From:	s22 [redacted]
To:	Catherine Gwynne
Cc:	s22 [redacted]; s22 [redacted]
Subject:	Early Draft TGA Safety Review on Sunscreen Ingredients [SEC=OFFICIAL]
Date:	Tuesday, 6 August 2024 12:01:00 PM
Attachments:	image001.png Literature search and summaries for seven sunscreen active ingredients as of 1 August 2024 - DRAFT.DOCX

Dear Catherine,

Thank you for your time on the phone earlier this morning. I hope you and the team get a well-deserved break soon from all the consultations that have been coming your way!

As previously advised, the TGA has been conducting a thorough literature review to identify safety data for seven common sunscreen active ingredients used in therapeutic sunscreens in Australia. These ingredients include

- butyl methoxydibenzoylmethane (avobenzone)
- ethylhexyl triazone
- homosalate
- octocrylene
- octyl methoxycinnamate (octinoxate)
- oxybenzone
- phenylbenzimidazole sulfonic acid

Our Toxicology team has completed the review following an extensive literature search to determine the No Observed Adverse Effect Level (NOAEL) and Dermal Absorption (DA) for each of these ingredients. This information will be required to finalise our risk assessments for these ingredients.

Given the tight timeframe we are working within, we would like to provide you with an early draft of our findings as soon as possible. The attached document is intended to give you a preliminary understanding of our review process and findings to date, however a risk assessment of each of these ingredients has not been finalised as this will depend on the outcomes of the consultation on a final sunscreen exposure model that will be suitable for Australian therapeutic sunscreens.

We are not requesting a detailed analysis or review, however, should you have any key information that has not been considered in our draft that could inform our review, we encourage you to share it with us as soon as possible.

Please note that in the future, if any regulatory changes are proposed as a result of our review, we expect they will be open to public consultation, allowing all stakeholders, including industry, the opportunity to provide feedback.

The attached draft document is provided to you in confidence, and we ask that it is not distributed publicly. We would welcome you to share it in confidence among your relevant sunscreen/technical working group and members that may have relevant information that needs to be brought to our attention.

If you have any questions or require further clarification, please feel free to contact us.

Could you kindly reply to advise when you have received this email.

Best regards,
[redacted]

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The Department of Health and Aged Care acknowledges First Nations peoples as the Traditional Owners of Country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to all Elders both past and present.

Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration

Literature search and summaries of seven sunscreen active ingredients (DRAFT)

Butyl methoxydibenzoylmethane (avobenzone), ethylhexyl triazone, homosalate, octocrylene, octyl methoxycinnamate (octinoxate), oxybenzone and phenylbenzimidazole sulfonic acid (PBSA)

1 August 2024

This is an early draft under development and is subject to change. It does not reflect the TGA's position or final conclusions regarding the safety of the ingredients noted herein.

This document is intended to provide a preliminary understanding of our review process and findings to date, however risk assessments have not been finalised and will depend on outcomes of TGA's current public consultation on a sunscreen exposure model suitable for Australia.

TGA Health Safety Regulation

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EXECUTIVE SUMMARY

The TGA has conducted a literature search investigating information relevant to the safety assessment of the following seven sunscreen active ingredients available for use in Australia:

- butyl methoxydibenzoylmethane (avobenzone)
- ethylhexyl triazone
- homosalate
- octocrylene
- octyl methoxycinnamate (octinoxate)
- oxybenzone
- phenylbenzimidazole sulfonic acid

The purpose of this review was to provide an overview of the publicly available safety information for these ingredients needed to assess their suitability for use in therapeutic sunscreens listed on the ARTG. The findings will inform the need for any risk management actions to ensure public safety.

These ingredients were prioritised for this targeted review based on the availability of nonclinical safety data to TGA, their reported use in a higher number of sunscreen products marketed in Australia, and safety signals reported overseas. The literature includes available national and international safety assessment reports and peer reviewed publications.

The two main issues considered in this review were the evidence for the ability of these ingredients to penetrate the skin to reach viable cells systemically, and the potential toxicity exerted by them.

INTRODUCTION

The *Therapeutic Goods (Permissible Ingredients) Determination (No. 2) 2024* currently lists 30 sunscreen active ingredients approved for use in Australia. The safety of these ingredients has been addressed by various means, including assessment of toxicological data, utilisation of overseas regulatory reports, and consideration by committees such as the then Medicines Evaluation Committee.

In 2019, the US FDA published a guidance for industry concerning safety and effectiveness data necessary to determine that a sunscreen active ingredient is generally recognized as safe and effective (GRASE) under the Sunscreen Innovation Act. This introduced a new requirement to conduct Maximal Usage Trials (MUsT) in order to study human absorption correlating to real-world use (FDA 2019a). This was followed by the publication of a US FDA proposed rule in 2019 elaborating the requirement for testing and labelling of sunscreens by manufacturers (FDA 2019b). The rule divided the 16 active ingredients approved in USA into three categories:

- category I (GRASE) includes ZnO and TiO_2;
- category II (not GRASE) includes trolamine salicylate and para-aminobenzoic acid (PABA) (neither of which is used in products currently marketed in Australia); and
- category III (additional data needed) includes the remaining 12 organic filters (cinoxate, dioxybenzone, ensulizole, homosalate, meradimate, octinoxate, octisalate, octocrylene, padimate O, sulisobenzone, oxybenzone, avobenzone; (FDA 2019b)). Ensulizole, homosalate, octinoxate, octisalate, octocrylene, oxybenzone, avobenzone are currently used in Australian products.

The US FDA has proposed that the category III ingredients are not GRASE, because the public record does not currently contain sufficient data to support positive GRASE determinations and additional data is required. The US FDA has also emphasised that they have not concluded that the active ingredients proposed as non-GRASE are unsafe for use in sunscreens, but have requested additional information to evaluate their GRASE status in light of changed conditions, including substantially increased sunscreen usage and evolving information about potential risks since their original evaluation. The US FDA has yet to publish their findings or final order and have noted they are reviewing these ingredients to determine if they are GRASE before they can establish a final order.

Given the greater use and importance of sunscreens in Australia; and the current interest by the US FDA in the ongoing safety of sunscreen active ingredients, the TGA has conducted an audit of its safety data holdings to better understand the safety profile of these ingredients.

As part of this audit, it was noted that some of the category III (additional data needed) organic filters have been widely used in sunscreen products in Australia. One of them was octisalate (octyl salicylate also known as ethylhexyl salicylate). Based on the available information, the Cosmetic Ingredient Review Expert Panel (Cosmetic Ingredient Review 2019) reached the conclusion that octisalate is safe when used in cosmetics in the European use settings and concentration (at 0.003% to 5% concentration as of 2018 data) described in the safety assessment when formulated to be non-irritating and non-sensitizing, which may be based on a quantitative risk assessment (QRA). As such, the literature review was not conducted for octisalate (octyl salicylate).

A literature search was conducted for the scientific information available for seven active ingredients avobenzone, ethylhexyl triazone (EHT), homosalate, octinoxate, octocrylene, oxybenzone and phenylbenzimidazole sulfonic acid (PBSA) for use in sunscreens. These ingredients have been widely used in sunscreen products in Australia. The review is intended to provide an overview of the publicly available safety information for these ingredients needed to assess the suitability of these ingredients for use in therapeutic sunscreens.

WHAT ARE THESE INGREDIENTS

The chemical and physical properties and the molecular structures of these seven ingredients are provided in the following tables (Yap *et al.* 2017; Gilbert *et al.* 2013).

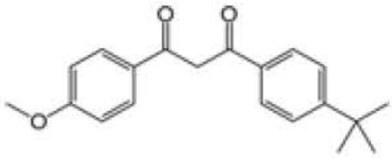
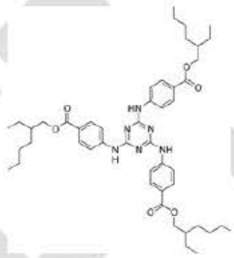
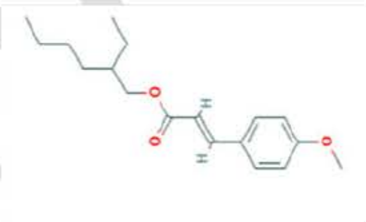
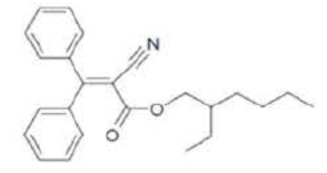
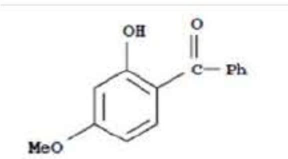
Table 0-1 Chemical and Physical Properties of the active ingredients under review

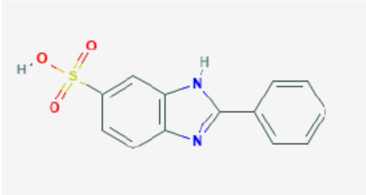
Active ingredient (*absorption spectrum*)	CAS no.	Chemical name	Molecular formula	Physical properties				Other names
				Water solubility	MW g/mol	Density	Log P_{ow}	
Avobenzone (BMDM or BMDBM) *UVA*	70356-09-1	1,3-Propanedione, 1-[4-(1,1-dimethylethyl)phenyl]-3-(4-methoxyphenyl)-	$C_{20}H_{22}O_3$	0.01 mg/L	310.4	1.1±0.1 g/cm³	4.5-6.1	Butyl methoxydibenzoylmethane, Eusolex® 020, Parsol® 1789, 4-tert-butyl-4'methoxydibenzoyl methane, BMDBM
Ethylhexyl triazone (EHT) *UVB*	88122-99-0	2,4,6-Trianilino-(p-carbo-2'-ethylhexyl-l'-oxy)-1,3,5-triazine	$C_{48}H_{66}N_6O_6$	0.005 mg/L at 20°C	823.1	1.1±0.1 g/cm³	15.5	Uvinul T150, (octyl triazone)
Homosalate *UVB*	118-56-9	3,3,5-trimethylcyclohexyl) 2-hydroxybenzoate	$C_{16}H_{22}O_3$	0.4 mg/L at 25°C	262.3	1.045 g/cm³	4.7	Benzoic Acid, 2-Hydroxy-, 3,3,5-Trimethylcyclohexyl Ester Cyclohexanol,

Active ingredient (*absorption spectrum*)	CAS no.	Chemical name	Molecular formula	Physical properties				Other names
				Water solubility	MW g/mol	Density	Log P_{ow}	
								3,3,5-trimethyl-, salicylate. Homomethyl salicylate Salicylic acid, 3,3,5-trimethylcyclohexyl ester Caswell No. 482B, Neo Heliopan® HMS, CCRIS 4885, Filtersol "A"
Octinoxate (OMC or EHMC) *UVB*	5466-77-3	2-Ethylhexyl 4-methoxycinnamate	$C_{18}H_{26}O_3$	0.1 g/100 mL at 27°C	290.4	1.01 to 1.02 g/cm³	5.9	EHMC or octyl-methoxycinnamate (OMC)
Octocrylene (OC) *UVB*	6197-30-4	2-Propenoic acid, 2-cyano-3,3-diphenyl-, 2-ethylhexyl ester	$C_{24}H_{27}NO_2$	40 µg/L at 20 °C	361.5	1.051 g/mL	6.1	2-Cyano-3,3-diphenyl acrylic acid, 2-ethylhexyl ester, 2-Ethylhexyl-2-cyano-3,3 diphenylacrylate, K.SORB 1139, Octocrylene USP, Parsol 340, Sunkem OTC, Sunobel®23 OCT, Uvinul 3039, 24 UVINUL N 539 T
Oxybenzone (BP-3) *UVB*	131-57-7	2-benzoyl-5-methoxyphenol; 4-Methoxy-2-hydroxybenzophenone	$C_{14}H_{12}O_3$	0.0037 g/L at 20°C	228.3	1.32 g/mL	>3.7	Benzophenone-3
Phenylbenz-imidazole sulfonic acid (PBSA) *UVB*	27503-81-7	2-Phenylbenzimidazole-5-sulfonic acid	$C_{13}H_{10}N_2O_3S$	> 30%	274.3	1.5 g/cm³	-1.1 at pH 5	Ensulizole, Benzimidazole, 2-phenyl, 5-sulfonic acid

*the active ingredients are referred to throughout the report as either their AAN, INN or the abbreviated names.

Table 0-2 Molecular structure of the active ingredients under review

Active ingredient	Structure
Avobenzone	
Ethylhexyl triazone	
Homosalate	
Octinoxate	
Octocrylene	
Oxybenzone	

Active ingredient	Structure
Phenylbenzimidazole sulfonic acid	

Current restrictions in Australia and overseas

The following ingredients are currently approved in Australia for use as active ingredients in therapeutic sunscreens for dermal application (see the table below), not to be used in topical products for eyes, with appropriate safety warnings mandated on the label. It is noted that the regulation of sunscreens differs internationally, for example the USA regulate these as OTC drugs while they are regulated as cosmetics in the EU.

Active ingredient	Maximum % approved				
	Australia	EU	USA	Canada[1]	Japan[2]
Avobenzone	5	5	3	3	10
Ethylhexyl triazone †	5	5	Not approved	Not approved	5
Homosalate	15	7.34 (restricted to face product)	15	15	10 (restricted in all types of cosmetics)
Octinoxate	10	10	7.5	7.5	10
Octocrylene**	10	9 (propellant spray products); 10 (other products)	10	10	10 (restricted in all types of cosmetics)
Oxybenzone[Δ]	10	6 (for face /hand products, excluding propellent and pump spray products); 2.2 (for body products)	6	6	5 (cosmetics not used for mucosa and not to be washed away)
Phenylbenzimidazole sulfonic acid [γ]	4	8	4 (referred to as Ensulizole)	4	3 (cosmetics not used for mucosa and to be/not to be washed away)

**Octocrylene is approved as a UV filter in cosmetic formulation at ≤10% (as acid) in both Europe (Annex VI/10) and USA. The specific migration limit (SML) of octocrylene from food contact materials is 0.05 mg/kg (FDA 2018); European Parliament and the Council (2009); Restriction in EU - Benzophenone as an impurity and/or degradation product of

[1] http://webprod.hc-sc.gc.ca/nhpid-bdipsn/atReq.do?atid=sunscreen-ecransolaire&lang=eng
[2](https://www.mhlw.go.jp/english/dl/cosmetics.pdf

Octocrylene shall be kept at trace level.
†EU: Annex VI, Regulation (EC) No. 1223/2009; γ EU: cosmetics directive in annex VII, part 1 list of permitted UV filters under entry 6;
Δ Annex VI/4, oxybenzone is also allowed at concentrations of up to 0.5 % to protect product formulations in all other cosmetic products (Annex VI/4).

LITERATURE SEARCH SUMMARY

METHOD OF DATA SEARCH

The literature review was conducted using keywords such as the chemical name, Australian Approved Name (AAN) or the International Nomenclature Cosmetic Ingredient (INCI) names, and "sunscreen" as the search items. Publications during a 15 year period were searched (between 2008 and March 2023). See the Appendix 0 for details.

In summary, the following data sources have been used for the literature search:

- Assessments from national regulatory agencies (e.g., AICIS, previously known as NICNAS) where available.
- Opinions from the Scientific Committee on Consumer Safety (SCCS, previously known as SCCNFP/SCCP/SCC) where available.[3]
- Information identified through literature search in PubMed and on the internet where a newer SCCS is not available.
- The publicly available registration dossiers for the ingredients submitted by industry under the EU REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) Regulation and available on the website of the European Chemicals Agency (ECHA). This information includes unpublished study summaries submitted by industry, in response to the standard data requirements of the REACH Regulation. Data from key studies in the registration dossiers have been considered for assessment in this review.

Information on the health hazards is available for all the selected ingredients considered, although the amount of information available varies considerably and does not cover all toxicological endpoints for all ingredients. Endocrine activity modulation properties of ingredients may give rise to a concern for human health. The evaluation of endocrine activity modulation properties was described collectively. Of note, all articles dealing with environmental matters relating to the ingredients were excluded as they do not fall under Australian therapeutic goods legislation.

PHARMACOKINETICS

The main safety concerns for these active ingredients arise from the knowledge gap around the toxicokinetic and pharmacokinetics data. Cutaneous permeation is a critical parameter in the kinetics of these active ingredients. Although most organic UV filters are lipophilic, *in vitro* cell permeation studies were also conducted with some of these ingredients to demonstrate systemic absorption by intact skin. Dermal absorption data from either relevant SCCS opinion, ECHA dossiers, AICIS assessments or published literature were reviewed in this document. Limited permeation data were noted for some active ingredients. In the absence of dermal toxicity data, oral toxicity data were considered when considering systemic toxicity in the worst case scenario. Where appropriate, the dermal absorption value from the most recent SCCS opinions for the relevant active ingredients, were

[3] https://ec.europa.eu/health/ph_risk/committees/04_sccp/sccp_opinions_en.htm

noted. Note that dermal absorption values apply to intact skin and may not be applicable for abraded skin or areas of sensitive skin e.g. lips.

Avobenzone

The molecular weight of avobenzone is in the range (MW < 500 D) where skin penetration can occur but the log P_{ow} is slightly above the range favouring penetration (log P_{ow} in range -1 to +4). Avobenzone has a low water solubility. Based on these physico-chemical data, only low dermal penetration is expected.

The toxicokinetic data for avobenzone were assessed in ECHA 2021 (ECHA 2021A). The executive summary of the assessed data is given below (for details see ECHA 2021A).

- In a 21 day dermal rabbit toxicity study (Keller 1980), there was an absence of a biological response (no adverse effects were observed in rats up to the high dose of 360 mg/kg bw/day, both in groups with intact skin or with abraded skin), and there was no indication of systemic bioavailability following dermal exposure.

- *In vitro* studies with isolated pig skin using ^{14}C-labelled BMBDM (avobenzone) at a concentration of 2% or 7.5 % in cream formulations exposed for 6 hours, showed that majority of the topically applied BMDBM remained on the skin surface (95%), 1.0-1.7% were found on the stratum corneum, 0.9-3.4% absorbed in the skin and only a minimum (≤ 0.5%) was found to pass the skin. Briefly, the results indicate a low penetration rate of avobenzone when applied on pig skin (up to 1.5 % of applied radioactivity 6 h post application). Dermal penetration in pig skin was not influenced by UV light (ECHA 2021A).

- In an *in vitro* study (DSM 1982) with ^{14}C-labelled BMDBM (avobenzone) using isolated human abdominal cadaver skin, up to 2.7 % of the applied radioactivity was observed in the epidermis, 7.3 % in the dermis 18 hr post dose but no activity was found in the collection fluid at any time and lower skin corium contained only 0.34 % after the longest exposure period (ECHA 2021A).

- A human *in vivo* study also indicated a very low level of systemic penetration of BMDBM (avobenzone) or its metabolites. In the study, a preliminary study (occluded) was followed by the main study where human volunteers were exposed to a 10% solution of ^{14}C-labelled BMBDM in carbitol for 8 hours.[4] The amounts of BMDBM found in the urine were 0.08 and 0.016 % for the occluded and non-occluded experiment, respectively. No radioactivity was found in the blood or faeces in any subject. Therefore, these data confirm only a very low level of systemic penetration of BMDBM or its metabolites (ECHA 2021A).

A recent study demonstrated that there was very poor skin permeation of avobenzone after single or repeated applications of sunscreens (Montenegro *et al.* 2018). However, recent randomised clinical trials indicate that avobenzone was systemically absorbed in humans (see Clinical Trials).

In the absence of further kinetic data for avobenzone and based on the data from the *in vitro* study using isolated human abdominal cadaver skin ((ECHA 2021A), **a 7.3% dermal absorption** of avobenzone was assumed.

[4] The dose was applied to a small square of gauze (10 cm^2) taped to the skin.

Ethylhexyl triazone

No specific pharmacokinetic data are available for ethylhexyl triazone. The ingredient is expected to have low oral and dermal bioavailability based on its physiochemical properties (Molecular weight > 500 Dalton and Log P_{ow} > 4; Table 2.1)

Ethylhexyl triazone did not penetrate the receptor fluid in an *in vitro* study by Monti *et al.* (2008) when applied to the reconstructed human skin model and the rat skin. However, BASF (1995) reported *in vitro* permeation of ethylhexyl triazone in the sunscreen formulation, but no value was provided.

In an *in vitro* diffusion study (6-h exposure of the *ex-vivo* porcine-ear skin to the sunscreen, water-oil emulsion containing 10% oxybenzone and 5% ethylhexyl triazone, doses of 1 mg/cm² and 2 mg/cm²), 23.2 ± 4.1 mg/cm² and 18.3 ± 2.5 µg/cm² of oxybenzone and ethylhexyl triazone, respectively were found in the stratum corneum, whereas 1.5 ± 0.3 mg/cm² of oxybenzone was found in the receptor fluid (Hojerová *et al.* 2017). Ethylhexyl triazone was not determined in the receptor fluid. The study authors concluded, that approximately 0.54 mg/cm² of ethylhexyl triazone (i.e., ~1.08% of the amount of ingredient applied) permeated the excised human epidermis into the receptor fluid. Approximately 1.3 and 1.8 × higher content of oxybenzone and ethylhexyl triazone were found in the viable epidermis and dermis, respectively, and 2.3- and 1.5-times higher content in the receptor fluid, respectively, when the study was conducted on shaved skin. Insignificant percutaneous absorption of ethylhexyl triazone across the shaved skin was noted. The total recovery in the whole study (intact and/or shaved skin) was 87.5- 90.4% consistent with the recovery (85-115%) allowed by the SCCS (2016). The SED after the sunscreen application at 1 mg/cm² for 6 h on the: (i) face; and (ii) whole-body skin, was (i) 136 and 30; (ii) 4200 and 933 mg/kg bw/day for oxybenzone and ethylhexyl triazone, respectively. Reapplication caused approximately 1.4 -fold increase in the SED values indicating partial saturation after the first application.

Preferential ethylhexyl triazone distribution into stratum corneum was also noted by Sauce *et al.* (2020) in tape strip samples obtained from human volunteers (n = 12) treated with 100 µg/mL of the compound emulsified in cosmetic oil/water formulation (5% w/w) and applied at 2.0 mg/2.25 cm² for 2 h. However, only first 10 µm of the upper layers was collected (thickness of stratum corneum is ~30 µm) and given that the total recovery observed in this section was 56.34 %, the authors concluded that the remaining 44.66% of the dose penetrated deeper strata.

An *in vivo* study investigating the penetration of ethylhexyl triazone in human stratum corneum demonstrated that 21.9% (± 4.9) of the applied ethylhexyl triazone dose diffused into the stratum corneum. However, the skin penetration reduced significantly (by 45.7%) when ethylhexyl triazone was applied in microencapsulated form (Scalia *et al.* 2019).

In the absence of an appropriate dermal absorption value for ethylhexyl triazone, a **dermal absorption of 10%** was assumed based upon physicochemical parameters.

Homosalate

Studies in animals and human skin showed that homosalate could penetrate the skin in a variable manner. *In vitro* experiments indicated that about 1.1% of the applied dose was absorbed by human skin (range: 0.9-2.0%) (CTFA 2005).

Maximum plasma concentrations of homosalate after topical application varied between 13.9 and 23.1 ng/ml and $t_{½}$ between 46.9 and 78.4 h in clinical trials (see Clinical Trials). Homosalate was also detected in human milk samples after topical application in samples from different cohorts (2004, 2005, 2006) (Schlumpf *et al.* 2010). 15.1% of mothers reported use of homosalate exclusively in sunscreens with no additional use of other cosmetics. Homosalate was detected in 5.56% of total milk samples. However, homosalate could not be detected in human breast tissue samples (Barr 2018).

The *in vitro* metabolism of homosalate was investigated in rat and human liver microsomes. Homosalate (10 mM) incubated with human or rat liver microsomes (1 mg/ml protein) was hydrolysed into salicylic acid and 3,3, 5-trimethylcyclohexanol. In addition, conjugation and hydroxylation of intact homosalate was detected *in vitro*.

Commercial products often contain mixtures of cis- and trans-homosalate isomers (*cis*-HMS and *trans*-HMS respectively). Ebert *et al.* (2022) reported 87.2 - 91.9% of *cis*-HMS and 8.1-12.8% of *trans*-HMS in total homosalate content in 10 examined sunscreen products. However, following oral administration, homosalate isomers displayed diastereoselective metabolism, which was skewed towards *trans*-HMS e.g., metabolite levels derived from *trans*-HMS (6.4 %), including carboxylic acid and alkyl-hydroxylated compounds, were 142-fold higher compared to *cis*-HMS (0.045 %) while its bioavailability was 10-times higher. Although it is currently unknown whether homosalate applied dermally also undergoes divergent isomer metabolism, preliminary data of Ebert *et al.* agree with the findings from the oral study.

The SCCS selected a new skin penetration study using human skin from which **a dermal absorption of 5.3%** (mean + 1SD: 3.86±1.43) was derived (SCCS 2020).[5]

Octocrylene

Octocrylene is expected to be absorbed in the GI tract by micellar solubilisation based on its physicochemical properties (ECHA 2020b). The inhalational uptake of octocrylene is likely to be low due to the very low vapour pressure (4×10^{-7} Pa at 20°C) (ECHA 2020b).

Octocrylene has been found to induce xenobiotic-metabolising enzymes based on mechanistic studies, oral repeated dose toxicity and reproductive/developmental toxicity studies (SCCS 2021a; ECHA 2020b). An *in vitro* study on the hydrolysis-stability in rat liver S9 fraction indicated that octocrylene was metabolized in liver S9 fraction only (ECHA 2020b).

Human octocrylene metabolism and the pathways were described by Bury *et al.*, (2019). Six metabolites of octocrylene were detected in human urine after both oral and dermal exposure simulating a regular-use scenario with whole body application to octocrylene. 2-cyano-3,3-diphenylacrylic acid (CDAA) was identified as the major urinary metabolite (~45% of the octocrylene dose) followed by 2-ethyl-5-hydroxyhexyl 2-cyano-3,3-diphenyl acrylate (5OH–OC) and 2-(carboxymethyl) butyl 2-cyano-3,3-diphenyl acrylate (dinor OC carboxylic acid, DOCCA). Faecal excretion was observed. *In vitro* study with human and rat liver microsomes in the presence of NADPH and glutathione (GSH) suggested that the ester bond of octocrylene can be hydrolysed to form 3,3-diphenyl cyanoacrylate (DPCA) and 2-ethylhexanol based on the chemical structure of octocrylene (Guesmi *et al.* 2020).

Dermal exposure resulted in much lower concentrations of metabolites with considerably delayed elimination despite much higher octocrylene (> 25-fold) applied dermally (dermal dose 217 mg *vs* oral dose ~5 mg). This suggests a slower uptake of octocrylene through the skin.

[5] The June 2021 SCCS opinion for homosalate uses a different dermal absorption value for the SED calculation. The systemic exposure dose for homosalate used as a UV filter in cosmetic products is calculated using a dermal absorption value of 5.3% derived from an *in vitro* dermal penetration study using viable human skin (Finlayson 2021, as cited in SCCS 2020) and a standard sunscreen formulation containing 10% homosalate.

Table 0-1 Toxicokinetic data in urine after oral and dermal exposure to octocrylene (adapted from Bury *et al* 2019)*

Ingredient			CDAA	5OH-OC	DOCCA
Oral (*n*=3)	Concentration (µg/g creatinine)		2450 (1150-4410)	1.85 (1.62-2.11)	10.6 (9.94-11.1)
	t_{max} (hours)		4.2 (2.7-5.0)	3.2 (1.4-4.4)	3.6 (1.4-5.0)
	$t_{½}$ (hours)	1st phase	5.7 (3.8-7.1)	1.3 (1.1-1.5)	3.0 (2.1-3.6)
		2nd phase	16 (14-20)	6.4 (5.7-7.5)	16 (10-21)
Dermal (*n*=1)	Concentration (µg/g creatinine)		71.4	0.14	1.15

*Median (range) values are reported.

Following dermal application of octocrylene (8-10%) in *in vitro* studies, poor skin penetration (< 5%) of octocrylene was observed with mostly remaining in the stratum corneum (Freitas *et al.* 2015; Potard *et al.* 2000; Hayden *et al.* 2005). The dermal absorption (%) was not determined in these studies. Similar findings were observed in a study with a formulation (8% octocrylene) applied on freshly dermatomized human skin (344 ± 61 µm) in static diffusion cells at a dose of 3 mg/cm^2 for a 16-hour period. 0.1%, 0.005% and 4.3% of the applied dose were found in epidermis, dermis and in the stratum corneum, respectively (ECHA 2020b). No octocrylene was detectable in the receptor fluid. After 24 hours of dosing, octocrylene bioavailability (epidermis, dermis and receptor fluid) was estimated ~ 0.1% of the applied dose (ECHA 2020b; SCCS 2021a). In another study, a cream formulation (8% octocrylene) was applied for 16 hours (3 mg formulation/cm^2) on freshly dermatomed pig (700 ± 50 µm) and human (350 ± 50 µm) skin in static diffusion cells (ECHA 2020b). In the study with pig skin, no octocrylene was detectable in the receptor fluid whereas 2.8% and 0.3% of the applied dose were found in pig epidermis and dermis, respectively, and 14% were detected in the stratum corneum. In the study with human epidermis and dermis, only 0.125% of the applied dose were found, whereas 5.4% was determined for human stratum corneum. Based on these data, the amount bioavailable (epidermis, dermis and receptor fluid) represents approximately 0.2% and 3% of the applied dose in the human and pig skin, respectively (ECHA 2020b). The SCCS (2021a) also referred to the octocrylene Chemical Safety Report (2010) which indicated a low dermal absorption rate (≤ 0.25%).

A recent *in vitro* study (Fabian and Landsiedel 2020, as cited in SCCS 2021a) with a formulation (10% octocrylene) applied at a dose of 3 mg formulation/cm^2 on dermatomized human skin preparations (*n* =12 skin samples from six females) for 24 hours was evaluated by SCCS (2021a). At 24 hours post-dose, the amount considered as absorbed (epidermis, dermis and receptor fluid) was estimated to be a maximum of 0.45±0.52 µg/cm^2 (~ 0.15% of the applied dose) consistent with previous findings. The **dermal absorption of 0.97 µg/cm^2** (Fabian and Landsiedel 2020, as cited in SCCS 2021a) was considered a worst-case scenario for octocrylene and was used in the calculation of SED and MoS by the SCCS (2021a).

Octinoxate

Octinoxate absorption studies (oral and dermal) in rats and mice indicate octinoxate can be absorbed dermally and orally (Fennell *et al.* 2018). Octinoxate was rapidly cleared from rat hepatocytes (half-life ≤3.16 min) compared to human hepatocytes (half-life ≤48 min). [^{14}C]-octinoxate was extensively absorbed and excreted primarily in urine by 72 h after oral administration (65-80%) and a lesser extent (3-8%) in faeces and as CO_2 (1-4%).

Five metabolites were found in rat urine after oral exposure to octinoxate (200 mg/kg bw and 1000 mg/kg bw) (Huang *et al.* 2019). The major metabolites of octinoxate were 4-methoxycinnamic acid (4-MCA) and 4′-methoxyacetophenone (4′-MAP). The concentration of two metabolites was found to be much higher than octinoxate, highlighting that measuring octinoxate alone could not comprehensively evaluate the human exposure to octinoxate.

Dermal penetration was observed to be dependent on the vehicles, when using the tape-stripping technique. Significantly greater amounts were absorbed when the chemical was applied in emulsions than when microencapsulated (HSDB). Octinoxate was able to penetrate the skin, and derivatives were formed when it was applied with oleaginous cream as a vehicle on excised rat skin. In contrast, octinoxate penetration was not observed following the administration of octinoxate as entrapped into solid lipid microspheres (SLM) (Yener *et al.* 2003).

Studies with porcine skin showed that about 9% of the applied dose of octinoxate penetrates the skin with a flux of 27 $\mu g/cm^2 \cdot h$ (Touitou and Godin 2008). An accumulation of ~9% of octinoxate in epidermis and ~2-3% in dermis were observed following application of 2 mg/cm^2 and 0.5 mg/cm^2 of octinoxate, respectively for 6 h exposure (Schneider *et al.* 2005). Octinoxate accumulation is expected to increase over time as the accumulation in dermis was found to be ~12-15% of the dose applied and 2-4% of the dose was found to cross the dermis and enter into the circulation after 24 hours.

An *in vitro* absorption study with sunscreen (O/W , oil in water emulsion and W/O, water in oil emulsion) containing octinoxate or EHMC (10%) on full-thickness pig-ear skin, mimicking human in-use conditions revealed the skin distribution of octinoxate from the sunscreen dose of 0.5 mg/cm^2 after 6-h exposure to the epidermis of frozen-stored skin was 4.8± 0.7 $\mu g/cm^2$, dermis 1.2 ± 0.1 $\mu g/cm^2$ and undetectable in receptor fluid, whereas 3.4 ± 0.6 $\mu g/cm^2$, 2.1 ± 0.4 $\mu g/cm^2$ and 0.9 ± 0.1 $\mu g/cm^2$ of octinoxate was distributed to epidermis, dermis and receptor fluid after following 18-h permeation, respectively (Klimova *et al.* 2015). Almost two-fold higher absorption was noted when water in oil emulsion containing 10% octinoxate was applied on pig skin in the same study (Klimova *et al.* 2015).

In this study, the authors "*tried to mimic the real-life habits of consumers when applying sunscreen as closely as possible*". In this way the time of exposition was reduced to 6 hours (in contrast of classic studies using long skin exposure), and a smaller dose of sunscreen was used (0.5 mg/cm^2) (Klimova *et al.* 2015). Considering that some chemical substances, instead of passing entirely through the skin, can remain partly in the skin and released later in time, the dermal absorption was evaluated at the end of the exposure period and then following washing and an 18-h permeation.

The dermal absorption was obtained by the sum of the filter absorbed in the dermis and the receptor fluid (RF) (which was considered systematically available), corrected by the fresh/frozen – stored skin permeability coefficient. It is noted that pig-ear skin has been recognized by the international authorities and scientists as a practical alternative and relevant model for predicting permeability of cosmetic ingredients in humans (Klimova *et al.* 2015).

