Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

# Literature Review

## Avobenzone, ethylhexyl triazone, homosalate, octocrylene, octinoxate, oxybenzone and phenylbenzimidazole sulfonic acid

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June 2021



TGA Health Safety Regulation

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**RECOMMENDATION**

- The report is sent to COMB and discuss with COMB to ascertain how the TGA should proceed.
- The TGA can inform the Sponsors that a literature review of these seven ingredients has been completed triggered by FDA proposed rule and media concerns.
- The TGA can send the Sponsors a letter detailing the summary of the assessment. Sponsors can be given 4-12 weeks to provide more information/data/scientific justification to establish favourable safety profile of **homosalate and oxybenzone**.
- The TGA can seek further data from the Sponsors for the rest of the ingredients to determine their endocrine disrupting potential.
- After receiving the sponsor's response, the TGA can establish the final compliance status of the active ingredients, and whether any further regulatory actions were required (COMB can remove homosalate and oxybenzone from the permitted list of active ingredients in the sunscreens following further review of the latest use pattern of the sunscreens containing these ingredients).
- The TGA can publish a summary of the review on TGA website for public knowledge.

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## EXECUTIVE SUMMARY

- The literature review of seven active ingredients (avobenzone, ethylhexyl triazone, homosalate, octocrylene, octinoxate, oxybenzone and phenylbenzimidazole sulfonic acid) was based on the national and international safety assessment reports and available peer reviewed publications investigating the safety and toxicokinetics of the ingredients, where available.
- These ingredients were selected for this targeted priority review considering the status of the availability of nonclinical safety data to TGA and their reported use in higher number of sunscreen products marketed in Australia in addition to the safety signals reported in media and overseas.
- The two main issues considered in this review are the evidence for the ability of these ingredients to penetrate the skin to reach viable cells systemically and the potential toxicity exerted by them. Based on the data available for these ingredients, a Margin of Safety (MoS) was determined for each of the ingredients as per relevant guidelines.
- The systemic absorption of avobenzone, homosalate, octocrylene, octinoxate and oxybenzone was noted in a limited number of clinical trials.
- Based on limited data available, avobenzone, ethylhexyl triazone, octocrylene, octinoxate and phenylbenzimidazole sulfonic acid are unlikely to cause any significant systemic toxicity (MoS >100). However, MoS was less than 100 for **homosalate and oxybenzone** when used as active ingredients in sunscreens in the current use scenario. The calculation was based on available dermal absorption data and data from a combined repeated dose toxicity study with the Reproduction/Developmental Toxicity and pre- and post-natal developmental toxicity study for homosalate and oxybenzone, respectively.
- The available information on avobenzone, homosalate, octocrylene, octinoxate and oxybenzone indicate potential endocrine effects, however, the data are not adequate to derive a conclusion. Further data on the endocrine disrupting potential of these chemicals are warranted.
- The following challenges were identified during the literature review.
    a) The NOAELs were determined from published international safety assessment reports. Actual firsthand evaluation of the data, study quality, compliance were not possible.
    b) Additional clinical studies would be required to fully evaluate the pharmacokinetics of the active ingredients.
    c) Due to a lack of specific data, the safety of these ingredients is uncertain when used on infants and children.
    d) International safety assessments were conducted considering the use pattern of sunscreens within specific countries and regulatory framework. There is a lack of information surrounding the typical use patterns (frequency of use, duration of use, how much is applied etc.) of sunscreens in Australia.

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## ASSESSMENT

Maintaining public confidence in the safety and effectiveness of sunscreens is an important part of the TGA's role in therapeutic sunscreen regulation. Concerns about the safety of sunscreens expressed in the media and by consumer groups could lead to a loss of public confidence in this key component of Australia's skin cancer-prevention strategy.

Recent concerns about the skin absorption of active ingredients in sunscreens have arisen in part by the FDA's proposed changes in the regulation of sunscreen ingredients (US FDA 2019). The proposed changes state that the FDA considers that a sunscreen active ingredient is safe and effective, if it demonstrates a steady-state blood level of an ingredient under 0.5 ng/mL, and an adequately conducted toxicological study does not raise any other safety concerns (US FDA 2019). The FDA

published two studies in 2019 and 2020 looking at the dermal absorption of the most common active ingredients in sunscreens (Matta *et al.,* 2020; 2019). Both studies demonstrated that the studied sunscreen active ingredients were absorbed in appreciable quantities and that active ingredients can remain in plasma for an extended time after the last application.

