume. This effect was greater when avobenzone was combined with other UV filters (e.g. octinoxate, and octocrylene plus titanium dioxide) (Bode and Roh 2020).

Table 8. Genotoxicity/mutagenicity studies of avobenzone.

Testing guidelines	Assay	Test organism	Doses or concentrations	Results	Reference
In vitro studies					
OECD TG 471 (GLP)	Bacterial reverse mutation assay	*Salmonella typhimurium* TA98, TA100, TA102, TA1535, TA1537, TA1538	Up to 5,000 µg/plate for *S. typhimurium*	Negative ± S9 for *S. typhimurium*	(ECHA 2022)
OECD TG 476	*In vitro* gene mutation (at the HGPRT locus)	Chinese hamster lung fibroblasts (V79)	24-h exposure duration; 0, 5, 15 and 20 µg/mL ± S9	Negative ± S9	(ECHA 2022)
In vivo studies					
OECD TG 474 (GLP)	Mammalian erythrocyte micronucleus test	Mouse (Füllinsdorf albino)	Avobenzone doses 2-fold oral applications of 0, 100, 2500, and 5000 mg/kg administered 30 min and 6 h prior to sacrifice	Negative	(ECHA 2022)

±S9: With and without metabolic activation; GLP: Good laboratory practices; 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.
Note: This table includes only studies evaluating avobenzone alone (not in multi-ingredient formulations).

Genotoxicity and carcinogenicity

Avobenzone was negative when tested for mutagenicity in an *in vitro* Ames assay and an *in vitro* mammalian cell gene mutation assay, as well as in an *in vivo* mammalian erythrocyte micronucleus assay (see Table 8). Details of these and other genotoxicity studies are provided below.

Avobenzone was not genotoxic in a bacterial reverse mutation assay (GLP-compliant study, conducted in 2000 according to OECD TG 471) in *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535, TA1537, and TA1538 at concentrations of 50 to 5000 µg/plate with metabolic activation and at concentrations of 5 to 5000 µg/plate without metabolic activation (ECHA 2022). Cytotoxicity was noted in TA102 at 500 µg/plate (without metabolic activation) and 1500 µg/plate (with metabolic activation).

The *in vitro* gene mutation potential (at the *HGPRT* locus) of avobenzone was investigated in a GLP-compliant OECD TG 476 study in Chinese hamster lung fibroblasts (V79), in the presence or absence of metabolic activation (S9) (ECHA 2022). The cytotoxicity and gene mutation in V79 cells was evaluated following exposure to avobenzone at concentrations of 0 to 20 µg/mL for 24 h. Under these test conditions, avobenzone did not induce mutation in V79 cells up to the highest concentration evaluated (20 µg/mL), which was cytotoxic (i.e., reduced plating efficiency or cell survival).

Avobenzone was also negative for genotoxicity in a GLP-compliant *in vivo* mammalian somatic cell study (erythrocyte micronucleus assay) performed according to OECD TG 474 (ECHA 2022). In this study, three male and three female Füllinsdorf albino SPF mice per group were twice administered oral doses of 100, 2500, and 5000 mg/kg avobenzone at 30 min and 6 h prior to termination. No avobenzone-related increases in micronuclei in bone marrow cells were noted; therefore, avobenzone was not classified as a clastogen or aneugen.

The genotoxicity of avobenzone was investigated in a novel combination sun protective dermal formulation containing melatonin and pumpkin seed oil (Bora et al. 2017). This study evaluated the preclinical safety of the formulation, which contained the FDA-approved UV filters avobenzone (0.9% to 1.35%), octinoxate (1.5% to 2.25%), oxybenzone (0.6% to 0.9%), and titanium dioxide (3.0% to 6.0%), with melatonin (0.9% to 2.5%) and pumpkin seed oil (5.6% to 10.0%), using OECD guidelines for genotoxicity testing. Genotoxicity was tested in the following assays: the bacterial reverse mutation test (OECD TG 471) in four strains of *S. typhimurium* with or without metabolic activation (S9) at 5000 µg/plate of the sunscreen formulation; the mammalian erythrocyte micronucleus test (OECD TG 474-like) in Wistar albino rats at a dermal dose of up to of 2000 mg/kg of the sunscreen formulation for 2 consecutive days; and the mammalian bone marrow chromosome aberration test (OECD TG 475 with modifications) in Wistar albino rats at a dermal dose of up to 2000 mg/kg of the sunscreen formulation for 2 consecutive days. The sunscreen formulation did not result in an increase in genotoxicity in any of the tests at any concentration. It should be noted that exposure of the target tissue (bone marrow) is likely very low after dermal application. Because the sunscreen formulation contained both a variety of UV filters, melatonin, and pumpkin seed oil, extrapolation of the results for avobenzone alone is not possible. Therefore, results of this study are reported for reference purposes only and are not used for limit derivation purposes.

The mutagenicity of four organic UV filters (including avobenzone) in nonchlorinated and chlorinated bromide-rich water (artificial seawater that is sometimes used in swimming pools) was investigated *in vitro* in an Ames test (Manasfi et al. 2019) using a modified assay method (Maron and Ames 1983; De Méo et al. 1996). The mutagenicity of avobenzone in *S. typhimurium* TA98 at different concentrations (4 to 10 µL/plate of a 10 µM stock solution added to 0.2 mL medium) without metabolic activation (-S9) was investigated for up to 48 h after exposure. Avobenzone was not mutagenic in either nonchlorinated or chlorinated water *in vitro*. It was noted that the protocol used in this study was very limited by modern standards (e.g. one strain, no metabolic activation).

Although no long-term rodent carcinogenicity studies have been performed with avobenzone, there are no indicators of potential hazard based on the available genetic toxicology data. The lack of carcinogenic hazard potential is further supported by empirical evidence from the repeated-dose toxicity studies. No increase in pre-neoplastic/non-neoplastic histopathological changes were reported in a

subchronic 90-day oral toxicity study of avobenzone in rats (ECHA 2022).

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 nongenotoxic chemicals (Woutersen et al. 2016). Although 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 the human relevance of animal tumors was considered. The authors concluded that their results *"support the concept that chemicals showing no histopathological risk factors for neoplasia in a sub-chronic study in rats 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). Moreover, Cohen et al. 2025 found no evidence of biologically relevant carcinogenic modes of action for avobenzone. Furthermore, systemic exposure levels in humans were well below concentrations that have any reported biological activity (Matta et al. 2019, 2020). Taken together with the lack of genotoxicity, although no long-term carcinogenicity study on avobenzone has been performed, a repeated-dose toxicity study up to 90 days demonstrated no evidence for induction of hyperplasia and/or pre-neoplastic lesions, suggesting long-term carcinogenicity studies are not warranted (see Cohen et al. 2025 for further details). There was no evidence of an estrogenic effect or immunosuppressive effect of avobenzone (see below), providing additional evidence that it does not have carcinogenic activity. The finding of increased liver weight in the 90-day study (ECHA 2022) was described as adaptive rather than adverse and was most likely related to either CAR or PPARα activation. Such activation could potentially lead to liver tumors in rats and/or mice, but these modes of action have been shown to not be relevant to human cancer risk (Corton et al. 2014, 2018; Elcombe et al. 2014; Yamada et al. 2021, 2025).