Human *in vitro* and *in vivo* studies showed that the permeation of octinoxate in human skin was dependent on both the lipid lipophilicity and structure of the lipid used in the microemulsion and the type of surfactant used (Montenegro *et al.* 2011; TGA 2020).

The systemic absorption of octinoxate in humans was demonstrated by Janjua *et al* (2008). Maximum plasma concentration of octinoxate was reached at ~ 3 h (10 ng/ml for females and 20 ng/ml for males) following daily whole-body topical application of 2 mg/cm^2 of cream formulation with 10% octinoxate. Octinoxate was also detected in urine (5 and 8 ng/mL in females and males, respectively). Similar findings were reported following a 4-day exposure to this ingredient, which were detectable in the human plasma just 2 h following application (Janjua *et al.* 2004).

Another human study reported in SCC (2000) with a cream formulation containing 10% octinoxate suggested that an insignificant amount of octinoxate was absorbed under the conditions of the experiment (SCC 2000). Applications were made to the interscapular area and there was no evidence of any rise in plasma levels after 24 h. In addition, the urine concentration of octinoxate did not change during the experiment (collected until 96 h).

Based on all dermal absorption studies described above, no clear relationship between applied dose and dermal absorption could be established for octinoxate. Therefore, a **dermal absorption of 1.77 μg/cm^2** was considered a worst-case scenario (Klimova *et al.* 2015).

Oxybenzone

Oxybenzone is expected to be rapidly absorbed after oral, intravenous or topical skin administration based upon studies in rats and piglets as per European Safety assessment reports (SCCS 2021c). Oxybenzone was well absorbed following a single gavage administration of [^{14}C]-oxybenzone (3.01 to 2570 mg/kg) in male rats, with the administered dose excreted primarily *via* urine (63.9% to 72.9%) and faeces (19.3% to 41.7%) by 72 hours post-administration. The radioactivity remaining in tissues 72 hours after administration was low (~0.1%) in all dose groups. Oxybenzone is widely distributed in rats. Jung *et al.* (2022) assessed that bioavailability in rats following topical application as 6.9%.

Oxybenzone is metabolised in rats to 2-OH BP and BP-1, with a trace of 2, 3, 4-triOH BP. The major metabolite of oxybenzone, 2,4-diOH BP (BP-1) was present in most tissues including the liver, kidney, testes, intestine, spleen and skin six hours post-dose. Liver was the major distribution site of oxybenzone and BP-1 (SCCS 2021c). BP-1 is also the major metabolite in humans. Oxybenzone metabolites were detected in piglet plasma 2 hours post dose after dermal administration of oxybenzone (SCCS 2021c). Systemic absorption of oxybenzone has been demonstrated in recent clinical studies (Section 2.1). Oxybenzone binds to human serum albumin with Ka= 1.32 x 10^5 L/mol.

Elimination of oxybenzone is predominately *via* the urine (39-57%) and faeces (24-42%) in rats and mice, with differences observed between the species or the route of administration (oral or dermal). Following topical application studies in piglets, the elimination half-lives of oxybenzone ranged from 7.14 and 8.04 h (SCCS 2021c), while in rats it was 18.3 h (Jung *et al.* 2022).

A number of *in vitro* and *in vivo* dermal absorption studies have been evaluated by the SCCP 2008 and SCCS 2021c. Following application of 6% oxybenzone, the **dermal absorption of oxybenzone was determined to be 9.9%.** The dermal absorption value of 9.9% was calculated by the SCCP using an *in vitro* study using pig ear skin and applying a safety factor of 2 standard deviations to account for limitations in the data set (3.1% + 2 SD [2 x 3.4%] = 9.9%) (SCCS 2021c). This *in vitro* study was chosen for oxybenzone in the absence of adequate information from *in vivo* studies.

Phenylbenzimidazole sulfonic acid

Absorption and plasma kinetics of PBSA were examined in pregnant rats (SCCP 2006b). [^{14}C]-PBSA sodium salt was administered to pregnant rats on day 18 of gestation (1 mg/kg bw IV or 1000 mg/kg bw PO, single dose). The pharmacokinetic parameters were: T_{max} 5 min (IV) and 15 min (oral), with a $t_{½}$ of 0.4 h (IV) and 24 h (oral). The amount of absorption from the gastrointestinal tract was estimated to be 3 – 4%.

Dermal penetration was examined in male volunteers (SCCP 2006b). Although the penetration rate of PBSA was not established, cumulative penetration of 0.159% (range 0.107-0.259%) of the applied dose (8% formulation of PBSA), was derived from total excretion. Total recovery of radioactivity was 78.8%. There was no indication of accumulation in any of the organs investigated. Trace amounts of radioactivity are found in brain and fetuses after IV administration but not following oral administration. This indicates that both blood/brain- and placental barriers were not passed. No data on metabolism were available.

Excretory pathways were examined in male rats (SCCP 2006b). Elimination of PBSA sodium salt was virtually completed by 72 hours. Elimination occurs *via* urine and faeces in male rats. In pregnant rats, elimination predominantly occurred *via* the faeces following oral administration and *via* both the urine and faeces following IV administration. Maximum **absorption through the skin of 0.259% (0.416 μg/cm²) determined** in the *in vivo* study in humans following application of an 8% formulation of PBSA was used by the SCCP to determine the margin of safety for PBSA (SCCP 2006b).

Clinical trials

In a recent randomised clinical trial, healthy volunteers (*n*=24; 6/ group) were treated with four sunscreen products, four times per day for 4 days, in indoor conditions, at a rate of 2 mg/cm² on 75% of body surface area. The sunscreen products were spray 1 (3% avobenzone/ 6% oxybenzone/2.35 % octocrylene/ 0% ecamsule[6]), spray 2 (3% avobenzone/5% oxybenzone/ 10% octocrylene/ 0% ecamsule), lotion (3% avobenzone/ 4% oxybenzone/ 6% octocrylene/ 0% ecamsule); and cream (2% avobenzone/ 0% oxybenzone/ 10% octocrylene/ 2% ecamsule). The overall maximum plasma concentrations (C_{max}) of avobenzone, oxybenzone and octocrylene ranged from 4 to 4.3 ng/mL, 169.3 to 209.6 ng/mL and 2.9 to 7.8 ng/mL, respectively. The AUC increased from day 1 to day 4 and terminal half-life ($t_{½}$) was relatively long (33-55 h, 27-31 h and 42–84 h, respectively), suggesting a possible accumulation of the ingredients (Matta *et al.* 2019). The systemic exposure of avobenzone and oxybenzone in human plasma was re-quantified by Pilli *et al.* (2021) using novel UHPLC-MS/MS method and in general, the C_{max} values were comparable to the results obtained previously.

Similar findings were observed in a follow up study with six active ingredients (avobenzone, oxybenzone, octocrylene, homosalate, octisalate[7], and octinoxate) (Matta *et al.* 2020). Four groups (*n*=12) of healthy adults received 2 mg/cm² (75% of body surface area) on day 1 and 4 times on day 2 to day 4 at 2-hour intervals and blood samples were collected over 21 days from each participant.

[6] Ecamsule (CAS 92761-26-7) is commonly used as an active ingredient in sunscreen. However, currently it is not used in any sunscreen product marketed in Australia.

[7] Octisalate or octyl salicylate is an active ingredient used in sunscreen. This has been evaluated by TGA as an excipient to be used in prescription medicines.

The C_{max} of all these ingredients exceeded the US FDA threshold (> 0.5 ng/mL) after a single application and remained above the threshold until day 7 for avobenzone (95%; *n* = 42/44), octisalate (75%; *n* = 24/32), and octinoxate (90%; *n* = 18/20); day 10 for octocrylene (67%; *n* = 22/33); and day 21 for homosalate (55%; *n* = 17/31) and oxybenzone (96%; *n* = 22/23). The overall exposure throughout the study (Days 1-21) is summarised in the following table taken from Matta *et al.* (2020).

	Geometric mean maximum plasma concentration, ng/mL (coefficient of variation, %)			
	Lotion	**Aerosol spray**	**Nonaresol spray**	**Pump spray**
Avobenzone	7.1 (73.9)	3.5 (70.9)	3.5 (73.0)	3.3 (47.8)
Oxybenzone	258.1 (53.0)	180.1 (57.3)	NA	NA
Octocrylene	7.8 (87.1)	6.6 (78.1)	6.6 (103.9)	NA
Homosalate	NA	23.1 (68.0)	17.9 (61.7)	13.9 (70.2)
Octisalate	NA	5.1 (81.6)	5.9 (77.4)	4.6 (97.6)
Octinoxate	NA	NA	7.9 (86.5)	5.2 (68.2)

Another study investigating systemic absorption of avobenzone and octocrylene using real-life exposure scenario demonstrated similar systemic absorption of the ingredients (Hiller *et al.* 2018). Following dermal exposure, avobenzone, octocrylene and CDAA (major urinary metabolite of octocrylene) reached concentrations up to 11.3 µg/L, 25 µg/L and 1352 µg/L, respectively, in plasma (Table 0-2). When kinetic models were fitted for octocrylene and CDAA in plasma and CDAA in urine, concentration peaks reached between 10 and 16 h after first application and elimination half-life ($t_{½}$) were 36-48 hours. Octocrylene and CDAA showed slower elimination.

Table 0-2 Toxicokinetic data in humans following dermal exposure to octocrylene and avobenzone

Study details		***n*=20; commercial sunscreen lotion containing octocrylene was applied three times (2 mg/cm² initially, then 1 mg/cm² after 2 h and 4 h) to 75–80% BSA)**		
Ingredient		**Octocrylene**	**Avobenzone**	**CDAA**
Concentration	(%)	10.85	2.34	NA
C_{max} plasma (µg/L)	Mean (max)	11.7 (25)	4(11.3)	570 (1352)
C_{max} in urine (µg/g creatinine)	Median (max)	9.6 (< LOD–91.4)	3.4 (< LOD–25.2)	2072 (5207)
T_{max} plasma (hours), day 1	Median (95% CI)	10 (6.9-13.4)	ND	14.5 (13.2-15.9)
T_{max} urine (hours), day 1		ND	ND	15.9 (15.2-16.7)
$t_{½}$ plasma (hours)		43.9 (19.0-68.7)	ND	36.1 (31.0-41.2)
$t_{½}$ urine (hours)		ND	ND	37.7 (35.1-40.4)

*81% of samples < LOD' c: concentration; C_{max}: max plasma concentration; ND: not determinable; T_{max}: time to maximum concentration; $t_{½}$: half-life; CDAA: 2-cyano-3,3-diphenylacrylic acid

Toxicity

The information on the safety of avobenzone, ethylhexyl triazone, homosalate, octinoxate, octocrylene, oxybenzone and PBSA using various toxicological endpoints, has been summarised in the following sections. It is important to note that the original toxicological study reports were not available for independent verification and therefore this report is reliant on the accuracy of various published safety assessment reviews (reviews by SCCS/SCC/SCCP, NICNAS, ECHA etc. see bibliography).

Acute toxicity

Avobenzone, ethylhexyl triazone, homosalate, oxybenzone, octocrylene, PBSA and octinoxate displayed low acute oral toxicity. Low acute dermal toxicity was observed for homosalate, oxybenzone, octocrylene, PBSA and octinoxate. Information for acute inhalational toxicity is only available for octinoxate (shown below).

Table 3-3. Summary of acute toxicity studies for sunscreen ingredients

Avobenzone (ECHA (2021a; DEPA 2015)	Ethylhexyl triazone (ECHA 2021b; DEPA 2015)	Homosalate (SCCS 2020; ECHA 2021c)	Octinoxate (ECHA 2021e)	Octocrylene (SCCS 2021a; ECHA 2021d)	Oxybenzone (SCCP 2006a; 2021c)	PBSA (SCCP 2006b)
Oral >16000 mg/kg bw (rats) Dermal, inconclusive*	Oral > 5000 mg/kg bw (rats)	Oral > 5000 mg/kg (rats) Dermal > 5000 mg/kg bw (rabbits)	Oral >8 g/kg (mice) >20 mL/kg (20.0 mg/kg) (rats) Dermal >126.5 mg/kg (rats) Inhalation LC50 >0.511 mg/L (rats)	Oral > 5000 mg/kg bw (rats) Dermal > 2000 mg/kg bw (rats)	Oral > 6000 mg/kg bw (rats) Dermal > 16000 mg/kg bw (rabbits)	Oral >5000 mg/kg bw (mice) >1600 mg/kg bw (rats) Dermal >3000 mg/kg bw (rats) IP 1000 – 1500 mg/kg bw (rats)

The values are LD_{50} determined in relevant studies extracted from the safety assessment reviews; *Acute dermal toxicity was tested up to a dose of 1000 mg/kg bw in rats showing no deaths. Slight erythema was observed in treated animals and in the vehicle control, assuming that the vehicle, carbitol, has a slight irritant effect to skin. Concerning acute dermal toxicity, the test item was only tested up to a maximum dose of 1000 mg/kg bw, whereas the regulatory cut-off level for classification according to Regulation (EC) No 1272/2008 (CLP) is 2000 mg/kg bw.

Local tolerance

Skin irritation and eye irritation studies were generally conducted as per the OECD TG 404 and 405 guidelines, respectively. All ingredients examined were found to be non-irritants to the skin and eye in *in vivo* studies in animals (see below).

Table 3-4. Summary of skin and eye irritation studies for sunscreen ingredients

Study	Avobenzone (ECHA (2021a; DEPA 2015)	Ethylhexyl triazone (ECHA (2021b; DEPA 2015	Homosalate (SCCS 2020; ECHA 2021c)	Octinoxate (ECHA 2021e)	Octocrylene (SCCS 2021a; ECHA 2021d)	Oxybenzone (SCCP 2006a; 2021c)	PBSA (SCCP 2006b)
Skin	Non-irritant (at 10% in rabbits)	Non-irritant, undiluted(rabbits)	Non-irritant (mice, Guinea pigs)	Non-irritant, undiluted (rabbits, guinea pigs)	Non-irritant (rabbits)	Non-irritant (rabbits)	Non-irritant (rabbits)
Eye	Non-irritant (at 5-20% in rabbits)	Non-irritant, undiluted (rabbits)	Non-irritant (at 10%)	Non-irritant, undiluted (rabbits)	Non-irritant (rabbits)	Non-irritant (rabbits)	Non-irritant (rabbits)

Sensitisation

With the exception of octocrylene, all the ingredients were not found to be skin sensitisers in *in vivo* studies in animals (see below).

Table 3-5. Summary of skin sensitisation studies for sunscreen ingredients

Avobenzone (ECHA 2021a; DEPA 2015)	Ethylhexyl triazone (ECHA (2021b; DEPA 2015	Homosalate (SCCS 2020; ECHA 2021c)	Octinoxate (ECHA 2021e)	Octocrylene (SCCS 2021a; ECHA 2021d)	Oxybenzone (SCCP 2006a; 2021c)	PBSA (SCCP 2006b)
Not sensitizing (at 6% and 20% in GPMT)	Not sensitizing (GPMT)	Not sensitizing (GPMT and mice) Not sensitizing (at 15%, HRIPT)	Not sensitizing (GPMT)	Not sensitizing (GPMT) Moderate sensitising in a LLNA (not properly conducted)	Not sensitizing (GPMT) Not sensitising (LLNA)	Not sensitizing (GPMT)

GPMT: Guinea Pig Maximization Test; LLNA: Local Lymph Node Assay; HRIPT: Human repeated insult patch test

Repeat dose toxicity

A summary of repeat-dose toxicity studies for each sunscreen ingredient is shown in the table below:

Table 3-6. Repeat-dose toxicity studies for sunscreen ingredients

Active ingredient	Study details$^{\Delta}$	Major findings
Avobenzone (ECHA 2021a; DEPA 2015)	Rats (*n*=12/sex/dose), doses: 0, 200, 450, and 1000 mg /kg bw/day (diet), 13 weeks	No treatment-related mortality. No effect on the body weight and food consumption. ↓ RBC in ♀ rats at 1000 mg/kg bw/day. No findings in eyes. No treatment-related necropsy findings.

Active ingredient	Study details[Δ]	Major findings
		Treatment-related ↑ liver weights at 1000 mg/kg bw/day in ♂ and at 200, 450, and 1000 mg/kg bw/day in ♀ compared to control. All effects were fully reversed after a treatment-free period of 4 weeks. Hypertrophic hepatic parenchyma cells in ♀ at 1000 mg/kg bw/day. **NOAEL: 450 mg/kg bw/day** *Applying route to route extrapolation, by assuming that penetration of avobenzone through skin is equal to penetration through the intestinal wall, the same effect levels as for oral route shall apply for the dermal route of exposure (ECHA 2021)*
	Rabbits (*n*=10/sex/group), 1.5, 5 and 18 % w/v solutions in carbitol (vehicle) (30, 100 and 360 mg/kg bw/day) (dermal once daily), exposure: 6 hours/day, 28 days	No treatment-related mortality. ↑ dose dependent severe dermal reactions ≥ 30 mg/kg/day, more persistent at 100 mg/kg bw/day. ↑ Incidence of epidermal thickening in both vehicle control and treatment groups compared to the untreated control group. NOAEL: 360 mg/kg bw/day (based on systemic effects). LOAEL: 30 mg/kg/bw/day (dermal)
Octocrylene (ECHA 2021d; SCCS 2021a)	Rats (Wistar), *n* = 10/sex/dose 0, 58, 175, 340 and 1085 mg/kg bw/day (diet), 13 weeks Study BASF 50S0227/92059	No treatment-related mortality. No treatment-related clinical signs. Body weight gain: ↓ at HD in both sexes along with decreased food consumption Haematology: RBC affected (↓MCV, ↓MCH, ↓MCHC) at HD in both sexes Organ weights (bodyweight-relative): ↑ absolute and relative weight of liver at 340 and 1085 mg/kg bw/day Histopathology: hypertrophy of periacinar and centriacinar hepatocytes at 340 and 1085 mg/kg bw/day; Slight or moderate hypertrophy of the thyroid, follicular epithelium and associated pale staining colloid at 340 and 1085 mg/kg bw/day NOAEL: 175 mg/kg bw/day
	Rabbits (NZW), *n* = 5/sex/dose 0, 130, 264, 534 mg/kg bw/day (dermal) 5 days/week; 13 weeks (Odio *et al.*, 1994)	Slight to moderate skin irritation (erythema and desquamation) at all doses at the site of application correlated to ↓ bodyweight gain at 264 and 534 m/kg bw/day. No evidence for haematological or macroscopic and histopathological abnormalities No effects were reported on testicular and epididymal morphology as well as on sperm count and motility NOAEL: 534 mg/kg bw/day (systemic toxicity) NOAEL: 130 mg/kg bw/day (dermal)
	A follow up mechanistic study was conducted in rats to investigate mechanisms related to potential thyroid effects of octocrylene observed in the 13-week oral repeat dose study in rats Rats (Wistar), *n* = 5/sex/dose 72, 215, 720 mg/kg bw/day PO (Subset A) 63, 188, 630 mg/kg bw/day PO (Subset B) 28 days (Subset A) 14 days (Subset B)	No treatment-related mortality No treatment-related clinical signs. Body weight gain: ↓ at HD in both subsets Serum chemistry: ↑ TSH at 630 mg/kg bw/day in ♀ in subset B; ↑ TSH at 720 mg/kg bw/day in both sexes in subset A Organ weights (bodyweight-relative): ↑ absolute and relative weight of liver at high doses in both sexes in both subsets Histopathology: minimal follicular cell hypertrophy/hyperplasia of the thyroid gland at high doses in both sexes in both subsets NOAEL: 188-215 mg/kg/day

Active ingredient	Study details[Δ]	Major findings
Octinoxate (ECHA 2021e)	Rats (not specified), *n*=5/sex/dose, at 300, 900 and 2700 mg/kg bw/day (gavage), 3 weeks	↓ body weight, ↓ relative and absolute weight of the thymus at HD, ↓absolute weight of the left kidney (♂) and ↓ absolute weight of the heart (♀) at HD. NOAEL: 900 mg/kg bw/day.
	Rats (SPF), *n*=12/ sex/dose, at 200, 450 and 1000 mg/kg/day (oral), 13 weeks with recovery period of 5 weeks	↑ Kidney weights at HD, reversed during the recovery period (5 weeks). ↓ glycogen in the liver and ↑ iron in the Kupfer cells at HD, ↑ GLDH in ♀ at HD. Some of the effects were reversed during the recovery period; however, then reversed effects were not listed in the AICIS report. NOAEL: 450 mg/kg/day based on the minor and reversible changes at 1000 mg/kg bw/day
	Rats (SD), *n*=10/sex/dose, 55.5, 277 and 555 mg/kg/day, 5 days/ week, 13 weeks (dermal)	Mortality: none treatment-related ↑ (non-significant) serum alanine phosphatase (SAP) levels and ↑ relative liver weight at HD. Liver effects were not observable upon microscopic examination. NOAEL: 555 mg/kg bw/day based on no significant adverse effects at the highest treated dose
	Rats (SD), *n*=15/sex/dose; 0, 500, 1500 or 5000 mg/kg/day applied occlusively on the abraded skin, 6 days/ week, 28 days (dermal)	No systemic effects, body weight changes, ocular defects, haematology effects or changes in blood chemistry parameters were observed. Dose dependent low-grade epidermal proliferation at all doses (more prominent in ♂). The chemical was considered as a low-grade irritant under the conditions of this study (OECD TG 410) NOAEL: 5000 mg/kg bw/day
	Rabbits (NZW), *n* = 10/sex/dose, 500, 1500 or 5000 mg/kg bw/day applied occlusively on the abraded skin, 6 hours/day, 21 days (dermal)	Mortality: 3 at HD Lethargy, hunched posture, hair loss, soiled coats, emaciation, increased respiration, swelling of the conjunctivae, and reproductive effects (retardation of testicular growth) at HD. Haematological changes including ↑ neutrophils and urea nitrogen, and ↓ lymphocytes and alkaline phosphatase activity at HD. Dermal irritation effects (erythema, oedema, desquamation, cracking and atonia) were observed at all doses but were more severe at the HD. Histopathology of the skin sites showed an epidermal proliferative response with low grade inflammatory reaction (dose dependent). NOAEL: 1500 mg/kg bw/day
Ethyl hexyl triazone (ECHA 2021b; DEPA 2015)	Rats (Wistar), *n*=10/sex/group, 0, 1000, 4000, and 16000 mg/kg bw/day;7 days/week, 90 days (oral)	Slight variations in the haematological and clinical chemistry parameters corresponded to the range of biological variation in the species. ↑ Liver-weight without histological correlates among treated female animals could not be interpreted as being treatment-related. **NOAEL: 1000 mg/kg bw/day** (nominal) was mentioned.
	Rats, *n* = 10/sex/group, 0, 1000, 4000, and 16000 mg/kg bw/day (diet); 7 days/week, 90 days	Clinical signs: none treatment-related in the haematological and clinical chemistry parameters No treatment-related effects on organs NOAEL: ≤ 1275 mg/kg bw/day (nominal)
Oxybenzone (SCCP 2006a; 2021c)	Mice (B6C3F1; *n* = 5/sex/group), 0, 3125, 6250, 12500, 25000, 50000 ppm (equivalent to 1021, 2041, 4430, 8648, 20796 mg/kg bw/day), 14 days (diet)	Mortality: none Bodyweight gain: ↓ in ♂at HD. Organ weight: ↑ liver weights (♂ & ♀) from LD, associated histopathology observed at 2041 mg/kg bw/day; ↓ kidney weight in ♂ from 8648 mg/kg bw/day. NOAEL: 992 (♂)/1050 (♀) mg/kg/day

Active ingredient	Study details[Δ]	Major findings
	Mice (B6C3F1; *n* = 10/sex), doses: 0, 0, 3125, 6250, 12500, 25000, 50000 ppm (equivalent to 554, 1246, 2860, 6780, 16238 mg/kg bw/day), 90 days (diet)	Mortality: none Bodyweight: ↓ BW gain in ♂ & ♀ from 6780 mg/kg bw/day Organ weights: ↑ liver weight from 1246 mg/kg bw/day with histopathology from 6780 mg/kg bw/day. Renal histopathology at HD in ♂. Reproductive parameters: ↓ sperm density and ↑ abnormal sperm in ♂ and ↑ oestrus cycle length in ♀ at HD NOAEL: 2860 mg/kg/day (equivalent to 1068 and 1425 mg/kg/day in ♂ and ♀, respectively)
	Rats (F344/N; *n* = 5/sex/group), Doses: 0, 3125, 6250, 12500, 25000, 50000 ppm (equivalent to 303, 576, 1132, 2238, 3868 mg/kg bw/day), 14 days (diet)	Mortality: none Bodyweight gain: ↓ in ♂at HD. Organ weight: ↑ liver (♂ & ♀) and kidney (♂) weights from LD, associated histopathology observed at 576 mg/kg bw/day in liver and at HD in kidney . NOAEL: 303 mg/kg/day (equivalent to 295 and 311 mg/kg/day in ♂ and ♀, respectively)
	Rats (F344/N; *n* = 10/sex/group), Doses: 0, 3125, 6250, 12500, 25000, 50000 ppm (equivalent to 0, 204, 411, 828, 1702, 3458 mg/kg bw/day), 90 days (diet)	Mortality: none. Clinical signs: coloured urine from LD. Bodyweights: ↓ BW gain in ♂ & ♀ from 1702 mg/kg bw/day. Clinical pathology: serum protein levels from 411 mg/kg bw/day, ↑ platelet counts from 1702 mg/kg bw/day Organ weights: ↑ liver weight from LD; ↑ kidney weight in ♀ from 1702 mg/kg bw/day with dilation of renal tubules, inflammation with fibrosis in renal interstitium at HD. Reproductive parameters: ↓ sperm motility in ♂ and ↑ oestrus cycle length in ♀ at HD. NOAEL: 411 mg/kg bw/day (equivalent to 429 and 393 in ♂ and ♀, respectively)
	Mice (B6C3F1; *n* = 5/sex/group), Doses: 0, 0.5, 1.0, 2.0, 4.0, 8.0 mg/mouse in acetone or lotion* (equivalent to 24.8, 48.4, 100, 196, 388 mg/kg bw/day), 14 days (dermal)	Mortality: none Organ weights: ↑ liver weight from 196 mg/kg bw/day. NOAEL: 388 (♀) mg/kg bw/day (equivalent to 384 and 432 mg/kg/day in ♂ and ♀, respectively)
	Mice (B6C3F1; *n* = 10/sex/group), Doses: 0, 22.8, 45.5, 91, 183, 364 mg/kg bw/day in acetone or lotion*, 90 days (dermal, 5 days/week)	Mortality: none. Organ weights: ↑ kidney weight in ♂ at all doses Reproductive parameters: ↓ epididymal sperm density in ♂ at all doses. NOAEL: 364mg/kg bw/day in ♂ and ♀
	Rats (F344/N; *n* = 5/sex/group), doses: 0, 1.25, 2.5, 5, 10, 20 mg/rat in acetone or lotion* (equivalent to 7, 13.6, 27.7, 54.9 and 110 mg/kg bw/day), 14 days (dermal) (5 days/week for 2 weeks)	Mortality: none Organ weights: ↑ liver weight in ♀ from 27.7 mg/kg bw/day, ↑ kidney weight in ♀ at HD NOAEL: 100 (♂)/140 (♀) mg/kg bw/day
	Rats (SD; *n* = 6♂/group), 0, 100 mg/kg bw/day, 28 days (twice daily)(dermal)	No treatment-related effects (limited evaluation). NOAEL: 100 (♂) mg/kg bw/day
	Rats (F344/N; *n*-10/sex/group), doses: 0, 12.5, 25, 50, 100, 200 mg/rat in acetone or lotion* (equivalent to 12.5, 25, 50, 100, 200 mg/kg bw/day), 90 days (dermal)(5 days/week)	Mortality: none. Clinical pathology: ↓ reticulocyte counts from LD, ↑ platelet counts from 50 mg/kg bw/day, ↑ whole blood cell count produced by lymphocytosis at HD. NOAEL: 200 mg/kg bw/day
PBSA	Rats (Wistar; *n* = 5/sex/group)	No treatment-related effects.

Active ingredient	Study details[Δ]	Major findings
(SCCP 2006b)	Doses: 0, 100, 330 and 1000 mg/kg bw, 13 weeks (oral)	NOAEL: 1000 mg/kg bw/day
Homosalate (SCCS 2020; ECHA 2021c)	Rats, n=5/sex/dose, 0, 100, 300, 1000 mg/kg bw/day, 2 weeks (gavage)	Mortality: none Clinical signs: none treatment related Body weight gain: ↓ at HD in ♂ along with decreased food consumption Haematology: none treatment related Serum chemistry: ↑ Triglycerides in both sexes at HD ↑APTT in ♂ at MD NOAEL: > 300 mg/kg bw/day ♂ NOAEL: >1000 mg/kg bw/day ♀
	Repeat dose/ reproduction/ developments study Rats (Wistar), *n* =10/sex, 0, 60, 120, 300, 750 mg/kg bw/day (gavage), 7 weeks duration (ECHA 2020)	*Mortality:* 2 ♀ at 750 mg/kg bw/day *Clinical signs:* none treatment-related *Body weight gain:* ↓ at 750 mg/kg bw/day in ♂ and ♀ *Haematology:* none treatment-related *Serum chemistry:* ↑ Albumin and ↓ Globulin in ♂ at 300 mg/kg bw/day *Urinalysis:* not conducted *Organ weights (bodyweight-relative):* ↑ absolute and relative weight of liver in both sexes at 300 and 750 mg/kg bw/day, ↑ kidney in ♀ at 300 mg/kg bw/day. ↓ thymus in both sexes at 750 mg/kg bw/day. ↓ prostate and seminal vesicles at HD 750 mg/kg bw/day. *Gross pathology:* no treatment-related findings *Histopathology:* ↑ Minimal/moderate intra-epithelial hyaline droplets in the kidneys ♂ from 60 mg/kg bw/day (associated with ↑ in foci of basophilic tubules, single cell death and/or the presence of granular casts). * Minimal/mild hypertrophy of hepatocytes (1/5 ♂) at 120 mg/kg bw/day, and almost every ♂ and ♀ from 300 mg/kg bw/day. Hypertrophy of the follicular epithelium of thyroid gland in ♂ at 750 mg/kg bw/day and in ♀ from 300 mg/kg bw/day. ↓ Cortical lymphocytes in males from 300 mg/kg bw/day and in ♀ at 750 mg/kg bw/day *NOAEL:* ** mg/kg bw/day *The REACH registrants considered this as manifestations of hyaline droplet nephropathy without giving further evidence. **Based on this study, the REACH registrants derived a NOAEL of 300 mg/kg/day for general toxicity based on mortality in HD females. However, at this dose effects on kidneys, liver, thyroid and thymus occurred. In males, effects were noted **from the lowest dose of 60 mg/kg bw/d**, therefore the SCCS considers this dose as LOAEL.

Δ GLP compliance was not specified in the reviews

Genotoxicity

A summary of genotoxicity studies for each sunscreen ingredient is shown in the table below. With the exception of homosalate, all sunscreen ingredients were negative in *in vitro* and *in vivo* tests. Homosalate was negative in the Ames test and the gene mutation test in Chinese hamster cells *in vitro*. However homosalate induced DNA damage the Comet assay in isolate human peripheral lymphocytes and in the micronucleus assay *in vivo*.

Table 3-7. Summary of genotoxicity studies with sunscreen ingredients

Avobenzone (ECHA (2021a; DEPA 2015)	Ethylhexyl triazone (ECHA (2021b; DEPA 2015	Homosalate (SCCS 2020; ECHA 2021c)	Octinoxate (ECHA 2021e)	Octocrylene (SCCS 2021a; ECHA 2021d)	Oxybenzone (SCCP 2006a; 2021c)	PBSA (SCCP 2006b)
In vitro Negative AMES test and gene mutation study V79 Chinese hamster cells In vivo Negative Bone marrow polychromatic erythrocytes (mice)	*In vitro* Negative AMES test, Chinese hamster lung fibroblasts for chromosome aberration, Chinese hamster ovary (CHO) cells, in vivo chromosome aberration test	*In vitro* Negative AMES test and gene mutation study in V79 Chinese hamster cells Findings from the SCGE comet assay in isolated human peripheral lymphocytes and micronucleus assay in MCF-7 cells suggest that homosalate induced DNA damage in a dose dependent manner and it is clastogenic when the cells were incubated at cytotoxic concentrations (Yazar et al. 2018; 2019)	*In vitro* Negative AMES test, mammalian cell transformation assay (BALB/c-3T3 clone A31-11 cells), micronucleus test (mice), Unscheduled DNA synthesis assay (rat primary hepatocytes), Chromosomal aberrations (human peripheral blood lymphocytes) In vivo Negative Chromosomal aberrations in micronucleus assay in bone marrow polychromatic erythrocytes, Cell gene mutation assay (V79, ± S9) showed a very slight increase in mutant colonies (up to 20 mg/mL)	*In vitro* Negative AMES test, gene mutation test, cytogenicity test in mammalian cells, chromosome aberrations tests In vivo Negative Cytogenicity test in mice (ECHA 2020, SCCS 2021a)	*In vitro* Negative AMES test (weak positive: TA97 (30% hamster +S9), 10% hamster or 10% and 30% rat S9), Chinese hamster lung fibroblasts for chromosome aberration ±S9, CHO cells –S9; Sister-chromatid exchanges and chromosomal aberrations + S9 In vivo Negative micronucleus test (mice), chromosome aberration test (rats), Drosophila (SMART)†	*In vitro* Negative AMES test and chromosome aberration test in human peripheral blood lymphocytes In vivo No data

† In a recently published study (Majhi *et al.* 2020), benzophone-3 (1 and 5 μM) increased DNA damage similar to that of E2 treatment in a ERα-dependent manner. Benzophone-3 exposure caused R-loop formation in a normal epithelial cell line when ERα was introduced. R-loops and DNA damage were also detected in mammary epithelial cells of mice treated with benzophone-3.