In response to the findings from the FDA and given the greater use of sunscreens in Australia from a higher frequency of use and longer-term use by the population as whole, the TGA is undertaking its own audit to understand the safety profile of the active ingredients approved for use in sunscreens in Australia. An audit to review the safety information of ingredients currently approved by TGA as actives in sunscreens revealed safety data for existing 'grandfathered' ingredients were limited. Subsequently, following consideration of the highest reported use of the sunscreen products in Australia containing these active ingredients and international safety signals (FDA, 2019) related to these ingredients, a targeted safety assessment of seven ingredients (avobenzone, ethylhexyl triazone, homosalate, octocrylene, octinoxate, oxybenzone and phenylbenzimidazole sulfonic acid) was undertaken by the TGA.

The safety assessment of the selected ingredients was based on information provided in the newest opinions from the Scientific Committee on Consumer Safety (SCCS) where available, and information identified from a literature search in PubMed and an open search for information on specific endpoints from published reports from the internet. Review articles and documents focusing on the individual toxicological endpoints were featured in the hazard assessment where no recent SCCS opinions were available. REACH registration dossiers for individual ingredients published by ECHA and risk assessment by national regulatory agencies (i.e., AICIS) were also considered if available. Exposure to these selected ingredients from other products than sunscreens has not been considered. Exposure to metabolites of these ingredients or impurities present in these ingredients has not been considered for safety assessment in this review.

Within 2020-21, the European Commission has published opinions (preliminary and/or final) on the safety of oxybenzone, homosalate and octocrylene. Based on the available information, risk assessments of each of these ingredients were conducted and a Margin of Safety (MoS) determined for each of the ingredients as per relevant guidelines (SCC, 2000; SCCS, 2016). It found that the levels of oxybenzone and homosalate were not safe in the current use scenarios and proposed a concentration limit of 2.2% and 1.4% (0.5% in the final opinion) for oxybenzone and homosalate, respectively when used in sunscreens.

The TGA literature review follows a similar approach of risk assessment based on a MoS determination while recognising limited available data (2008-2020). It is noted that current evidence may not be sufficient to support the causal relationship between the elevated systemic level of the ingredients and adverse health outcomes. To accurately evaluate the long-term risk of exposure to these active ingredients from sunscreen, further randomized controlled trial may need to be conducted.

### 1.1. Margin of Safety

As per the *SCCNFP's notes of guidance for the testing of cosmetic ingredients and their safety evaluation, 9th revision* (SCCS, 2016), the risk assessment of active ingredients in sunscreens can be conducted by calculating the MoS using uncertainty factors. MoS can be extrapolated from animals to humans to predict the potential risk in human. Usually, a MoS > 100 would indicate that the ingredient is safe under the proposed use conditions. MoS is the ratio between a NOAEL and a Systemic Exposure Dose (SED).

$$\text{MoS} = \frac{\text{NOAEL(mg/kg bw/d)}}{\text{SED(mg/kg bw/d)}}$$



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The SED of a cosmetic substance is the amount expected to enter the blood stream (and therefore be systemically available) per kg body weight and per day. It is expressed in mg/kg body weight/day. For this definition, the human body weight of 60 kg is commonly accepted; however, the TGA usually consider a more conservative approach to calculate the SED, with a typical body weight for adults of 50 kg.

**SED can be calculated using either of the following two formulas depending on the method of reporting for the dermal absorption value.**

***Option 1: Dermal absorption reported as a percentage of the amount of substance applied in in vitro studies:***

**The percentage of dermal absorption is expected to be calculated from *in vitro* studies with doses, concentrations and amounts mimicking, but not exceeding the intended use conditions. Otherwise, the studies may result in an underestimation of the penetration.**

**SED= A (mg/kg bw/day) × C (%)/100 × $DA_p$(%)/100**

**A= Estimated daily exposure to a cosmetic product per kg body weight[1], based upon the amount applied and the frequency of application, For sunscreen lotion, an application of 18 g/d is used in the MoS calculation (SCCS, 2016, also Table 3 in appendix) C (%) = concentration of the ingredient under study in the finished product on the application site**