Estrogenic, androgenic, and thyroid activity

Table 9 summarizes the available studies *in vitro* and *in vivo* that have evaluated the potential estrogenic, androgenic, and thyroid activity of avobenzone.

The EPA Tox 21 database (USEPA 2023) reported that avobenzone was positive in six of 12 ER assays and in one of six androgen receptor (AR) assays. An independent evaluation of this database was performed (Onyango et al. 2023), in which the results were curated to exclude those assays with multiple flags indicating questionable data (e.g. borderline activity, low efficacy, curve overfitting, noise, etc.) or did not have a clear concentration-response curve (Onyango et al. 2023). It was concluded that avobenzone was active in two ER, one AR, one thyroid hormone, and 0 steroidogenesis assays (out of six, eight, six, and two tests, respectively) (Onyango et al. 2023). All biologically effective concentrations of avobenzone in these assays were well above the cytotoxic limit, indicating general cell toxicity rather than specific endocrine pathway activity, and were appreciably higher than the plasma C_{max} of 0.0229 μM noted by Matta et al. (2019, 2020). Studies *in vitro* have demonstrated that avobenzone has no progesterone-like activity (Rehfeld et al. 2018) or anti-progestagenic activity (Schreurs et al. 2005). These are summarized in Table 9.

Schreurs et al. (2002) assessed the estrogenic activity of avobenzone *in vitro* (human embryonal kidney 293 [HEK293] cells transfected with human ER [hER]α and hERβ) and *in vivo* (juvenile transgenic zebrafish with a luciferase reporter gene stably introduced as a marker for ER transactivation) (Schreurs et al. 2002; ECHA 2022). Avobenzone induced ERα transcription at concentrations of 10 and 100 μM up to approximately 40% of the maximal estradiol (E_2) induction. ERβ was slightly induced only at the highest avobenzone concentration of 100 μM (10% to 15% of the maximal E_2 induction). Avobenzone showed no anti-estrogenic effect on transcription of either receptor when assessed by competition with a submaximal concentration of E_2. There was a slight, non-concentration dependent inhibitory effect on hERα and no effect on hERβ transcription and estradiol. The avobenzone concentrations that were estrogenic (10 to 100 μM) had no estrogenic activity in the *in vivo* zebrafish follow-up assay conducted by the same group (Schreurs et al. 2002; ECHA 2022). Avobenzone (10 μM) exposure in the zebrafish assay *via* water for 96 h showed no estrogenic activity, based on a lack of whole-body luciferase activity (Schreurs et al. 2002). This study was not conducted according to GLP standards or OECD testing guidelines.

In another study, Schreurs et al. evaluated seven UV filters (including avobenzone) for their (anti)estrogenic, (anti)androgenic, and (anti)progestagenic activity using *in vitro* reporter gene assays (Schreurs et al. 2005). Avobenzone showed weak activation of hERα. The dose-response curve reached its plateau level at 37% (percentage of maximal estradiol induction [EC_{50} hERα of E_2 was 2.1 pM]), and no EC_{50} was achieved. Avobenzone did not show hERβ activation or anti-estrogenic effects toward either receptor subtype. Avobenzone did not show AR activation, progesterone receptor (PR) activation, or PR repression, but showed weak AR repression. Avobenzone showed only weak transcriptional repression for AR within the tested concentration range; however, extrapolation to concentrations slightly outside the tested range indicate an IC_{50} of 11 μM. Based on these data, the ECHA registrant reported that avobenzone may be a weak ERα agonist and a weak AR antagonist, and that it has no influence on PR (ECHA 2022). This study was not conducted according to GLP standards or OECD testing guidelines.

Schlumpf et al. evaluated the *in vitro* and *in vivo* estrogenicity of six UV filters (including avobenzone) (Schlumpf et al. 2001). In the *in vitro* E-SCREEN, avobenzone did not increase cellular proliferation in MCF-7 human breast cancer cells compared to control over the range of concentrations tested (1×10^{-7} to 5×10^{-5} M), and avobenzone (10 μM) did not induce the estrogen-regulated pS2 protein. The authors reported that avobenzone was clearly inactive for both endpoints, suggesting a lack of estrogenic activity (Schlumpf et al. 2001). In the *in vivo* uterotrophic assay, immature female Long-Evans rats received avobenzone at dose levels