Carcinogenicity

No carcinogenicity data were available for avobenzone, octinoxate, octocrylene, ethylhexyltriazone, homosalate or PBSA. Oxybenzone was carcinogenic in mice (bone marrow, spleen, kidney and liver), with equivocal evidence of carcinogenicity observed in rats (brain, spinal cord, thyroid and uterus). Findings are provided in the following table.

Table 3-8. Summary of carcinogenicity studies with sunscreen ingredients

Active ingredient	Study details	Major findings
Avobenzone	–	No data
Ethyl hexyl triazone	–	No data
Homosalate	–	No data
Octinoxate	–	No data
Octocrylene	–	No data
Oxybenzone (SCCP 2006a; 2021c)	Mice (B6C3F1/N; *n*=50/sex/group), 0, 1000, 3000, 10000 ppm (equivalent to 113/109, 339/320, 1207/1278 mg/kg bw/day in ♂/♀)	Mice: ↑ lesions in the bone marrow, spleen, and kidney of both sexes and in the liver in ♂
	Rats (SD; *n*=10/sex/group), 0, 1000, 3000, 10000 ppm (equivalent to 58/60, 168/180, 585/632 mg/kg bw/day in ♂/♀) Two years (beginning on GD6 in ♀)	Rats: ↑ incidence of brain and spinal cord malignant meningiomas at 3000 ppm in ♂ and thyroid C-cell adenomas at 3000 ppm) and uterine stromal polyps at 3000 ppm in ♀ without any dose-response relationship. These findings are considered equivocal evidence of carcinogenicity.
PBSA	–	No data

Reproductive and developmental studies

A summary of reproductive and developmental toxicity studies for each sunscreen ingredient is shown in the table below.

Table 3-9. Summary of reproductive and developmental toxicity studies with sunscreen ingredients

Active ingredient	Study details	Major findings
Avobenzone (ECHA 2021a; DEPA 2015)	Rats at 0, 250, 500 and 1000 mg/kg bw/day (oral gavage), GD 7 -16.	No treatment-related skeletal malformations were observed. One pup with two fused sternal elements was seen at LD. A slight increase of incised neural arches and sternebrae was seen at 500 mg/kg/day. The soft tissue examination displayed one fetus of the 500 mg/kg dose group with unilateral missing ovarium and uterus. No effects were considered treatment related in the absence of dose dependence. In the rearing group, all measured parameters were well comparable to concurrent control group values. Maternal and developmental NOAEL: 1000 mg/kg bw/day.
	Rabbits, single dose of 500 mg/kg bw/day GD 7-19 (oral, daily)	No treatment-related effects or teratogenicity.

Active ingredient	Study details	Major findings
Octinoxate (ECHA 2021e)	Rats (Wistar); *n* = 25/sex/dose. 0, 150, 450 or 1000 mg/kg bw/day (oral), The parental (F0) generation was exposed throughout premating period (73 days), mating (21 days), gestation (21 days), and up to weaning of the F1 offspring (21 days). The duration of exposure for the F1 generation was similar to F0.	No adverse effects were observed on oestrous cycles, sperm and follicle parameters, mating, fertility, morphology and motility, gestation and parturition. ↓ food consumption and body weight, ↑ liver weight and hepatic cytoplasmic eosinophilia related to hepatic enzyme induction, and ↑ ulceration of the glandular stomach mucosa at HD. In the offspring, ↓ lactation weight gain and organ weights, and slightly delayed sexual maturation (vaginal opening and preputial separation) at HD. **NOAEL: 450 mg/kg bw/day** for fertility and reproduction parameters, and for systemic parental and developmental toxicity (Schneider *et al.* 2005, REACH).
	Pregnant rabbits (*n*=20/dose), 80, 200 or 500 mg/kg bw/day on GD 7–20.	Reproductive parameters were not affected. Except for a slight reduction of maternal and foetal weight at HD, no abnormality was found. The fetuses did not show any skeletal or visceral abnormalities. ↓ body weight at HD, but within the range of other doses and the controls. NOAELs: 500 mg/kg bw/day (Maternal and developmental).
	Rats (albino, ♀), single dose of 1000 mg/kg bw/day on GD 7–16 (oral gavage)	No maternal, embryotoxic or teratogenic effects were observed. No other information was provided.
	NTP-DART-06 (2022b) Modified one-generation study Rats (SD); *n*=26/dose; exposure through feed and/or lactation 1000, 3000, 6000 ppm (equivalent to 70 to 87, 207-418 , 419-842 mg/kg/day) F_0 dams: GD6 - LD 28 F_1 offspring were exposed in utero and during lactation through postnatal day (PND) 28 and evaluated for signs of toxicity. After weaning, F_1 offspring were allocated into prenatal, reproductive performance or subchronic exposure cohorts. Exposure to test article continued in feed until necropsy on PND96, 120 or 150. F_2 offspring were exposed in utero, during lactation and postweaning until necropsy on GD21 or PND28.	Octinoxate did not induce overt F_0 or F_1 maternal toxicity or affected mating or pregnancy indices. Reproductive performance (fertility and fecundity), numbers of live fetuses and pups ware not affected. Octinoxate exposure was not associated with any effects on fetal weight or the incidences of external, visceral, or skeletal malformations. Equivocal evidence of developmental toxicity was observed: ↓ Mean pup body weight (F1) at HD ↑ Vaginal opening (F_1) from MD ↑ Balanopreputial separation (F_1) at HD NOAEL: 6000 ppm for parental systemic toxicity, fertility and reproduction performance NOAEL: 1000 ppm for developmental toxicity
Octocrylene (SCCS 2021a; ECHA 2021d)	Extended one generation reproductive toxicity study (EOGRTS), GLP Rat (Wistar); Dose: (diets) 55, 153, 534 mg/kg bw/day ♂ 58, 163, 550 mg/kg bw/day ♀ *n*= 27 or 28 /sex /dose F1: Cohort 1A: 19/sex/ dose Cohort 1B: 25/sex/dose Cohort 2A: 10/sex/ dose Cohort 2B: 10/sex/dose ♂: 10-week premating period, during mating up to the day of sacrifice (~ 13 weeks)	↓ number of implantation sites and consequently a lower number of pups at HD ↓ bodyweight of pups at HD No effects on male fertility and male and female reproductive parameters such as oestrus cycle, epididymal and testicular sperm parameters at all doses. No effects on sexual and neurodevelopmental parameters in pups. Based on effects on parental and pup body weights, a lower number of implantation sites and lower number of pups delivered. **NOAEL: 153/163 mg/kg bw/day for males/females** for parental systemic toxicity, fertility/reproduction performance, and general and sexual development

Active ingredient	Study details	Major findings
	♀: P: 10-week premating period, termination on LD 21 F1: from weaning up to sacrifice (~ 10 weeks in Cohort 1A, ~ 13 weeks (♂) and approx. 18 weeks (♀) in Cohort 1B; ~ 8 weeks in cohort 2A) F2: until weaning (indirectly) (ECHA 2021d; SCCS 2021a)	
	Pregnant rats (Wistar); *n* = 25/♀/dose, Dose: 0, 100, 400, 1000 mg/kg bw/day PO GD6–GD15; termination on GD21	F0: Transient salivation at HD. ↑ relative liver weight at MD and HD F1: No treatment related effects. NOAEL: ≥ 1000 mg/kg bw/day (teratogenicity)
	Mice (CD-1); *n*= 12 ♀/dose, Dose: 0, 100, 300, 1000 mg/kg bw/day (oral gavage); GD8–GD12; termination on LD3 Odio *et al.* (1994)	No treatment related adverse effects. NOEL: 1000 mg/kg bw/day (mice)
	Rabbit (NZW); *n* = 17 ♀/dose Dose: 0, 65, 267 mg/kg bw/day, (Dermal, open, clipped area on the back), dosing GD6–GD18; termination on GD21 Odio *et al.* (1994)	No treatment related adverse effects. NOEL (percutaneous): 267 mg/kg bw/day (rabbits)
Ethylhexyl triazone (ECHA 2021b; DEPA 2015	Rats (wistar), Prenatal Developmental Toxicity study (*n*=25/dose). Dosing the dams 7 days/week for an unspecified period (0, 100, 400 and 1000 mg/kg bw/day).	No treatment-related effects reported. Maternal NOAEL = 1000 mg/kg bw/day; Developmental NOAEL = 1000 mg/kg bw/day
Homosalate (SCCS 2020; ECHA 2021c)	The evaluation of potential toxicity of homosalate on fertility and development was performed in a combined repeat dose toxicity study with the reproduction/developmental toxicity-screening test (described above in repeat-dose toxicity section). The study findings were considered as inconclusive and unreliable due to a technical error that maintained the animals under a constant light. In the context of a compliance check process under REACH, the ECHA adopted a decision in 2018 requesting a sub-chronic toxicity study, a prenatal developmental toxicity study, an extended one-generation reproductive toxicity study, and the identification of degradation products (ECHA 2018, ECHA decision CCH-D-2114386909-26-01/F). An appeal was filed against this decision; however, the Board of Appeal dismissed the appeal and decided that the information must be provided by 25 February 2024.	
Oxybenzone (SCCP 2006a; 2021c)	Mice (CD-1), RACB (Reproductive Assessment by Continuous Breeding): 1850, 3950, 9050 mg/kg bw/day (14 days; *n*=20/sex); 1000, 2100, 4700, 10200, 15700 mg/kg bw/day (14 weeks; *n*=8/sex)	No effect on fertility at doses up to 8600/9500 mg/kg bw/day in♂ /♀ mice (highest dose). Effects on reproductive performance included a slightly lower number of live pups at birth. Impaired body weight/body weight gain in pups was also observed. All effects were observed at dose levels resulting maternal toxicity including decreased bodyweight and premature death at doses of 1850 mg/kg bw/day. The NOAEL for systemic, reproductive and developmental toxicity was 1800/1900 mg/kg bw/day in males/females.
	Rats (F344/N; *n*=10/sex) and mice (B6C3F1; *n*=10/sex): 0, 3125, 12500, 50000 ppm (equivalent to 204, 828, 3458 mg/kg bw/day in rats and 554, 2860, 16238 mg/kg bw/day in mice);13 weeks (dietary)	↓ Epididymal sperm counts, and decreased absolute cauda, epididymal and testis weight as a consequence of the reduced body weight in male rats and ↑ in the length of the oestrous cycle in female rats. ↓ in the epididymal sperm count and ↑ the incidence of abnormal sperm was observed in male mice, and there was an ↑ in the length of the oestrous cycle in female mice (as seen in rats).

Active ingredient	Study details	Major findings
		Oestrous cyclicity was not affected in either rats or mice. NOAEL for reproductive parameters was established at 828 mg/kg bw/day in rats and 2860 mg/kg bw/day in mice (SCCP 2006a).
	Rats (SD; n=not reported) doses up to 200 mg/kg bw/day and mice (B6C3F1; n= x ♂);0, 20, 100, 400 mg/kg bw/day; 13 weeks (dermal)	No effects on selective reproduction parameters and a NOAEL was established at 200 mg/kg bw/day, the highest dose tested in rats. In mice, there were no effects on reproductive organ weight, cauda epididymal sperm concentration, sperm parameters, testicular spermatid concentration or testicular histology. NOAEL: 400 mg/kg bw/day, the highest dose tested.
	Prenatal developmental toxicity study in rats (Wistar; *n*=25 ♀), at doses of 0, 40, 200, 1000 mg/kg bw/day PO	Slight ↑ rates of fetuses/litter with skeletal variations (incomplete ossification of different skull bones and cervical arch, supernumerary 14th ribs) and therefore ↑ rates of total variations were observed at 1000 mg/kg bw/day. These effects were associated with maternal toxicity (clinical signs, reduced bodyweight and food consumption). The NOAEL was established at 200 mg/kg bw/day.
	Reproductive toxicity study in rats (SD) at doses of 3000, 10000 and 30000 ppm (equivalent to 242, 725 and 3689 mg/kg bw/day) in the diet from GD 5-15.	The maternal NOAEL was established at 3000 ppm (206-478 mg/kg bw/day) based on reduced bodyweight gain during GD 6-9 and lactation day 4-21. The developmental NOEL was established at 3000 ppm (206-478 mg/kg bw/day) based on impaired postnatal bodyweight performance at 10000 ppm (660-1609 mg/kg bw/day) (SCCS 2021c).
	Nakamura *et al.* (2015) Reproductive toxicity study in rats (SD; *n*=7-8 mated ♀); Doses: 0, 1000, 3000, 10,000, 25,000, or 50,000 ppm, equivalent to 67.9, 207.1, 670.8, 1798.3, and 3448.2 mg/kg bw/day, respectively. Treatment from GD6-PND23. The effects of maternal exposure during gestation and lactation on development and reproductive organs of offspring of mated female rats was examined.	Exposure to <10,000 ppm oxybenzone was not associated with adverse effects on the reproductive system in rats. At higher doses, a decrease in the normalised anogenital distance in male pups at PND 23, impairment of spermatocyte development in testes of male offspring, delayed follicular development in females was observed at doses of ≥207 mg/kg bw/day. The **NOAEL was established at 67.9 mg/kg bw/day.**
	Han *et al.* (2022) Reproductive toxicity study in mice (ICR; *n*=13-15 mated ♀) Doses: 0, 0.1, 10, 1000 mg/kg/day PO Treatment from GD1-GD13	No adverse effect on maternal body weight and the relative weights of the liver, brain and the uterus Slight ↑ rate of fetal loss at HD; ↑ placental thrombosis and necrosis from LD (severity not assessed)
	NTP-DART-05 (2022a) Modified one-generation study Rats (SD; mated ♀; *n*= 25/dose) Doses: 0, 3000,10000, 30000 ppm; exposure through feed and/or lactation (equivalent of 205 to 426, 697 to 1621, and 2,644 to 5944 mg/kg/day respectively) F_0 GD6 - LD28 F_1 GD6 - LD28; after weaning, F_1 offspring were allocated into cohorts for prenatal, reproductive performance, or additional assessments (e.g., subchronic or biological sampling cohorts) and exposure to test article in feed	There was equivocal evidence of reproductive toxicity of oxybenzone based on ↓ F_2 litter size at HD. There was some evidence of developmental toxicity from MD based on ↓ F_1 and F_2 mean body weights; this effect on body weight contributed to the apparent oxybenzone -related ↓ in male reproductive organ weights from MD. The relationship of the ↑ occurrence of diaphragmatic and hepatodiaphragmatic hernias in F_1 adults and F_2 pups from MD is unclear. Exposure to oxybenzone was associated with ↑ nonneoplastic kidney lesions in the F_0, F_1, and F_2 generations at HD Exposure to oxybenzone was not associated with signals consistent with alterations in estrogenic, androgenic, or antiandrogenic action. NOAEL: 3000 ppm

Active ingredient	Study details	Major findings
	continued until necropsy on PND96, PND120 or PND150 F_2 offspring were exposed in utero, during lactation and postweaning until necropsy on GD21 or PND28.	
PBSA (SCCP 2006b)	A prenatal developmental study (rats, *n*=25♀/group), treatment GD 6-15, doses: 0 and 1000 mg/kg bw/day (gavage)	No treatment-related findings were noted in the study. The NOAEL for maternal and fetal toxicity was 1000 mg/kg bw/day.

Active ingredients in human milk

In a cohort study between 2004 and 2006, 54 human milk samples were analysed; UV filters were detectable in 46 samples and levels were positively correlated with the reported usage of UV filter products (Schlumpf *et al.*, 2010). Concentrations of octinoxate or ethylhexyl methoxy cinnamate (EHMC), octocrylene (OC), 4-methylbenzylidene camphor (4-MBC), homosalate (HMS) and oxybenzone (BP-3) ranged 2.10–134.95 ng/g lipid, with octinoxate/EHMC and octocrylene being most prevalent (42 and 36 positive samples, respectively) and an average of 7 positive samples for the other three (Schlumpf *et al.*, 2010). In another study, levels of oxybenzone in maternal urinary samples taken in gestational weeks 6–30 were positively correlated with the overall weight and head circumference of the baby (Philippat *et al.* 2012). These reports raise concerns about potential prenatal exposure and developmental toxicity of UV filters.

Endocrine activity modulation

Chemicals with endocrine activity modulation are exogenous chemicals that can alter hormone action, thereby potentially increasing the risk of adverse health outcomes, including cancer, reproductive impairment, cognitive deficits and obesity. In 2013, publicly available data on endocrine disruptive properties of 23 ingredients including the ingredients reviewed in this document were collected and evaluated by the Danish Centre on Endocrine Disruptors (Axelstad *et al.* 2013). The overall conclusion of the evaluation was that there were not enough data to conclude whether the ingredients have endocrine disruptive properties or not.

> *"In conclusion, very little is known on the endocrine disrupting potential of these 23 UV-filters. For 14 of the 23 assessed UV-filters[8] no in vivo studies in rodents, assessing endpoint that are sensitive to endocrine disruption, have been performed, and it was therefore not possible to conclude anything on their endocrine disrupting potential, with regard to human health...*
>
> *Two of these (octocrylene and butyl methoxydibenzoylmethane) showed no adverse effects in the used test systems. Seven of the UV-filters (placed in groups C & D) were tested in the Uterotrophic assay, and regardless of their estrogenic potential in vitro, none of them caused increased uterine weights, indicating lack of estrogenic potential in vivo. The three compounds in-group E[9] were also investigated for androgen receptor (AR) agonism/antagonism in vitro, and the results differed somewhat depending on which type of study had been performed. However, since no in vivo studies investigating the anti androgenic effects of the compounds were present, it is difficult to conclude anything on their endocrine disrupting potential with regard to the possible androgenic/antiandrogenic mode of action. Information on human health endocrine disrupting potential of last two UV-filters (octocrylene and titanium dioxide)*

[8] EHT was included in these 14 ingredients
[9] Homosalate and avobenzone were included

was also scarce. Since no adverse effects on testicular and epididymal morphology or on sperm quality were seen in a 90-day study of octocrylene, this UV filter did not seem to be a potent anti-androgen. Read across assessment showed possible resemblance of the chemical structures of some of the presently evaluated UV-filters to known or suspected endocrine disrupting UV-filters, however more knowledge on the endocrine disrupting potential of the presently evaluated UV-filters could be obtained by doing QSAR analyses. Unfortunately no published reports of such analysis were present in the open literature."

An extensive review in 2016 also discussed the potential endocrine disruption of typical UV filters including benzophenones (i.e. oxybenzone), camphor derivatives and cinnamate derivatives (i.e., octocrylene, Octinoxate etc.) (Wang *et al.* 2016). The review (Wang *et al.* 2016) concluded:

"These UV filters are generally involved in the disruption of the hypothalamic–pituitary–gonadal system. As revealed by in vivo and in vitro assays, exposure to these chemicals induced various endocrine disrupting effects such as estrogenic disrupting effects, androgenic disrupting effects as well as the disrupting effects towards TR, PR. The underlying mechanism of endocrine disruption was summarized (Table 2). The minor structural changes of these kinds of UV filters have influence on the potency of their endocrine disrupting effects."

The Table 2 (summarising the Endocrine Activity Modulation effects of the commonly used UV filters) from the Wang review is provided in the Appendix.

In a recent *in vitro* study, Rehfeld *et al.* (2018) found that the homosalate, oxybenzone, avobenzone, octinoxate and octocrylene induced Ca^{2+} influx in human sperm cells whereas ethylhexyl triazone did not. It concluded:

"In conclusion, chemical UV filters that mimic the effect of progesterone on Ca^{2+} signaling in human sperm cells can similarly mimic the effect of progesterone on acrosome reaction and sperm penetration. Human exposure to these chemical UV filters may impair fertility by interfering with sperm function, e.g. through induction of premature acrosome reaction. Further studies are needed to confirm the results in vivo".

Lee *et al.* (2022) screened octinoxate, octocrylene, avobenzone and homosalate among 35 other chemicals used in consumer products, for their ability to modulate estrogen receptor (ER) or androgen receptor (AR) *in vitro*. Octinoxate was a weak agonist of ER, while octocrylene acted both as a very weak agonist or a weak antagonist of ER, but both were negative for AR. Avobenzone and homosalate did not activate either ER or AR.

In the light of increased safety concerns regarding the Endocrine Activity Modulation potential of the active ingredients in sunscreens, in 2018, the ECHA and the European Food Safety Authority (EFSA) published "Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009 (Andersson *et al.* 2018). The Biocidal Products Regulation (EU No 528/2012; BPR) restricts approvals of the active substances considered to have endocrine disruption properties, unless the risk from exposure to the active substance is shown to be negligible or unless there is evidence that the active substance is essential to prevent or control a serious danger to human health, animal health, or the environment.

A recent Consensus Statement discussed ten key characteristics (KCs) of Endocrine Activity Modulation based on hormone actions and Endocrine Activity Modulation effects, the logic behind the identification of these KCs and the assays that could be used to assess several of these KCs (la Merrill *et al.* 2020).

A systematic review assessed 29 studies that addressed the impact of oxybenzone on human health (Suh 2020). The review suggests increased systemic level of oxybenzone had no adverse effect on male and female fertility, female reproductive hormone level, adiposity, fetal growth, child's neurodevelopment and sexual maturation (Suh 2020). However, the association of oxybenzone level on thyroid hormone, testosterone level, kidney function and pubertal timing has been reported warranting further investigations to validate a true association. The health effects of an increased octinoxate level have been less extensively studied presumably. The current evidence shows that topical application of octinoxate does not have biologically significant effect on thyroid and reproductive hormone levels (Suh 2020). However, the topical application of octinoxate results in systemic absorption greater than 0.5 ng/mL, a threshold established by the FDA for waiving toxicology assessment, and therefore further drug safety assessment on octinoxate is crucial.

The review concluded that:

> *"To evaluate the long-term risk of exposure to BP-3 or OMC from sunscreens, a well-designed longitudinal randomized controlled trial is of high priority."*

The latest SCCS opinions on these ingredients considered available information on the endocrine activity of these active ingredients and suggested inadequate evidence is available for relevant safety determination.

The key conclusions from the evidence above are given below.

Avobenzone

The Danish Centre on Endocrine Disruptors (Axelstad *et al.* 2013) evaluated publicly available data on endocrine disruptive properties of substances and based on the assessment it concluded, that there were not enough data to conclude whether avobenzone has endocrine disruptive properties or not.

Homosalate

According to Danish QSAR database, homosalate was predicted to activate the E2R (Leadscope and SciQSAR)[10] and to act as an antagonist of androgen receptor (AR)(CASE Ultra and Leadscope).[10]

The SCCS (2020) conclusion was based on a Risk Management Options Analysis (RMOA) 2016 by ANSES[11]. As per the RMOA, *the available data from non-testing methods and in vitro assay and the inadequate in vivo studies provide indications for an ED potential of homosalate, whereas the rest of the studies were of limited relevance and do not indicate the potential for ED concern. Despite the poor quality of the in vivo studies, findings that could be linked to an endocrine disruption were identified, in particular fluctuations of hormones, sperm changes and effects on the thyroid*. These effects raised some concerns regarding ED properties of homosalate.

Therefore, the SCCS (2020) concluded:

> *"It needs to be noted that the SCCS has regarded the currently available evidence for endocrine disrupting properties of homosalate as inconclusive, and at best equivocal. This applies to all of the available data derived from in silico modelling, in vitro tests and in vivo studies, when considered individually or taken together. The SCCS considers that, whilst there are indications from some studies to suggest that homosalate may have endocrine effects, the evidence is not*

[10] QSAR software for modelling and predicting toxicity of chemicals. CASE Ultra has both methodologies (statistics based and expert rule based) built in for a complete ICH M7 compliant assessment. Leadscope Model Applier (Leadscope, Inc.) is a chemoinformatic platform that provides QSAR models for the prediction of potential toxicity and adverse human clinical effects of pharmaceuticals, cosmetics, food ingredients and other chemicals.

[11] French Agency for Food, Environmental and Occupational Health & Safety (ANSES) – See Eurometaux (2016).

conclusive enough at present to enable deriving a specific endocrine-related toxicological point of departure for use in safety assessment."

Octocrylene

The endocrine activity modulation potential of octocrylene was extensively discussed in SCCS (2021a). The SCCS opinion concluded that:

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

Oxybenzone

The endocrine activity modulation potential of oxybenzone was extensively discussed in SCCS (2021c). The SCCS (2020) evaluated the potential endocrine mode of action for oxybenzone (BP-3) *in vitro* and *in vivo* and endocrine-related adverse effects in humans and animals.

The SCCS concluded:

> *"The currently available evidence for endocrine disrupting properties of BP-3 is not conclusive, and is at best equivocal. This applies to the data derived from in silico modelling, in vitro tests and in vivo studies, when considered individually or taken together. There are either contradictory results from different studies, or the reported data do not show dose-response relationship, and/or the effect are seen only at relatively very high doses that can only be considered far beyond the human exposure range. In view of this, the SCCS considers that whilst there are indications from some studies to suggest that BP-3 may have endocrine effects, it is not conclusive enough at present to enable deriving a new endocrine-related toxicological point of departure for use in safety assessment."*

Octinoxate

Most of the available data suggest that octinoxate has an estrogenic activity, androgenic and anti-thyroid activity in rats and humans [NICNAS (currently known as AICIS), 2017; Lorigo *et al.* 2018].

Regarding the octinoxate mechanism of action, several studies showed that the effects exerted by Estradiol (E2) and octinoxate were not always totally shared and it is possible that octinoxate could act by a mechanism different from the classic E2R (α y β). There are few data regarding the anti-androgenic activity of octinoxate, and the studies suggest that octinoxate is not able to bind to androgen receptors. Studies in rats showed that octinoxate could disturb the homeostasis of the thyroid hormones by mechanisms different from the classical ones of hormone-dependent regulation and feedback.

More studies in rodents and very few in humans, suggest that an increase exposure to octinoxate could be related to infertility or changes in GnRH and disturbance of reproductive hormone levels. A public call by the European Commission for data on the endocrine activity modulation potential of ingredients used in cosmetics, including octinoxate, was undertaken from 15 February to 15 November 2021 (EU 2021).

A recent review summarises the endocrine effects of these ingredients recognising limited data availability (Fivenson 2020). This was a retrospective literature review that involved many different types of studies across a variety of species. Comparison between reports is limited by variations in methodology and criteria for toxicity.

OTHER STUDIES

The photo-allergic potential of avobenzone has been extensively reviewed in several publications (Nash and Tanner 2014). However, given the mechanistic understanding and known photo-degradation of avobenzone, the findings were inconsistent. For example, the *in vitro* skin phototoxicity of cosmetic formulations containing avobenzone, other UV filters and vitamin A palmitate was assessed by two *in vitro* techniques [3T3 Neutral Red Uptake Phototoxicity Test (3T3-NRU-PT) and Human 3-D Skin Model *In Vitro* Phototoxicity Test (H3D-PT)](Gaspar *et al.* 2013).The phototoxicity potential was 'positive' for avobenzone alone and in combination with other UV filters (3T3-NRU-PT). However, when tested on a human skin model, the 'positive' results were no longer observed. It has been suggested by several studies and reviews that the photoallergic potential of avobenzone may be the result of the photoproducts formed following exposure to UV. These data suggest that photo-degradation of avobenzone forms classes of photoproducts (arylglyoxals and benzils) which have strong potential for sensitization (Karlsson *et al.* 2009).

A survey in Canada (2001-2010) indicated that the most common photoallergens were oxybenzone, octyl dimethyl para-amino- benzoic acid and avobenzone whereas the most common contact allergens were octyl dimethyl para-aminobenzoic acid, oxybenzone and sandalwood (Yap 2017).

The SCCS (SCCS 2000) stated that octinoxate did not have phototoxic potential based on one study of 10 subjects exposed to patches of octinoxate for 24 hours and then exposed to a sub-erythematous dose of UV irradiation. No further details were supplied in the SCCS report. Recent *in vitro* (3T3 viable monolayer fibroblast cultures) and *in vivo* studies indicated that octinoxate was not phototoxicity (Gomes *et al.* 2015).

A human repeated insult patch test (HRIPT) was carried out at a concentration of 2% octinoxate in 53 subjects. There was no sensitisation. Similar studies using different formulations (7.5 % octinoxate in petrolatum or 10 % octinoxate in dimethylphthalate) also did not show any adverse reaction after 24 and 48 h. In a study in 32 healthy volunteers, daily whole–body topical application of 2 mg/cm² of cream formulation without (week 1) and with (week 2) the sunscreen (octinoxate 10%) for one week was performed. Hormone changes (testosterone, oestradiol and inhibin B levels) were observed following treatment but were not considered to be biologically significant. Following 1–2 hours of application, the chemical was detected in the parent form both in plasma and in urine (more than 86 % of the applied dose).

Oxybenzone was not phototoxic in the 3T3-NRU-PT test and was not phototoxic in *S. cerevisiae* or *E. coli in vitro*. Oxybenzone was not phototoxic in guinea pigs *in vivo* at a concentration of 10% (oxybenzone applied to shaven and depilated skin for 30 minutes followed by irradiation (UV-A) for 60 minutes). Oxybenzone did not cause photosensitisation in rabbits *in vivo* (study details not available). Oxybenzone was not photomutagenic in the photo Ames test or an *in vitro* chromosome aberration assay in CHO cells.

Oxybenzone was tested for photobinding to human serum albumin and histidine photo-oxidation potential in a mechanistic *in vitro* test for the discrimination of the photo-allergic and photo-irritants where oxybenzone revealed no phototoxic potential (SCCP 2006a). However, in a recent study, oxybenzone was shown to cause photoallergenic reactions being second most frequent photo contact allergen among the UV filters (European photo patch test task force) (Subiabre-Ferrer *et al.* 2019).

Ethylhexyl triazone (10%) did not cause photosensitisation in guinea pigs. Separate tests with *Saccharomyces cerevisiae* and CHO cells exposed to the ethylhexyl triazone and UVA and UVB irradiation did not show any potential photomutagenic effects of ethylhexyl triazone.

Phototoxicity, photosensitisation and photomutagenicity of phenylbenzimidazole sulfonic acid was examined in the SCCP opinion on phenylbenzimidazole sulfonic acid and its salts (SCCP 2006b).

Phenylbenzimidazole sulfonic acid was not a photo-irritant in mice or guinea pigs *in vivo*, or in 3T3 cells *in vitro* (Photo irritation factor of 1.4). In addition, phenylbenzimidazole sulfonic acid was not photomutagenic in the photo Ames test, a yeast gene conversion assay or an *in vitro* chromosome aberration assay in CHO cells. A few cases of photoallergic contact dermatitis reactions have been reported in the literature following use of products containing phenylbenzimidazole sulfonic acid, however no skin reactions have been observed in dedicated patch tests studies in human volunteers at concentrations up to 10%, with or without irradiation (SCCP 2006b).

The incidence of positive reactions (0.08%) was reported in a recent patch study among patients administered with octocrylene at 10% in petrolatum (n = 2577) (Uter *et al.* 2017). Similar findings were reported in an EU multicentre photopatch test study where contact allergy was reported in only 0.7% of the 1031 patients patch tested with 10% octocrylene in petrolatum for suspected photoallergic contact dermatitis (Klimova *et al.* 2015).

Contact allergy to octocrylene appears to be more frequent and severe in children (EMCPPTSA 2012; Gilaberte and Carrascosa 2014) whereas photoallergic contact dermatitis to octocrylene was found to be much more frequent in adults (NICNAS 2017). Photocontact allergy to octocrylene was reported in 4% of the 1031 adult patients patch-tested for suspected photoallergic contact dermatitis (EMCPPTSA 2012). The occurrence of photoallergic contact dermatitis to octocrylene was found to be related to a previous photoallergy to topical ketoprofen (Loh and Cohen 2016). Patients with photoallergic contact dermatitis caused by sunscreens and positive photopatch tests to octocrylene have been mainly reported in France, Belgium, Italy and Spain, countries in which topical ketoprofen is used regularly in consumer products (de Groot and Roberts 2014). This was confirmed in a recent study conducted in Italy where concomitant photocontact allergy to ketoprofen was reported in 61.5% of 156 patients (Romita *et al.* 2018). A very recent review has evaluated these findings extensively (Berardesca *et al.* 2019).

Several hypotheses were proposed to illustrate the mechanism for the co-reactivity of octocrylene namely: (i) the role of the benzophenone moiety of ketoprofen (although the benzophenone moiety is not part of the octocrylene structure, aminolysis and hydrolysis of octocrylene in the skin may result in the formation of benzophenone which then can lead to cross-reactivity); (ii) hyper-photo susceptibility to ingredients that are nonrelevant allergens; and (iii) co-reactivity – i.e. concomitant sensitization or prior or subsequent *de novo* photosensitisation – may be involved in place of cross-reaction.

The presence of sensitizing impurities in some commercial batches of octocrylene were also suspected to be allergens contributing to photocontact allergy (Aerts *et al.* 2016).

Neurotoxic effects of active ingredients in sunscreens were reviewed extensively (Ruszkiewcz *et al.* 2017). The table listing the effects from the treatment of octinoxate, oxybenzone and octocrylene is shown below. However, this is not reviewed in this discussion elaborately as similar mechanisms apply on endocrine activity modulation potential of these ingredients (Ruszkiewcz *et al.* 2017).

Obesogenic potential of avobenzone was demonstrated *in vitro* by Shin et al. (2020) and Ahn et al. (2019). In normal human epidermal keratinocytes, avobenzone (10 μM) increased expression of genes associated with lipid metabolism, including peroxisome proliferator-activated receptor γ (PPARγ) and promoted adipogenesis in human bone marrow mesenchymal stem cells (EC_{50} = 14.1 μM). Nevertheless, avobenzone did not bind PPARγ and the avobenzone-induced adipogenesis-promoting activity was not affected by PPARγ antagonists (Ahn *et al.* 2019). Even though potential obesogenic effect in human subject cannot be unequivocally excluded, it is unlikely given that mean C_{max} (12.89 nM or 4 μg/L; see **Clinical Trials**) of avobenzone following a dermal application was ~1000 lower than concentrations promoting adipogenesis *in vitro*.