**DA= Dermal Absorption expressed as a percentage of the test dose assumed to be applied in real-life conditions.**

**Note: In the case that the molecular weight (MW) > 500 Da and the log $P_{ow}$ (octanol-water partition coefficient) is less than -1 or higher than 4, the value of 10% dermal absorption may be considered appropriate to use in the absence of empirical data.**

***Option 2: Dermal absorption of test substance reported in µg/cm²***

**For calculating the SED, the skin surface envisaged to be treated with the finished cosmetic product containing the substance under study has to be taken into account, as well as its frequency of application per day. All other variables should have been taken into consideration in the proper design of the dermal absorption study itself (SCCS, 2016).**

**SED = $\frac{DA_a\ (\mu g/cm^2) \times SSA\ (cm^2) \times F\ (day^{-1})}{50\ kg^1} \times 10^{-3}$**

**$DA_a$ (µg/cm²) = Dermal Absorption reported as amount/cm², resulting from an assay under in-use mimicking conditions**

**SSA (cm²) = Skin Surface Area expected to be treated with the finished cosmetic product (See Table 3 in appendix)**

**F ($day^{-1}$) = Frequency of application of the finished product (F ≥ 1)**

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[1] TGA usually consider a more conservative approach to calculate the SED, with a typical body weight for adults of 50 kg.

## 1.2. RISK ASSESSMENT OF THE ACTIVE INGREDIENTS IN SUNSCREENS

### Avobenzone

This review is based on the international safety assessment reports for avobenzone (SCC; 2000; ECHA, 2021a; DEPA, 2015) and available peer reviewed publications investigating the safety and toxicokinetics of avobenzone.

The ECHA dossier suggested low percutaneous absorption of avobenzone. Potential systemic availability of avobenzone or metabolites at a high oral dosage was suggested from the oral toxicity studies in rats with up to 3 months exposure. Low systemic exposure from dermal contact was also noted in the ECHA dossier and insignificant inhalation exposure was assumed due to the low vapour pressure. In a study with pigskin (2% and 7.5% avobenzone containing formulations), about 95 % of avobenzone remained on the skin surface, 1-2 % were in the stratum corneum, 1 - 3.4 % in the skin and only ≤0.5 % was found to pass the skin (DSM, 1982). In an *in vitro* dermal absorption study with human skin (2% avobenzone in water-oil cream) dermal absorption increased with exposure time from 0.3% to 7.3% (this value is used in the MoS calculation, see below) after 18 hours (DSM, 1982). In a recent study (Montenegro *et al.* 2018) to investigate the effects of the vehicle and repeated applications of sunscreens on skin permeation, the skin permeation was demonstrated to be very poor after single or repeated applications leading to a MoS above the accepted safety limit (>100).

Nonetheless, recent randomised clinical trials indicate that avobenzone could be systemically absorbed (Matta *et al.*, 2020; 2019). The systemic exposure of avobenzone in all product types (spray, lotion, aerosol spray) exceeded 0.5 ng/mL on single application and remained above the threshold until 23 hours after application, and up to 7 days in more than 50% of participants. The long terminal half-life typically exceeded 48 hours and the ingredient remained detectable through to day 21, suggesting absorption through the skin is the rate-limiting step. However, further studies are required to determine other kinetic parameters e.g. elimination rate constants.

The available information reported for avobenzone indicate it has low acute toxicity (rats) and it is not an irritant to skin (very slight irritation at 10%) and eye (≤ 20%) in rabbits. No treatment-related effects were seen in guinea pig studies investigating irritation, sensitization, phototoxicity, and photoallergenicity potential. The ingredient was not found to be genotoxic, mutagenic, photo mutagenic or teratogenic in animals. Clinical data have shown the ingredient to be a rare allergen and/or photoallergen. Based on a 13-week oral repeated dose toxicity study in rats, the NOAEL of avobenzone was considered to be 450 mg/kg bw/day and used for the MoS calculation given the longer duration of the study and a better reflection of systemic toxicity using a conservative approach. Dose related local dermal effects like erythema and oedema were seen in a 28 day dermal repeat dose study in rabbits with no systemic effects, therefore the NOAEL was not used in the calculation of the MoS. In this study, the systemic NOAEL was determined to be 360 mg/kg/day bw (18% avobenzone) whereas the LOAEL (dermal) was 30 mg/kg/day bw (1.5% avobenzone) based on topical local effects. A NOAEL (oral) for maternal, developmental and embryotoxicity of 1,000 mg/kg bw/day was determined in rats.