Table 9. Assessment of avobenzone estrogen, androgen, thyroid, 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	*In silico* prediction models (Leadscope): NEGATIVE in prediction models: fetal death, post-implantation loss rat & rabbit, pre-implantation loss rat & rabbit, dysmorphia rat, rabbit & mouse, repro female mouse, repro male mouse, repro rat sperm. POSITIVE in prediction models: repro male rat, repro mouse sperm	(Leadscope Version 2023.0.2)
Level 2 - In vitro (mammalian and nonmammalian) assays: select endocrine mechanism(s)/pathways(s)		
ER binding assay (rat uterine cytosol) (OPPTS 890.1250, GLP-compliant)	Avobenzone was classified as "non-interacting" with the ER at concentrations of 10^{-10}, 10^{-9}, 10^{-8}, 10^{-7}, 10^{-6}, and 10^{-5} M (precipitation occurred at 10^{-4} and 10^{-3} M).	(CeeTox 2013c; NTP 2024)*
AR binding assay (rat prostate cytosol) (OPPTS 890.1150, GLP-compliant)	Avobenzone was classified as a "non-binder" (mean specific binding >75%) of the AR at concentrations of 10^{-10}, 10^{-9}, 10^{-8}, 10^{-7}, 10^{-6}, 10^{-5}, 10^{-4}, and/or 10^{-3} M).	(CeeTox 2013a; NTP 2024)*
Human recombinant aromatase assay (OPPTS 890.1200, GLP-compliant)	Avobenzone was classified as a noninhibitor (mean aromatase activity of 115% ± 9% SD) at the highest feasible concentration of 10^{-5} M.	(CeeTox 2013f; NTP 2024)*
AR transactivation activity assay (MDA-kb2 cells) (GLP-compliant)	Avobenzone did not show induction or repression of AR-mediated transactivation in the test system.	(CeeTox 2013b; NTP 2024)*
ER transcriptional activation assay (human cell line [HeLa-9903]) (OECD 455, OPPTS 890.1300, GLP-compliant)	Avobenzone was not an inducer of hERα expression in the test system.	(CeeTox 2013d; NTP 2024)*
H295R steroidogenesis assay (OPPTS 890.1550, GLP-compliant)	Decreases (∼20-25%, not statistically significant) in mean testosterone and estradiol levels were noted at multiple avobenzone concentrations (0.1-10 μM).	(CeeTox 2013e; NTP 2024)*
Kidney 293 (HEK 293)	ERα induction was noted at concentrations of 10 and 100 μM (no anti-estrogenic activity was noted). Slight ERβ induction occurred at a concentration of 100 μM.	(Schreurs et al. 2002)
MCF-7 cell proliferation assay	No increase in cell proliferation was noted at a concentration of up to 10 μM.	(Schlumpf et al. 2001)
AR CALUX® bioassay in U2-OS cells	No antagonism was observed.	(Schreurs et al. 2005)
MDA-kb2 cells	Avobenzone did not show androgenic or antiandrogenic activity.	(Ma et al. 2003)
PR CALUX® bioassay in U2-OS cells	Avobenzone did not show progesterone receptor induction or repression.	(Schreurs et al. 2005)
Human trophoblast cell line HRT8/SVneo cells	Avobenzone increased the expression of *IFI27* (a transient gene involved in decreasing cell viability) but did not alter any other cell properties.	(Yang C et al. 2018)
Acrosome reaction assay	No progesterone-like activity was observed up to a 10 μM concentration.	(Rehfeld et al. 2018)
Steroid hormone biosynthesis study in male zebrafish and human adrenocortical carcinoma (H295R) cells	The presence of avobenzone (0.72 μg/L) in binary mixture with homosalate (1.02 or 103 μg/L) appeared to augment the anti-androgenic responses in male fish exposed to homosalate (decreased gonadosomatic index, testosterone level, and transcription of several genes e.g., *hsd3b2*, *cyp17a1*, and *hsd17b1*) and increased hepatosomatic index, liver steatosis, 17β-estradiol level, and transcription of *vtg* gene and was associated with decreased testosterone level in H295R cells. Avobenzone alone had no effect in H295R cells.	(Lee et al. 2023)
Level 3 - In vivo (mammalian) assays: select endocrine mechanism(s)/pathway(s)		
Uterotrophic assay	No uterotrophic effect was noted.	(Schlumpf et al. 2001)
Uterotrophic assay (OPPTS 890.1600, GLP-compliant)	Ovariectomized adult female Harlan Sprague-Dawley rats were orally administered avobenzone at 0 (vehicle control), 320, or 1000 mg/kg/day in corn oil or 0.5 mg/kg/day 17α-ethinyl estradiol (positive control) for 3 consecutive days. Avobenzone at 1000 mg/kg/day significantly decreased body weight gain compared to vehicle controls, but similar effects were not observed at 320 mg/kg/day. No estrogenic (uterotrophic) effects were noted at either dose level.	(ILS 2012b; NTP 2024)*
Hershberger assay (OPPTS 890.1400, GLP-compliant)	Groups of 8 castrated male Harlan Sprague-Dawley rats were orally dosed for 10 consecutive days with avobenzone 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 avobenzone in corn oil at 0, 100, 320, or 1000 mg/kg/day or 3 mg/kg/day of flutamide (antagonist positive control). No androgenic or anti-androgenic effects were noted at either dose level.	(ILS 2012a; NTP 2024)*

(*continued*)

Table 9. Continued.

Assay/data	Results	References
Level 4 - In vivo (mammalian) assays: adverse effects on endocrine relevant endpoints		
Prenatal developmental toxicity study (OECD TG 414-like)	In a prenatal developmental toxicity study in rats with avobenzone doses up to 1000 mg/kg/day from gestational days 7-16, no treatment-related adverse effects were reported for dams or pups at any of the doses tested.	(Eckhardt 1984; ECHA 2022)
Prenatal developmental toxicity study	In a prenatal developmental toxicity study in rabbits with avobenzone doses up to 500 mg/kg/day from gestational days 7-19, no treatment-related adverse effects were reported for does or pups at any of the doses tested.	(Hummler and McKinney 1983; EC 2000)
Level 5 - In vivo (mammalian) assays: more comprehensive data over more extensive parts of an organism's lifecycle		
No study identified	Not applicable	Not applicable

ADME: absorptiona, distribution, metabolism, and excretion; AR: androgen receptor; ER: estrogen receptor; GLP: good laboratory practices; hERα: human ER α; *IFI27*: mitochondrial gene interferon alpha inducible protein 27; 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.
* Unpublished study report (sponsored by the U.S. National Toxicology Program).

of 421 or 636 mg/kg/day in powdered feed from postnatal day 21 to 25. Based on no statistical changes in uterine weights or other treatment-related effects, it was concluded that avobenzone was inactive in the *in vivo* uterotrophic assay at the doses tested.

In a study conducted by Ma et al., avobenzone was evaluated for its (anti)androgenic activity in an *in vitro* luciferase reporter gene assay using the human breast carcinoma cell line MDA-kb2, which expresses functional endogenous AR and is stably transfected with a luciferase reporter plasmid (Ma et al. 2003). Over the wide range of concentrations tested, avobenzone did not cause AR transactivation, nor did it inhibit dihydrotestosterone-induced AR activation.

In an *in vitro* study, avobenzone exposure at a concentration range of 0 to 50 μM (0 to 15.52 mg/L) for 48 h resulted in the inhibition of the proliferation of the immortalized human trophoblast cell line HRT8/SVneo, used as a model for possible effects on development (Yang et al. 2018). A significant concentration-related inhibition of proliferation was observed starting at 5 μM. Further, in a separate assay (Annexin V and PI staining), it was noted that avobenzone at concentrations of ≥10 μM resulted in a concentration-dependent increase in apoptotic cells. Additionally, avobenzone (20 μM) time-dependently increased the activity (increased phosphorylation) of AKT and ERK1/2 in HRT8/SVNeo cells, resulting in an increase in AKT-regulated downstream proteins, an effect that was attenuated by AKT and ERK1/2 inhibitors. Avobenzone concentrations of 20 and 50 μM promoted Ca^{2+} overload into mitochondria, which subsequently resulted in the depolarization of the mitochondrial membrane. Avobenzone increased the expression of the mitochondrial gene, interferon alpha inducible protein 27 (*IFI27*; a transient gene involved in decreasing cell viability), but did not alter any other cell properties, suggesting that avobenzone may induce mitochondrial dysfunction-mediated apoptosis. It is unlikely that these *in vitro* effects would be observed *in vivo* given the maximum concentrations achieved after dermal application; further, no reproductive or developmental toxicity was noted in an OECD TG 414 study conducted in rats (described below). Hence the relevance of these findings, which occurred at high concentrations, is highly questionable under physiologically relevant concentrations.

Multiple chemical UV filters induced Ca^{2+} influx through the cationic channel of sperm (CatSper) Ca^{2+}-channel, mimicking the effect of progesterone on Ca^{2+} signaling, an endogenous mechanism that controls sperm function (Rehfeld et al. 2018). To determine whether UV filters may similarly mimic the effect of progesterone on sperm function, 29 UV filters were examined for their ability to affect the acrosome reaction of sperm cells and sperm penetration into a viscous medium, as well as hyperactivation and viability of human sperm cells. Specifically, the sperm acrosome reaction was investigated following the addition of 10 μM of each UV filter to capacitated human sperm cells for 30 min using an image-cytometer-based assay. Although several UV filters were found to induce an acrosome reaction, avobenzone did not; additionally, avobenzone did not affect sperm penetration. Further, none of the UV filters induced a change in the proportion of hyperactivated cells, although cell viability was decreased after treatment with avobenzone, which, according to the authors, was independent of any Ca^{2+} effects. This study demonstrated that avobenzone has no progesterone-like activity on sperm *in vitro*.