Similarly, obesogenic potential of octocrylene was postulated by Ko *et al.* (2022), but in contrast to avobenzone, octocrylene directly bound PPARγ, although with a relatively low affinity (Ki = 37.8 µM). *In vitro* octocrylene induced (EC_{50}= 29.6 µM) adiponectin secretion by human bone marrow mesenchymal stem. However, like avobenzone, the obesogenic impact of octocrylene applied dermally is not expected, as mean plasma C_{max} of (32 nM or 11.7 µg/L; see **Clinical Trials**) was 925 lower than the EC_{50} of adiponectin secretion *in vitro*.

The immunomodulatory effect of avobenzone was reported *in vitro*. At 50 µM the compound increased IL-8 secretion by monocyte-like THP-1 cells as well as by THP-1 derived macrophages (Weiss *et al.* 2023). However, the immunomodulatory effect of avobenzone in sunscreen applications is not predicted considering low systemic exposures (C_{max} = 12.89 nM) and relatively low impact *in vitro* (fold changes of affected factors were generally < 2) at concentrations exceeding C_{max} ~4000 times.

Table 0-30 Summaries of other studies

Compound	Exposure model	Experimental design	Effect
Octyl methyoxycinnamate or octinoxate	Wistar rats	Oral (gavage) administration during gestation and lactation	Decreased motor activity in female offspring, increased spatial learning in male offspring.
	Sprague-Dawley rats, female	Oral (gavage) administration for 5 days; 10–1000 mg/kg/day	Non-estrogenic interference within the rodent HPT axis; no changes in pre-proTRH mRNA in mediobasal-hypothalamus.
	Wistar rats	In vitro incubation of hypothalamus isolated from adult rats; 60 min; 0.263 µM	Decreased hypothalamic release of GnRH. Increased GABA release and decreased Glu production in males. Decreased Asp and Glu production in females.
	Wistar rats	in vitro incubation of hypothalamus isolated from immature rats; 60 min; 0.263µM	Decreased hypothalamic release of LHRH. Increased GABA release in males, decreased Asp and Glu levels in females.
	SH-SY5Y neuroblastoma cell line	72 h; 10^{-8}–10^{-4}M	Decreased cell viability and increased caspase-3 activity.
	Rainbow trout (Cahova *et al.* 2023)	Administered with food; 6 weeks; 6.9 – 395 µg/kg/day	Increased plasma thyroxine levels at 395/kg/day (~325 ng/mL) *c.f.* controls (~200 ng/mL)
	Wistar rats (Lorigo and Cairrao 2022)	*In vitro*; isolated rat aortas 0.001–50 µmol/L	Increased vasorelaxant effect by endothelium-dependent mechanisms
	Human umbilical arteries (Lorigo *et al.* 2021, 2022)	*In vitro*, 24h incubation; 1 -50 µmol/L	Decreased vasorelaxation response by interference with NO/sGC/cGMP/PKG pathway Increased reactivity to the contractile agents – serotonin, histamine and KCl In silico analysis suggests that octinoxate might compete with T3 for the binding centre of THRα.
Benzophenone-3 or oxybenzone	Zebrafish	Waterborne; 14 days for adult, 120 h for embryos; 10–600 µg/L	Anti-androgenic activity: decreased expression of *esr1*, *ar* and *cyp19b* expression in the brain of males.
	Zebrafish (Babich *et al.* 2020)	Embryonic oxygen consumption rate; 0.004 – 4 mg/L	Negligible effect on mitochondrial respiration

	Zebrafish (Xu *et al.* 2021)	Waterborne; 0.056 -38 µg/L 42 days post fertilization	Decreased female to male ratio from 2.3 µg/L Increased expression of estrogen receptors *esr2a* and *vtg2* in the brain and hepatic *vtg2* at HD
	Zebrafish (Bai *et al.* 2023)	Waterborne; 6 h post fertilisation to adulthood(~5months); 10 µg/mL (0.04 µM)	Reduced social aggression, learning and memory in ♀; cognition deficits in ♀ correlated with neurotoxicity and increased brain cell apoptosis. Reduced social preference in ♂ and ♀.
	Sprague-Dawley rats	Dermal application; 30 days; 5 mg/kg/day	No changes in behavioural tests (locomotor and motor co-ordination).
	Rat primary cortical astrocytes and neurones	1–7 days; 1–10 µg/mL	Decreased cell viability of neurons but not of astrocytes.
	Kumming (KM) mice (Zhang *et al.* 2021)	*In vitro*; Sertoli cells; 24 h; 5-150 µM	Impaired cell viability and disturbed cell morphology from 100 µM and increased Bcl-2 levels. Reduced expression of Rictor (component of mTORC2 complex) from 50 µM
	SH-SY5Y neuroblastoma cell line	72 h; 10^{-8}–10^{-4}M	Decreased cell viability and increased caspase-3 activity.
Octocrylene	Zebrafish	Waterborne; 14 days; 22–383 µg/L	Impaired expression of genes related with development and metabolism in the brain.
	Zebrafish (Meng *et al.* 2021)	96 h incubation; hatching rates of zebrafish (50-250uM) 96 h incubation; larvae death and zebra fish liver cell line (ZFL) – concentration range not reported.	Impaired hatching from 200 µM and increased larvae death (LC_{50} = 251.8 µM) Increased cytotoxicity (96 h LC_{50} = 5.5 µM) and expression of *cyp1a, cyp3a65,* estrogen receptors (*erα, erβ1, gper, vtg1*) and sex determination genes (*brca2, drtm1, cyp19a sox9a)* in ZFL at 10% LC_{50}
	ICR mice (Chang *et al.* 2022)	*In vitro;* oocytes incubated until maturation; 8-50 nM	Disturbed meiotic maturation and reduced oocyte quality from 40 nM, likely due to impaired mitochondrial function.
	Human bone marrow mesenchymal stem cells (Ko *et al.* 2022)	*In vitro*; 72h; concentration range was not reported	Octocrylene directly binds to PPARγ with K_i = 37.8 µM and acts as a partial agonist Increased adipogenesis and secretion of adiponectin (EC_{50} = 29.6 µM).

Abbreviations: ar: androgen receptor; Asp: aspartate; cyp19b: cytochrome P450 aromatase b; esr1: estrogen receptor; GABA: gamma amino butyric acid; Glu: glutamate; GnRH: gonadotrophin-releasing hormone; HPT: hypothalamo-pituitary-thyroid; pre-proTRH: pre-pro-thyrotrophin-releasing hormone.

NOAEL AND DA VALUES FOR RISK ASSESSMENT

Based on the information/data reviewed above, the TGA has concluded on the following NOAEL and dermal absoprtion values for risk assessment of the respective suncreen active ingredients.

Table 3-11. NOAEL selected from available information.

Active ingredient	NOAEL	Rationale
Avobenzone	450 mg/kg bw/day	Oral 13-week repeat dose toxicity study in rats. (ECHA 2021)
Ethylhexyl triazone	1000 mg/kg bw/day	Oral 90 day repeat dose toxicity study in rats. (ECHA 2021b; DEPA 2015).
Homosalate	10 mg/kg bw/day	Based upon a LOAEL of 60 mg/kg bw/day from combined repeat dose toxicity study and reproduction/developmental toxicity screening test. Uncertainty factor of 3 applied for conversion of LOAEL to NOAEL. A further adjustment made (50% reduction) due to absence of oral bioavailability data consistent with SCCS approach.
Octinoxate	450 mg/kg bw/day	Fertility and reproduction oral study in rats (Schneider *et al.* 2005).
Octocrylene	76.5 mg/kg bw/day	Extended one generation reproductive toxicity study (EOGRTS) in rats via diet. Adjustment of (50%) based on oral bioavailability data made to male NOAEL of 153 mg/kg bw/da, consistent with SCCS approach. (ECHA 2021d; SCCS 2021a).
Oxybenzone	67.9 mg/kg bw/day	Reproductive and developmental toxicity studies in rats via diet (Nakamura *et al.* 2015).
PBSA	40 mg/kg bw/day	Oral 90-day repeat dose/reproduction/developmental toxicity study in rats. Adjustment made to NOAEL (1000 mg/kg bw/day to account for 4% oral absorption. (ECHA 2020).

Table 3-12. Dermal absorption factor selected from available information.

Active ingredient	DA	Rationale
Avobenzone	7.3%	Based upon *in vitro* study using isolated human abdominal cadaver skin (ECHA 2021a).
Ethylhexyl triazone	10%	Based upon physicochemical properties, (molecular weight > 500 and a $\log P_{ow}$ > 4).
Homosalate	5.3%	Based upon dermal absorption (mean +1SD) derived from study using human split thickness skin preparations (Finlayson 2021, as cited in SCCS 2020).
Octinoxate	1.77 $\mu g/cm^2$	Based upon 6-hour pig ear skin exposure + 18-h free permeation of oil-in-water emulsion study (Klimova *et al.* 2015)
Octocrylene	0.97 $\mu g/cm^2$	Based upon dermal absorption (mean +1SD) derived from study using dermatomized human skin preparations (Fabian and Landsiedel 2020, as cited in SCCS 2021a).
Oxybenzone	9.9%	Based upon *in vitro* study using pig skin and applying a safety factor of 2 standard deviations to account for limitations in the data set, i.e, mean (3.1%) + 2 SD (2 x 3.4%) dermal absorption study consistent with SCCS. (SCCS 2021c).
PBSA	0.416 $\mu g/cm^2$	Based upon *in vivo* study in humans (SCCP 2006b).

APPENDIX

SEARCH STRATEGY

Search criteria (word input)

Keywords included the chemical name, AAN or the INCI names, and "sunscreen" were used as the search items. Publications in last 15 years were searched (between 2008 and March 2023). Following toxicological endpoints were included.

Nonclinical (toxicology) data:

• Dermal carcinogenicity

• Systemic carcinogenicity

• Developmental and reproductive toxicity (DART)

• Toxicokinetics

• Additional testing when data suggest a concern about other long-term effects, such as **endocrine effects**

Clinical data:

• Dermal irritation and sensitization

• Phototoxicity and photoallergenicity testing

• Human maximal use bioavailability studies

Websites searched for the sunscreen active ingredients:

WHO

USA:

- PubChem https://pubchem.ncbi.nlm.nih.gov
- GOLD FFX database / ChemWatch (TGA subscribed)
- FDA
- US EPA (www.epa.gov).
- NIOSH CDC https://www.cdc.gov/niosh/index.htm
- National Center for Toxicological Research (NCTR) https://ntp.niehs.nih.gov/nctr/
- National Toxicology program (NTP), U.S. Department of Health and Human Services https://ntp.niehs.nih.gov/publications/index.html.
- BUND (Federal Mnistry for the Environment, Nature Conservation, Building and Nuclear Safety)
- Comparative Toxicogenomics Database http://ctdbase.org/
- Consumer Product Information Database (cpid) https://www.whatsinproducts.com/. similar to and linked to PubChem.
- US EPA (United States Environmental Protection Agency) IRIS Assessments https://cfpub.epa.gov/ncea/iris_drafts/atoz.cfm
- Integrated Risk Information System (IRIS) https://www.epa.gov/iris
- ChemView https://chemview.epa.gov/chemview/
- Science Inventory https://cfpub.epa.gov/si/

UK:

- Cancer Research UK https://www.cancerresearchuk.org/

EU:

- Registered substances - Chemical property data search / European Chemicals Agency (ECHA)
- Scientific Committee on Consumer Safety (SCCS), European Commission https://op.europa.eu/en/
- SafetyNL; National Institute for Public Health and the Environment (RIVM), The Netherlands www.rivm.nl
- CosIng Database https://cosmeticseurope.eu/library/
- European Medicines Agency (EMA)
- OECD OECD Existing Chemicals Database https://hpvchemicals.oecd.org
- Environmental Protection Agency in Denmark www.mst.dk
- Nature Agency in Denmark www.nst.dk
- Swedish Chemicals Agency (KEMI) in Sweden www.kemi.se
- Environment Agency in Norway www.miljodirektoratet.no
- ANSES in France www.anses.fr
- The Environment Agency in the UK www.environment-agency.gov.uk
- ChemSec - International Chemical Secretariat www.chemsec.org
- Information Centre for Environment and Health www.forbrugerkemi.dk
- National Institute for Public Health and the Environment https://www.rivm.nl/en

Australia:

- NICNAS
- Safe Work Australia - Hazardous Chemical Information System (HCIS) http://hcis.safeworkaustralia.gov.au/
- FSANZ

Canada:

- DRUGBANK / University of Alberta et al., Canada
- Health Canada

Non-Government:

- Environmental Working Group https://www.ewg.org/ (non-profit)
- Food Packaging Forum https://www.foodpackagingforum.org/
- International Toxicity Estimates for Risk (ITER) http://www.iter.tera.org/. similar to PubChem.
- Cosmetic Ingredient Review (CIR) https://www.cir-safety.org/

TABLE 2: LIST OF ENDOCRINE ACTIVITY MODULATION EFFECTS OF COMMONLY USED UV FILTERS

UV Filters	Endocrine disrupting effects	
Benzophenones	Estrogenic disrupting effects	Activation of ERα, ERβ; Inhibition of the activity of 17β-Estradiol; Induction of proliferation of MCF-7 cell; Induction of VTG in fathead minnow; Reduction of the uterine weight in immature Long-Evans rats.
	Androgenic disrupting effects	Antagonists of human AR transactivation; Repression of 4.5dihydrotestosterone-induced transactivational activity; Inhibition of testosterone formation in mice and rats.
	Disrupting effects toward other nuclear receptors	Inhibition of human recombinant TPO; Interference with THR; Inhibition of TPO activity in rats; Antagonists of PR
Camphor derivatives	Disrupting effects toward estrogen receptor	Activation of ERα, ERβ; Inhibition of the activity of 17β-Estradiol; Inhibition of testosterone formation in HEK-293 cells; Antagonist of Human AR.
	Disrupting effects toward androgen receptor	Repression of 4,5-dihydrotestosterone-induced transactivational activity; Inhibition of testosterone formation in HEK-293 cells; Antagonists of Human AR.
	Disrupting effects toward estrogen receptor	Antagonists of PR; Increase of PR mRNA levels in rats; Inhibition of the expression of PR protein in rats; Disturbance of the expression of membrane-associate PR in insects.
Cinnamate derivatives	Disrupting effects toward estrogen receptor	Activation of ERα; Inhibition of the activity of 17β-Estradiol; Induction of proliferation of MCF-7 cell; Reduction of uterine weight in rats; Induction of VTG in fish.
	Disrupting effects toward thyroid hormone receptor	Decrease of T4 levels; Inhibition of the conversion of T4 to triiodothyronine in rats.
	Disrupting effects toward other nuclear receptors	Antagonists of PR and AR; Inhibition of 4,5-dihydrotestosterone activity; Reduction of prostate and testicular weight in rats.

AR: androgen receptor; ER: estrogen receptor alpha; PR: progesterone receptor; T4: thyroxine; THR: thyroid hormone receptor; TPO: thyroid peroxidase; VTG: vitellogenin.

Source: Wang *et al.*, 2016

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Yazar S., & Krtekin S.K. (2019). Assessment of the cytotoxicity and genotoxicity of homosalate in MCF-7. S. *J. Cosmetic Dermatol.* 19: 246-252.

Yener G., *et al.* (2003). Importance of using lipid microspheres as carriers for UV filters on the example octyl methoxy cinnamate. *Int. J. Pharmaceutics.* 258: 203-207.

Zhang X.Y., Jiao X.F., Wu D., Chen F., Ding Z.M., Wang Y.S. et al. (2022). Benzophenone-3 breaches mouse Sertoli cell barrier and alters F-actin organization without evoking apoptosis. *Environ. Toxicol.* 37: 28–40.

From: [redacted]
To: Catherine Oh
Cc: [redacted]; [redacted]
Subject: Early Draft TGA Safety Review on Sunscreen Ingredients [SEC=OFFICIAL]
Date: Tuesday, 6 August 2024 1:50:00 PM
Attachments: image001.png
Literature search and summaries for seven sunscreen active ingredients as of 1 August 2024 - DRAFT.DOCX

Dear Catherine,

I tried calling you at different times today but could only reach your answering machine. I wanted to touch base with you regarding how Accord is tracking with the Australian Sunscreen Exposure Model consultation and if there was anything we could assist with. I also wanted to provide you with an update on TGA's literature review, which I have done below.

As previously advised, the TGA has been conducting a thorough literature review to identify safety data for seven common sunscreen active ingredients used in therapeutic sunscreens in Australia. These ingredients include

- butyl methoxydibenzoylmethane (avobenzone)
- ethylhexyl triazone
- homosalate
- octocrylene
- octyl methoxycinnamate (octinoxate)
- oxybenzone
- phenylbenzimidazole sulfonic acid

Our Toxicology team has completed the review following an extensive literature search to determine the No Observed Adverse Effect Level (NOAEL) and Dermal Absorption (DA) for each of these ingredients. This information will be required to finalise our risk assessments for these ingredients.

Given the tight timeframe we are working within, we would like to provide you with an early draft of our findings as soon as possible. The attached document is intended to give you a preliminary understanding of our review process and findings to date, however a risk assessment of each of these ingredients has not been finalised as this will depend on the outcomes of the consultation on a final sunscreen exposure model that will be suitable for Australian therapeutic sunscreens.

We are not requesting a detailed analysis or review, however, should you have any information that has not been considered in our draft that could inform our review, we encourage you to share it with us as soon as possible.

Please note that in the future, if any regulatory changes are proposed as a result of our review, we expect they will be open to public consultation, allowing all stakeholders, including industry, the opportunity to provide feedback.

The attached draft document is provided to you in confidence, and we ask that it is not distributed publicly. We would welcome you to share it in confidence among your relevant sunscreen/technical working group and members that may have relevant information that needs to be brought to our attention. I have also shared the document with Catherine Gwynne from CHP Australia this morning on the same basis.

If you have any questions or require further clarification, please feel free to contact us.

Could you kindly reply to advise when you have received this email.

Kind regards,
[redacted]

[redacted] **Sunscreen Taskforce**
Complementary & OTC Medicines Branch
Medicines Regulation Division | Health Products Regulation Group
Australian Government Department of Health and Aged Care
T: [redacted] | E: [redacted]@health.gov.au
Location: Level 1, 27 Sherger Drive, Fairbairn 2609
PO Box 100, Canberra ACT 2601, Australia

The Department of Health and Aged Care acknowledges First Nations peoples as the Traditional Owners of Country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to all Elders both past and present.

From: [redacted]
To: Catherine Oh
Cc: [redacted] [redacted]
Subject: RE: Early Draft TGA Safety Review on Sunscreen Ingredients [SEC=OFFICIAL]
Date: Wednesday, 7 August 2024 10:18:00 AM
Attachments: image001.png

Thank you for your email Catherine, and for the update on Accord's progress.
We're looking forward to receiving your comments.

Regarding the literature review, we are not seeking a detailed analysis or review, so Accord are welcome to review when convenient. If you wish to provide input, then I anticipate we would require this by no later than the first week of September so that it can be evaluated. For context, the Sunscreen Taskforce is only running for 6 months and ceasing operation in November, so we are expecting to finalise both the sunscreen exposure model and literature review/risk assessment by then.

Kind regards,

[redacted]

[redacted] Sunscreen Taskforce
Complementary & OTC Medicines Branch
Medicines Regulation Division | Health Products Regulation Group
Australian Government Department of Health and Aged Care
T: [redacted] | E: [redacted]@health.gov.au
Location: Level 1, 27 Sherger Drive, Fairbairn 2609
PO Box 100, Canberra ACT 2601, Australia

From: Catherine Oh <coh@accord.asn.au>
Sent: Tuesday, August 6, 2024 5:21 PM
To: [redacted]
Cc: [redacted] [redacted]
Subject: Re: Early Draft TGA Safety Review on Sunscreen Ingredients [SEC=OFFICIAL]

Document 3

Dear [redacted]

I was caught up in several meetings today and missed your call. Confirming I have received the email and thanks for the outreach.

The ASEM submission is coming along. So that I can give you a heads up, our comments will focus on the improving the flexibility of the Option 1 approach. The risk assessment 'tool' that the TGA Toxicology Team has come up with is quite a powerful risk assessment tool, that can provide a nuanced risk management. It has the potential to be flexible to support innovation, both in product types e.g. facial sunscreens, and technologies e.g. microencapsulation. The way that the consultation question is posed seems to suggest that the flexibility of the risk assessment tool would not be fully utilised. I hope this is not the case - I will be putting in some comments around that. We will also have comments around some exposure assumptions - young toddlers are generally not awake for long enough during the day, or mobile enough for the level of sun exposure assumed.

Thank you for sharing the literature review of sunscreen active ingredients, and for allowing us to share with our Sunscreen Working Group. Could I ask for your timeline for review? Between Rianna and I, we have six submissions we are working on that are due in August, and we are out of the office most of the week next week for our Canberra Day events.

Kind regards,
Catherine

From: s22 [redacted]
Sent: Tuesday, August 6, 2024 1:51 PM
To: Catherine Oh <coh@accord.asn.au>
Cc: s22 [redacted] s22 [redacted]
Subject: Early Draft TGA Safety Review on Sunscreen Ingredients [SEC=OFFICIAL]

Dear Catherine,

I tried calling you at different times today but could only reach your answering machine. I wanted to touch base with you regarding how Accord is tracking with the Australian Sunscreen Exposure Model consultation and if there was anything we could assist with. I also wanted to provide you with an update on TGA's literature review, which I have done below.

As previously advised, the TGA has been conducting a thorough literature review to identify safety data for seven common sunscreen active ingredients used in therapeutic sunscreens in Australia. These ingredients include

- butyl methoxydibenzoylmethane (avobenzone)
- ethylhexyl triazone
- homosalate

- octocrylene
- octyl methoxycinnamate (octinoxate)
- oxybenzone
- phenylbenzimidazole sulfonic acid

Our Toxicology team has completed the review following an extensive literature search to determine the No Observed Adverse Effect Level (NOAEL) and Dermal Absorption (DA) for each of these ingredients. This information will be required to finalise our risk assessments for these ingredients.

Given the tight timeframe we are working within, we would like to provide you with an early draft of our findings as soon as possible. The attached document is intended to give you a preliminary understanding of our review process and findings to date, however a risk assessment of each of these ingredients has not been finalised as this will depend on the outcomes of the consultation on a final sunscreen exposure model that will be suitable for Australian therapeutic sunscreens.

We are not requesting a detailed analysis or review, however, should you have any information that has not been considered in our draft that could inform our review, we encourage you to share it with us as soon as possible.

Please note that in the future, if any regulatory changes are proposed as a result of our review, we expect they will be open to public consultation, allowing all stakeholders, including industry, the opportunity to provide feedback.

The attached draft document is provided to you in confidence, and we ask that it is not distributed publicly. We would welcome you to share it in confidence among your relevant sunscreen/technical working group and members that may have relevant information that needs to be brought to our attention. I have also shared the document with Catherine Gwynne from CHP Australia this morning on the same basis.

If you have any questions or require further clarification, please feel free to contact us.

Could you kindly reply to advise when you have received this email.

Kind regards,
[redacted] s22

[redacted] s22 **Sunscreen Taskforce**
Complementary & OTC Medicines Branch
Medicines Regulation Division | Health Products Regulation Group
Australian Government Department of Health and Aged Care
T: [redacted] s22 | E: [redacted] s22 @health.gov.au
Location: Level 1, 27 Sherger Drive, Fairbairn 2609
PO Box 100, Canberra ACT 2601, Australia

The Department of Health and Aged Care acknowledges First Nations peoples as the Traditional Owners of Country throughout Australia, and their continuing connection to land, sea and community.

We pay our respects to them and their cultures, and to all Elders both past and present.

Document 4

From: CLARKE, Avinash
To: s 22 [redacted]
Cc: s 22 [redacted]; VUCKOVIC, George
Subject: Fwd: Sunscreen Safety Report - FOI Release [SEC=OFFICIAL]
Date: Monday, 3 February 2025 10:32:02 AM
Attachments: image001.png
Summary of sunscreen roundtable discussion Deb182024.docx
Expert stakeholder roundtable - TGA"s toxicology review of sunscreen ingredients - Attendance report 12-18-24.csv

---

FYI

Sent from Workspace ONE Boxer
---------- Forwarded message ----------

From: LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>
Date: February 3, 2025 at 10:22:47 AM GMT+11
Subject: Re: Sunscreen Safety Report - FOI Release [SEC=OFFICIAL]
To: CLARKE, Avinash <Avinash.CLARKE@Health.gov.au>
Cc: s22 [redacted]
s22 [redacted]

attached..

i have included the file from the Teams meeting of attendees.. let me know if you need info about the expertise of each invitee.

There is also some commentary included in the Teams meeting. - hope i have incorporated all.

Robyn

From: CLARKE, Avinash <Avinash.CLARKE@Health.gov.au>
Sent: Sunday, February 2, 2025 10:33 PM
To: LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>
Cc: s22 [redacted]
s22 [redacted]
Subject: RE: Sunscreen Safety Report - FOI Release [SEC=OFFICIAL]

Hi Robyn,

Any chance we can get that summary of the expert stakeholder roundtable on sunscreen ingredients (ideally tomorrow AM) – even if it is in draft and not finalised. Be useful to include relevant advice in talking points and min brief.

Thanks!

Document 4

A

Avinash Clarke

02 5132 1436

From: HENDERSON, Nick <Nick.Henderson@health.gov.au>
Sent: Friday, 31 January 2025 11:26 AM
To: MOODIE, Grant <Grant.MOODIE@Health.gov.au>; LAWLER, Tony <Anthony.LAWLER@Health.gov.au>
Cc: CLARKE, Avinash <Avinash.CLARKE@Health.gov.au>; VUCKOVIC, George <George.VUCKOVIC@Health.gov.au>
Subject: RE: Sunscreen Safety Report - FOI Release [SEC=OFFICIAL]

Ok

Avi and George, we'll need to have TPs and comms (including web content) ready by COB Monday. I advised the MO this morning we will also provide Min Brief with key points, this will need to go to MO COB Monday as well

[redacted]

s 22

s 22

Document 4

[redacted]

[SEC=OFFICIAL]

Summary of roundtable discussion

TGA's risk assessment of sunscreen ingredients

11.00am- 1pm, Wednesday 18 December 2024

Teleconference

Chair: Professor Robyn Langham AM

Attendees: see attached

Agenda item 1: Welcome and introductions

Professor Langham opened the meeting. The list of attendees is included at Attachment 1.

Agenda item 2: Sunscreen risk assessment- current status and possible future direction

- Professor Langham presented on the risk management of sunscreen chemicals in Australia.
- It was reiterated that skin cancer is a major health issue in Australia. The age-standardised rate of melanoma in Australia increased from 46 cases per 100,000 persons in 2000 to an estimated 55 cases per 100,000 persons in 2021.
- It was noted that the TGA undertook a review of sunscreen ingredients following regulatory changes progressed by the FDA in 2019, with a single change to maximum concentration of one chemical by the EMA in 2022.
- An overview of the AICIS review of homosalate was provided.
- It was noted that the TGA conducted two recent reviews;
    - The first review led to the development of the Australian Sunscreen Exposure Model (ASEM). The ASEM was proposed to provide a standardised method for calculating sunscreen exposure, reducing discrepancies in risk assessments. It was developed to align with Australian conditions (i.e. high UV light levels) and consumer practices (i.e. outdoor lifestyle), ensuring sunscreens are safe and effective when used as directed. The TGA undertook extensive targeted pre-public consultation between May-July 2024 to develop the ASEM and public consultation again between July and August 2024. There was broad in-principle support from this consultation for the adoption of the ASEM for estimating therapeutic sunscreen exposure for ingredient risk assessments.
    - The second review is the risk assessment of seven chemicals in Australian sunscreens, the Draft Risk Assessment of 7 Active Sunscreen Ingredients, noting a theoretical risk with two of the seven chemicals from the extensive literature review and with the application of the ASEM to allow for a local contextualisation.

Following a brief overview of the proposed next steps, including a proposed scheduling change to limit concentrations of the chemicals in question in therapeutic sunscreens, the proposed messaging was also presented, forming the basis of the subsequent roundtable discussion.

Agenda item 3: Roundtable discussion

The group felt that the work undertaken was thorough and detailed. There was concern that the term ‘low risk’ was not one that the public would readily understand in applying to their own context.

There was discussion on the utility of the ASEM (particularly with respect to calculation of surface area), and some questions regarding the specifics of the PK analysis of some chemicals in the draft document.

There was a clear and consistent view of the group that supporting the use of sunscreens to prevent skin cancers should be front and centre of any campaign. Any messaging that advises reduction or avoidance would result in the risk of shunning sunscreen.

The advice from the group was that there was no clear evidence to bring about a change in practice at this time. There was support for an ongoing measured regulatory approach, ensuring an ongoing message of the safety and utility of sunscreens. A number of examples and approaches concerning sunscreen use were shared, particularly Queensland Health and also a strong social media presence.

Further discussion regarding advice to infants and pregnant women were discussed. Advice was on softening the advice from an absolute, particularly with respect to advice for pregnant women. Providing clear and correct advice in the first instance will avoid the need to dispel myths down the track. Advice was on providing a balanced approach (avoiding skin cancer, maintaining Vitamin D levels through sun exposure rather than advice to avoid using sunscreen when pregnant because of a minimal theoretical risk of harm)

The group also gave clear advice that messaging from all sectors should be aligned, and that advice to apply to certain body parts only would result in a reduced and harmful use of sunscreen. There was also a request for new educational resources for primary care.

Prof Langham concluded the meeting by thanking all those present for their time and efforts, with an undertaking to keep the group informed of ongoing work.