The Danish EPA (DEPA, 2015) calculated the MoS with the maximum allowed concentration of 5% and determined a MoS around 300 for sunscreens containing avobenzone applied on people with mean average weight of 60 kg. Assuming the mean average body weight of 50 kg for Australian public, the SED is determined 1.3 mg/kg bw/day resulting in a MoS of 346 (see below).

| Description | Parameter | Sunscreen |
|---|---|---|
| Amount of sunscreen applied daily | Q (mg/day) | 18000 |
| Concentration of ingredient in finished product | C (%) | 5 |
| Total amount of active ingredient applied | Qi = Q x C (mg/day) | 90000 |

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| | | |
|---|---|---|
| Absorption of active ingredient | Dap (%) | 7.3 |
| Total amount absorbed | Abs =Qi x Dap × 0.01 × 0.01 mg/day | 65.7 |
| **SED** | ABs/body weight (50 kg) | 1.3 |

**No Observed Adverse Effect Level (NOAEL) = 450 mg/kg bw/day**

**MoS= NOAEL/SED= 346**

The Danish EPA (DEPA, 2015) also concluded that avobenzone did not pose a risk to consumers based on the REACH registration dossier assuming 36 g was applied daily (MoS ≥ 100). In 2013, publicly available data on endocrine disruptive properties of the substance were collected and evaluated by the Danish Centre on Endocrine Disruptors which concluded that there was not enough data to conclude whether the substance had endocrine disruptive properties or not.

Based on the information available and MoS determined to be more than 100, there are no immediate systemic safety concerns with the use of avobenzone at 5% in sunscreens. However, the primary data and analysis have not been subject to scrutiny by the evaluator.

**Ethylhexyl triazone (EHT)**

The summary is primarily based on the REACH dossier (ECHA, 2021b) and published peer reviewed articles.

The ECHA registration dossier indicated the dermal uptake of ethylhexyl triazone was negligible or low (maximum uptake of 1.3%). Recent *in vitro* experiments with a static skin diffusion cell design under real life conditions indicated that 18.3 ± 2.5 µg/cm² of ethylhexyl triazone was found in the stratum corneum, whereas no ethylhexyl triazone was determined in the receptor fluid following the application of a sunscreen with 5% ethylhexyl triazone on the intact human skin at the dose of 1mg/cm² for 6 h (Hojerová *et al.* 2017). 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. Higher ethylhexyl triazone absorption was noted on shaved skin.

Undiluted ethylhexyl triazone is not expected to be a skin or eye irritant. There are no data for respiratory irritation. It was not found to be sensitising in guinea pigs. The NOAELs were determined 1000 mg/kg/day and ≤ 1275 mg/kg/day in two 90 day oral repeat dose studies in rats, respectively. Ethylhexyl triazone was not found to be genotoxic in *in vivo* and *in vitro* studies. No carcinogenicity data were available, and no adverse effects were reported in a pre-natal developmental study (maternal and developmental NOAEL 1000 mg/kg/day bw).

Because no dermal repeated-dose toxicity study for ethylhexyl triazone was available from the literature, and in accordance with the guidance provided in SCCS (2016), the NOAEL value (1000 mg/kg bw/day) from oral repeated dose toxicity studies in rats was used in the MoS determination.