In a number of unpublished studies (see details in Table 9) sponsored by the U.S. 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 estrogenic or androgenic activity or inhibition of aromatase activity by avobenzone (CeeTox 2013c, 2013a, 2013f, 2013b, 2013d). Decreased testosterone and estradiol levels were noted in the H295R steroidogenesis assay at avobenzone concentrations ranging from 0.1 to 10 μM (CeeTox 2013e; NTP 2024). There were no estrogenic (uterotrophic) effects noted in the uterotrophic assay at avobenzone doses up to 1000 mg/kg/day (ILS 2012b; NTP 2024). There were no androgenic or anti-androgenic effects noted in the Hershberger assay at avobenzone doses up to 1000 mg/kg/day (ILS 2012a; NTP 2024).

In summary, although the *in vitro* results from the literature for avobenzone are mixed with respect to (anti)estrogenic activity, albeit at high concentrations, the *in vivo* data clearly demonstrate a lack of (anti)estrogenic activity. There was no response in the uterotrophic assay (Schlumpf et al. 2001) and no estrogenic activity in a juvenile transgenic

zebrafish assay with 10 μM exposure via water for 96 h (Schreurs et al. 2002). As for the potential (anti)androgenic activity of avobenzone, the literature is limited largely to *in vitro* data, which were mixed, though again at high concentrations (Ma et al. 2003; Schreurs et al. 2005). Avobenzone did not alter androgen-dependent tissue weight at doses up to 1000 mg/kg in the Hershberger assay (ILS 2012a).

Developmental and reproductive toxicity

No clinical study has been conducted to determine whether the presence of avobenzone in sunscreen has any reproductive or developmental effects in humans. However, the available nonclinical data presented in Table 10 and discussed in detail in the following subsection indicate avobenzone does not pose a reproductive or developmental hazard.

There are no *in vivo* reproductive toxicity studies on avobenzone, but there are two developmental toxicity studies. Both studies, one in rats and another in rabbits, demonstrated no evidence of developmental toxicity following gestational exposure (i.e. no effects were observed even at the highest dose tested) (Hummler and McKinney 1983; Eckhardt 1984).

A GLP-compliant prenatal developmental toxicity study was performed according to FDA guidelines (USFDA 1966) and the UK Committee on Safety of Medicines (CSM) guidance (CSM 1974), equivalent or similar to the current OECD TG 414. Füllinsdorf albino rats (n = 36 dams per dose) were administered avobenzone (purity not specified) via oral gavage at doses of 0, 250, 500, and 1000 mg/kg/day on gestational day (GD) 7 to 16 (the ECHA entry for the same study noted that exposure was from GD 6 to 17 [12 days total]) (Eckhardt 1984; ECHA 2022). Based on increased embryonic resorptions (19.5%) at 1000 mg/kg/day in a preliminary dose range-finding study, the dose of 1000 mg/kg/day was chosen as the upper limit for the main study. In the definitive study, half of the animals were terminated on GD 21, while the other half of the females were allowed to litter and to rear the pups until weaning on postnatal day 23. Examination of dams, including reproductive endpoints (corpora lutea, implantations, early resorptions, and late resorptions), indicated no treatment-related effects. Only one complete resorption was observed in the lowest dose group (250 mg/kg/day), which was considered an incidental finding and not substance-related. Thus, the possible effect on resorptions observed in the range-finding study was not confirmed in the main study. Further, there was no treatment-related embryotoxicity or teratogenicity; the pups were examined for developmental toxicity, including external, soft tissue, and skeletal abnormalities. Delayed ossification of neural arches and sternebrae were observed in 500 mg/kg dose group fetuses, but not in fetuses of the 250 and 1000 mg/kg dose groups (Eckhardt et al. 1984). Due to the lack of a dose-response, the ECHA registrant of this study concluded that this effect was probably not treatment-related (ECHA 2022). The NOAEL for maternal and developmental toxicity (embryotoxicity or teratogenicity) was 1000 mg/kg/day, the highest dose tested (Eckhardt 1984).

In another study, the embryotoxicity and teratogenicity of avobenzone was investigated in rabbits according to the guidelines established by the FDA and UK CSM (USFDA 1966; CSM 1974; Hummler and McKinney 1983). Rabbits were administered avobenzone at doses of 0, 80, 200, and 500 mg/kg/day *via* oral gavage on GD 7 to 19 ($n = 17$ to 19 per dose group) (Hummler and McKinney 1983; EC 2000). Does were terminated on GD 30, and fetuses were monitored for viability for 24 h and examined for external, visceral, and skeletal anomalies (Hummler and McKinney 1983). No maternal toxicity was evident during the study (Hummler and McKinney 1983). Although it was reported that there were some maternal deaths (dose group not specified), and a higher prevalence of resorption in the lowest dose group, it was unclear whether these effects were treatment-related (EC 2000). There was no treatment-related teratogenicity; although malformations were noted in the control, low-dose, and mid-dose groups, no malformations were noted in the highest treatment group (Hummler and McKinney 1983). The NOAEL for maternal toxicity and embryotoxicity/teratogenicity was the highest dose tested (i.e. 500 mg/kg/day).

No extended 1-generation or 2-generation reproductive toxicity studies were identified for avobenzone.

Immunotoxicity

One *in vitro* study reported that exposure to organic UV filters, including avobenzone, significantly increased the production of various inflammatory cytokines in macrophages, particularly tumor necrosis factor (TNF)–α and interleukin (IL)–6 (Ao et al. 2018). In this study, THP-1 cells were treated with phorbol 12-myristate 13-acetate to transform THP-1 cells into macrophage-like cells. Cell viability was not affected after 24 h of exposure to increasing concentrations of avobenzone (10^{-8} to 10^{-5} M). TNF-α and IL-6 were significantly increased at avobenzone concentrations of 10^{-6} to 10^{-5} M; however, exposure to lower concentrations did not induce a significant increase in cytokine levels compared with controls. Evaluation of mRNA expression demonstrated that both *TNF-α* and *IL-6* mRNA levels increased after 24 h of exposure to 10^{-6} M avobenzone (only concentration tested). It was further reported that avobenzone may activate the phosphorylation of the p38 MAPK and NF-κB pathways (which are

Table 10. *In vivo* developmental and reproductive toxicity studies of avobenzone.

Species/strain	Route of exposure/ Guideline study	NOAEL for maternal or developmental toxicity (mg/kg/day)	Adverse endpoint(s)	Reference
Rat/Füllinsdorf albino	Oral/similar to OECD TG 414	1000	Highest dose tested	(Eckhardt 1984; ECHA 2022)
Rabbits	Oral	500	Highest dose tested	(Hummler and McKinney 1983; EC 2000)

NOAEL: No-observed-adverse-effect level; OECD: Organization for Economic Co-operation and Development; TG: Test guideline.

important in cytokine expression) in human macrophages, leading to the production of TNF-α and IL-6.