Document 4

1. Summary

Meeting title	Expert stakeholder roundtable - TGA's toxicology review of sunscreen ingredients
Attended participants	22
Start time	12/18/24, 10:46:41 AM
End time	12/18/24, 1:00:57 PM
Meeting duration	2h 14m 16s
Average attendance time	1h 47m 7s

2. Participants

Name	First Join	Last Leave	In-Meeting Duration	Email	Participant ID (UPN)	Role
s22 [redacted]	12/18/24, 10:55:43 AM	12/18/24, 12:59:34 PM	2h 3m 51s	s22 [redacted]@Health.gov.au	s22 [redacted]@Health.gov.au	Presenter
Robyn Langham (Unverified)	12/18/24, 10:56:05 AM	12/18/24, 12:59:29 PM	2h 3m 24s			Presenter
s22 [redacted]	12/18/24, 10:58:05 AM	12/18/24, 12:59:21 PM	2h 1m 15s	s22 [redacted]@health.gov.au	s22 [redacted]@health.gov.au	Presenter
s22 [redacted]	12/18/24, 10:58:27 AM	12/18/24, 12:59:18 PM	2h 51s	s22 [redacted]@health.gov.au	s22 [redacted]@health.gov.au	Presenter
s22 [redacted]	12/18/24, 11:01:49 AM	12/18/24, 12:59:19 PM	1h 57m 30s	s22 [redacted]@Health.gov.au	s22 [redacted]@Health.gov.au	Presenter
s47F [redacted]	12/18/24, 11:01:49 AM	12/18/24, 12:59:22 PM	1h 57m 32s			Presenter
s47F [redacted]	12/18/24, 11:01:50 AM	12/18/24, 12:59:21 PM	1h 57m 30s	s47F [redacted]	s47F [redacted]	Presenter
s47F [redacted]	12/18/24, 11:01:53 AM	12/18/24, 12:59:24 PM	1h 57m 31s	s47F [redacted]	s47F [redacted]	Presenter
s47F [redacted]	12/18/24, 11:01:54 AM	12/18/24, 12:59:31 PM	1h 57m 37s			Presenter
s47F [redacted]	12/18/24, 11:01:55 AM	12/18/24, 12:59:21 PM	1h 57m 26s			Presenter
s47F [redacted]	12/18/24, 11:01:58 AM	12/18/24, 12:18:13 PM	1h 16m 14s	s47F [redacted]	s47F [redacted]	Presenter
Monika Janda (External)	12/18/24, 11:02:06 AM	12/18/24, 12:59:20 PM	1h 57m 14s	m.janda@uq.edu.au	uqmjanda@uq.edu.au	Presenter
Amanda Gwee (External)	12/18/24, 11:02:11 AM	12/18/24, 12:59:19 PM	1h 57m 8s	Amanda.Gwee@rch.org.au	gweea@rch.org.au	Presenter
s22 [redacted]	12/18/24, 11:02:39 AM	12/18/24, 12:59:25 PM	42m 35s	s22 [redacted]@Health.gov.au	s22 [redacted]@Health.gov.au	Presenter
WEARNE, Susan	12/18/24, 11:03:24 AM	12/18/24, 12:59:17 PM	1h 55m 53s	Susan.Wearne@health.gov.au	Susan.Wearne@health.gov.au	Presenter
Debra Kennedy (External)	12/18/24, 11:04:24 AM	12/18/24, 12:59:27 PM	1h 55m 3s	debra.kennedy@unsw.edu.au	z3067469@ad.unsw.edu.au	Presenter
s47F [redacted]	12/18/24, 11:05:45 AM	12/18/24, 12:59:18 PM	1h 53m 32s			Presenter
Melissa Eastgate	12/18/24, 11:06:14 AM	12/18/24, 12:59:18 PM	1h 53m 3s	s47F [redacted]	s47F [redacted]	Presenter
Euan Walpole	12/18/24, 11:07:05 AM	12/18/24, 12:59:19 PM	1h 52m 14s	Euan.Walpole@health.qld.gov.au	Euan.Walpole@health.qld.gov.au	Presenter
Darren Roberts (Sydney LHD)	12/18/24, 11:08:38 AM	12/18/24, 12:59:23 PM	1h 50m 44s	Darren.Roberts1@health.nsw.gov.au	Darren.Roberts1@health.nsw.gov.au	Presenter
Ju Oei (South Eastern Sydney LHD)	12/18/24, 11:16:09 AM	12/18/24, 12:59:24 PM	1h 43m 15s	Ju.Oei@health.nsw.gov.au	Ju.Oei@health.nsw.gov.au	Presenter
s22 [redacted]	12/18/24, 12:35:46 PM	12/18/24, 1:00:57 PM	25m 11s	s22 [redacted]@health.gov.au	s22 [redacted]@health.gov.au	Presenter

3. In-Meeting Activities

Name	Join Time	Leave Time	Duration	Email	Role
s22 [redacted]	12/18/24, 10:55:43 AM	12/18/24, 12:59:34 PM	2h 3m 51s	s22 [redacted]@Health.gov.au	Presenter
Robyn Langham (Unverified)	12/18/24, 10:56:05 AM	12/18/24, 12:59:29 PM	2h 3m 24s		Presenter
s22 [redacted]	12/18/24, 10:58:05 AM	12/18/24, 12:59:21 PM	2h 1m 15s	s22 [redacted]@health.gov.au	Presenter
s22 [redacted]	12/18/24, 10:58:27 AM	12/18/24, 12:59:18 PM	2h 51s	s22 [redacted]@health.gov.au	Presenter
s22 [redacted]	12/18/24, 11:01:49 AM	12/18/24, 12:59:19 PM	1h 57m 30s	s22 [redacted]@Health.gov.au	Presenter
s47F [redacted]	12/18/24, 11:01:49 AM	12/18/24, 12:59:22 PM	1h 57m 32s		Presenter
s47F [redacted]	12/18/24, 11:01:50 AM	12/18/24, 12:59:21 PM	1h 57m 30s	s47F [redacted]	Presenter
s47F [redacted]	12/18/24, 11:01:53 AM	12/18/24, 12:59:24 PM	1h 57m 31s	s47F [redacted]	Presenter
s47F [redacted]	12/18/24, 11:01:54 AM	12/18/24, 12:59:31 PM	1h 57m 37s		Presenter
s47F [redacted]	12/18/24, 11:01:55 AM	12/18/24, 12:59:21 PM	1h 57m 26s		Presenter
s47F [redacted]	12/18/24, 11:01:58 AM	12/18/24, 12:18:13 PM	1h 16m 14s	s47F [redacted]	Presenter
Monika Janda (External)	12/18/24, 11:02:06 AM	12/18/24, 12:59:20 PM	1h 57m 14s	m.janda@uq.edu.au	Presenter
Amanda Gwee (External)	12/18/24, 11:02:11 AM	12/18/24, 12:59:19 PM	1h 57m 8s	Amanda.Gwee@rch.org.au	Presenter
s22 [redacted]	12/18/24, 11:02:39 AM	12/18/24, 11:36:03 AM	33m 23s	s22 [redacted]@Health.gov.au	Presenter
s22 [redacted]	12/18/24, 12:50:12 PM	12/18/24, 12:59:25 PM	9m 12s	s22 [redacted]@Health.gov.au	Presenter
WEARNE, Susan	12/18/24, 11:03:24 AM	12/18/24, 12:59:17 PM	1h 55m 53s	Susan.Wearne@health.gov.au	Presenter
Debra Kennedy (External)	12/18/24, 11:04:24 AM	12/18/24, 12:59:27 PM	1h 55m 3s	debra.kennedy@unsw.edu.au	Presenter
s47F [redacted]	12/18/24, 11:05:45 AM	12/18/24, 12:59:18 PM	1h 53m 32s		Presenter
Melissa Eastgate	12/18/24, 11:06:14 AM	12/18/24, 12:59:18 PM	1h 53m 3s	s47F [redacted]	Presenter
Euan Walpole	12/18/24, 11:07:05 AM	12/18/24, 12:59:19 PM	1h 52m 14s	Euan.Walpole@health.qld.gov.au	Presenter
Darren Roberts (Sydney LHD)	12/18/24, 11:08:38 AM	12/18/24, 12:59:23 PM	1h 50m 44s	Darren.Roberts1@health.nsw.gov.au	Presenter
Ju Oei (South Eastern Sydney LHD)	12/18/24, 11:16:09 AM	12/18/24, 12:59:24 PM	1h 43m 15s	Ju.Oei@health.nsw.gov.au	Presenter
s22 [redacted]	12/18/24, 12:35:46 PM	12/18/24, 1:00:57 PM	25m 11s	s22 [redacted]@health.gov.au	Presenter

Document 5

From: LANGHAM, Robyn
To: CLARKE, Avinash; s22 [redacted]; SYME, Sarah
Subject: Re: Sunscreen Safety Report - FOI Release [SEC=OFFICIAL]
Date: Tuesday, 4 February 2025 12:02:45 PM
Attachments: image001.png

---

thanks for this Avi.. i think that makes perfect sense.

Robyn

From: CLARKE, Avinash <Avinash.CLARKE@Health.gov.au>
Sent: Tuesday, February 4, 2025 11:09 AM
To: LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>; KRASOWSKI, s22 [redacted]; SYME, Sarah <Sarah.Syme@health.gov.au>
Subject: RE: Sunscreen Safety Report - FOI Release [SEC=OFFICIAL]

Hi All,

We has a change of tack last night and now plan to only release the literature reviews. Have update covering text accordingly. Appreciate and comments/input. Plan is to release today.

Thanks, Avi

Avinash Clarke
02 5132 1436

From: LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>
Sent: Monday, 3 February 2025 10:14 PM
To: CLARKE, Avinash <Avinash.CLARKE@Health.gov.au>; s22 [redacted], Sarah <Sarah.Syme@health.gov.au>
Subject: Re: Sunscreen Safety Report - FOI Release [SEC=OFFICIAL]

Thanks all - apologies for being late on this one..

Reads really well..

Regards

Robyn

Sent from Workspace ONE Boxer
On 3 February 2025 at 4:21:03 pm AEDT, CLARKE, Avinash <Avinash.CLARKE@Health.gov.au> wrote:

> Thanks. That's my thinking.
>
> And we have tweaked the web page content a little more (attached).
>
> Thanks, Avi
>
> Avinash Clarke
> 02 5132 1436
>
> ---
>
> **From:** s22 [redacted]
> **Sent:** Monday, February 3, 2025 4:16 PM
> **To:** CLARKE, Avinash <Avinash.CLARKE@Health.gov.au>; s22 [redacted] SYME, Sarah <Sarah.Syme@health.gov.au>
> **Subject:** RE: Sunscreen Safety Report - FOI Release [SEC=OFFICIAL]
>
> Great, thanks Avi.
>
> Could I please confirm that we won't push this content out through social media or our email newsletters at this stage?
>
> Once there is further information and resources available, we can then promote through our usual channels.
>
> Thanks
> s22 [redacted]
>
> ---
>
> **From:** CLARKE, Avinash <Avinash.CLARKE@Health.gov.au>
> **Sent:** Monday, 3 February 2025 3:57 PM
> **To:** s22 [redacted]
> LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>; s22 [redacted] SYME, Sarah <Sarah.Syme@health.gov.au>
> **Subject:** RE: Sunscreen Safety Report - FOI Release [SEC=OFFICIAL]
>
> Thanks s22 [redacted] Looks really good. Have talked through with Nick and made a couple of minor changes (FYI attached). Will progress with Web Team. Unfortunately Robyn is in a meeting till 8pm today so won't have a chance to take a look.

A

Avinash Clarke
02 5132 1436

From: [redacted]
Sent: Monday, February 3, 2025 2:53 PM
To: [redacted] LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>; [redacted] CLARKE, Avinash <Avinash.CLARKE@Health.gov.au>; SYME, Sarah <Sarah.Syme@health.gov.au>
Subject: RE: Sunscreen Safety Report - FOI Release [SEC=OFFICIAL]

Hi all

Please find attached a draft news article for publishing on the TGA website to accompany the publication of the safety review report.

[redacted] – I'll hand this over to you now to coordinate clearances and provide to the web team once finalised.

Kind regards
[redacted]

From: [redacted]
Sent: Monday, 3 February 2025 1:19 PM
To: [redacted]
Subject: RE: Sunscreen Safety Report - FOI Release [SEC=OFFICIAL]

And I don't have anything for the web content, as I was hoping you and team could assist using the dot points that I have provided:

- The TGA created an Australian Sunscreen Exposure Model (ASEM). This model estimates how much sunscreen Australians use. Read about our previous public consultation on the ASEM.
- The TGA completed a comprehensive review of active ingredients used in sunscreens to ensure their safety. The ASEM model was used to ensure our safety assessments on ingredients in sunscreens considered average and heavy rates of sunscreen use by both children and adults in Australia,.
- The safety review aimed to identify any new evidence that would help us to keep the public safe.
- The TGA will publish the safety review in early 2025.

That consumers continue to use sunscreens to prevent skin cancers.

Nick is discussing this with Tony, and will try to get the green light for the 'go ahead' with publishing of web news. Do you think you can provide me with a initial draft by 3 pm so Avi can send through to Nick? Sorry if this is a bit of a stretch!

s2 [redacted]

From: s22 [redacted]
Sent: Monday, 3 February 2025 12:48 PM
To: s22 [redacted]
Subject: RE: Sunscreen Safety Report - FOI Release [SEC=OFFICIAL]

Hi s22 [redacted]

You beat me to it. I've been working on these docs just.

Sending through latest drafts.

Kind regards,
s22 [redacted]

From: s22 [redacted]
Sent: Monday, 3 February 2025 12:34 PM
To: s22 [redacted]
Subject: RE: Sunscreen Safety Report - FOI Release [SEC=OFFICIAL]

Thanks s22 [redacted]

Do you also have the latest versions of the TPs and web content referenced below?

ta

From: s22 [redacted]
Sent: Monday, 3 February 2025 12:06 PM
To: s22 [redacted]
Subject: FW: Sunscreen Safety Report - FOI Release [SEC=OFFICIAL]

From: CLARKE, Avinash <Avinash.CLARKE@Health.gov.au>
Sent: Monday, 3 February 2025 10:32 AM

To: s22 [redacted]
Cc: s22 [redacted] VUCKOVIC, George <George.VUCKOVIC@Health.gov.au>
Subject: Fwd: Sunscreen Safety Report - FOI Release [SEC=OFFICIAL]

FYI

Sent from Workspace ONE Boxer
---------- Forwarded message ----------

From: LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>
Date: February 3, 2025 at 10:22:47 AM GMT+11
Subject: Re: Sunscreen Safety Report - FOI Release [SEC=OFFICIAL]
To: CLARKE, Avinash <Avinash.CLARKE@Health.gov.au>
Cc: s22 [redacted]

attached..

i have included the file from the Teams meeting of attendees.. let me know if you need info about the expertise of each invitee.

There is also some commentary included in the Teams meeting. - hope i have incorporated all.

Robyn

From: CLARKE, Avinash <Avinash.CLARKE@Health.gov.au>
Sent: Sunday, February 2, 2025 10:33 PM
To: LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>
Cc: s22 [redacted]
Subject: RE: Sunscreen Safety Report - FOI Release [SEC=OFFICIAL]

Hi Robyn,

Any chance we can get that summary of the expert stakeholder roundtable on sunscreen ingredients (ideally tomorrow AM) – even if it is in draft and not finalised. Be useful to include relevant advice in talking points and min brief.

Thanks!

A

Avinash Clarke
02 5132 1436

From: HENDERSON, Nick <Nick.Henderson@health.gov.au>
Sent: Friday, 31 January 2025 11:26 AM
To: MOODIE, Grant <Grant.MOODIE@Health.gov.au>; LAWLER, Tony <Anthony.LAWLER@Health.gov.au>
Cc: CLARKE, Avinash <Avinash.CLARKE@Health.gov.au>; VUCKOVIC, George <George.VUCKOVIC@Health.gov.au>
Subject: RE: Sunscreen Safety Report - FOI Release [SEC=OFFICIAL]

Ok

Avi and George, we'll need to have TPs and comms (including web content) ready by COB Monday. I advised the MO this morning we will also provide Min Brief with key points, this will need to go to MO COB Monday as well

[redacted]

s 22

s 22

Document 5

[redacted]

TGA publishes literature review of sunscreen ingredients

The TGA has released a literature review of certain active ingredients used in sunscreens.

This review aims to identify any new evidence about the use of these ingredients.

Clinical advice remains that the benefits of sunscreen continue to far outweigh any risks.

Tragically, around 2,000 people die each year from skin cancer in Australia. Sun protection, which includes the use of sunscreen, remains the best way to prevent skin cancer.

While some theoretical risks associated with frequent sunscreen use over a lifetime have been identified, they are minimal compared with the proven dangers of prolonged sun exposure and sun burn.

This process is part of the TGA's ongoing role to continually monitor and review ingredients used in therapeutic goods, including sunscreens, to maintain the highest standards of quality, safety and efficacy in the Australian market.

The assessment of sunscreen ingredients will also be informed by the Australian Sunscreen Exposure Model (ASEM). The ASEM model takes account of the Australian context and what would be considered average and heavy rates of sunscreen use by both children and adults.

The ASEM model was developed by the TGA following significant public consultation, with the results available on our Consultation Hub.

[To upload PDF (D25-483182) and word documents (D25-483061)]

Summary of Comments on Document 6.PDF

Page: 1

Number: 1 Author: s22 [redacted] Date: 3/02/2025 2:01:00 PM

Web team: Insert link to safety review report

Number: 2 Author: s22 [redacted] Date: 4/02/2025 1:06:00 PM

Trim link: PDF - D25-483182
Word: D25-483061

Number: 3 Author: s22 [redacted] Date: 3/02/2025 1:58:00 PM

Web team link to: https://consultations.tga.gov.au/tga/proposed-model-for-assessing-sunscreen-ingredients/

Number: 4 Author: s22 [redacted] Date: 3/02/2025 9:04:00 PM

Web team, if this is not encouraged, can you please create a child page for the document, titled 'Literature search and summaries of seven active sunscreen ingredients'.

Document 7

From: [redacted]
To: [redacted]
Cc: [redacted]
Subject: Update on your web publishing request WEB-2037
Date: Tuesday, 4 February 2025 4:30:48 PM

Please do not reply to this automated email as we will not receieve it.

Hi [redacted]

Your web publishing request WEB-2037 has an approval outcome of Approved.

Approver name:
CLARKE, Avinash.

Approver comments:
Please use updated TRIM document. Thanks.

If your request was approved it will be actioned by the Web Team.
If your request was rejected it will not be actioned.

You can check the status of your web publishing request at any time. You will be notified when the request has been actioned.

If an approved web publishing job is no longer required, please contact us at [redacted]@tga.gov.au.

Thank you.
Publishing Team

[redacted]
E: [redacted]@tga.gov.au

Web Experience Section
HPRG Digital Branch
Regulatory Practice and Support Division | Health Products Regulation Group
Australian Government, Department of Health and Aged Care
27 Scherger Drive, Level G, Fairbairn Business Park
FAIRBAIRN, ACT 2600

See the HPRG Service gateway for direct access to our services and resources

Need help writing Guidance? Check out our Guidance template and drafting guide.

From: [redacted]
To: [redacted]
Cc: [redacted]; CLARKE, Avinash; [redacted]
Subject: Web publishing request WEB-2037 is complete
Date: Tuesday, 4 February 2025 4:53:31 PM

Hi [redacted]

Your web publishing request for WEB-2037 is now complete.

Title:
Publication of literature review of sunscreen active ingredients

New or updated pages:
Please check any new or updated pages as soon as possible and let me know if there are any problems. Please note, you may need to refresh your browser or clear your browsing history to see changes:

https://www.tga.gov.au/news/news/tga-publishes-literature-review-sunscreen-ingredients

Kind regards

[redacted]

Publishing Team

[redacted]

E: [redacted]@tga.gov.au

Web Experience Section
HPRG Digital Branch
Regulatory Practice and Support Division | Health Products Regulation Group
Australian Government, Department of Health and Aged Care
27 Scherger Drive, Level G, Fairbairn Business Park
FAIRBAIRN, ACT 2600

See the HPRG Service gateway for direct access to our services and resources

Need help writing Guidance? Check out our Guidance template and drafting guide.

From: [redacted]
To: [redacted]
Cc: CLARKE, Avinash; VUCKOVIC, George
Subject: RE: Documents to be released today [SEC=OFFICIAL]
Date: Tuesday, 4 February 2025 9:27:56 AM
Attachments: TGA publishes literature search and summaries of sunscreen ingredients.docx
image003.png
image004.png
image005.png

Hi [redacted]

The document has been updated as requested below with new Trim links for the word and PDF (word: D25-483061; PDF: D25-483182). These trim links have also been added to the document attached.

Please let me know if there is anything further I can do.

Regards
[redacted]

[redacted] – Toxicology Section
Scientific Evaluation Branch

Medicines Regulation Division | Health Products Regulation Group
Australian Government, Department of Health and Aged Care
T: [redacted] | E: [redacted]@health.gov.au

Location: Fairbairn ACT
PO Box 100, Canberra ACT 2601, Australia

From: [redacted]
Sent: Monday, 3 February 2025 9:07 PM
To: [redacted]
Cc: CLARKE, Avinash <Avinash.CLARKE@Health.gov.au>; VUCKOVIC, George <George.VUCKOVIC@Health.gov.au>
Subject: Re: Documents to be released today [SEC=OFFICIAL]
Importance: High

Hi [redacted]

We're planning on publishing a news page on the TGA's website to publish the literature review that has been released via FOI. Nick, Avi and George have had discussions and George is aware.

Do you mind cleaning up the literature search and summaries document D24-3104014, including:

- update the publication to reflect tomorrow's date on the front cover;

- removing the 'DRAFT' watermarks;
- creating a PDF version; and
- creating new TRIM links to the pdf and word document for the purpose of publication?

I have attached the web content as a word document in this email and left 2 comments in there for your addressing.

As we're intending to publish this as soon as practicable, I'd appreciate if you can attend to this first thing tomorrow morning.

Chat tomorrow,
s22 [redacted]

From: VUCKOVIC, George <George.VUCKOVIC@Health.gov.au>
Sent: Monday, 3 February 2025 1:50 PM
To: HENDERSON, Nick <Nick.Henderson@health.gov.au>; CLARKE, Avinash <Avinash.CLARKE@Health.gov.au>
Cc: s22 [redacted]
Subject: FW: Documents to be released today [SEC=OFFICIAL]

Hi Nick and Avi – confirmation from the FOI team that documents relating to FOI 25-0104 - For electronic signature - Notice of Decision- Joseph Mizikovsky - Draft sunscreen ingredient safety assessment document prepared as part of the TGA review of sunscreen active ingredients will be released today.

Dr George Vuckovic
Assistant Secretary
Scientific Evaluation Branch
TGA Chief Regulatory Scientist

Medicines Regulation Division | Health Products Regulation Group
Australian Government, Department of Health and Aged Care
T: 02 5132 0130| E: george.vuckovic@health.gov.au

Location: Fairbairn ACT
PO Box 100, Canberra ACT 2601, Australia

From: s22 [redacted]
Sent: Monday, 3 February 2025 1:46 PM
To: VUCKOVIC, George <George.VUCKOVIC@Health.gov.au>
Cc: TGA FOI <TGAFOI@health.gov.au>

Subject: Documents to be released today [SEC=OFFICIAL]

Hi George

As you know, we will be releasing the attached decision and documents to the applicant today, this generally occurs in the afternoon after 4 pm.

Just a heads up for your visibility.

Regards
s22 [redacted]

s22 [redacted] [redacted]

FOI, Decision Review and Business Support Section | Regulatory Legal Services Branch
Health Products Regulation Group
Australian Government Department of Health
T: s22 [redacted] | E: TGAFOI@health.gov.au

I may send emails out of hours at a time that suits me.. I look forward to receiving your response during your normal working hours.
The Department of Health and Aged Care acknowledges First Nations peoples as the Traditional Owners of Country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to all Elders both past and present.

News Page to be created

1. **TGA publishes literature search and summaries of sunscreen ingredients**

The TGA has released a literature search and summaries of certain active ingredients used in sunscreens.

The literature search and summaries are intended to provide a preliminary understanding of the TGA's review process and findings to date, however risk assessments have not been finalised.

This process is part of the TGA's ongoing role to continually monitor and review ingredients used in therapeutic goods including sunscreens to maintain the highest standards of quality, safety and efficacy in the Australian market.

The risk assessments of certain sunscreen ingredients will be informed by the Australian Sunscreen Exposure Model (ASEM). The ASEM model takes account of the Australian context and what would be considered average and heavy rates of sunscreen use by both children and adults.

The ASEM model was developed by the TGA following significant public consultation, with the results available on our Consultation Hub.

[To upload PDF (D25-483182) and word documents (D25-483061)]

Document 9

Author: [redacted] Date: 3/02/2025 2:01:00 PM
Web team: Insert link to safety review report

Author: [redacted] Date: 3/02/2025 8:37:00 PM
Child page to 'Literature search and summaries of seven active sunscreen ingredients'. Nicole, please let web team know the TRIM link.

Author: [redacted] Date: 4/02/2025 9:16:00 AM
Trim link: PDF - D25-483182
Word: D25-483061

Author: [redacted] Date: 3/02/2025 1:58:00 PM
Web team link to: https://consultations.tga.gov.au/tga/proposed-model-for-assessing-sunscreen-ingredients/

Author: [redacted] Date: 3/02/2025 9:04:00 PM
Web team, if this is not encouraged, can you please create a child page for the document, titled 'Literature search and summaries of seven active sunscreen ingredients'.

Author: [redacted] Date: 3/02/2025 9:03:00 PM
Nicole: TRIM link to PDF and word documents.

Document 10

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Literature search and summaries of seven sunscreen active ingredients

Butyl methoxydibenzoylmethane (avobenzone), ethylhexyl triazone, homosalate, octocrylene, octyl methoxycinnamate (octinoxate), oxybenzone and phenylbenzimidazole sulfonic acid (PBSA)

4 February 2025

TGA Health Safety Regulation

Table of Contents

Executive summary

The TGA has conducted a literature search investigating information relevant to the safety assessment of the following seven sunscreen active ingredients available for use in Australia:

- butyl methoxydibenzoylmethane (avobenzone)
- ethylhexyl triazone
- homosalate
- octocrylene
- octyl methoxycinnamate (octinoxate)
- oxybenzone
- phenylbenzimidazole sulfonic acid

The purpose of this review was to provide an overview of the publicly available safety information for these ingredients needed to assess their suitability for use in therapeutic sunscreens listed on the ARTG. The findings will inform the need for any risk management actions to ensure public safety.

These ingredients were prioritised for this targeted review based on the availability of nonclinical safety data to TGA, their reported use in a higher number of sunscreen products marketed in Australia, and safety signals reported overseas. The literature includes available national and international safety assessment reports and peer reviewed publications.

The two main issues considered in this review were the evidence for the ability of these ingredients to penetrate the skin to reach viable cells systemically, and the potential toxicity exerted by them.

Introduction

The Therapeutic Goods (Permissible Ingredients) Determination (No. 3) 2024 currently lists 30 sunscreen active ingredients approved for use in Australia. The safety of these ingredients has been addressed by various means, including assessment of toxicological data, utilisation of overseas regulatory reports, and consideration by committees such as the then Medicines Evaluation Committee.

In 2019, the US FDA published a guidance for industry concerning safety and effectiveness data necessary to determine that a sunscreen active ingredient is generally recognized as safe and effective (GRASE) under the Sunscreen Innovation Act. This introduced a new requirement to conduct Maximal Usage Trials (MUsT) in order to study human absorption correlating to real-world use (FDA 2019a). This was followed by the publication of a US FDA proposed rule in 2019 elaborating the requirement for testing and labelling of sunscreens by manufacturers (FDA 2019b). The rule divided the 16 active ingredients approved in USA into three categories:

- category I (GRASE) includes ZnO and TiO_2;
- category II (not GRASE) includes trolamine salicylate and para-aminobenzoic acid (PABA) (neither of which is used in products currently marketed in Australia); and
- category III (additional data needed) includes the remaining 12 organic filters (cinoxate, dioxybenzone, ensulizole, homosalate, meradimate, octinoxate, octisalate, octocrylene, padimate O, sulisobenzone, oxybenzone, avobenzone; (FDA 2019b)). Ensulizole, homosalate, octinoxate, octisalate, octocrylene, oxybenzone, avobenzone are currently used in Australian products.

The US FDA has proposed that the category III ingredients are not GRASE, because the public record does not currently contain sufficient data to support positive GRASE determinations and additional data is required. The US FDA has also emphasised that they have not concluded that the active ingredients proposed as non-GRASE are unsafe for use in sunscreens, but have requested additional information to evaluate their GRASE status in light of changed conditions, including substantially increased sunscreen usage and evolving information about potential risks since their original evaluation. The US FDA has yet to publish their findings or final order and have noted they are reviewing these ingredients to determine if they are GRASE before they can establish a final order.

Given the greater use and importance of sunscreens in Australia; and the current interest by the US FDA in the ongoing safety of sunscreen active ingredients, the TGA has conducted an audit of its safety data holdings to better understand the safety profile of these ingredients.

As part of this audit, it was noted that some of the category III (additional data needed) organic filters have been widely used in sunscreen products in Australia. One of them was octisalate (octyl salicylate also known as ethylhexyl salicylate). Based on the available information, the Cosmetic Ingredient Review Expert Panel (Cosmetic Ingredient Review 2019) reached the conclusion that octisalate is safe when used in cosmetics in the European use settings and concentration (at 0.003% to 5% concentration as of 2018 data) described in the safety assessment when formulated to be non-irritating and non-sensitizing, which may be based on a quantitative risk assessment (QRA). As such, the literature review was not conducted for octisalate (octyl salicylate).

A literature search was conducted for the scientific information available for seven active ingredients avobenzone, ethylhexyl triazone (EHT), homosalate, octinoxate, octocrylene, oxybenzone and phenylbenzimidazole sulfonic acid (PBSA) for use in sunscreens. These ingredients have been widely used in sunscreen products in Australia. The review is intended to provide an overview of the publicly available safety information for these ingredients needed to assess the suitability of these ingredients for use in therapeutic sunscreens.

What are these ingredients

The chemical and physical properties and the molecular structures of these seven ingredients are provided in the following tables (Yap *et al.* 2017; Gilbert *et al.* 2013).

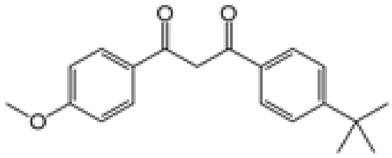
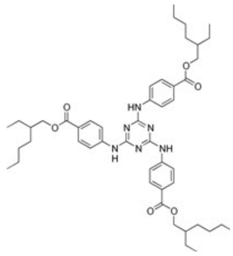
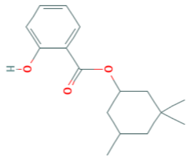
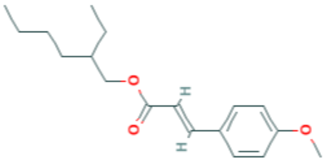
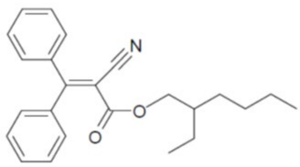
Table 0-1 Chemical and Physical Properties of the active ingredients under review

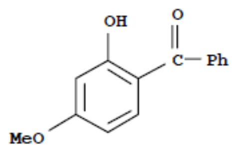
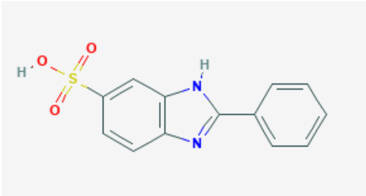
Active ingredient (*absorption spectrum*)	CAS no.	Chemical name	Molecular formula	Physical properties				Other names
				Water solubility	MW g/mol	Density	Log P_{ow}	
Avobenzone (BMDM or BMDBM) *UVA*	70356-09-1	1,3-Propanedione, 1-[4-(1,1-dimethylethyl)phenyl]-3-(4-methoxyphenyl)-	$C_{20}H_{22}O_3$	0.01 mg/L	310.4	1.1±0.1 g/cm^3	4.5-6.1	Butyl methoxydibenzoylmethane, Eusolex® 020, Parsol® 1789, 4-tert-butyl-4'methoxydibenzoylmethane, BMDBM
Ethylhexyl triazone (EHT) *UVB*	88122-99-0	2,4,6-Trianilino-(p-carbo-2'-ethylhexyl-l'-oxy)-1,3,5-triazine	$C_{48}H_{66}N_6O_6$	0.005 mg/L at 20°C	823.1	1.1±0.1 g/cm^3	15.5	Uvinul T150, (octyl triazone)

Active ingredient (*absorption spectrum*)	CAS no.	Chemical name	Molecular formula	Physical properties				Other names
				Water solubility	MW g/mol	Density	Log P_{ow}	
Homosalate *UVB*	118-56-9	3,3,5-trimethylcyclohexyl) 2-hydroxybenzoate	$C_{16}H_{22}O_3$	0.4 mg/L at 25°C	262.3	1.045 g/cm^3	4.7	Benzoic Acid, 2-Hydroxy-, 3,3,5-Trimethylcyclohexyl Ester Cyclohexanol, 3,3,5-trimethyl-, salicylate. Homomethyl salicylate Salicylic acid, 3,3,5-trimethylcyclohexyl ester Caswell No. 482B, Neo Heliopan® HMS, CCRIS 4885, Filtersol ''A''
Octinoxate (OMC or EHMC) *UVB*	5466-77-3	2-Ethylhexyl 4-methoxycinnamate	$C_{18}H_{26}O_3$	0.1 g/100 mL at 27°C	290.4	1.01 to 1.02 g/cm^3	5.9	EHMC or octyl-methoxycinnamate (OMC)
Octocrylene (OC) *UVB*	6197-30-4	2-Propenoic acid, 2-cyano-3,3-diphenyl-, 2-ethylhexyl ester	$C_{24}H_{27}NO_2$	40 µg/L at 20 °C	361.5	1.051 g/mL	6.1	2-Cyano-3,3-diphenyl acrylic acid, 2-ethylhexyl ester, 2-Ethylhexyl-2-cyano-3,3 diphenylacrylate, K.SORB 1139, Octocrylene USP, Parsol 340, Sunkem OTC, Sunobel®23 OCT, Uvinul 3039, 24 UVINUL N 539 T
Oxybenzone (BP-3) *UVB*	131-57-7	2-benzoyl-5-methoxyphenol; 4-Methoxy-2-hydroxybenzophenone	$C_{14}H_{12}O_3$	0.0037 g/L at 20°C	228.3	1.32 g/mL	>3.7	Benzophenone-3
Phenylbenz-imidazole sulfonic acid (PBSA) *UVB*	27503-81-7	2-Phenylbenzimidazole-5-sulfonic acid	$C_{13}H_{10}N_2O_3S$	> 30%	274.3	1.5 g/cm^3	-1.1 at pH 5	Ensulizole, Benzimidazole, 2-phenyl, 5-sulfonic acid

*the active ingredients are referred to throughout the report as either their AAN, INN or the abbreviated names.

Table 0-2 Molecular structure of the active ingredients under review

Active ingredient	Structure
Avobenzone	
Ethylhexyl triazone	
Homosalate	
Octinoxate	
Octocrylene	

Active ingredient	Structure
Oxybenzone	
Phenylbenzimidazole sulfonic acid	

Current restrictions in Australia and overseas

The following ingredients are currently approved in Australia for use as active ingredients in therapeutic sunscreens for dermal application (see the table below), not to be used in topical products for eyes, with appropriate safety warnings mandated on the label. It is noted that the regulation of sunscreens differs internationally, for example the USA regulate these as OTC drugs while they are regulated as cosmetics in the EU.

Active ingredient	Maximum % approved				
	Australia	EU	USA	Canada[1]	Japan[2]
Avobenzone	5	5	3	3	10
Ethylhexyl triazone †	5	5	Not approved	Not approved	5
Homosalate	15	7.34 (restricted to face product)	15	15	10 (restricted in all types of cosmetics)
Octinoxate	10	10	7.5	7.5	10
Octocrylene**	10	9 (propellant spray products); 10 (other products)	10	10	10 (restricted in all types of cosmetics)
Oxybenzone∆	10	6 (for face /hand products, excluding propellent and pump spray products); 2.2 (for body products)	6	6	5 (cosmetics not used for mucosa and not to be washed away)

[1] http://webprod.hc-sc.gc.ca/nhpid-bdipsn/atReq.do?atid=sunscreen-ecransolaire&lang=eng
[2](https://www.mhlw.go.jp/english/dl/cosmetics.pdf

Active ingredient	Maximum % approved				
	Australia	EU	USA	Canada[1]	Japan[2]
Phenylbenzimidazole sulfonic acid γ	4	8	4 (referred to as Ensulizole)	4	3 (cosmetics not used for mucosa and to be/not to be washed away)

**Octocrylene is approved as a UV filter in cosmetic formulation at ≤10% (as acid) in both Europe (Annex VI/10) and USA. The specific migration limit (SML) of octocrylene from food contact materials is 0.05 mg/kg (FDA 2018); European Parliament and the Council (2009); Restriction in EU - Benzophenone as an impurity and/or degradation product of Octocrylene shall be kept at trace level.
†EU: Annex VI, Regulation (EC) No. 1223/2009; γ EU: cosmetics directive in annex VII, part 1 list of permitted UV filters under entry 6;
Δ Annex VI/4, oxybenzone is also allowed at concentrations of up to 0.5 % to protect product formulations in all other cosmetic products (Annex VI/4).

Literature search summary

Method of data search

The literature review was conducted using keywords such as the chemical name, Australian Approved Name (AAN) or the International Nomenclature Cosmetic Ingredient (INCI) names, and "sunscreen" as the search items. Publications during a 15 year period were searched (between 2008 and March 2023). See the Appendix 0 for details.

In summary, the following data sources have been used for the literature search:

- Assessments from national regulatory agencies (e.g., AICIS, previously known as NICNAS) where available.

- Opinions from the Scientific Committee on Consumer Safety (SCCS, previously known as SCCNFP/SCCP/SCC) where available.[3]

- Information identified through literature search in PubMed and on the internet where a newer SCCS is not available.