Public exposure to ethylhexyl triazone is expected to be widespread and frequent through a daily use of listed products containing the ingredient at concentrations up to 5% (approved on TGA permitted list). In the absence of an appropriate dermal absorption value for ethylhexyl triazone, a 10% dermal absorption was assumed for SED calculation in the worst case scenario using option 1 (Section 1.1, Page Error! Bookmark not defined.7) considering physiochemical properties (molecular weight > 500 and a $\log P_{ow} > 4$).

| Description | Parameter | Sunscreen |
|---|---|---|
| Amount of sunscreen applied daily | Q (mg/day) | 18000 |

| | | |
|---|---|---|
| Concentration of ingredient in finished product | C (%) | 5 |
| Total amount of active ingredient applied | Qi = Q x C (mg/day) | 90000 |
| Absorption of active ingredient | Dap (%) | 10 |
| Total amount absorbed | Abs =Qi x Dap × 0.01 × 0.01 mg/day | 90 |
| **SED** | ABs/body weight (50 kg) | 1.8 |

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**No Observed Adverse Effect Level (NOAEL) = 1000 mg/kg bw/day**

**Therefore, the MoS was determined = NOAEL/SED= 1000/1.8 = 555 (> 100)**

**Homosalate**

This review is based on the published literature, ECHA dossier and SCCS opinions (ECHA, 2021c; SCCS, 2020). The SCCS has published their opinion on homosalate in 2007, and recently extended their preliminary opinion based on new information of homosalate in 2020 (SCCS, 2020).[2]

Animal studies and studies with human skin showed that homosalate could penetrate the skin. Evidence from *in vitro* experiments indicates that about 1.1% of the applied dose was absorbed in human skin (range: 0.9-2.0%)(CTFA, 2005). The maximal absorption value observed in the donor with highest absorption values (2%) was taken for MoS calculation.[3]

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 Section 2.1). Homosalate was also detected in human milk samples after topical application in human volunteers (Schlumpf *et al.* 2010).

Homosalate was found to be systemically absorbed in recent randomised clinical trials (Matta *et al.*, 2020, 2021). The systemic exposure of homosalate in sunscreens (spray) exceeded 0.5 ng/mL on single application and repeated applications (in > 50% of participants up to 21 days). The continued presence of homosalate at skin up to 21 days and long terminal half-life (> 48 hours) suggest skin absorption of homosalate (Matta *et al.*, 2020). Intravenous studies would be required to determine elimination rate constants.

*In vitro*, homosalate was hydrolysed into salicylic acid and 3,3,5-trimethylcyclohexano associated with conjugation and hydroxylation of intact homosalate.

Based on available safety information from animal studies, homosalate was found to be of low acute oral and dermal toxicity, not a skin or eye irritant (at 10%) and with no sensitising potential. Undiluted homosalate was also found to be a non-irritant in a human epidermis skin test with no sensitising potential at 15% in a human repeat patch test.

A general toxicity NOAEL of 300 mg/kg bw/day was established in a combined repeat dose and reproductive/developmental screening study in rats based on mortality in female rats at the highest dose. However, treatment-related effects were observed in kidneys, liver, thyroid and thymus in male rats at 60 mg/kg bw/day. Therefore, the SCCS concluded that this dose should be considered LOAEL. The SCCS also states that technical errors might have contributed to the effects observed, influencing the reliability of the study. A NOAEL of > 300 mg/kg bw/day in males and >1000 mg/kg bw/day in females was established in a two-week study in rats. Both these studies indicate that the treatment-related effects were more adverse in males. The human relevance of this species specific effect is uncertain.

[2] The final opinion was published in June 2021, after this review was drafted.

[3] A 5% dermal absorption value was used in the final SCCS opinion on homosalate (June 2021) resulting in a MoS value of 6. This does not change the safety assessment of homosalate as the current MoS is not acceptable (< 100).

Homosalate was not found to be genotoxic in a standard battery of tests. While two recent studies indicated that there was a genotoxic potential for homosalate, the studies were found inadequate due to methodological errors (Yazar *et al.* 2018; 2019). No carcinogenicity data were available. A combined repeated dose and reproductive/developmental screening study in rats by gavage up to 750 mg/kg bw/day was recently reported (SCCS, 2020; ECHA, 2018). The SCCS noted that the occurrence of constant lighting (illumination) during the conduct of the study significantly affected the reliability of this study, especially for developmental/reproductive effects. In addition, the low number of pregnancies per group questions the validity of the data on the development of offspring in this study. Homosalate was found to adversely affect the survival, proliferation, and invasiveness of human trophoblast cells which highly associated with the development of human placenta during early pregnancy and, as such, may pose a threat to pregnant women (Yang *et al.* 2018).