In a systematic evaluation, the potential for immune-regulatory cytokines and chemical allergens to produce vascular endothelial growth factor (VEGF) in normal human epidermal keratinocytes (NHKs) was investigated *in vitro* (Bae et al. 2015). VEGF is a major cytokine in the regulation of angiogenesis and lymphangiogenesis, which are important components in chronic inflammation. In this study, reference chemicals for human sensitizers as noted in OECD TG 429 and "common" human haptenic allergens, including avobenzone, were investigated for any potential to induce IL-8 and VEGF in NHKs (Bae et al. 2015). Following treatment, 10 of 16 potential sensitizers identified in OECD TG 429, along with avobenzone, induced IL-8 and VEGF production in NHKs. Specifically, IL-8 was induced at 10 and 50 μM and VEGF was induced at 2 and 10 μM avobenzone concentrations in culture. At a concentration of 50 μM, VEGF production was significantly reduced, although cell viability was also significantly decreased at this high concentration.

In another *in vitro* study, high concentrations of avobenzone initially dissolved in dipropylene glycol (0.5% v/v) before addition of medium were required to cause cytotoxicity in human THP-1 monocytes and in THP-1 monocyte-derived macrophages after 24 h of exposure (O'Keefe et al. 2016). Of note, avobenzone exhibited a shallow cytotoxicity concentration-response curve for both monocytes and macrophages and did not achieve an EC_{50} value even at the highest concentration (200 μg/mL) tested. In monocytes and macrophages, avobenzone exposure increased IL-8, whereas in macrophages, avobenzone exposure increased IL-1β levels. Together, these results indicate that there is potential for immunotoxicity following avobenzone exposure *in vitro*; however, whether these *in vitro* effects are translated *in vivo*, where achieved systemic concentrations are appreciably lower, e.g. 0.023 μM (Matta et al. 2019; 2020), is questionable. Moreover, no nonclinical repeated-dose toxicity studies have identified any immune-related organ weight changes or corresponding gross pathology or histopathological changes in avobenzone-treated animals, indicating a lack of immunological concerns for avobenzone.

An investigation of the potential immunomodulatory properties of eight UV filters, including avobenzone, demonstrated that none of the filters were cytotoxic to THP-1 cells at concentrations up to 50 μM (Weiss et al. 2023). Nontoxic concentrations of avobenzone were shown to increase the secretion of IL-8 from both THP-1 cells and THP-1–derived macrophages and decrease IL-6 and IL-10 release from lipopolysaccharide-stimulated peripheral blood mononuclear cells, suggesting that avobenzone exposure could be involved in immune deregulation.

Neurotoxicity

No *in vivo* animal studies have identified any neurobehavioral changes, neurotoxicity-related organ weight changes, or corresponding gross pathology or histopathological changes in avobenzone-treated animals. Additionally, developmental exposure to avobenzone has not been associated with any neurotoxicity-related adverse effects. In a 2017 review of the neurotoxic effects associated with active ingredients (UV filters) in sunscreen products, avobenzone was not identified as a neurotoxicant (Ruszkiewicz et al. 2017).

Obesogenicity

In a microarray study conducted in NHKs, exposure to 10 μM avobenzone resulted in genome-scale transcriptional profile changes, including the upregulation of 272 and downregulation of 274 differentially expressed genes (Ahn et al. 2019). No significant cytotoxicity was observed at the 10 μM test concentration; the half maximal cell viable concentration of avobenzone was 34.9 μM. Among the genes investigated, avobenzone increased transcription of those associated with lipid metabolism (such as cholesterol biosynthetic processes). To confirm the avobenzone-induced upregulation of genes associated with cholesterol metabolism in NHKs, the gene transcriptional changes of insulin-induced gene 1 (*INSIG1*), 3-hydroxy-3-methylglutaryl-CoA reductase (*HMGCR*), and 3-hydroxy-3-methylglutaryl-CoA synthase 1 (*HMGCS1*) were investigated at 4, 24, and 48 h after avobenzone treatment by quantitative reverse-transcription polymerase chain reaction. Consistent with the microarray results, the mRNA levels of *INSIG1*, *HMGCR*, and *HMGCS1* were upregulated in NHKs at 24 h after the avobenzone treatment, whereas only *HMGCS1* remained upregulated at 48 h. Avobenzone increased gene transcription of the peroxisome proliferator-activated receptor γ (PPARγ; gene name *PPARG*) and fatty acid binding protein 4, indicating that avobenzone exposure may cause metabolic effects. The obesogenic potential of avobenzone was further investigated by evaluating the adipogenesis in human bone marrow mesenchymal stem cells (hBM-MSCs), in which avobenzone significantly promoted adipogenicity with an EC_{50} of 14.1 μM. Additionally, avobenzone significantly upregulated PPARγ (i.e. *PPARG*) mRNA levels during adipogenesis of hBM-MSCs, although it was noted that avobenzone did not directly bind to PPARγ. Therefore, the authors concluded that the avobenzone-associated adipogenesis occurred via a PPARγ-independent mechanism *in vitro*. However, the relevance of these *in vitro* effects *in vivo*, where achieved concentrations are appreciably lower, e.g. 0.023 μM (Matta et al. 2019, 2020), is not known. No effect on body weight was observed in a 90-day repeated-dose oral toxicity study, at doses up to 1000 mg/kg/day.

Risk characterization

To characterize the risk associated with the use of an avobenzone-containing sunscreen product, a margin of safety (MoS) approach was used. This is a well-established risk assessment approach in which a selected reference or benchmark dose is divided by the measured or expected human exposure to quantify how many times lower the exposure is relative to the reference or benchmark dose. The MoS, also known by some as a MoE, was calculated as the ratio of the NOAEL obtained, in this case, from animal toxicology studies to the estimated human systemic exposure dose (SED) as shown in Equation (1). Although an MoS is not a probabilistic

statement of risk, the concern regarding the exposure evaluated decreases as the value of the MoS increases. Accordingly, MoS values greater than 100 are generally interpreted to be acceptable and protective for nongenotoxic and noncarcinogenic effects, whereas values lower than 100 suggest that the risk from chemical exposure is likely not to be acceptable (SCCS 2018).

$$MoS = \frac{NOAEL}{SED} \tag{1}$$

Estimation of systemic exposure dose

The expected exposure (i.e. SED) to avobenzone through use of an avobenzone-containing sunscreen product was calculated using Equation (2). Terms of the equation included the daily sunscreen application (A), unit conversion factor (UC), avobenzone concentration in the sunscreen (C), dermal absorption of avobenzone (D), and a typical individual's body weight (BW). Conservative assumptions were used in selecting values for these terms (see Table 11).

$$SED(\mathrm{mg/kg/day}) = A\left(\frac{g}{day}\right) \times UC\left(1000\frac{mg}{g}\right) \times C\left(\frac{\%}{100}\right) \times \left(\frac{D(\%)}{BW}\right) \tag{2}$$

Avobenzone systemic exposures resulting from the application of avobenzone-containing sunscreen products were calculated for three separate scenarios: 1) 97.2 g/day maximum amount based on the maximal usage trial, 2) 28 g/day based on the recommended sunscreen application per day by the American Academy of Dermatology, and 3) 3.46 g/day based on estimates for facial application of a sunscreen product.