- The publicly available registration dossiers for the ingredients submitted by industry under the EU REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) Regulation and available on the website of the European Chemicals Agency (ECHA). This information includes unpublished study summaries submitted by industry, in response to the standard data requirements of the REACH Regulation. Data from key studies in the registration dossiers have been considered for assessment in this review.

Information on the health hazards is available for all the selected ingredients considered, although the amount of information available varies considerably and does not cover all toxicological endpoints for all ingredients. Endocrine activity modulation properties of ingredients may give rise to a concern for human health. The evaluation of endocrine activity modulation properties was described collectively. Of note, all articles dealing with environmental matters relating to the ingredients were excluded as they do not fall under Australian therapeutic goods legislation.

[3] https://ec.europa.eu/health/ph_risk/committees/04_sccp/sccp_opinions_en.htm

Pharmacokinetics

The main safety concerns for these active ingredients arise from the knowledge gap around the toxicokinetic and pharmacokinetics data. Cutaneous permeation is a critical parameter in the kinetics of these active ingredients. Although most organic UV filters are lipophilic, *in vitro* cell permeation studies were also conducted with some of these ingredients to demonstrate systemic absorption by intact skin. Dermal absorption data from either relevant SCCS opinion, ECHA dossiers, AICIS assessments or published literature were reviewed in this document. Limited permeation data were noted for some active ingredients. In the absence of dermal toxicity data, oral toxicity data were considered when considering systemic toxicity in the worst case scenario. Where appropriate, the dermal absorption value from the most recent SCCS opinions for the relevant active ingredients, were noted. Note that dermal absorption values apply to intact skin and may not be applicable for abraded skin or areas of sensitive skin e.g. lips.

Avobenzone

The molecular weight of avobenzone is in the range (MW < 500 D) where skin penetration can occur but the log P_{ow} is slightly above the range favouring penetration (log P_{ow} in range -1 to +4). Avobenzone has a low water solubility. Based on these physico-chemical data, only low dermal penetration is expected.

The toxicokinetic data for avobenzone were assessed in ECHA 2021 (ECHA 2021A). The executive summary of the assessed data is given below (for details see ECHA 2021A).

- In a 21 day dermal rabbit toxicity study (Keller 1980), there was an absence of a biological response (no adverse effects were observed in rats up to the high dose of 360 mg/kg bw/day, both in groups with intact skin or with abraded skin), and there was no indication of systemic bioavailability following dermal exposure.

- *In vitro* studies with isolated pig skin using ^{14}C-labelled BMBDM (avobenzone) at a concentration of 2% or 7.5 % in cream formulations exposed for 6 hours, showed that majority of the topically applied BMDBM remained on the skin surface (95%), 1.0-1.7% were found on the stratum corneum, 0.9-3.4% absorbed in the skin and only a minimum (≤ 0.5%) was found to pass the skin. Briefly, the results indicate a low penetration rate of avobenzone when applied on pig skin (up to 1.5 % of applied radioactivity 6 h post application). Dermal penetration in pig skin was not influenced by UV light (ECHA 2021A).

- In an *in vitro* study (DSM 1982) with ^{14}C-labelled BMDBM (avobenzone) using isolated human abdominal cadaver skin, up to 2.7 % of the applied radioactivity was observed in the epidermis, 7.3 % in the dermis 18 hr post dose but no activity was found in the collection fluid at any time and lower skin corium contained only 0.34 % after the longest exposure period (ECHA 2021A).

- A human *in vivo* study also indicated a very low level of systemic penetration of BMDBM (avobenzone) or its metabolites. In the study, a preliminary study (occluded) was followed by the main study where human volunteers were exposed to a 10% solution of ^{14}C-labelled BMBDM in carbitol for 8 hours.[4] The amounts of BMDBM found in the urine were 0.08 and 0.016 % for the occluded and non-occluded experiment, respectively. No radioactivity was found in the blood or faeces in any subject. Therefore, these data confirm only a very low level of systemic penetration of BMDBM or its metabolites (ECHA 2021A).

[4] The dose was applied to a small square of gauze (10 cm^2) taped to the skin.

A recent study demonstrated that there was very poor skin permeation of avobenzone after single or repeated applications of sunscreens (Montenegro *et al.* 2018). However, recent randomised clinical trials indicate that avobenzone was systemically absorbed in humans (see **Clinical Trials**).

In the absence of further kinetic data for avobenzone and based on the data from the *in vitro* study using isolated human abdominal cadaver skin ((ECHA 2021A), **a 7.3% dermal absorption** of avobenzone was assumed.

Ethylhexyl triazone

No specific pharmacokinetic data are available for ethylhexyl triazone. The ingredient is expected to have low oral and dermal bioavailability based on its physiochemical properties (Molecular weight > 500 Dalton and Log P_{ow} > 4; Table 2.1)

Ethylhexyl triazone did not penetrate the receptor fluid in an *in vitro* study by Monti *et al.* (2008) when applied to the reconstructed human skin model and the rat skin. However, BASF (1995) reported *in vitro* permeation of ethylhexyl triazone in the sunscreen formulation, but no value was provided.

In an *in vitro* diffusion study (6-h exposure of the *ex-vivo* porcine-ear skin to the sunscreen, water-oil emulsion containing 10% oxybenzone and 5% ethylhexyl triazone, doses of 1 mg/cm^2 and 2 mg/cm^2), 23.2 ± 4.1 mg/cm^2 and 18.3 ± 2.5 µg/cm^2 of oxybenzone and ethylhexyl triazone, respectively were found in the stratum corneum, whereas 1.5 ± 0.3 mg/cm^2 of oxybenzone was found in the receptor fluid (Hojerová *et al.* 2017). Ethylhexyl triazone was not determined in the receptor fluid. The study authors concluded, that approximately 0.54 mg/cm^2 of ethylhexyl triazone (i.e., ~1.08% of the amount of ingredient applied) permeated the excised human epidermis into the receptor fluid. Approximately 1.3 and 1.8 × higher content of oxybenzone and ethylhexyl triazone were found in the viable epidermis and dermis, respectively, and 2.3- and 1.5-times higher content in the receptor fluid, respectively, when the study was conducted on shaved skin. Insignificant percutaneous absorption of ethylhexyl triazone across the shaved skin was noted. The total recovery in the whole study (intact and/or shaved skin) was 87.5- 90.4% consistent with the recovery (85-115%) allowed by the SCCS (2016). The SED after the sunscreen application at 1 mg/cm^2 for 6 h on the: (i) face; and (ii) whole-body skin, was (i) 136 and 30; (ii) 4200 and 933 mg/kg bw/day for oxybenzone and ethylhexyl triazone, respectively. Reapplication caused approximately 1.4 -fold increase in the SED values indicating partial saturation after the first application.

Preferential ethylhexyl triazone distribution into stratum corneum was also noted by Sauce *et al*. (2020) in tape strip samples obtained from human volunteers (*n* = 12) treated with 100 µg/mL of the compound emulsified in cosmetic oil/water formulation (5% w/w) and applied at 2.0 mg/2.25 cm^2 for 2 h. However, only first 10 µm of the upper layers was collected (thickness of stratum corneum is ~30 µm) and given that the total recovery observed in this section was 56.34 %, the authors concluded that the remaining 44.66% of the dose penetrated deeper strata.

An *in vivo* study investigating the penetration of ethylhexyl triazone in human stratum corneum demonstrated that 21.9% (± 4.9) of the applied ethylhexyl triazone dose diffused into the stratum corneum. However, the skin penetration reduced significantly (by 45.7%) when ethylhexyl triazone was applied in microencapsulated form (Scalia *et al.* 2019).

In the absence of an appropriate dermal absorption value for ethylhexyl triazone, a **dermal absorption of 10%** was assumed based upon physicochemical parameters.

Homosalate

Studies in animals and human skin showed that homosalate could penetrate the skin in a variable manner. *In vitro* experiments indicated that about 1.1% of the applied dose was absorbed by human skin (range: 0.9-2.0%) (CTFA 2005).

Maximum plasma concentrations of homosalate after topical application varied between 13.9 and 23.1 ng/ml and $t_{½}$ between 46.9 and 78.4 h in clinical trials (see **Clinical Trials**). Homosalate was also detected in human milk samples after topical application in samples from different cohorts (2004, 2005, 2006) (Schlumpf *et al.* 2010). 15.1% of mothers reported use of homosalate exclusively in sunscreens with no additional use of other cosmetics. Homosalate was detected in 5.56% of total milk samples. However, homosalate could not be detected in human breast tissue samples (Barr 2018).

The *in vitro* metabolism of homosalate was investigated in rat and human liver microsomes. Homosalate (10 mM) incubated with human or rat liver microsomes (1 mg/ml protein) was hydrolysed into salicylic acid and 3,3, 5-trimethylcyclohexanol. In addition, conjugation and hydroxylation of intact homosalate was detected *in vitro*.

Commercial products often contain mixtures of cis- and trans-homosalate isomers (*cis*-HMS and *trans*-HMS respectively). Ebert *et al.* (2022) reported 87.2 - 91.9% of *cis*-HMS and 8.1-12.8% of *trans*-HMS in total homosalate content in 10 examined sunscreen products. However, following oral administration, homosalate isomers displayed diastereoselective metabolism, which was skewed towards *trans*-HMS e.g., metabolite levels derived from *trans*-HMS (6.4 %), including carboxylic acid and alkyl-hydroxylated compounds, were 142-fold higher compared to *cis*-HMS (0.045 %) while its bioavailability was 10-times higher. Although it is currently unknown whether homosalate applied dermally also undergoes divergent isomer metabolism, preliminary data of Ebert *et al.* agree with the findings from the oral study.

The SCCS selected a new skin penetration study using human skin from which **a dermal absorption of 5.3%** (mean + 1SD: 3.86±1.43) was derived (SCCS 2020).[5]

Octocrylene

Octocrylene is expected to be absorbed in the GI tract by micellar solubilisation based on its physicochemical properties (ECHA 2020b). The inhalational uptake of octocrylene is likely to be low due to the very low vapour pressure (4 $x10^{-7}$ Pa at 20°C) (ECHA 2020b).

Octocrylene has been found to induce xenobiotic-metabolising enzymes based on mechanistic studies, oral repeated dose toxicity and reproductive/developmental toxicity studies (SCCS 2021a; ECHA 2020b). An *in vitro* study on the hydrolysis-stability in rat liver S9 fraction indicated that octocrylene was metabolized in liver S9 fraction only (ECHA 2020b).

Human octocrylene metabolism and the pathways were described by Bury *et al.,* (2019). Six metabolites of octocrylene were detected in human urine after both oral and dermal exposure simulating a regular-use scenario with whole body application to octocrylene. 2-cyano-3,3-diphenylacrylic acid (CDAA) was identified as the major urinary metabolite (~45% of the octocrylene dose) followed by 2-ethyl-5-hydroxyhexyl 2-cyano-3,3-diphenyl acrylate (5OH–OC) and 2-(carboxymethyl) butyl 2-cyano-3,3-diphenyl acrylate (dinor OC carboxylic acid, DOCCA). Faecal excretion was observed. *In vitro* study with human and rat liver microsomes in the presence of

[5] The June 2021 SCCS opinion for homosalate uses a different dermal absorption value for the SED calculation. The systemic exposure dose for homosalate used as a UV filter in cosmetic products is calculated using a dermal absorption value of 5.3% derived from an *in vitro* dermal penetration study using viable human skin (Finlayson 2021, as cited in SCCS 2020) and a standard sunscreen formulation containing 10% homosalate.

NADPH and glutathione (GSH) suggested that the ester bond of octocrylene can be hydrolysed to form 3,3-diphenyl cyanoacrylate (DPCA) and 2-ethylhexanol based on the chemical structure of octocrylene (Guesmi *et al.* 2020).

Dermal exposure resulted in much lower concentrations of metabolites with considerably delayed elimination despite much higher octocrylene (> 25-fold) applied dermally (dermal dose 217 mg *vs* oral dose ~5 mg). This suggests a slower uptake of octocrylene through the skin.

Table 0-1 Toxicokinetic data in urine after oral and dermal exposure to octocrylene (adapted from Bury *et al* 2019)*

Ingredient			CDAA	5OH-OC	DOCCA
Oral (n=3)	Concentration (µg/g creatinine)		2450 (1150-4410)	1.85 (1.62-2.11)	10.6 (9.94-11.1)
	t_{max} (hours)		4.2 (2.7-5.0)	3.2 (1.4-4.4)	3.6 (1.4-5.0)
	$t_{½}$ (hours)	1st phase	5.7 (3.8-7.1)	1.3 (1.1-1.5)	3.0 (2.1-3.6)
		2nd phase	16 (14-20)	6.4 (5.7-7.5)	16 (10-21)
Dermal (n=1)	Concentration (µg/g creatinine)		71.4	0.14	1.15

*Median (range) values are reported.

Following dermal application of octocrylene (8-10%) in *in vitro* studies, poor skin penetration (< 5%) of octocrylene was observed with mostly remaining in the stratum corneum (Freitas *et al.* 2015; Potard *et al.* 2000; Hayden *et al.* 2005). The dermal absorption (%) was not determined in these studies. Similar findings were observed in a study with a formulation (8% octocrylene) applied on freshly dermatomized human skin (344 ± 61 µm) in static diffusion cells at a dose of 3 mg/cm^2 for a 16-hour period. 0.1%, 0.005% and 4.3% of the applied dose were found in epidermis, dermis and in the stratum corneum, respectively (ECHA 2020b). No octocrylene was detectable in the receptor fluid. After 24 hours of dosing, octocrylene bioavailability (epidermis, dermis and receptor fluid) was estimated ~ 0.1% of the applied dose (ECHA 2020b; SCCS 2021a). In another study, a cream formulation (8% octocrylene) was applied for 16 hours (3 mg formulation/cm^2) on freshly dermatomed pig (700 ± 50 µm) and human (350 ± 50 µm) skin in static diffusion cells (ECHA 2020b). In the study with pig skin, no octocrylene was detectable in the receptor fluid whereas 2.8% and 0.3% of the applied dose were found in pig epidermis and dermis, respectively, and 14% were detected in the stratum corneum. In the study with human epidermis and dermis, only 0.125% of the applied dose were found, whereas 5.4% was determined for human stratum corneum. Based on these data, the amount bioavailable (epidermis, dermis and receptor fluid) represents approximately 0.2% and 3% of the applied dose in the human and pig skin, respectively (ECHA 2020b). The SCCS (2021a) also referred to the octocrylene Chemical Safety Report (2010) which indicated a low dermal absorption rate (≤ 0.25%).

A recent *in vitro* study (Fabian and Landsiedel 2020, as cited in SCCS 2021a) with a formulation (10% octocrylene) applied at a dose of 3 mg formulation/cm^2 on dermatomized human skin preparations (n =12 skin samples from six females) for 24 hours was evaluated by SCCS (2021a). At 24 hours post-dose, the amount considered as absorbed (epidermis, dermis and receptor fluid) was estimated to be a maximum of 0.45±0.52 µg/cm^2 (~ 0.15% of the applied dose) consistent with previous findings. The **dermal absorption of 0.97 µg/cm^2** (Fabian and Landsiedel 2020, as cited in SCCS 2021a) was considered a worst-case scenario for octocrylene and was used in the calculation of SED and MoS by the SCCS (2021a).

Octinoxate

Octinoxate absorption studies (oral and dermal) in rats and mice indicate octinoxate can be absorbed dermally and orally (Fennell *et al.* 2018). Octinoxate was rapidly cleared from rat hepatocytes (half-life ≤3.16 min) compared to human hepatocytes (half-life ≤48 min). [^{14}C]-octinoxate was extensively absorbed and excreted primarily in urine by 72 h after oral administration (65-80%) and a lesser extent (3-8%) in faeces and as CO_2 (1-4%).

Five metabolites were found in rat urine after oral exposure to octinoxate (200 mg/kg bw and 1000 mg/kg bw) (Huang *et al.* 2019). The major metabolites of octinoxate were 4-methoxycinnamic acid (4-MCA) and 4′-methoxyacetophenone (4′-MAP). The concentration of two metabolites was found to be much higher than octinoxate, highlighting that measuring octinoxate alone could not comprehensively evaluate the human exposure to octinoxate.

Dermal penetration was observed to be dependent on the vehicles, when using the tape-stripping technique. Significantly greater amounts were absorbed when the chemical was applied in emulsions than when microencapsulated (HSDB). Octinoxate was able to penetrate the skin, and derivatives were formed when it was applied with oleaginous cream as a vehicle on excised rat skin. In contrast, octinoxate penetration was not observed following the administration of octinoxate as entrapped into solid lipid microspheres (SLM) (Yener *et al.* 2003).

Studies with porcine skin showed that about 9% of the applied dose of octinoxate penetrates the skin with a flux of 27 μg/cm^2·h (Touitou and Godin 2008). An accumulation of ~9% of octinoxate in epidermis and ~2-3% in dermis were observed following application of 2 mg/cm^2 and 0.5 mg/cm^2 of octinoxate, respectively for 6 h exposure (Schneider *et al.* 2005). Octinoxate accumulation is expected to increase over time as the accumulation in dermis was found to be ~12-15% of the dose applied and 2-4% of the dose was found to cross the dermis and enter into the circulation after 24 hours.

An *in vitro* absorption study with sunscreen (O/W , oil in water emulsion and W/O, water in oil emulsion) containing octinoxate or EHMC (10%) on full-thickness pig-ear skin, mimicking human in-use conditions revealed the skin distribution of octinoxate from the sunscreen dose of 0.5 mg/cm^2 after 6-h exposure to the epidermis of frozen-stored skin was 4.8± 0.7 μg/cm^2, dermis 1.2 ± 0.1 μg/cm^2 and undetectable in receptor fluid, whereas 3.4 ± 0.6 μg/cm^2 , 2.1 ± 0.4 μg/cm^2 and 0.9 ± 0.1 μg/cm^2 of octinoxate was distributed to epidermis, dermis and receptor fluid after following 18-h permeation, respectively (Klimova *et al.* 2015). Almost two-fold higher absorption was noted when water in oil emulsion containing 10% octinoxate was applied on pig skin in the same study (Klimova *et al.* 2015).

In this study, the authors "*tried to mimic the real-life habits of consumers when applying sunscreen as closely as possible".* In this way the time of exposition was reduced to 6 hours (in contrast of classic studies using long skin exposure), and a smaller dose of sunscreen was used (0.5 mg/cm^2) (Klimova *et al.* 2015). Considering that some chemical substances, instead of passing entirely through the skin, can remain partly in the skin and released later in time, the dermal absorption was evaluated at the end of the exposure period and then following washing and an 18-h permeation.

The dermal absorption was obtained by the sum of the filter absorbed in the dermis and the receptor fluid (RF) (which was considered systematically available), corrected by the fresh/frozen – stored skin permeability coefficient. It is noted that pig-ear skin has been recognized by the international authorities and scientists as a practical alternative and relevant model for predicting permeability of cosmetic ingredients in humans (Klimova *et al.* 2015).

Human *in vitro* and *in vivo* studies showed that the permeation of octinoxate in human skin was dependent on both the lipid lipophilicity and structure of the lipid used in the microemulsion and the type of surfactant used (Montenegro *et al*. 2011; TGA 2020).

The systemic absorption of octinoxate in humans was demonstrated by Janjua *et al* (2008). Maximum plasma concentration of octinoxate was reached at ~ 3 h (10 ng/ml for females and 20 ng/ml for males) following daily whole-body topical application of 2 mg/cm^2 of cream formulation with 10% octinoxate. Octinoxate was also detected in urine (5 and 8 ng/mL in females and males, respectively). Similar findings were reported following a 4-day exposure to this ingredient, which were detectable in the human plasma just 2 h following application (Janjua *et al.* 2004).

Another human study reported in SCC (2000) with a cream formulation containing 10% octinoxate suggested that an insignificant amount of octinoxate was absorbed under the conditions of the experiment (SCC 2000). Applications were made to the interscapular area and there was no evidence of any rise in plasma levels after 24 h. In addition, the urine concentration of octinoxate did not change during the experiment (collected until 96 h).

Based on all dermal absorption studies described above, no clear relationship between applied dose and dermal absorption could be established for octinoxate. Therefore, a **dermal absorption of 1.77 µg/cm^2** was considered a worst-case scenario (Klimova *et al.* 2015).

Oxybenzone

Oxybenzone is expected to be rapidly absorbed after oral, intravenous or topical skin administration based upon studies in rats and piglets as per European Safety assessment reports (SCCS 2021c). Oxybenzone was well absorbed following a single gavage administration of [^{14}C]-oxybenzone (3.01 to 2570 mg/kg) in male rats, with the administered dose excreted primarily *via* urine (63.9% to 72.9%) and faeces (19.3% to 41.7%) by 72 hours post-administration. The radioactivity remaining in tissues 72 hours after administration was low (~0.1%) in all dose groups. Oxybenzone is widely distributed in rats. Jung *et al.* (2022) assessed that bioavailability in rats following topical application as 6.9%.

Oxybenzone is metabolised in rats to 2-OH BP and BP-1, with a trace of 2, 3, 4-triOH BP. The major metabolite of oxybenzone, 2,4-diOH BP (BP-1) was present in most tissues including the liver, kidney, testes, intestine, spleen and skin six hours post-dose. Liver was the major distribution site of oxybenzone and BP-1 (SCCS 2021c). BP-1 is also the major metabolite in humans. Oxybenzone metabolites were detected in piglet plasma 2 hours post dose after dermal administration of oxybenzone (SCCS 2021c). Systemic absorption of oxybenzone has been demonstrated in recent clinical studies (Section 2.1). Oxybenzone binds to human serum albumin with Ka= 1.32 x 10^5 L/mol.

Elimination of oxybenzone is predominately *via* the urine (39-57%) and faeces (24-42%) in rats and mice, with differences observed between the species or the route of administration (oral or dermal). Following topical application studies in piglets, the elimination half-lives of oxybenzone ranged from 7.14 and 8.04 h (SCCS 2021c), while in rats it was 18.3 h (Jung *et al.* 2022).

A number of *in vitro* and *in vivo* dermal absorption studies have been evaluated by the SCCP 2008 and SCCS 2021c. Following application of 6% oxybenzone, the **dermal absorption of oxybenzone was determined to be 9.9%.** The dermal absorption value of 9.9% was calculated by the SCCP using an *in vitro* study using pig ear skin and applying a safety factor of 2 standard deviations to account for limitations in the data set (3.1% + 2 SD [2 x 3.4%] = 9.9%) (SCCS 2021c). This *in vitro* study was chosen for oxybenzone in the absence of adequate information from *in vivo* studies.

Phenylbenzimidazole sulfonic acid

Absorption and plasma kinetics of PBSA were examined in pregnant rats (SCCP 2006b). [^{14}C]-PBSA sodium salt was administered to pregnant rats on day 18 of gestation (1 mg/kg bw IV or 1000 mg/kg bw PO, single dose). The pharmacokinetic parameters were: T_{max} 5 min (IV) and 15 min (oral), with a $t_{½}$ of 0.4 h (IV) and 24 h (oral). The amount of absorption from the gastrointestinal tract was estimated to be 3 – 4%.

Dermal penetration was examined in male volunteers (SCCP 2006b). Although the penetration rate of PBSA was not established, cumulative penetration of 0.159% (range 0.107-0.259%) of the applied dose (8% formulation of PBSA), was derived from total excretion. Total recovery of radioactivity was 78.8%. There was no indication of accumulation in any of the organs investigated. Trace amounts of radioactivity are found in brain and fetuses after IV administration but not following oral administration. This indicates that both blood/brain- and placental barriers were not passed. No data on metabolism were available.

Excretory pathways were examined in male rats (SCCP 2006b). Elimination of PBSA sodium salt was virtually completed by 72 hours. Elimination occurs *via* urine and faeces in male rats. In pregnant rats, elimination predominantly occurred *via* the faeces following oral administration and *via* both the urine and faeces following IV administration. Maximum **absorption through the skin of 0.259% (0.416 μg/cm^2) determined** in the *in vivo* study in humans following application of an 8% formulation of PBSA was used by the SCCP to determine the margin of safety for PBSA (SCCP 2006b).

Clinical trials

In a recent randomised clinical trial, healthy volunteers (*n*=24; 6/ group) were treated with four sunscreen products, four times per day for 4 days, in indoor conditions, at a rate of 2 mg/cm^2 on 75% of body surface area. The sunscreen products were spray 1 (3% avobenzone/ 6% oxybenzone/2.35 % octocrylene/ 0% ecamsule[6]), spray 2 (3% avobenzone/5% oxybenzone/ 10% octocrylene/ 0% ecamsule), lotion (3% avobenzone/ 4% oxybenzone/ 6% octocrylene/ 0% ecamsule); and cream (2% avobenzone/ 0% oxybenzone/ 10% octocrylene/ 2% ecamsule). The overall maximum plasma concentrations (C_{max}) of avobenzone, oxybenzone and octocrylene ranged from 4 to 4.3 ng/mL, 169.3 to 209.6 ng/mL and 2.9 to 7.8 ng/mL, respectively. The AUC increased from day 1 to day 4 and terminal half-life ($t_{½}$) was relatively long (33-55 h, 27-31 h and 42–84 h, respectively), suggesting a possible accumulation of the ingredients (Matta *et al.* 2019). The systemic exposure of avobenzone and oxybenzone in human plasma was re-quantified by Pilli *et al.* (2021) using novel UHPLC-MS/MS method and in general, the C_{max} values were comparable to the results obtained previously.

Similar findings were observed in a follow up study with six active ingredients (avobenzone, oxybenzone, octocrylene, homosalate, octisalate[7], and octinoxate) (Matta *et al.* 2020). Four groups (*n*=12) of healthy adults received 2 mg/cm^2 (75% of body surface area) on day 1 and 4 times on day 2 to day 4 at 2-hour intervals and blood samples were collected over 21 days from each participant.

The C_{max} of all these ingredients exceeded the US FDA threshold (> 0.5 ng/mL) after a single application and remained above the threshold until day 7 for avobenzone (95%; *n* = 42/44), octisalate (75%; *n* = 24/32), and octinoxate (90%; *n* = 18/20); day 10 for octocrylene (67%; *n* = 22/33); and day 21 for homosalate (55%; *n* = 17/31) and oxybenzone (96%; *n* = 22/23). The overall exposure throughout the study (Days 1-21) is summarised in the following table taken from Matta *et al.* (2020).

[6] Ecamsule (CAS 92761-26-7) is commonly used as an active ingredient in sunscreen. However, currently it is not used in any sunscreen product marketed in Australia.

[7] Octisalate or octyl salicylate is an active ingredient used in sunscreen. This has been evaluated by TGA as an excipient to be used in prescription medicines.

	Geometric mean maximum plasma concentration, ng/mL (coefficient of variation, %)			
	Lotion	**Aerosol spray**	**Nonaresol spray**	**Pump spray**
Avobenzone	7.1 (73.9)	3.5 (70.9)	3.5 (73.0)	3.3 (47.8)
Oxybenzone	258.1 (53.0)	180.1 (57.3)	NA	NA
Octocrylene	7.8 (87.1)	6.6 (78.1)	6.6 (103.9)	NA
Homosalate	NA	23.1 (68.0)	17.9 (61.7)	13.9 (70.2)
Octisalate	NA	5.1 (81.6)	5.9 (77.4)	4.6 (97.6)
Octinoxate	NA	NA	7.9 (86.5)	5.2 (68.2)

Another study investigating systemic absorption of avobenzone and octocrylene using real-life exposure scenario demonstrated similar systemic absorption of the ingredients (Hiller *et al.* 2018). Following dermal exposure, avobenzone, octocrylene and CDAA (major urinary metabolite of octocrylene) reached concentrations up to 11.3 µg/L, 25 µg/L and 1352 µg/L, respectively, in plasma (Table 0-2). When kinetic models were fitted for octocrylene and CDAA in plasma and CDAA in urine, concentration peaks reached between 10 and 16 h after first application and elimination half-life ($t_{½}$) were 36-48 hours. Octocrylene and CDAA showed slower elimination.

Table 0-2 Toxicokinetic data in humans following dermal exposure to octocrylene and avobenzone

Study details		***n*=20; commercial sunscreen lotion containing octocrylene was applied three times (2 mg/cm² initially, then 1 mg/cm² after 2 h and 4 h) to 75–80% BSA)**		
Ingredient		**Octocrylene**	**Avobenzone**	**CDAA**
Concentration	(%)	10.85	2.34	NA
C_{max} plasma (µg/L)	Mean (max)	11.7 (25)	4(11.3)	570 (1352)
C_{max} in urine (µg/g creatinine)	Median (max)	9.6 (< LOD–91.4)	3.4 (< LOD–25.2)	2072 (5207)
T_{max} plasma (hours), day 1	Median (95% CI)	10 (6.9-13.4)	ND	14.5 (13.2-15.9)
T_{max} urine (hours), day 1		ND	ND	15.9 (15.2-16.7)
$t_{½}$ plasma (hours)		43.9 (19.0-68.7)	ND	36.1 (31.0-41.2)
$t_{½}$ urine (hours)		ND	ND	37.7 (35.1-40.4)

*81% of samples < LOD' c: concentration; C_{max}: max plasma concentration; ND: not determinable; T_{max}: time to maximum concentration; $t_{½}$: half-life; CDAA: 2-cyano-3,3-diphenylacrylic acid

Toxicity

The information on the safety of avobenzone, ethylhexyl triazone, homosalate, octinoxate, octocrylene, oxybenzone and PBSA using various toxicological endpoints, has been summarised in the following sections. It is important to note that the original toxicological study reports were not available for independent verification and therefore this report is reliant on the accuracy of various published safety assessment reviews (reviews by SCCS/SCC/SCCP, NICNAS, ECHA etc. see bibliography).

Acute toxicity

Avobenzone, ethylhexyl triazone, homosalate, oxybenzone, octocrylene, PBSA and octinoxate displayed low acute oral toxicity. Low acute dermal toxicity was observed for homosalate, oxybenzone, octocrylene, PBSA and octinoxate. Information for acute inhalational toxicity is only available for octinoxate (shown below).

Table 3-3. Summary of acute toxicity studies for sunscreen ingredients

Avobenzone (ECHA (2021a; DEPA 2015)	Ethylhexyl triazone (ECHA 2021b; DEPA 2015)	Homosalate (SCCS 2020; ECHA 2021c)	Octinoxate (ECHA 2021e)	Octocrylene (SCCS 2021a; ECHA 2021d)	Oxybenzone (SCCP 2006a; 2021c)	PBSA (SCCP 2006b)
Oral >16000 mg/kg bw (rats) Dermal, inconclusive*	Oral > 5000 mg/kg bw (rats)	Oral > 5000 mg/kg (rats) Dermal > 5000 mg/kg bw (rabbits)	Oral >8 g/kg (mice) >20 mL/kg (20.0 mg/kg) (rats) Dermal >126.5 mg/kg (rats) Inhalation LC50 >0.511 mg/L (rats)	Oral > 5000 mg/kg bw (rats) Dermal > 2000 mg/kg bw (rats)	Oral > 6000 mg/kg bw (rats) Dermal > 16000 mg/kg bw (rabbits)	Oral >5000 mg/kg bw (mice) >1600 mg/kg bw (rats) Dermal >3000 mg/kg bw (rats) IP 1000 – 1500 mg/kg bw (rats)

The values are LD_{50} determined in relevant studies extracted from the safety assessment reviews; *Acute dermal toxicity was tested up to a dose of 1000 mg/kg bw in rats showing no deaths. Slight erythema was observed in treated animals and in the vehicle control, assuming that the vehicle, carbitol, has a slight irritant effect to skin. Concerning acute dermal toxicity, the test item was only tested up to a maximum dose of 1000 mg/kg bw, whereas the regulatory cut-off level for classification according to Regulation (EC) No 1272/2008 (CLP) is 2000 mg/kg bw.

Local tolerance

Skin irritation and eye irritation studies were generally conducted as per the OECD TG 404 and 405 guidelines, respectively. All ingredients examined were found to be non-irritants to the skin and eye in *in vivo* studies in animals (see below).

Table 3-4. Summary of skin and eye irritation studies for sunscreen ingredients

Study	Avobenzone (ECHA (2021a; DEPA 2015)	Ethylhexyl triazone (ECHA (2021b; DEPA 2015	Homosalate (SCCS 2020; ECHA 2021c)	Octinoxate (ECHA 2021e)	Octocrylene (SCCS 2021a; ECHA 2021d)	Oxybenzone (SCCP 2006a; 2021c)	PBSA (SCCP 2006b)
Skin	Non-irritant (at 10% in rabbits)	Non-irritant, undiluted(rabbits)	Non-irritant (mice, Guinea pigs)	Non-irritant, undiluted (rabbits, guinea pigs)	Non-irritant (rabbits)	Non-irritant (rabbits)	Non-irritant (rabbits)
Eye	Non-irritant (at 5-20% in rabbits)	Non-irritant, undiluted (rabbits)	Non-irritant (at 10%)	Non-irritant, undiluted (rabbits)	Non-irritant (rabbits)	Non-irritant (rabbits)	Non-irritant (rabbits)

Sensitisation

With the exception of octocrylene, all the ingredients were not found to be skin sensitisers in *in vivo* studies in animals (see below).