Therefore, further studies (e.g. a sub-chronic toxicity study, a prenatal developmental toxicity study, an extended one-generation reproductive toxicity study, and the identification of degradation products) would be required to fully allay concerns related to homosalate exposure and reproductive and developmental concerns.

The SED for homosalate when used as a UV filter in cosmetic products, was calculated using a dermal absorption value of 2% derived from an *in vitro* dermal penetration study using viable human skin and a standard sunscreen formulation containing 10% homosalate.

The SCCS (2020) report takes into account the following consideration to calculate the margin of safety:

> *As point of departure for risk assessment, a LOAEL of 60 mg/kg bw/day was used, based on a combined repeated dose toxicity study with the Reproduction/Developmental Toxicity Screening Test. Since the point of departure was based on a LOAEL, an additional uncertainty factor of 3 was added. Furthermore, due to lack of information on oral bioavailability, 50% of the administered dose was used as the default oral absorption value, resulting in an adjusted NOAEL of 10 mg/kg bw/day.*

- *Amount of sunscreen applied A (g/d) = 18*
- *Concentration in the finished product C (%) = 10 %*
- *Dermal Absorption $DA_p$ (%) = 2 %*
- *Typical bodyweight of human = 60 kg*

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*Systemic exposure dose (SED) A x 1000 mg/kg x C/100 x Dap/100/60 = 0.6 mg/kg*

*LOAEL = 60 mg/kg; NOAEL/LOAEL adjustment 20 mg/kg*

*Bioavailability 50% = 10 mg*

*Margin of Safety (MoS): adjusted NOAEL/SED = 10/0.6 = **17.0***

*In order to derive at MoS of 100, the SED should be maximally 0.1 mg/kg meaning that*

*A x 1000 mg/kg x C/100 x Dap/100/60 = 0.1.*

With the above values, C is 1.666, meaning the safe level is maximally 1.7 % homosalate in sunscreen.

TGA usually consider a more conservative approach to calculate the SED, with a typical body weight for adults of 50 kg, using this parameter the MoS obtained (~14.0) is similar to the result calculated in SCCS report **(MoS = 17)**.

The SCCS concluded:

> *"On the basis of safety assessment of homosalate, and considering the concerns related to potential endocrine disrupting properties, the SCCS has concluded that homosalate is not safe when used as a UV-filter in cosmetic products at concentrations of up to 10%.*
>
> *In the SCCS's opinion, the use of homosalate as a UV filter in cosmetic products is safe for the consumer up to a maximum concentration of 1.4% homosalate in the final product.*
> *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**

This review aims to present review the main safety data on octocrylene from the ECHA website (ECHA, 2020), as well as those reported in the SCCS opinions (SCCS, 2021a) and scientific articles from peer-reviewed journals. In a recently published SCCS opinion on the safety of octocrylene (SCCS, 2021a), the SCCS considered that octocrylene was safe at concentrations of up to 10% when used individually or together as a UV-filter in cosmetic products, i.e. in sunscreen cream/lotion, sunscreen pump spray, face cream, hand cream and lipstick (SCCS, 2021a). However, a lower concentration of octocrylene (9%) is considered safe in sunscreen propellant spray when the sunscreen propellent spray is used along with face cream, hand cream, and lipstick (containing 10% octocrylene).

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Extensive studies were available investigating octocrylene pharmacokinetics, and these have been summarised in Section 3 (Page 2334).

Octocrylene is a lipophilic substance, and it is reported to be metabolised to a variety of metabolites where CDAA is the main metabolite. Information was lacking on whether the most significant toxic agent was octocrylene or its metabolites. Considering the relatively long half-life of both octocrylene and CDAA in plasma and the low elimination rate of CDAA in urine, an accumulation of octocrylene and CDAA in the human body following repeated dermal applications would be expected.

The higher maximum observed concentration of CDAA (1351.7 ng/mL) *vs* octocrylene (25.0 ng/mL) also suggested that measuring only unmetabolized octocrylene might underestimate total systemic absorption and thereby influencing the safety assessment of octocrylene. In addition, it was noted that higher absolute concentrations of octocrylene were observed from exposure to "real-life" conditions compared to "indoor maximal use conditions", indicating peak plasma concentrations may be even higher in real-world usage conditions.