Scenario 1. Assuming that a 60-kg individual applies 97.2 g of a 3% avobenzone-containing sunscreen product per day with 0.59% dermal absorption of avobenzone, the SED of avobenzone was calculated below to be 0.29 mg/kg/day:

$$SED = \left(97.2\frac{g}{day}\right) \times \left(1000\frac{mg}{g}\right) \times 0.03 \times \left(\frac{0.0059}{60\ kg}\right) = 0.29\ mg/kg/day$$

Scenario 2. Assuming that a 60-kg individual applies 28 g of a 3% avobenzone-containing sunscreen product per day with 0.59% dermal absorption of avobenzone, the SED of avobenzone was calculated below to be 0.083 mg/kg/day:

$$SED = \left(28\frac{g}{day}\right) \times \left(1000\frac{mg}{g}\right) \times 0.03 \times \left(\frac{0.0059}{60\ kg}\right) = 0.083\ mg/kg/day$$

Scenario 3. Assuming that a 60-kg individual applies 3.46 g (facial application only) of a 3% avobenzone-containing sunscreen product per day with 0.59% dermal absorption of avobenzone, the SED of avobenzone was calculated below to be 0.010 mg/kg/day:

$$SED = \left(3.46\frac{g}{day}\right) \times \left(1000\frac{mg}{g}\right) \times 0.03 \times \left(\frac{0.0059}{60\ kg}\right) = 0.010\ mg/kg/day$$

Avobenzone-specific margin of safety calculations

For avobenzone MoS calculations, NOAELs were considered from the available animal toxicology studies (Table 12). Given the short exposure duration in the reported dermal toxicity studies in rats (4 weeks) and rabbits (21 days), these studies were not used for risk assessment purposes. Because no

Table 11. Parameters used for avobenzone 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	Recommended amount of sunscreen applied per day to cover human adult body (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)
UCC (unit conversion factor)	1000 mg/g	
C (avobenzone concentration within product)	0.03	3% is the maximum concentration of avobenzone allowed in product formulations in the United States (Jansen et al. 2013; Kockler et al. 2013)
D (dermal absorption of avobenzone)	0.59	0.59% of the applied dermal dose of avobenzone penetrated the skin in a clinical study; other studies indicate lower bioavailability via the dermal route
BW (body weight)	60 kg	Typical body weight of an adult human female
	70 kg	Typical body weight of an adult human male

Table 12. NOAELs From key animal toxicology studies on avobenzone.

Study	NOAEL (basis) [detailed basis]	Reference
21-day dermal toxicity study in rabbits (OECD TG 410)	360 mg/kg/day [no avobenzone-related toxicity at the highest dose tested]	(ECHA 2022)
90-day toxicity study in rats (OECD TG 408)	450 mg/kg/day (hematologic effects)	(ECHA 2022)

NOAEL: No-observed-adverse-effect level; OECD: Organization for Economic Co-operation and Development; TG: Test guideline.

dermal repeated-dose toxicity study of sufficient duration was available for avobenzone, in accordance with SCCS guidelines, the NOAEL value from an oral repeated-dose toxicity study was considered with an applicable conservative oral bioavailability assumption. Therefore, the critical study for MoS derivation was the 90-day oral toxicity study in rats (OECD TG 408) (ECHA 2022). In this study, treatment-related decreases in mean red blood cells and hemoglobin were noted at the highest exposure dose of 1000 mg/kg/day at week 14 of treatment in females (at the end of the study). Therefore, the NOAEL for hematologic effects was 450 mg/kg/day. Indications of hepatic weight changes were considered to be related to liver adaptations to treatment and not adverse. Although there is no empirical information for avobenzone bioavailability via the oral route, based on SCCS recommendations, a 50% oral bioavailability was assumed (SCCS 2018).

The following section describes the calculations used to derive a MoS value (based on various exposure scenarios) for general toxicity, using the 90-day toxicity study data. This MoS value would be applicable to nonadult populations as well. According to the SCCS, although 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× that is already considered in the interpretation of the MoS (SCCS 2018).

Based on the rat 90-day oral toxicity study NOAEL of 450 mg/kg/day (OECD TG 408) (ECHA 2022) and an oral bioavailability of 50% for rats based on the SCCS guidelines for when empirical data are missing (SCCS 2018), the following calculations were used to obtain MoS values for potential adverse toxic effects for the three previously described exposure scenarios. The MoS for these scenarios was ≥776. The MoS was also calculated for the most conservative exposure scenario (60-kg individual applies 97.2 g) for a 10% avobenzone containing sunscreen (the highest concentration allowed globally) with 0.59% dermal absorption of avobenzone, the SED was calculated to be 0.956 mg/kg/day, and the MoS was 235:

Scenario 1.

$$MoS = \frac{450 mg/kg/day \ (NOAEL) \times 0.50(bioavailability)}{0.29 \ mg/kg/day(SED)} = 776$$

Scenario 2.

$$MoS = \frac{450 mg/kg/day \ (NOAEL) \times 0.50(bioavailability)}{0.083 \ mg/kg/day(SED)} = 2710$$

Scenario 3.

$$MoS = \frac{450 mg/kg/day \ (NOAEL) \times 0.50(bioavailability)}{0.010 \ mg/kg/day(SED)} = 22,500$$

Although oral bioavailability was conservatively assumed to be 50%, other risk evaluations of avobenzone, 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. 1552; 5420; or 45,000 for Scenarios 1, 2, and 3, respectively).

The risk characterization of avobenzone based on a reported dermal penetration of 0.59% in a clinical trial suggests that risks are actually lower. This estimate was reported by the SCC with limited study details, which precludes evaluation of study quality. Therefore, an alternative risk characterization of avobenzone based on FDA's clinical MUsT study data was also conducted.

Estimation of systemic exposure to avobenzone from FDA's maximal usage trial studies

The highest C_{max} value reported for avobenzone in the MUsT studies was 7.1 ng/mL from a lotion formulation (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 (Mathew et al. 2021). Assuming a volume of distribution (V_d) of 944 L (Lukacova et al. 2008), the total internal (systemic) dose of avobenzone is the product of the C_{max} and V_d as follows:

$$Total \ Internal \ Avobenzone \ Dose = 7.1 ng/mL \times 10^{-6} \ mg/ng \times 944,000 \ mL = 6.70 \ mg$$

The total applied dose in the MUsT study was 2.916 g (97.2 g x 0.03) (Matta et al. 2020). Therefore, the percentage dermal penetration for avobenzone is calculated as 0.23% (0.0067 g total internal dose divided by 2.916 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 estimate has numerous uncertainties including lack of consideration for metabolite formation, elimination rate, and area under the curve 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 the value of 0.59% derived from *in vitro* skin penetration studies that was used in the MoS calculations.