Table 3-5. Summary of skin sensitisation studies for sunscreen ingredients

Avobenzone (ECHA 2021a; DEPA 2015)	Ethylhexyl triazone (ECHA (2021b; DEPA 2015	Homosalate (SCCS 2020; ECHA 2021c)	Octinoxate (ECHA 2021e)	Octocrylene (SCCS 2021a; ECHA 2021d)	Oxybenzone (SCCP 2006a; 2021c)	PBSA (SCCP 2006b)
Not sensitizing (at 6% and 20% in GPMT)	Not sensitizing (GPMT)	Not sensitizing (GPMT and mice) Not sensitizing (at 15%, HRIPT)	Not sensitizing (GPMT)	Not sensitizing (GPMT) Moderate sensitising in a LLNA (not properly conducted)	Not sensitizing (GPMT) Not sensitising (LLNA)	Not sensitizing (GPMT)

GPMT: Guinea Pig Maximization Test; LLNA: Local Lymph Node Assay; HRIPT: Human repeated insult patch test

Repeat dose toxicity

A summary of repeat-dose toxicity studies for each sunscreen ingredient is shown in the table below:

Table 3-6. Repeat-dose toxicity studies for sunscreen ingredients

Active ingredient	Study details$^{\Delta}$	Major findings
Avobenzone (ECHA 2021a; DEPA 2015)	Rats (*n*=12/sex/dose), doses: 0, 200, 450, and 1000 mg /kg bw/day (diet), 13 weeks	No treatment-related mortality. No effect on the body weight and food consumption. ↓ RBC in ♀ rats at 1000 mg/kg bw/day. No findings in eyes. No treatment-related necropsy findings. Treatment-related ↑ liver weights at 1000 mg/kg bw/day in ♂ and at 200, 450, and 1000 mg/kg bw/day in ♀ compared to control. All effects were fully reversed after a treatment-free period of 4 weeks. Hypertrophic hepatic parenchyma cells in ♀ at 1000 mg/kg bw/day. **NOAEL: 450 mg/kg bw/day** *Applying route to route extrapolation, by assuming that penetration of avobenzone through skin is equal to penetration through the intestinal wall, the same effect levels as for oral route shall apply for the dermal route of exposure (ECHA 2021)*
	Rabbits (*n*=10/sex/group), 1.5, 5 and 18 % w/v solutions in carbitol (vehicle) (30, 100 and 360 mg/kg bw/day) (dermal once daily), exposure: 6 hours/day, 28 days	No treatment-related mortality. ↑ dose dependent severe dermal reactions ≥ 30 mg/kg/day, more persistent at 100 mg/kg bw/day. ↑ Incidence of epidermal thickening in both vehicle control and treatment groups compared to the untreated control group. NOAEL: 360 mg/kg bw/day (based on systemic effects). LOAEL: 30 mg/kg/bw/day (dermal)
Octocrylene (ECHA 2021d; SCCS 2021a)	Rats (Wistar), *n* = 10/sex/dose 0, 58, 175, 340 and 1085 mg/kg bw/day (diet), 13 weeks Study BASF 50S0227/92059	No treatment-related mortality. No treatment-related clinical signs. Body weight gain: ↓ at HD in both sexes along with decreased food consumption Haematology: RBC affected (↓MCV, ↓MCH, ↓MCHC) at HD in both sexes Organ weights (bodyweight-relative): ↑ absolute and relative weight of liver at 340 and 1085 mg/kg bw/day Histopathology: hypertrophy of periacinar and centriacinar hepatocytes at 340 and 1085 mg/kg bw/day; Slight or moderate hypertrophy of the thyroid,

Active ingredient	Study details^Δ	Major findings
		follicular epithelium and associated pale staining colloid at 340 and 1085 mg/kg bw/day NOAEL: 175 mg/kg bw/day
	Rabbits (NZW), *n* = 5/sex/dose 0, 130, 264, 534 mg/kg bw/day (dermal) 5 days/week; 13 weeks (Odio *et al.,* 1994)	Slight to moderate skin irritation (erythema and desquamation) at all doses at the site of application correlated to ↓ bodyweight gain at 264 and 534 m/kg bw/day. No evidence for haematological or macroscopic and histopathological abnormalities No effects were reported on testicular and epididymal morphology as well as on sperm count and motility NOAEL*:* 534 mg/kg bw/day (systemic toxicity) NOAEL: 130 mg/kg bw/day (dermal)
	A follow up mechanistic study was conducted in rats to investigate mechanisms related to potential thyroid effects of octocrylene observed in the 13-week oral repeat dose study in rats Rats (Wistar), *n* = 5/sex/dose 72, 215, 720 mg/kg bw/day PO (Subset A) 63, 188, 630 mg/kg bw/day PO (Subset B) 28 days (Subset A) 14 days (Subset B)	No treatment-related mortality No treatment-related clinical signs. Body weight gain: ↓ at HD in both subsets Serum chemistry: ↑ TSH at 630 mg/kg bw/day in ♀ in subset B; ↑ TSH at 720 mg/kg bw/day in both sexes in subset A Organ weights (bodyweight-relative): ↑ absolute and relative weight of liver at high doses in both sexes in both subsets Histopathology: minimal follicular cell hypertrophy/hyperplasia of the thyroid gland at high doses in both sexes in both subsets NOAEL: 188-215 mg/kg/day
Octinoxate (ECHA 2021e)	Rats (not specified), *n*=5/sex/dose, at 300, 900 and 2700 mg/kg bw/day (gavage), 3 weeks	↓ body weight, ↓ relative and absolute weight of the thymus at HD, ↓absolute weight of the left kidney (♂) and ↓ absolute weight of the heart (♀) at HD. NOAEL: 900 mg/kg bw/day.
	Rats (SPF), *n*=12/ sex/dose, at 200, 450 and 1000 mg/kg/day (oral), 13 weeks with recovery period of 5 weeks	↑ Kidney weights at HD, reversed during the recovery period (5 weeks). ↓ glycogen in the liver and ↑ iron in the Kupfer cells at HD, ↑ GLDH in ♀ at HD. Some of the effects were reversed during the recovery period; however, then reversed effects were not listed in the AICIS report. NOAEL: 450 mg/kg/day based on the minor and reversible changes at 1000 mg/kg bw/day
	Rats (SD), *n*=10/sex/dose, 55.5, 277 and 555 mg/kg/day, 5 days/ week, 13 weeks (dermal)	Mortality: none treatment-related ↑ (non-significant) serum alanine phosphatase (SAP) levels and ↑ relative liver weight at HD. Liver effects were not observable upon microscopic examination. NOAEL: 555 mg/kg bw/day based on no significant adverse effects at the highest treated dose
	Rats (SD), *n*=15/sex/dose; 0, 500, 1500 or 5000 mg/kg/day applied occlusively on the abraded skin, 6 days/ week, 28 days (dermal)	No systemic effects, body weight changes, ocular defects, haematology effects or changes in blood chemistry parameters were observed. Dose dependent low-grade epidermal proliferation at all doses (more prominent in ♂). The chemical was considered as a low-grade irritant under the conditions of this study (OECD TG 410) NOAEL: 5000 mg/kg bw/day
	Rabbits (NZW), *n* = 10/sex/dose, 500, 1500 or 5000 mg/kg bw/day applied occlusively on the abraded skin, 6 hours/day, 21 days (dermal)	Mortality: 3 at HD Lethargy, hunched posture, hair loss, soiled coats, emaciation, increased respiration, swelling of the conjunctivae, and reproductive effects (retardation of testicular growth) at HD.

Active ingredient	Study details^Δ	Major findings
		Haematological changes including ↑ neutrophils and urea nitrogen, and ↓ lymphocytes and alkaline phosphatase activity at HD. Dermal irritation effects (erythema, oedema, desquamation, cracking and atonia) were observed at all doses but were more severe at the HD. Histopathology of the skin sites showed an epidermal proliferative response with low grade inflammatory reaction (dose dependent). NOAEL: 1500 mg/kg bw/day
Ethyl hexyl triazone (ECHA 2021b; DEPA 2015)	Rats (Wistar), *n*=10/sex/group, 0, 1000, 4000, and 16000 mg/kg bw/day;7 days/week, 90 days (oral)	Slight variations in the haematological and clinical chemistry parameters corresponded to the range of biological variation in the species. ↑ Liver-weight without histological correlates among treated female animals could not be interpreted as being treatment-related. **NOAEL: 1000 mg/kg bw/day** (nominal) was mentioned.
	Rats, *n* = 10/sex/group, 0, 1000, 4000, and 16000 mg/kg bw/day (diet); 7 days/week, 90 days	Clinical signs: none treatment-related in the haematological and clinical chemistry parameters No treatment-related effects on organs NOAEL: ≤ 1275 mg/kg bw/day (nominal)
Oxybenzone (SCCP 2006a; 2021c)	Mice (B6C3F1; *n* = 5/sex/group), 0, 3125, 6250, 12500, 25000, 50000 ppm (equivalent to 1021, 2041, 4430, 8648, 20796 mg/kg bw/day), 14 days (diet)	Mortality: none Bodyweight gain: ↓ in ♂at HD. Organ weight: ↑ liver weights (♂ & ♀) from LD, associated histopathology observed at 2041 mg/kg bw/day; ↓ kidney weight in ♂ from 8648 mg/kg bw/day. NOAEL: 992 (♂)/1050 (♀) mg/kg/day
	Mice (B6C3F1; *n* = 10/sex), doses: 0, 0, 3125, 6250, 12500, 25000, 50000 ppm (equivalent to 554, 1246, 2860, 6780, 16238 mg/kg bw/day), 90 days (diet)	Mortality: none Bodyweight: ↓ BW gain in ♂ & ♀ from 6780 mg/kg bw/day Organ weights: ↑ liver weight from 1246 mg/kg bw/day with histopathology from 6780 mg/kg bw/day. Renal histopathology at HD in ♂. Reproductive parameters: ↓ sperm density and ↑ abnormal sperm in ♂ and ↑ oestrus cycle length in ♀ at HD NOAEL: 2860 mg/kg/day (equivalent to 1068 and 1425 mg/kg/day in ♂ and ♀, respectively)
	Rats (F344/N; *n* = 5/sex/group), Doses: 0, 3125, 6250, 12500, 25000, 50000 ppm (equivalent to 303, 576, 1132, 2238, 3868 mg/kg bw/day), 14 days (diet)	Mortality: none Bodyweight gain: ↓ in ♂at HD. Organ weight: ↑ liver (♂ & ♀) and kidney (♂) weights from LD, associated histopathology observed at 576 mg/kg bw/day in liver and at HD in kidney . NOAEL: 303 mg/kg/day (equivalent to 295 and 311 mg/kg/day in ♂ and ♀, respectively)
	Rats (F344/N; *n* = 10/sex/group), Doses: 0, 3125, 6250, 12500, 25000, 50000 ppm (equivalent to 0, 204, 411, 828, 1702, 3458 mg/kg bw/day), 90 days (diet)	Mortality: none. Clinical signs: coloured urine from LD. Bodyweights: ↓ BW gain in ♂ & ♀ from 1702 mg/kg bw/day. Clinical pathology: serum protein levels from 411 mg/kg bw/day, ↑ platelet counts from 1702 mg/kg bw/day Organ weights: ↑ liver weight from LD; ↑ kidney weight in ♀ from 1702 mg/kg bw/day with dilation of renal tubules, inflammation with fibrosis in renal interstitium at HD. Reproductive parameters: ↓ sperm motility in ♂ and ↑ oestrus cycle length in ♀ at HD. NOAEL: 411 mg/kg bw/day (equivalent to 429 and 393 in ♂ and ♀, respectively)

Active ingredient	Study details[Δ]	Major findings
	Mice (B6C3F1; *n* = 5/sex/group), Doses: 0, 0.5, 1.0, 2.0, 4.0, 8.0 mg/mouse in acetone or lotion* (equivalent to 24.8, 48.4, 100, 196, 388 mg/kg bw/day), 14 days (dermal)	Mortality: none Organ weights: ↑ liver weight from 196 mg/kg bw/day. NOAEL: 388 (♀) mg/kg bw/day (equivalent to 384 and 432 mg/kg/day in ♂ and ♀, respectively)
	Mice (B6C3F1; *n* = 10/sex/group), Doses: 0, 22.8, 45.5, 91, 183, 364 mg/kg bw/day in acetone or lotion*, 90 days (dermal, 5 days/week)	Mortality: none. Organ weights: ↑ kidney weight in ♂ at all doses Reproductive parameters: ↓ epididymal sperm density in ♂ at all doses. NOAEL: 364mg/kg bw/day in ♂ and ♀
	Rats (F344/N; *n* = 5/sex/group), doses: 0, 1.25, 2.5, 5, 10, 20 mg/rat in acetone or lotion* (equivalent to 7, 13.6, 27.7, 54.9 and 110 mg/kg bw/day), 14 days (dermal) (5 days/week for 2 weeks)	Mortality: none Organ weights: ↑ liver weight in ♀ from 27.7 mg/kg bw/day, ↑ kidney weight in ♀ at HD NOAEL: 100 (♂)/140 (♀) mg/kg bw/day
	Rats (SD; *n* = 6♂/group), 0, 100 mg/kg bw/day, 28 days (twice daily)(dermal)	No treatment-related effects (limited evaluation). NOAEL: 100 (♂) mg/kg bw/day
	Rats (F344/N; *n*-10/sex/group), doses: 0, 12.5, 25, 50, 100, 200 mg/rat in acetone or lotion* (equivalent to 12.5, 25, 50, 100, 200 mg/kg bw/day), 90 days (dermal)(5 days/week)	Mortality: none. Clinical pathology: ↓ reticulocyte counts from LD, ↑ platelet counts from 50 mg/kg bw/day, ↑ whole blood cell count produced by lymphocytosis at HD. NOAEL: 200 mg/kg bw/day
PBSA (SCCP 2006b)	Rats (Wistar; *n* = 5/sex/group) Doses: 0, 100, 330 and 1000 mg/kg bw, 13 weeks (oral)	No treatment-related effects. NOAEL: 1000 mg/kg bw/day
	Rats, n=5/sex/dose, 0, 100, 300, 1000 mg/kg bw/day, 2 weeks (gavage)	Mortality: none Clinical signs: none treatment related Body weight gain: ↓ at HD in ♂ along with decreased food consumption Haematology: none treatment related Serum chemistry: ↑ Triglycerides in both sexes at HD ↑APTT in ♂ at MD NOAEL: > 300 mg/kg bw/day ♂ NOAEL: >1000 mg/kg bw/day ♀
Homosalate (SCCS 2020; ECHA 2021c)	Repeat dose/ reproduction/ developments study Rats (Wistar), *n* =10/sex, 0, 60, 120, 300, 750 mg/kg bw/day (gavage), 7 weeks duration (ECHA 2020)	*Mortality:* 2 ♀ at 750 mg/kg bw/day *Clinical signs:* none treatment-related *Body weight gain:* ↓ at 750 mg/kg bw/day in ♂ and ♀ *Haematology:* none treatment-related *Serum chemistry:* ↑ Albumin and ↓ Globulin in ♂ at 300 mg/kg bw/day *Urinalysis:* not conducted *Organ weights (bodyweight-relative):* ↑ absolute and relative weight of liver in both sexes at 300 and 750 mg/kg bw/day, ↑ kidney in ♀ at 300 mg/kg bw/day. ↓ thymus in both sexes at 750 mg/kg bw/day. ↓ prostate and seminal vesicles at HD 750 mg/kg bw/day. *Gross pathology:* no treatment-related findings *Histopathology:* ↑ Minimal/moderate intra-epithelial hyaline droplets in the kidneys ♂ from 60 mg/kg bw/day (associated with ↑ in foci of basophilic tubules, single cell death and/or the presence of granular casts). * Minimal/mild hypertrophy of hepatocytes (1/5 ♂) at 120 mg/kg bw/day, and almost every ♂ and ♀ from 300 mg/kg bw/day.

Active ingredient	Study details^Δ	Major findings
		Hypertrophy of the follicular epithelium of thyroid gland in ♂ at 750 mg/kg bw/day and in ♀ from 300 mg/kg bw/day. ↓ Cortical lymphocytes in males from 300 mg/kg bw/day and in ♀ at 750 mg/kg bw/day *NOAEL:* ** mg/kg bw/day *The REACH registrants considered this as manifestations of hyaline droplet nephropathy without giving further evidence. **Based on this study, the REACH registrants derived a NOAEL of 300 mg/kg/day for general toxicity based on mortality in HD females. However, at this dose effects on kidneys, liver, thyroid and thymus occurred. In males, effects were noted **from the lowest dose of 60 mg/kg bw/d**, therefore the SCCS considers this dose as LOAEL.

Δ GLP compliance was not specified in the reviews

Genotoxicity

A summary of genotoxicity studies for each sunscreen ingredient is shown in the table below. With the exception of homosalate, all sunscreen ingredients were negative in *in vitro* and *in vivo* tests. Homosalate was negative in the Ames test and the gene mutation test in Chinese hamster cells *in vitro.* However homosalate induced DNA damage the Comet assay in isolate human peripheral lymphocytes and in the micronucleus assay *in vivo*.

Table 3-7. Summary of genotoxicity studies with sunscreen ingredients

Avobenzone (ECHA (2021a; DEPA 2015)	Ethylhexyl triazone (ECHA (2021b; DEPA 2015	Homosalate (SCCS 2020; ECHA 2021c)	Octinoxate (ECHA 2021e)	Octocrylene (SCCS 2021a; ECHA 2021d)	Oxybenzone (SCCP 2006a; 2021c)	PBSA (SCCP 2006b)
In vitro Negative AMES test and gene mutation study V79 Chinese hamster cells In vivo Negative Bone marrow polychromatic erythrocytes (mice)	*In vitro* Negative AMES test, Chinese hamster lung fibroblasts for chromosome aberration, Chinese hamster ovary (CHO) cells, in vivo chromosome aberration test	*In vitro* Negative AMES test and gene mutation study in V79 Chinese hamster cells Findings from the SCGE comet assay in isolated human peripheral lymphocytes and micronucleus assay in MCF-7 cells suggest that homosalate induced DNA damage in a dose	*In vitro* Negative AMES test, mammalian cell transformation assay (BALB/c-3T3 clone A31-11 cells), micronucleus test (mice), Unscheduled DNA synthesis assay (rat primary hepatocytes), Chromosomal aberrations (human peripheral blood lymphocytes) In vivo	*In vitro* Negative AMES test, gene mutation test, cytogenicity test in mammalian cells, chromosome aberrations tests In vivo Negative Cytogenicity test in mice (ECHA 2020, SCCS 2021a)	*In vitro* Negative AMES test (weak positive: TA97 (30% hamster +S9), 10% hamster or 10% and 30% rat S9), Chinese hamster lung fibroblasts for chromosome aberration ±S9, CHO cells –S9; Sister-chromatid exchanges and chromosomal aberrations + S9 In vivo Negative micronucleus test (mice),	*In vitro* Negative AMES test and chromosome aberration test in human peripheral blood lymphocytes In vivo No data

Avobenzone (ECHA (2021a; DEPA 2015)	Ethylhexyl triazone (ECHA (2021b; DEPA 2015	Homosalate (SCCS 2020; ECHA 2021c)	Octinoxate (ECHA 2021e)	Octocrylene (SCCS 2021a; ECHA 2021d)	Oxybenzone (SCCP 2006a; 2021c)	PBSA (SCCP 2006b)
		dependent manner and it is clastogenic when the cells were incubated at cytotoxic concentratio ns (Yazar et al. 2018; 2019)	Negative Chromosomal aberrations in micronucleus assay in bone marrow polychromatic erythrocytes, Cell gene mutation assay (V79, ± S9) showed a very slight increase in mutant colonies (up to 20 mg/mL)		chromosome aberration test (rats), Drosophila (SMART)†	

† In a recently published study (Majhi *et al.* 2020), benzophone-3 (1 and 5 μM) increased DNA damage similar to that of E2 treatment in a ERα-dependent manner. Benzophone-3 exposure caused R-loop formation in a normal epithelial cell line when ERα was introduced. R-loops and DNA damage were also detected in mammary epithelial cells of mice treated with benzophone-3.

Carcinogenicity

No carcinogenicity data were available for avobenzone, octinoxate, octocrylene, ethylhexyltriazone, homosalate or PBSA. Oxybenzone was carcinogenic in mice (bone marrow, spleen, kidney and liver), with equivocal evidence of carcinogenicity observed in rats (brain, spinal cord, thyroid and uterus). Findings are provided in the following table.

Table 3-8. Summary of carcinogenicity studies with sunscreen ingredients

Active ingredient	Study details	Major findings
Avobenzone	–	No data
Ethyl hexyl triazone	–	No data
Homosalate	–	No data
Octinoxate	–	No data
Octocrylene	–	No data

Active ingredient	Study details	Major findings
Oxybenzone (SCCP 2006a; 2021c)	Mice (B6C3F1/N; *n*=50/sex/group), 0, 1000, 3000, 10000 ppm (equivalent to 113/109, 339/320, 1207/1278 mg/kg bw/day in ♂/♀)	Mice: ↑ lesions in the bone marrow, spleen, and kidney of both sexes and in the liver in ♂
	Rats (SD; *n*=10/sex/group), 0, 1000, 3000, 10000 ppm (equivalent to 58/60, 168/180, 585/632 mg/kg bw/day in ♂/♀) Two years (beginning on GD6 in ♀)	Rats: ↑ incidence of brain and spinal cord malignant meningiomas at 3000 ppm in ♂ and thyroid C-cell adenomas at 3000 ppm) and uterine stromal polyps at 3000 ppm in ♀ without any dose-response relationship. These findings are considered equivocal evidence of carcinogenicity.
PBSA	–	No data

Reproductive and developmental studies

A summary of reproductive and developmental toxicity studies for each sunscreen ingredient is shown in the table below.

Table 3-9. Summary of reproductive and developmental toxicity studies with sunscreen ingredients

Active ingredient	Study details	Major findings
Avobenzone (ECHA 2021a; DEPA 2015)	Rats at 0, 250, 500 and 1000 mg/kg bw/day (oral gavage), GD 7 -16.	No treatment-related skeletal malformations were observed. One pup with two fused sternal elements was seen at LD. A slight increase of incised neural arches and sternebrae was seen at 500 mg/kg/day. The soft tissue examination displayed one fetus of the 500 mg/kg dose group with unilateral missing ovarium and uterus. No effects were considered treatment related in the absence of dose dependence. In the rearing group, all measured parameters were well comparable to concurrent control group values. Maternal and developmental NOAEL: 1000 mg/kg bw/day.
	Rabbits, single dose of 500 mg/kg bw/day GD 7-19 (oral, daily)	No treatment-related effects or teratogenicity.
Octinoxate (ECHA 2021e)	Rats (Wistar); *n* = 25/sex/dose. 0, 150, 450 or 1000 mg/kg bw/day (oral), The parental (F0) generation was exposed throughout premating period (73 days), mating (21 days), gestation (21 days), and up to weaning of the F1 offspring (21 days). The duration of exposure for the F1 generation was similar to F0.	No adverse effects were observed on oestrous cycles, sperm and follicle parameters, mating, fertility, morphology and motility, gestation and parturition. ↓ food consumption and body weight, ↑ liver weight and hepatic cytoplasmic eosinophilia related to hepatic enzyme induction, and ↑ ulceration of the glandular stomach mucosa at HD. In the offspring, ↓ lactation weight gain and organ weights, and slightly delayed sexual maturation (vaginal opening and preputial separation) at HD. **NOAEL: 450 mg/kg bw/day** for fertility and reproduction parameters, and for systemic parental and developmental toxicity (Schneider *et al.* 2005, REACH).
	Pregnant rabbits (*n*=20/dose), 80, 200 or 500 mg/kg bw/day on GD 7–20.	Reproductive parameters were not affected. Except for a slight reduction of maternal and foetal weight at HD, no abnormality was found. The fetuses did not show any skeletal or visceral abnormalities. ↓ body weight at HD, but within the range of other doses and the controls.

Active ingredient	Study details	Major findings
		NOAELs: 500 mg/kg bw/day (Maternal and developmental).
	Rats (albino, ♀), single dose of 1000 mg/kg bw/day on GD 7–16 (oral gavage)	No maternal, embryotoxic or teratogenic effects were observed. No other information was provided.
	NTP-DART-06 (2022b) Modified one-generation study Rats (SD); *n*=26/dose; exposure through feed and/or lactation 1000, 3000, 6000 ppm (equivalent to 70 to 87, 207-418 , 419-842 mg/kg/day) F_0 dams: GD6 - LD 28 F_1 offspring were exposed in utero and during lactation through postnatal day (PND) 28 and evaluated for signs of toxicity. After weaning, F_1 offspring were allocated into prenatal, reproductive performance or subchronic exposure cohorts. Exposure to test article continued in feed until necropsy on PND96, 120 or 150. F_2 offspring were exposed in utero, during lactation and postweaning until necropsy on GD21 or PND28.	Octinoxate did not induce overt F_0 or F_1 maternal toxicity or affected mating or pregnancy indices. Reproductive performance (fertility and fecundity), numbers of live fetuses and pups ware not affected. Octinoxate exposure was not associated with any effects on fetal weight or the incidences of external, visceral, or skeletal malformations. Equivocal evidence of developmental toxicity was observed: ↓ Mean pup body weight (F1) at HD ↑ Vaginal opening (F_1) from MD ↑ Balanopreputial separation (F_1) at HD NOAEL: 6000 ppm for parental systemic toxicity, fertility and reproduction performance NOAEL: 1000 ppm for developmental toxicity
Octocrylene (SCCS 2021a; ECHA 2021d)	Extended one generation reproductive toxicity study (EOGRTS), GLP Rat (Wistar); Dose: (diets) 55, 153, 534 mg/kg bw/day ♂ 58, 163, 550 mg/kg bw/day ♀ *n*= 27 or 28 /sex /dose F1: Cohort 1A: 19/sex/ dose Cohort 1B: 25/sex/dose Cohort 2A: 10/sex/ dose Cohort 2B: 10/sex/dose ♂: 10-week premating period, during mating up to the day of sacrifice (~ 13 weeks) ♀: P: 10-week premating period, termination on LD 21 F1: from weaning up to sacrifice (~ 10 weeks in Cohort 1A, ~ 13 weeks (♂) and approx. 18 weeks (♀) in Cohort 1B; ~ 8 weeks in cohort 2A) F2: until weaning (indirectly) (ECHA 2021d; SCCS 2021a)	↓ number of implantation sites and consequently a lower number of pups at HD ↓ bodyweight of pups at HD No effects on male fertility and male and female reproductive parameters such as oestrus cycle, epididymal and testicular sperm parameters at all doses. No effects on sexual and neurodevelopmental parameters in pups. Based on effects on parental and pup body weights, a lower number of implantation sites and lower number of pups delivered. **NOAEL: 153/163 mg/kg bw/day for males/females** for parental systemic toxicity, fertility/reproduction performance, and general and sexual development
	Pregnant rats (Wistar); *n* = 25/ ♀/dose, Dose: 0, 100, 400, 1000 mg/kg bw/day PO GD6–GD15; termination on GD21	F0: Transient salivation at HD. ↑ relative liver weight at MD and HD F1: No treatment related effects. NOAEL: ≥ 1000 mg/kg bw/day (teratogenicity)

Active ingredient	Study details	Major findings
	Mice (CD-1); *n*= 12 ♀/dose, Dose: 0, 100, 300, 1000 mg/kg bw/day (oral gavage); GD8–GD12; termination on LD3 Odio *et al*. (1994)	No treatment related adverse effects. NOEL: 1000 mg/kg bw/day (mice)
	Rabbit (NZW); *n* = 17 ♀/dose Dose: 0, 65, 267 mg/kg bw/day, (Dermal, open, clipped area on the back), dosing GD6–GD18; termination on GD21 Odio *et al*. (1994)	No treatment related adverse effects. NOEL (percutaneous): 267 mg/kg bw/day (rabbits)
Ethylhexyl triazone (ECHA 2021b; DEPA 2015	Rats (wistar), Prenatal Developmental Toxicity study (*n*=25/dose). Dosing the dams 7 days/week for an unspecified period (0, 100, 400 and 1000 mg/kg bw/day).	No treatment-related effects reported. Maternal NOAEL = 1000 mg/kg bw/day; Developmental NOAEL = 1000 mg/kg bw/day
Homosalate (SCCS 2020; ECHA 2021c)	The evaluation of potential toxicity of homosalate on fertility and development was performed in a combined repeat dose toxicity study with the reproduction/developmental toxicity-screening test (described above in repeat-dose toxicity section). The study findings were considered as inconclusive and unreliable due to a technical error that maintained the animals under a constant light. In the context of a compliance check process under REACH, the ECHA adopted a decision in 2018 requesting a sub-chronic toxicity study, a prenatal developmental toxicity study, an extended one-generation reproductive toxicity study, and the identification of degradation products (ECHA 2018, ECHA decision CCH-D-2114386909-26-01/F). An appeal was filed against this decision; however, the Board of Appeal dismissed the appeal and decided that the information must be provided by 25 February 2024.	
Oxybenzone (SCCP 2006a; 2021c)	Mice (CD-1), RACB (Reproductive Assessment by Continuous Breeding): 1850, 3950, 9050 mg/kg bw/day (14 days; *n*=20/sex); 1000, 2100, 4700, 10200, 15700 mg/kg bw/day (14 weeks; *n*=8/sex)	No effect on fertility at doses up to 8600/9500 mg/kg bw/day in♂ /♀ mice (highest dose). Effects on reproductive performance included a slightly lower number of live pups at birth. Impaired body weight/body weight gain in pups was also observed. All effects were observed at dose levels resulting maternal toxicity including decreased bodyweight and premature death at doses of 1850 mg/kg bw/day. The NOAEL for systemic, reproductive and developmental toxicity was 1800/1900 mg/kg bw/day in males/females.
	Rats (F344/N; *n*=10/sex) and mice (B6C3F1; *n*=10/sex): 0, 3125, 12500, 50000 ppm (equivalent to 204, 828, 3458 mg/kg bw/day in rats and 554, 2860, 16238 mg/kg bw/day in mice);13 weeks (dietary)	↓ Epididymal sperm counts, and decreased absolute cauda, epididymal and testis weight as a consequence of the reduced body weight in male rats and ↑ in the length of the oestrous cycle in female rats. ↓ in the epididymal sperm count and ↑ the incidence of abnormal sperm was observed in male mice, and there was an ↑ in the length of the oestrous cycle in female mice (as seen in rats). Oestrous cyclicity was not affected in either rats or mice. NOAEL for reproductive parameters was established at 828 mg/kg bw/day in rats and 2860 mg/kg bw/day in mice (SCCP 2006a).
	Rats (SD; n=not reported) doses up to 200 mg/kg bw/day and mice (B6C3F1; n= x ♂);0, 20, 100, 400 mg/kg bw/day; 13 weeks (dermal)	No effects on selective reproduction parameters and a NOAEL was established at 200 mg/kg bw/day, the highest dose tested in rats. In mice, there were no effects on reproductive organ weight, cauda epididymal sperm concentration, sperm parameters, testicular spermatid concentration or testicular histology. NOAEL: 400 mg/kg bw/day, the highest dose tested.
	Prenatal developmental toxicity study in rats (Wistar; *n*=25 ♀), at doses of 0, 40, 200, 1000 mg/kg bw/day PO	Slight ↑ rates of fetuses/litter with skeletal variations (incomplete ossification of different skull bones and cervical arch, supernumerary 14th ribs) and therefore ↑ rates of total variations were observed at 1000 mg/kg bw/day. These effects were associated with maternal toxicity (clinical signs, reduced

Active ingredient	Study details	Major findings
		bodyweight and food consumption). The NOAEL was established at 200 mg/kg bw/day.
	Reproductive toxicity study in rats (SD) at doses of 3000, 10000 and 30000 ppm (equivalent to 242, 725 and 3689 mg/kg bw/day) in the diet from GD 5-15.	The maternal NOAEL was established at 3000 ppm (206-478 mg/kg bw/day) based on reduced bodyweight gain during GD 6-9 and lactation day 4-21. The developmental NOEL was established at 3000 ppm (206-478 mg/kg bw/day) based on impaired postnatal bodyweight performance at 10000 ppm (660-1609 mg/kg bw/day) (SCCS 2021c).
	Nakamura *et al.* (2015) Reproductive toxicity study in rats (SD; *n*=7-8 mated ♀); Doses: 0, 1000, 3000, 10,000, 25,000, or 50,000 ppm, equivalent to 67.9, 207.1, 670.8, 1798.3, and 3448.2 mg/kg bw/day, respectively. Treatment from GD6-PND23. The effects of maternal exposure during gestation and lactation on development and reproductive organs of offspring of mated female rats was examined.	Exposure to <10,000 ppm oxybenzone was not associated with adverse effects on the reproductive system in rats. At higher doses, a decrease in the normalised anogenital distance in male pups at PND 23, impairment of spermatocyte development in testes of male offspring, delayed follicular development in females was observed at doses of ≥207 mg/kg bw/day. The **NOAEL was established at 67.9 mg/kg bw/day.**
	Han *et al.* (2022) Reproductive toxicity study in mice (ICR; *n*=13-15 mated ♀) Doses: 0, 0.1, 10, 1000 mg/kg/day PO Treatment from GD1-GD13	No adverse effect on maternal body weight and the relative weights of the liver, brain and the uterus Slight ↑ rate of fetal loss at HD; ↑ placental thrombosis and necrosis from LD (severity not assessed)
	NTP-DART-05 (2022a) Modified one-generation study Rats (SD; mated ♀; *n*= 25/dose) Doses: 0, 3000,10000, 30000 ppm; exposure through feed and/or lactation (equivalent of 205 to 426, 697 to 1621, and 2,644 to 5944 mg/kg/day respectively) F_0 GD6 - LD28 F_1 GD6 - LD28; after weaning, F_1 offspring were allocated into cohorts for prenatal, reproductive performance, or additional assessments (e.g., subchronic or biological sampling cohorts) and exposure to test article in feed continued until necropsy on PND96, PND120 or PND150 F_2 offspring were exposed in utero, during lactation and postweaning until necropsy on GD21 or PND28.	There was equivocal evidence of reproductive toxicity of oxybenzone based on ↓ F_2 litter size at HD. There was some evidence of developmental toxicity from MD based on ↓ F_1 and F_2 mean body weights; this effect on body weight contributed to the apparent oxybenzone -related ↓ in male reproductive organ weights from MD. The relationship of the ↑ occurrence of diaphragmatic and hepatodiaphragmatic hernias in F_1 adults and F_2 pups from MD is unclear. Exposure to oxybenzone was associated with ↑ nonneoplastic kidney lesions in the F_0, F_1, and F_2 generations at HD Exposure to oxybenzone was not associated with signals consistent with alterations in estrogenic, androgenic, or antiandrogenic action. NOAEL: 3000 ppm
PBSA (SCCP 2006b)	A prenatal developmental study (rats, *n*=25♀/group), treatment GD 6-15, doses: 0 and 1000 mg/kg bw/day (gavage)	No treatment-related findings were noted in the study. The NOAEL for maternal and fetal toxicity was 1000 mg/kg bw/day.