Systemic absorption of octocrylene was demonstrated in recent randomised clinical trials following dermal application. The plasma concentration of octocrylene from sunscreens exceeded 0.5 ng/mL on single application (until 23 hours after application) whereas the systemic exposure to octocrylene remained above the threshold of 0.5 ng/mL in plasma in more than 50% of participants for up to 10 days. The continued presence of octocrylene in skin at days 10 and its long terminal half-life suggested absorption through skin was the rate-limiting step. Intravenous studies with octocrylene would be required to determine elimination rate constants to the parent. Considering the above, the clinical significance of the systemic exposure and the metabolism of octocrylene in humans requires further investigation.

The SCCS determined that the SEDs for dermal exposures to octocrylene from sunscreen cream/lotion were 0.566 mg/kg bw/day. SEDs for inhalation exposures to sunscreen sprays were 0.176 and 0.002 mg/kg bw/day for propellant and pump spray, respectively (Matta *et al.,* 2019, 2020).

As tabulated in Section 4, Toxicity, octocrylene was found to be of low acute toxicity. Octocrylene was not an eye or skin irritant based on available data. It was found to not sensitising in a Guinea Pig Maximization Test (GPMT). Octocrylene was found to be a moderate skin sensitiser and a skin photosensitiser [local lymph nose assay (LLNA) with 1- 30% octocrylene, EC3: 7.7% and human patch studies with 10% octocrylene]. However, the LLNA study was not considered properly conducted and the occurrence of photoallergy to octocrylene was suspected to be related to a previous photoallergy to topical ketoprofen. Photoallergic contact dermatitis to octocrylene has been found to be much more frequent in adults than in children whereas contact allergy cases to octocrylene have been reported more in children compared to adults. This is likely due to the immaturity of the skin epidermal barrier and the prevalence of atopic dermatitis in young children as the study authors suggested (Gilaberte & Carrascosa, 2014). Considering the information above, octocrylene was considered a skin sensitiser at 10%.

No systemic effects were reported in rabbits after dermal exposure to octocrylene at 534 mg/kg bw/day. After oral exposure, effects on liver and thyroid were reported in a study in rats (males) at 340 and 1085 mg/ kg bw/day. These effects on liver and thyroid were investigated in an additional mechanistic study which showed that effects on thyroid were indirect and probably due to hepatic enzyme induction potential of octocrylene. Recently reported repeat dose toxicity studies with octocrylene (SCCS, 2021a; ECHA, 2020) do not alter the previously established NOAEL of 175 mg/kg bw/day, that was established in a previous SCCS report for octocrylene.

Octocrylene is not expected to be genotoxic. No carcinogenicity data were available. Based on the effects on parental and pup body weights, a lower number of implantation sites and lower number of pups in the extended one generation reproductive toxicity study (EOGRTS), a NOAEL was established at 153/163 mg/kg/day for parental systemic toxicity, fertility/reproduction performance, and general and sexual development. No neuro-/developmental effects were observed at the highest dose level tested (534/550 mg/kg/day). A monitoring study revealed that during the periods of pregnancy and lactation, > 78% of the women used some cosmetic product containing UV filters and UV filters were detected in 82.5% of human milk samples (Schlumpf *et al.* 2010, 2008). Octocrylene (OC) was one of the most frequently used UV filters and most frequently detected in milk samples (i.e. 27.50 ± 22.15 ng/g of lipids) (Schlumpf *et al.* 2010, 2008). Use of UV filters and concentration in human milk were significantly correlated. The results indicate transdermal passage of UV filters and potential placental transfer of octocrylene.

Public exposure to octocrylene would be expected to be widespread and frequent through a daily use of sunscreen products containing ingredient typically at concentrations up to 10%.

As per option 2 for SED calculation(Margin of Safety ~~Margin of Safety~~ ), the SED was determined to be 0.339 mg/kg bw/day for octocrylene in sunscreen (for a 60 kg bw person) (using a dermal absorption value of 0.97 µg/cm², ~~(~~Fabian & Landsiedel, 2020) and, ~~octocrylene concentration of 10%, see the table below~~ adopted from SCCS 2021a). Therefore, the MoS was calculated as:

MoS= NOAEL/SED= 76.5/0.339

= **225 (≥ 100).**

Assuming a body weight of 50 kg for an Australian adult, the SED was determined to be 0.679 mg/kg bw/day resulting in a MoS of 112. This value would still be above the accepted safety threshold.