Avobenzone safety conclusion

In conclusion, avobenzone can be considered safe when used as a sunscreen UV filter at concentrations up to 3%, the maximum permitted usage level in the United States and Canada. Furthermore, based on the limited longer-term toxicity studies (i.e. 90-day repeated-dose studies) and the results from genotoxicity and mutagenicity studies performed with avobenzone, it is not expected that avobenzone represents a carcinogenic hazard to humans.

Discussion

Based on the available nonclinical and human clinical safety test results, avobenzone has a favorable safety profile without any clear markers of toxicity or endpoints of concern. This conclusion has been reached and considered to be well

Table 13. Summary of avobenzone toxicological endpoints and risk characterization.

Property	Key avobenzone-related results
Pharmacokinetics	• Dermal absorption of avobenzone was minimal in clinical trials (≤0.59% of the applied dose) (EC 2000). • In an *ex vivo* dermal absorption study with human cadaver skin, 0.35% of the dermally applied avobenzone dose was found in the lower dermis after 16 h (EC 2000). • In an OECD TG 428 *ex vivo* study in minipigs, 0.9%-3.4% of the applied avobenzone dose was recovered from stratum corneum tape strips, and 0.5% was recovered in the receptor chamber (ECHA 2022). • No specific information regarding the distribution of avobenzone was identified. However, 4 tentative metabolites, including desmethylhydroxy avobenzone, hydroxyl avobenzone, desmethylavobenzone carboxylic acid, and dehydrated dihydrohydroxy avobenzone, have been identified for avobenzone (Klotz et al. 2019). • Avobenzone was minimally excreted in the urine at concentrations ranging from 0.012%-0.016% of the dermally applied dose in a clinical trial; no avobenzone was detected in plasma or feces (ECHA 2022).
Acute toxicity	• Rat dermal LD_{50} >1000 mg/kg (OECD TG 402) (ECHA 2022) • Rat oral LD_{50} >16,000 mg/kg (OECD TG 401) (ECHA 2022)
Repeated-dose toxicity	• A 4-week subacute dermal toxicity study in rats identified a NOAEL for general toxicity of 230 mg/kg/day (highest dose tested) for intact skin and 200 mg/kg/day for abraded skin (EC 2000). • A 21-day dermal toxicity study (OECD TG 410) in rabbits identified a NOAEL of 360 mg/kg/day (highest dose tested; no toxicological effects identified) (ECHA 2022). • A 90-day oral toxicity study in rats (OECD TG 408) identified a NOAEL of 450 mg/kg/day for hematological effects (ECHA 2022).
Irritation, skin sensitization, photoirritation, and photoallergenicity	• Clinical studies indicate that avobenzone is not a skin irritant. Similar findings of no dermal irritation are reported in nonclinical studies. • No eye irritation was observed in a standard Draize test in rabbits up to an avobenzone concentration of 20% (EC 2000). • Clinical studies indicate that avobenzone is not a sensitizer up to a dose of 10%. Avobenzone was not a skin sensitizer up to a concentration of 20% in the guinea pig maximization test (EC 2000). • The EMCPPTS Taskforce reported that only 0.1% of the study population (2715 patients) had a positive photoallergic contact dermatitis reaction to 2-10% avobenzone (Kerr et al. 2012). Further, other smaller scale clinical trials in individuals self-identified as having allergy or reaction to sunscreen ingredients found no positive patch test or photo patch test reactions to avobenzone.
Genotoxicity and carcinogenicity	• Avobenzone was negative for genotoxicity in the OECD TG 471 bacterial reverse mutation assay (Bora et al. 2017). • Avobenzone was negative for mutagenicity *in vitro* in Chinese hamster lung fibroblasts (V79) (OECD TG 476) up to 20 μg/mL (ECHA 2022). The 20 μg/mL dose (highest dose tested) increased cytotoxicity. • Avobenzone was negative for genotoxicity in the OECD TG 474 *in vivo* erythrocyte micronucleus test (ECHA 2022). • In a non-guideline clastogenicity study *in vitro*, avobenzone was non-photomutagenic up to 90 μg/mL (Chetelat et al. 1993). • A 90-day repeated-dose oral toxicity study in rats found no increase in hyperplasias or tumors (ECHA 2022). No longer-term carcinogenicity studies for avobenzone were identified. • Specific studies that have evaluated the photogenotoxicity or photocarcinogenicity potential of avobenzone were not identified. However, avobenzone was not mutagenic in photomutagenic studies.
Estrogen, androgen, thyroid, developmental, and reproductive toxicity	• Avobenzone was not active in most endocrine assays, either *in vitro* (e.g., estrogen and androgen competitive binding and progesterone assays) or *in vivo* (i.e., the rodent uterotrophic/Hershberger assays). • In an OECD TG 414 prenatal developmental toxicity study in rats, a NOAEL of 1000 mg/kg/day (maximum dose tested) was identified for effects on maternal and fetal development (Eckhardt 1984; ECHA 2022). • In a prenatal developmental toxicity study in rabbits, a NOAEL of 500 mg/kg/day (maximum dose tested) was identified for effects on maternal and fetal development (Hummler and McKinney 1983; EC 2000).
Immunotoxicity and neurotoxicity	• *In vitro* studies suggest the potential for various immune responses to avobenzone (Bae et al. 2015; O'Keefe et al. 2016; Ao et al. 2018), including some hematological effects; however, no immunological effects of avobenzone have been reported from any clinical or nonclinical *in vivo* studies. • Avobenzone is not recognized as a potential neurotoxicant (Ruszkiewicz et al. 2017).
Risk characterization	• Based on a NOAEL of 450 mg/kg/day from a 90-day toxicity study in rats (OECD TG 408), an adjusted margin of safety (MoS) of 776 was calculated. • No oral bioavailability data was available for avobenzone; therefore, a conservative 50% oral bioavailability was assumed based on SCCS guidelines (SCCS 2018). • A 90-day repeated-dose toxicity study in rats and genotoxicity and mutagenicity experiments *in vitro* and *in vivo* found no increased risk of carcinogenicity for avobenzone. • Together, the available data indicate avobenzone can be considered safe when used as a sunscreen UV filter in products at concentrations up to 3%.

EMCPPTS: European Multicenter Photopatch Test Study; NOAEL: No-observed-adverse-effect level; MoS: mmarginm of safety; OECD: Organization for Economic Co-operation and Development; SCCS: Scientific Committee on Consumer Safety; TG: test guideline.

supported by all 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 sunscreen UV filter, there are sufficient clinical use and nonclinical safety data on avobenzone to assess its safety as a sunscreen active ingredient 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 PK, pharmacodynamics, and potential toxicological properties (see Table 13 for a summary of the available data).