Active ingredients in human milk

In a cohort study between 2004 and 2006, 54 human milk samples were analysed; UV filters were detectable in 46 samples and levels were positively correlated with the reported usage of UV filter products (Schlumpf *et al.,* 2010). Concentrations of octinoxate or ethylhexyl methoxy cinnamate (EHMC), octocrylene (OC), 4-methylbenzylidene camphor (4-MBC), homosalate (HMS) and oxybenzone (BP-3) ranged 2.10–134.95 ng/g lipid, with octinoxate/EHMC and octocrylene being most prevalent (42 and 36 positive samples, respectively) and an average of 7 positive samples for the other three (Schlumpf *et al.,* 2010). In another study, levels of oxybenzone in maternal urinary samples taken in gestational weeks 6–30 were positively correlated with the overall weight and head circumference of the baby (Philippat *et al.* 2012). These reports raise concerns about potential prenatal exposure and developmental toxicity of UV filters.

Endocrine activity modulation

Chemicals with endocrine activity modulation are exogenous chemicals that can alter hormone action, thereby potentially increasing the risk of adverse health outcomes, including cancer, reproductive impairment, cognitive deficits and obesity. In 2013, publicly available data on endocrine disruptive properties of 23 ingredients including the ingredients reviewed in this document were collected and evaluated by the Danish Centre on Endocrine Disruptors (Axelstad *et al.* 2013). The overall conclusion of the evaluation was that there were not enough data to conclude whether the ingredients have endocrine disruptive properties or not.

> *"In conclusion, very little is known on the endocrine disrupting potential of these 23 UV-filters. For 14 of the 23 assessed UV-filters[8] no in vivo studies in rodents, assessing endpoint that are sensitive to endocrine disruption, have been performed, and it was therefore not possible to conclude anything on their endocrine disrupting potential, with regard to human health…*
>
> *Two of these (octocrylene and butyl methoxydibenzoylmethane) showed no adverse effects in the used test systems. Seven of the UV-filters (placed in groups C & D) were tested in the Uterotrophic assay, and regardless of their estrogenic potential in vitro, none of them caused increased uterine weights, indicating lack of estrogenic potential in vivo. The three compounds in-group E[9] were also investigated for androgen receptor (AR) agonism/antagonism in vitro, and the results differed somewhat depending on which type of study had been performed. However, since no in vivo studies investigating the anti androgenic effects of the compounds were present, it is difficult to conclude anything on their endocrine disrupting potential with regard to the possible androgenic/antiandrogenic mode of action. Information on human health endocrine disrupting potential of last two UV-filters (octocrylene and titanium dioxide) was also scarce. Since no adverse effects on testicular and epididymal morphology or on sperm quality were seen in a 90-day study of octocrylene, this UV filter did not seem to be a potent anti-androgen. Read across assessment showed possible resemblance of the chemical structures of some of the presently evaluated UV-filters to known or suspected endocrine disrupting UV-filters, however more knowledge on the endocrine disrupting potential of the presently evaluated UV-filters could be obtained by doing QSAR analyses. Unfortunately no published reports of such analysis were present in the open literature."*

An extensive review in 2016 also discussed the potential endocrine disruption of typical UV filters including benzophenones (i.e. oxybenzone), camphor derivatives and cinnamate derivatives (i.e., octocrylene, Octinoxate etc.) (Wang *et al.* 2016). The review (Wang *et al.* 2016) concluded:

> *"These UV filters are generally involved in the disruption of the hypothalamic–pituitary–gonadal system. As revealed by in vivo and in vitro assays, exposure to these chemicals induced various endocrine disrupting effects such as estrogenic disrupting effects, androgenic disrupting*

[8] EHT was included in these 14 ingredients
[9] Homosalate and avobenzone were included

effects as well as the disrupting effects towards TR, PR. The underlying mechanism of endocrine disruption was summarized (Table 2). The minor structural changes of these kinds of UV filters have influence on the potency of their endocrine disrupting effects."

The Table 2 (summarising the Endocrine Activity Modulation effects of the commonly used UV filters) from the Wang review is provided in the Appendix.

In a recent *in vitro* study, Rehfeld *et al.* (2018) found that the homosalate, oxybenzone, avobenzone, octinoxate and octocrylene induced Ca^{2+} influx in human sperm cells whereas ethylhexyl triazone did not. It concluded:

"*In conclusion, chemical UV filters that mimic the effect of progesterone on Ca^{2+} signaling in human sperm cells can similarly mimic the effect of progesterone on acrosome reaction and sperm penetration. Human exposure to these chemical UV filters may impair fertility by interfering with sperm function, e.g. through induction of premature acrosome reaction. Further studies are needed to confirm the results in vivo".*

Lee *et al.* (2022) screened octinoxate, octocrylene, avobenzone and homosalate among 35 other chemicals used in consumer products, for their ability to modulate estrogen receptor (ER) or androgen receptor (AR) *in vitro.* Octinoxate was a weak agonist of ER, while octocrylene acted both as a very weak agonist or a weak antagonist of ER, but both were negative for AR. Avobenzone and homosalate did not activate either ER or AR.

In the light of increased safety concerns regarding the Endocrine Activity Modulation potential of the active ingredients in sunscreens, in 2018, the ECHA and the European Food Safety Authority (EFSA) published "Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009 (Andersson *et al.* 2018). The Biocidal Products Regulation (EU No 528/2012; BPR) restricts approvals of the active substances considered to have endocrine disruption properties, unless the risk from exposure to the active substance is shown to be negligible or unless there is evidence that the active substance is essential to prevent or control a serious danger to human health, animal health, or the environment.

A recent Consensus Statement discussed ten key characteristics (KCs) of Endocrine Activity Modulation based on hormone actions and Endocrine Activity Modulation effects, the logic behind the identification of these KCs and the assays that could be used to assess several of these KCs (la Merrill *et al.* 2020).

A systematic review assessed 29 studies that addressed the impact of oxybenzone on human health (Suh 2020). The review suggests increased systemic level of oxybenzone had no adverse effect on male and female fertility, female reproductive hormone level, adiposity, fetal growth, child's neurodevelopment and sexual maturation (Suh 2020). However, the association of oxybenzone level on thyroid hormone, testosterone level, kidney function and pubertal timing has been reported warranting further investigations to validate a true association. The health effects of an increased octinoxate level have been less extensively studied presumably. The current evidence shows that topical application of octinoxate does not have biologically significant effect on thyroid and reproductive hormone levels (Suh 2020). However, the topical application of octinoxate results in systemic absorption greater than 0.5 ng/mL, a threshold established by the FDA for waiving toxicology assessment, and therefore further drug safety assessment on octinoxate is crucial.

The review concluded that:

"To evaluate the long-term risk of exposure to BP-3 or OMC from sunscreens, a well-designed longitudinal randomized controlled trial is of high priority."

The latest SCCS opinions on these ingredients considered available information on the endocrine activity of these active ingredients and suggested inadequate evidence is available for relevant safety determination.

The key conclusions from the evidence above are given below.

Avobenzone

The Danish Centre on Endocrine Disruptors (Axelstad *et al.* 2013) evaluated publicly available data on endocrine disruptive properties of substances and based on the assessment it concluded, that there were not enough data to conclude whether avobenzone has endocrine disruptive properties or not.

Homosalate

According to Danish QSAR database, homosalate was predicted to activate the E2R (Leadscope and SciQSAR)[10] and to act as an antagonist of androgen receptor (AR)(CASE Ultra and Leadscope).[10]

The SCCS (2020) conclusion was based on a Risk Management Options Analysis (RMOA) 2016 by ANSES[11]. As per the RMOA, *the available data from non-testing methods and in vitro assay and the inadequate in vivo studies provide indications for an ED potential of homosalate, whereas the rest of the studies were of limited relevance and do not indicate the potential for ED concern. Despite the poor quality of the in vivo studies, findings that could be linked to an endocrine disruption were identified, in particular fluctuations of hormones, sperm changes and effects on the thyroid*. These effects raised some concerns regarding ED properties of homosalate.

Therefore, the SCCS (2020) concluded:

> "*It needs to be noted that the SCCS has regarded the currently available evidence for endocrine disrupting properties of homosalate as inconclusive, and at best equivocal. This applies to all of the available data derived from in silico modelling, in vitro tests and in vivo studies, when considered individually or taken together. The SCCS considers that, whilst there are indications from some studies to suggest that homosalate may have endocrine effects, the evidence is not conclusive enough at present to enable deriving a specific endocrine-related toxicological point of departure for use in safety assessment.*"

Octocrylene

The endocrine activity modulation potential of octocrylene was extensively discussed in SCCS (2021a). The SCCS opinion concluded that:

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

Oxybenzone

The endocrine activity modulation potential of oxybenzone was extensively discussed in SCCS (2021c). The SCCS (2020) evaluated the potential endocrine mode of action for oxybenzone (BP-3) *in vitro* and *in vivo* and endocrine-related adverse effects in humans and animals.

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[10] QSAR software for modelling and predicting toxicity of chemicals. CASE Ultra has both methodologies (statistics based and expert rule based) built in for a complete ICH M7 compliant assessment. Leadscope Model Applier (Leadscope, Inc.) is a chemoinformatic platform that provides QSAR models for the prediction of potential toxicity and adverse human clinical effects of pharmaceuticals, cosmetics, food ingredients and other chemicals.

[11] French Agency for Food, Environmental and Occupational Health & Safety (ANSES) – See Eurometaux (2016).

The SCCS concluded:

> *"The currently available evidence for endocrine disrupting properties of BP-3 is not conclusive, and is at best equivocal. This applies to the data derived from in silico modelling, in vitro tests and in vivo studies, when considered individually or taken together. There are either contradictory results from different studies, or the reported data do not show dose-response relationship, and/or the effect are seen only at relatively very high doses that can only be considered far beyond the human exposure range. In view of this, the SCCS considers that whilst there are indications from some studies to suggest that BP-3 may have endocrine effects, it is not conclusive enough at present to enable deriving a new endocrine-related toxicological point of departure for use in safety assessment."*

Octinoxate

Most of the available data suggest that octinoxate has an estrogenic activity, androgenic and anti-thyroid activity in rats and humans [NICNAS (currently known as AICIS), 2017; Lorigo *et al.* 2018].

Regarding the octinoxate mechanism of action, several studies showed that the effects exerted by Estradiol (E2) and octinoxate were not always totally shared and it is possible that octinoxate could act by a mechanism different from the classic E2R (α y β). There are few data regarding the anti-androgenic activity of octinoxate, and the studies suggest that octinoxate is not able to bind to androgen receptors. Studies in rats showed that octinoxate could disturb the homeostasis of the thyroid hormones by mechanisms different from the classical ones of hormone-dependent regulation and feedback.

More studies in rodents and very few in humans, suggest that an increase exposure to octinoxate could be related to infertility or changes in GnRH and disturbance of reproductive hormone levels. A public call by the European Commission for data on the endocrine activity modulation potential of ingredients used in cosmetics, including octinoxate, was undertaken from 15 February to 15 November 2021 (EU 2021).

A recent review summarises the endocrine effects of these ingredients recognising limited data availability (Fivenson 2020). This was a retrospective literature review that involved many different types of studies across a variety of species. Comparison between reports is limited by variations in methodology and criteria for toxicity.

Other studies

The photo-allergic potential of avobenzone has been extensively reviewed in several publications (Nash and Tanner 2014). However, given the mechanistic understanding and known photo-degradation of avobenzone, the findings were inconsistent. For example, the *in vitro* skin phototoxicity of cosmetic formulations containing avobenzone, other UV filters and vitamin A palmitate was assessed by two *in vitro* techniques [3T3 Neutral Red Uptake Phototoxicity Test (3T3-NRU-PT) and Human 3-D Skin Model *In Vitro* Phototoxicity Test (H3D-PT)](Gaspar *et al.* 2013).The phototoxicity potential was 'positive' for avobenzone alone and in combination with other UV filters (3T3-NRU-PT). However, when tested on a human skin model, the 'positive' results were no longer observed. It has been suggested by several studies and reviews that the photoallergic potential of avobenzone may be the result of the photoproducts formed following exposure to UV. These data suggest that photo-degradation of avobenzone forms classes of photoproducts (arylglyoxals and benzils) which have strong potential for sensitization (Karlsson *et al.* 2009).

A survey in Canada (2001-2010) indicated that the most common photoallergens were oxybenzone, octyl dimethyl para-amino- benzoic acid and avobenzone whereas the most common contact allergens were octyl dimethyl para-aminobenzoic acid, oxybenzone and sandalwood (Yap 2017).

The SCCS (SCCS 2000) stated that octinoxate did not have phototoxic potential based on one study of 10 subjects exposed to patches of octinoxate for 24 hours and then exposed to a sub-erythematous dose of UV irradiation. No further details were supplied in the SCCS report. Recent *in vitro* (3T3 viable monolayer fibroblast cultures) and *in vivo* studies indicated that octinoxate was not phototoxicity (Gomes *et al.* 2015).

A human repeated insult patch test (HRIPT) was carried out at a concentration of 2% octinoxate in 53 subjects. There was no sensitisation. Similar studies using different formulations (7.5 % octinoxate in petrolatum or 10 % octinoxate in dimethylphthalate) also did not show any adverse reaction after 24 and 48 h. In a study in 32 healthy volunteers, daily whole–body topical application of 2 mg/cm^2 of cream formulation without (week 1) and with (week 2) the sunscreen (octinoxate 10%) for one week was performed. Hormone changes (testosterone, oestradiol and inhibin B levels) were observed following treatment but were not considered to be biologically significant. Following 1–2 hours of application, the chemical was detected in the parent form both in plasma and in urine (more than 86 % of the applied dose).

Oxybenzone was not phototoxic in the 3T3-NRU-PT test and was not phototoxic in *S. cerevisiae* or *E. coli in vitro*. Oxybenzone was not phototoxic in guinea pigs *in vivo* at a concentration of 10% (oxybenzone applied to shaven and depilated skin for 30 minutes followed by irradiation (UV-A) for 60 minutes). Oxybenzone did not cause photosensitisation in rabbits *in vivo* (study details not available). Oxybenzone was not photomutagenic in the photo Ames test or an *in vitro* chromosome aberration assay in CHO cells.

Oxybenzone was tested for photobinding to human serum albumin and histidine photo-oxidation potential in a mechanistic *in vitro* test for the discrimination of the photo-allergic and photo-irritants where oxybenzone revealed no phototoxic potential (SCCP 2006a). However, in a recent study, oxybenzone was shown to cause photoallergenic reactions being second most frequent photo contact allergen among the UV filters (European photo patch test task force) (Subiabre-Ferrer *et al.* 2019).

Ethylhexyl triazone (10%) did not cause photosensitisation in guinea pigs. Separate tests with *Saccharomyces cerevisiae* and CHO cells exposed to the ethylhexyl triazone and UVA and UVB irradiation did not show any potential photomutagenic effects of ethylhexyl triazone.

Phototoxicity, photosensitisation and photomutagenicity of phenylbenzimidazole sulfonic acid was examined in the SCCP opinion on phenylbenzimidazole sulfonic acid and its salts (SCCP 2006b). Phenylbenzimidazole sulfonic acid was not a photo-irritant in mice or guinea pigs *in vivo*, or in 3T3 cells *in vitro* (Photo irritation factor of 1.4). In addition, phenylbenzimidazole sulfonic acid was not photomutagenic in the photo Ames test, a yeast gene conversion assay or an *in vitro* chromosome aberration assay in CHO cells. A few cases of photoallergic contact dermatitis reactions have been reported in the literature following use of products containing phenylbenzimidazole sulfonic acid, however no skin reactions have been observed in dedicated patch tests studies in human volunteers at concentrations up to 10%, with or without irradiation (SCCP 2006b).

The incidence of positive reactions (0.08%) was reported in a recent patch study among patients administered with octocrylene at 10% in petrolatum (n = 2577) (Uter *et al.* 2017). Similar findings were reported in an EU multicentre photopatch test study where contact allergy was reported in only 0.7% of the 1031 patients patch tested with 10% octocrylene in petrolatum for suspected photoallergic contact dermatitis (Klimova *et al.* 2015).

Contact allergy to octocrylene appears to be more frequent and severe in children (EMCPPTSA 2012; Gilaberte and Carrascosa 2014) whereas photoallergic contact dermatitis to octocrylene was found to be much more frequent in adults (NICNAS 2017). Photocontact allergy to octocrylene was reported in 4% of the 1031 adult patients patch-tested for suspected photoallergic contact dermatitis (EMCPPTSA 2012). The occurrence of photoallergic contact dermatitis to octocrylene was found to be related to a previous photoallergy to topical ketoprofen (Loh and Cohen 2016). Patients with photoallergic contact dermatitis caused by sunscreens and positive photopatch tests to octocrylene have been mainly reported in France, Belgium, Italy and Spain, countries in which topical ketoprofen is used regularly in consumer products (de Groot and Roberts 2014). This was confirmed in a recent study conducted in Italy where concomitant photocontact allergy to ketoprofen was reported in 61.5% of 156 patients (Romita *et al.* 2018). A very recent review has evaluated these findings extensively (Berardesca *et al.* 2019).

Several hypotheses were proposed to illustrate the mechanism for the co-reactivity of octocrylene namely: (i) the role of the benzophenone moiety of ketoprofen (although the benzophenone moiety is not part of the octocrylene structure, aminolysis and hydrolysis of octocrylene in the skin may result in the formation of benzophenone which then can lead to cross-reactivity); (ii) hyper-photo susceptibility to ingredients that are nonrelevant allergens; and (iii) co-reactivity – i.e. concomitant sensitization or prior or subsequent *de novo* photosensitisation – may be involved in place of cross-reaction.

The presence of sensitizing impurities in some commercial batches of octocrylene were also suspected to be allergens contributing to photocontact allergy (Aerts *et al.* 2016).

Neurotoxic effects of active ingredients in sunscreens were reviewed extensively (Ruszkiewcz *et al.* 2017). The table listing the effects from the treatment of octinoxate, oxybenzone and octocrylene is shown below. However, this is not reviewed in this discussion elaborately as similar mechanisms apply on endocrine activity modulation potential of these ingredients (Ruszkiewcz *et al.* 2017).

Obesogenic potential of avobenzone was demonstrated *in vitro* by Shin et al. (2020) and Ahn et al. (2019). In normal human epidermal keratinocytes, avobenzone (10 μM) increased expression of genes associated with lipid metabolism, including peroxisome proliferator-activated receptor γ (PPARγ) and promoted adipogenesis in human bone marrow mesenchymal stem cells (EC_{50} = 14.1 μM). Nevertheless, avobenzone did not bind PPARγ and the avobenzone-induced adipogenesis-promoting activity was not affected by PPARγ antagonists (Ahn *et al.* 2019). Even though potential obesogenic effect in human subject cannot be unequivocally excluded, it is unlikely given that mean C_{max} (12.89 nM or 4 μg/L; see **Clinical Trials**) of avobenzone following a dermal application was ~1000 lower than concentrations promoting adipogenesis *in vitro*.

Similarly, obesogenic potential of octocrylene was postulated by Ko *et al.* (2022), but in contrast to avobenzone, octocrylene directly bound PPARγ, although with a relatively low affinity (Ki = 37.8 μM). *In vitro* octocrylene induced (EC_{50}= 29.6 μM) adiponectin secretion by human bone marrow mesenchymal stem. However, like avobenzone, the obesogenic impact of octocrylene applied dermally is not expected, as mean plasma C_{max} of (32 nM or 11.7 μg/L; see **Clinical Trials**) was 925 lower than the EC_{50} of adiponectin secretion *in vitro*.

The immunomodulatory effect of avobenzone was reported *in vitro*. At 50 μM the compound increased IL-8 secretion by monocyte-like THP-1 cells as well as by THP-1 derived macrophages (Weiss *et al.* 2023). However, the immunomodulatory effect of avobenzone in sunscreen applications is not predicted considering low systemic exposures (C_{max} = 12.89 nM) and relatively low impact *in vitro* (fold changes of affected factors were generally < 2) at concentrations exceeding C_{max} ~4000 times.

Table 0-30 Summaries of other studies

Compound	Exposure model	Experimental design	Effect
Octyl methyoxycinnamate or octinoxate	Wistar rats	Oral (gavage) administration during gestation and lactation	Decreased motor activity in female offspring, increased spatial learning in male offspring.
	Sprague-Dawley rats, female	Oral (gavage) administration for 5 days; 10–1000 mg/kg/day	Non-estrogenic interference within the rodent HPT axis; no changes in pre-proTRH mRNA in mediobasal-hypothalamus.
	Wistar rats	In vitro incubation of hypothalamus isolated from adult rats; 60 min; 0.263 µM	Decreased hypothalamic release of GnRH. Increased GABA release and decreased Glu production in males. Decreased Asp and Glu production in females.
	Wistar rats	in vitro incubation of hypothalamus isolated from immature rats; 60 min; 0.263µM	Decreased hypothalamic release of LHRH. Increased GABA release in males, decreased Asp and Glu levels in females.
	SH-SY5Y neuroblastoma cell line	72 h; 10^{-8}–10^{-4}M	Decreased cell viability and increased caspase-3 activity.
	Rainbow trout (Cahova *et al.* 2023)	Administered with food; 6 weeks; 6.9 – 395 µg/kg/day	Increased plasma thyroxine levels at 395/kg/day (~325 ng/mL) *c.f.* controls (~200 ng/mL)
	Wistar rats (Lorigo and Cairrao 2022)	*In vitro*; isolated rat aortas 0.001–50 µmol/L	Increased vasorelaxant effect by endothelium-dependent mechanisms
	Human umbilical arteries (Lorigo *et al.* 2021, 2022)	*In vitro,* 24h incubation; 1 -50 µmol/L	Decreased vasorelaxation response by interference with NO/sGC/cGMP/PKG pathway Increased reactivity to the contractile agents – serotonin, histamine and KCl In silico analysis suggests that octinoxate might compete with T3 for the binding centre of THRα.
Benzophenone-3 or oxybenzone	Zebrafish	Waterborne; 14 days for adult, 120 h for embryos; 10–600 µg/L	Anti-androgenic activity: decreased expression of *esr1*, *ar* and *cyp19b* expression in the brain of males.
	Zebrafish (Babich *et al.* 2020)	Embryonic oxygen consumption rate; 0.004 – 4 mg/L	Negligible effect on mitochondrial respiration
	Zebrafish (Xu *et al.* 2021)	Waterborne; 0.056 -38 µg/L 42 days post fertilization	Decreased female to male ratio from 2.3 µg/L Increased expression of estrogen receptors *esr2a* and *vtg2 i*n the brain and hepatic *vtg2* at HD
	Zebrafish (Bai *et al.* 2023)	Waterborne; 6 h post fertilisation to adulthood(~5months); 10 µg/mL (0.04 µM)	Reduced social aggression, learning and memory in ♀; cognition deficits in ♀ correlated with neurotoxicity and increased brain cell apoptosis. Reduced social preference in ♂ and ♀.
	Sprague-Dawley rats	Dermal application; 30 days; 5 mg/kg/day	No changes in behavioural tests (locomotor and motor co-ordination).
	Rat primary cortical astrocytes and neurones	1–7 days; 1–10 µg/mL	Decreased cell viability of neurons but not of astrocytes.
	Kumming (KM) mice (Zhang *et al.* 2021)	*In vitro*; Sertoli cells; 24 h; 5-150 µM	Impaired cell viability and disturbed cell morphology from

			100 µM and increased Bcl-2 levels. Reduced expression of Rictor (component of mTORC2 complex) from 50 µM
	SH-SY5Y neuroblastoma cell line	72 h; 10^{-8}–10^{-4}M	Decreased cell viability and increased caspase-3 activity.
Octocrylene	Zebrafish	Waterborne; 14 days; 22–383 µg/L	Impaired expression of genes related with development and metabolism in the brain.
	Zebrafish (Meng *et al.* 2021)	96 h incubation; hatching rates of zebrafish (50-250uM) 96 h incubation; larvae death and zebra fish liver cell line (ZFL) – concentration range not reported.	Impaired hatching from 200 µM and increased larvae death (LC_{50} = 251.8 µM) Increased cytotoxicity (96 h LC_{50} = 5.5 µM) and expression of *cyp1a, cyp3a65,* estrogen receptors (*erα, erβ1, gper, vtg1*) and sex determination genes (*brca2, drtm1, cyp19a sox9a)* in ZFL at 10% LC_{50}
	ICR mice (Chang *et al.* 2022)	*In vitro;* oocytes incubated until maturation; 8-50 nM	Disturbed meiotic maturation and reduced oocyte quality from 40 nM, likely due to impaired mitochondrial function.
	Human bone marrow mesenchymal stem cells (Ko *et al.* 2022)	*In vitro*; 72h; concentration range was not reported	Octocrylene directly binds to PPARγ with K_i = 37.8 µM and acts as a partial agonist Increased adipogenesis and secretion of adiponectin (EC_{50} = 29.6 µM).

Abbreviations: ar: androgen receptor; Asp: aspartate; cyp19b: cytochrome P450 aromatase b; esr1: estrogen receptor; GABA: gamma amino butyric acid; Glu: glutamate; GnRH: gonadotrophin-releasing hormone; HPT: hypothalamo-pituitary-thyroid; pre-proTRH: pre-pro-thyrotrophin-releasing hormone.

NOAEL and DA values for risk assessment

Based on the information/data reviewed above, the TGA has concluded on the following NOAEL and dermal absoprtion values for risk assessment of the respective suncreen active ingredients.

Table 3-11. NOAEL selected from available information.

Active ingredient	NOAEL	Rationale
Avobenzone	450 mg/kg bw/day	Oral 13-week repeat dose toxicity study in rats. (ECHA 2021)
Ethylhexyl triazone	1000 mg/kg bw/day	Oral 90 day repeat dose toxicity study in rats. (ECHA 2021b; DEPA 2015).
Homosalate	10 mg/kg bw/day	Based upon a LOAEL of 60 mg/kg bw/day from combined repeat dose toxicity study and reproduction/developmental toxicity screening test. Uncertainty factor of 3 applied for conversion of LOAEL to NOAEL. A further adjustment made (50% reduction) due to absence of oral bioavailability data consistent with SCCS approach.
Octinoxate	450 mg/kg bw/day	Fertility and reproduction oral study in rats (Schneider *et al.* 2005).
Octocrylene	76.5 mg/kg bw/day	Extended one generation reproductive toxicity study (EOGRTS) in rats via diet. Adjustment of (50%) based on oral bioavailability data made to male NOAEL of 153 mg/kg bw/da, consistent with SCCS approach. (ECHA 2021d; SCCS 2021a).

Active ingredient	NOAEL	Rationale
Oxybenzone	67.9 mg/kg bw/day	Reproductive and developmental toxicity studies in rats via diet (Nakamura *et al.* 2015).
PBSA	40 mg/kg bw/day	Oral 90-day repeat dose/reproduction/developmental toxicity study in rats. Adjustment made to NOAEL (1000 mg/kg bw/day to account for 4% oral absorption. (ECHA 2020).

Table 3-12. Dermal absorption factor selected from available information.

Active ingredient	DA	Rationale
Avobenzone	7.3%	Based upon *in vitro* study using isolated human abdominal cadaver skin (ECHA 2021a).
Ethylhexyl triazone	10%	Based upon physicochemical properties, (molecular weight > 500 and a $logP_{ow}$ > 4).
Homosalate	5.3%	Based upon dermal absorption (mean +1SD) derived from study using human split thickness skin preparations (Finlayson 2021, as cited in SCCS 2020).
Octinoxate	1.77 μg/cm^2	Based upon 6-hour pig ear skin exposure + 18-h free permeation of oil-in-water emulsion study (Klimova *et al.* 2015)
Octocrylene	0.97 μg/cm^2	Based upon dermal absorption (mean +1SD) derived from study using dermatomized human skin preparations (Fabian and Landsiedel 2020, as cited in SCCS 2021a).
Oxybenzone	9.9%	Based upon *in vitro* study using pig skin and applying a safety factor of 2 standard deviations to account for limitations in the data set, i.e, mean (3.1%) + 2 SD (2 x 3.4%) dermal absorption study consistent with SCCS. (SCCS 2021c).
PBSA	0.416 μg/cm^2	Based upon *in vivo* study in humans (SCCP 2006b).

APPENDIX

Search strategy

Search criteria (word input)

Keywords included the chemical name, AAN or the INCI names, and "sunscreen" were used as the search items. Publications in last 15 years were searched (between 2008 and March 2023). Following toxicological endpoints were included.

Nonclinical (toxicology) data:

- Dermal carcinogenicity
- Systemic carcinogenicity
- Developmental and reproductive toxicity (DART)
- Toxicokinetics

• Additional testing when data suggest a concern about other long-term effects, such as **endocrine effects**

Clinical data:

• Dermal irritation and sensitization

• Phototoxicity and photoallergenicity testing

• Human maximal use bioavailability studies

WEBSITES SEARCHED FOR THE SUNSCREEN ACTIVE INGREDIENTS:
WHO

USA:

- PubChem https://pubchem.ncbi.nlm.nih.gov
- GOLD FFX database / ChemWatch (TGA subscribed)
- FDA
- US EPA (www.epa.gov).
- NIOSH CDC https://www.cdc.gov/niosh/index.htm
- National Center for Toxicological Research (NCTR) https://ntp.niehs.nih.gov/nctr/
- National Toxicology program (NTP), U.S. Department of Health and Human Services https://ntp.niehs.nih.gov/publications/index.html.
- BUND (Federal Mnistry for the Environment, Nature Conservation, Building and Nuclear Safety)
- Comparative Toxicogenomics Database http://ctdbase.org/
- Consumer Product Information Database (cpid) https://www.whatsinproducts.com/. similar to and linked to PubChem.
- US EPA (United States Environmental Protection Agency) IRIS Assessments https://cfpub.epa.gov/ncea/iris_drafts/atoz.cfm
- Integrated Risk Information System (IRIS) https://www.epa.gov/iris
- ChemView https://chemview.epa.gov/chemview/
- Science Inventory https://cfpub.epa.gov/si/

UK:

- Cancer Research UK https://www.cancerresearchuk.org/

EU:

- Registered substances - Chemical property data search / European Chemicals Agency (ECHA)
- Scientific Committee on Consumer Safety (SCCS), European Commission https://op.europa.eu/en/
- SafetyNL; National Institute for Public Health and the Environment (RIVM), The Netherlands www.rivm.nl
- CosIng Database https://cosmeticseurope.eu/library/
- European Medicines Agency (EMA)
- OECD OECD Existing Chemicals Database https://hpvchemicals.oecd.org
- Environmental Protection Agency in Denmark www.mst.dk
- Nature Agency in Denmark www.nst.dk
- Swedish Chemicals Agency (KEMI) in Sweden www.kemi.se
- Environment Agency in Norway www.miljodirektoratet.no
- ANSES in France www.anses.fr

- The Environment Agency in the UK www.environment-agency.gov.uk
- ChemSec - International Chemical Secretariat www.chemsec.org
- Information Centre for Environment and Health www.forbrugerkemi.dk
- National Institute for Public Health and the Environment https://www.rivm.nl/en

Australia:

- NICNAS
- Safe Work Australia - Hazardous Chemical Information System (HCIS) http://hcis.safeworkaustralia.gov.au/
- FSANZ

Canada:

- DRUGBANK / University of Alberta et al., Canada
- Health Canada

Non-Government:

- Environmental Working Group https://www.ewg.org/ (non-profit)
- Food Packaging Forum https://www.foodpackagingforum.org/
- International Toxicity Estimates for Risk (ITER) http://www.iter.tera.org/. similar to PubChem.
- Cosmetic Ingredient Review (CIR) https://www.cir-safety.org/

Table 2: List of endocrine activity modulation effects of commonly used UV filters

UV Filters	Endocrine disrupting effects	
Benzophenones	Estrogenic disrupting effects	Activation of ERα, ERβ; Inhibition of the activity of 17β-Estradiol; Induction of proliferation of MCF-7 cell; Induction of VTG in fathead minnow; Reduction of the uterine weight in immature Long-Evans rats.
	Androgenic disrupting effects	Antagonists of human AR transactivation; Repression of 4.5dihydrotestosterone-induced transactivational activity; Inhibition of testosterone formation in mice and rats.
	Disrupting effects toward other nuclear receptors	Inhibition of human recombinant TPO; Interference with THR; Inhibition of TPO activity in rats; Antagonists of PR
Camphor derivatives	Disrupting effects toward estrogen receptor	Activation of ERα, ERβ; Inhibition of the activity of 17β-Estradiol; Inhibition of testosterone formation in HEK-293 cells; Antagonist of Human AR.
	Disrupting effects toward androgen receptor	Repression of 4,5-dihydrotestosterone-induced transactivational activity; Inhibition of testosterone formation in HEK-293 cells; Antagonists of Human AR.
	Disrupting effects toward estrogen receptor	Antagonists of PR; Increase of PR mRNA levels in rats; Inhibition of the expression of PR protein in rats; Disturbance of the expression of membrane-associate PR in insects.
Cinnamate derivatives	Disrupting effects toward estrogen receptor	Activation of ERα; Inhibition of the activity of 17β-Estradiol; Induction of proliferation of MCF-7 cell; Reduction of uterine weight in rats; Induction of VTG in fish.
	Disrupting effects toward thyroid hormone receptor	Decrease of T4 levels; Inhibition of the conversion of T4 to triiodothyronine in rats.
	Disrupting effects toward other nuclear receptors	Antagonists of PR and AR; Inhibition of 4,5-dihydrotestosterone activity; Reduction of prostate and testicular weight in rats.

AR: androgen receptor; ER: estrogen receptor alpha; PR: progesterone receptor; T4: thyroxine; THR: thyroid hormone receptor; TPO: thyroid peroxidase; VTG: vitellogenin.
Source: Wang *et al.,* 2016

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