Estimates of the dermal absorption of avobenzone have varied based on the model and dose/concentrations used. Although no harmonized dermal absorption value is available, the clinical data indicate very low percutaneous absorption in humans ($\leq$0.59% of the applied dose). There are no clinical or nonclinical data to assess the distribution of avobenzone; however, there is some information from human biomonitoring studies on its metabolism and excretion. Four metabolites of avobenzone have tentatively been identified, although metabolite-specific toxicity profiles were not available. Biomonitoring maximal use studies reported limited urinary excretion of avobenzone following normal use scenarios.

Indirect assessment of the bioaccumulation potential of avobenzone has been conducted in a case study of UV filters relative to the practical application of the interim internal threshold of toxicological concern (iTTC), 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 MUsT (Matta et al. 2019; 2020) showed that the experimentally determined internal exposure to avobenzone was an order of magnitude lower than the 1 µM interim iTTC threshold, in contrast to the external exposure of avobenzone, which exceeded the external dose limits of the standard TTC approach (Najjar et al. 2023). The first step of this assessment verified that the case study chemicals, including avobenzone, 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, avobenzone has not demonstrated mutagenicity/genotoxicity nor has it shown conclusive evidence of endocrine activity. Furthermore, avobenzone does not resemble known bioaccumulating chemicals such as 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).

Numerous studies have detected avobenzone in sediment samples (Tsui et al. 2015) and surface water samples collected worldwide (Kaiser et al. 2012; da Silva et al. 2022), leading to ecotoxicological concerns over the environmental impact of avobenzone dispersal from surface water runoff or wastewater treatment. The human health risk from consumption of seafood or other aquatic organisms with potential avobenzone-related health effects (Mitchelmore et al. 2019) has not been studied, as no bioaccumulation or biomagnification studies of the compound were identified. However, there is no conclusive evidence of avobenzone effects on the immune, estrogen, androgen, or thyroid systems, and laboratory studies of avobenzone have not reflected environmental concentrations (da Silva et al. 2022). Therefore, the effects of avobenzone on aquatic species (and subsequent biomagnification upward through the trophic chain to humans) are likely overestimated (da Silva et al. 2022).

The acute toxicity profile indicates that avobenzone is minimally toxic. The NOAEL for general toxicity from a subchronic oral rat toxicity study was 450 mg/kg/day, based on hematologic effects at the high dose of 1000 mg/kg/day. Additionally, some indications of sensitization have been reported in clinical case studies, but avobenzone generally did not cause dermal irritation or sensitization. Although there are no formal 2-year carcinogenicity studies for avobenzone, a subchronic (90-day) oral exposure study in rats did not reveal any increase in hyperplasia and avobenzone was found not to be genotoxic either *in vitro* or *in vivo*. Furthermore, there are no alerts for any other key events associated with carcinogenicity (e.g. endocrine activity or immunotoxicity) at concentrations achieved *in vivo*, which together indicate that carcinogenicity from use as a sunscreen in humans is very unlikely.

Overall, based on the NOAEL selected from the available animal toxicity studies as well as the use of conservative assumptions for estimating the systemic exposure dose from the application of sunscreen products, MoS one or more orders of magnitude greater than 100 are obtained for avobenzone. Therefore, the available data on avobenzone are supportive of a conclusion that it is safe and poses no human health risks when used in sunscreen products at concentrations up to 3%, the permitted maximum usage level in the United States and Canada, and at usage levels up to 5% in Europe, MERCOSUR, Australia, China, Korea, and ASEAN, or 10% in Japan. This conclusion is also consistent with the safety acceptance and global approval of avobenzone (DSM 2007; EP 2009; Jansen et al. 2013; Kockler et al. 2013; TGA 2021).

Acknowledgments

The authors would like to thank Stantec Chemrisk for their project assistance. We would also like to thank Shiva Noorchashm and Andrea Blevins Primeau of Medica Communications, LLC, for their assistance in project management and editorial reviews, and Jason Magby of Colgate-Palmolive Company for editorial review of the original draft. The authors would also like to acknowledge the expert views and comments of the journal Editor and the anonymous peer-reviewers.

Declaration of interest

This work was sponsored by the Personal Care Products Council (PCPC) Sunscreen Consortium. The following companies were members of the Sunscreen Consortium during the writing of this manuscript: Beiersdorf North America, Inc., Colgate-Palmolive Company, dsm-firmenich, Edgewell Personal Care, The Estee Lauder Companies, Inc., Kao USA, Inc, Kenvue (formerly Johnson & Johnson Consumer, Inc.), L'Oréal USA, Inc., Mary Kay, Inc., The Procter & Gamble Company, Shiseido America Corporation, Symrise, and Unilever North America.

The following authors declare the following sunscreen-related relationships: C. D'Ruiz is employed by dsm-firmenich, which was a member of the PCPC Sunscreen Consortium, and conducted this work as part of normal employment. J.F. Nash is employed by Procter & Gamble, which was a member of the PCPC Sunscreen Consortium, and conducted this work as part of normal employment. N.E. Kaminski and S.M. Cohen were scientific consultants for the Titanium Dioxide Manufacturers Association. S.M. Cohen serves on the Cosmetic Ingredient Review Expert Panel. The remaining authors have no relationships to disclose.

Medica Communications, LLC, is a medical communications company that was contracted by the PCPC Sunscreen Consortium to assist with project management and editorial assistance. Medica Communications

was not involved in the literature review, research, interpretation, or writing of the manuscript.

The roles of all the authors in the preparation of the manuscript were as follows: **K.G. Norman**: Investigation, Writing - Review & Editing, Project administration; **L. Kaufman**: Investigation, Writing – Original Draft, Writing- Review & Editing, Visualization; **C. D'Ruiz**: Conceptualization, Writing - Review & Editing; Supervision; **L. Loretz**: Conceptualization; Methodology, Investigation; Writing – Original Draft; **A. Kowcz**: Conceptualization; Writing - Review & Editing, Supervision, Project administration, Funding acquisition; **S.M. Cohen**: Conceptualization, Methodology, Investigation, Writing - Review & Editing, Supervision; **A.R. Scialli**: Conceptualization, Methodology, Investigation, Writing - Review & Editing; **A.R. Boobis**: Conceptualization, Methodology, Investigation, Writing - Review & Editing; **D. Jacobson-Kram**: Conceptualization, Methodology, Investigation, Writing - Review & Editing; **R. Schoeny**: Conceptualization, Methodology, Investigation, Writing - Review & Editing; **T.J. Rosol**: Conceptualization, Methodology, Investigation, Writing - Review & Editing; **G.M. Williams**: Conceptualization, Methodology, Investigation, Writing - Review & Editing; **N.E. Kaminski**: Conceptualization, Methodology, Investigation, Writing - Review & Editing; **F.P. Guengerich**: Conceptualization, Methodology, Investigation, Writing - Review & Editing; **J.F. Nash**: Conceptualization, Methodology, Investigation, Writing- Original Draft; Writing - Review & Editing, Supervision.

Supplemental material

Supplemental material for this article is available online here.

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