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**Octinoxate**

This review was based on the safety data from the ECHA website, the SCCS opinion (SCC, 2000), NICNAS Human Health Tier II Assessment Report, and scientific articles from peer-reviewed journals (NICNAS 2017, currently known as AICIS; ECHA 2021e).

Available *in vitro* and *in vivo* studies indicate octinoxate can poorly penetrate the skin. Systemic absorption of octinoxate was also demonstrated in recent randomised clinical trials (Matta et al., 2020). However, elimination rate constant was not determined due to the absence of intravenous studies.

Octinoxate was found to be of low and moderate acute oral toxicity in mice and rats, respectively. Based on the limited data available, the chemical is not considered to be a skin irritant or an eye irritant. The chemical is not considered to be a skin sensitiser in humans. There is potential for photosensitivity following UV exposure, but the results are inconclusive.

No systemic effects were reported in a 13-week dermal repeat dose study in rats administered up to 534 mg/kg/day. The NOAEL was determined 450 mg/kg/day in a 13-week oral repeat dose study. Based on the available studies, the chemical is not considered to cause serious damage to health from repeated dermal exposure.

Octinoxate is not expected to have genotoxic potential, however, the lack of studies with isomers *cis* and *trans* was noted.

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No carcinogenicity study was conducted as per ICH guidelines. The chemical has not been shown to be a tumour initiator in photocarcinogenesis studies in mice but is shown to delay tumour development. No genotoxic potential was observed. Quantitative Structure-Activity Relationship (QSAR) modelling gave an alert for potential non-genotoxic carcinogenicity, but no details are available (OECD QSAR Toolbox ver.3.2).

The SCC and NICNAS report stated that "*based on the available data, the chemical is not considered to be reproductively or developmentally toxic at doses relevant to human exposure*". A NOAEL of 450 mg/kg bw/day was established for fertility and reproduction parameters, and for systemic parental and developmental toxicity (Schneider *et al.* 2005).

A study (Axelstad *et al.* 2011) to investigate the effect of octinoxate treatment (500-1000 mg/kg/day, ~~PO~~oral) on the endocrinological and neurological development of rat offspring indicated decreased motor activity in female offspring and increased spatial learning in male offspring (transient effects on thyroid axis, and in oestrogen level were also observed). The effects were observed at a much higher doses compared to clinical doses (Axelstad *et al.* 2011).

The value of 1.7 µg/cm² following 6-h pig-ear skin exposure + 18-h free permeation after an application of oil-in-water emulsion sunscreen dose (0.5 mg/cm²) containing 10% octinoxate was used in the SED calculation in this review (**Klimova *et al.* 2015**).

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The parameters used were:

- DA (µg/cm²) = dermal absorption reported as amount/ cm²: 1.77 µg/cm²
- SSA (cm²) = Skin surface area expected to be treated: 17500 cm² *
- F (day⁻¹)= frequency of application of the finished product: 2 *
- Body weight = default human body weight: 50 kg

(*) value comply with the SCCS 2016 (Appendix 5.3)

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SED= 1.24 mg/kg/day

For the calculation of MoS the NOAEL that correspond to the worst-case scenario (rat, 13 week oral study), 450 mg/kg was selected.

**MoS = NOAEL/SED= 450/1.24= 363 ≥ 100.**

**Oxybenzone**

This review was based on peer-reviewed publications and the SCCS opinion on benzophenone-3 (2021c; SCCP, 2006a; SCCP, 2008).

Oxybenzone was shown to be rapidly absorbed after oral, intravenous, or topical skin administration and widely distributed in animals, 2,4-diOH BP (BP-1) was the major metabolite of oxybenzone in rats and humans. Oxybenzone was primarily excreted though urine.

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A number of *in vitro* and *in vivo* dermal absorption studies have been evaluated by the SCCS. A dermal absorption value of 9.9% was used to calculate the MoS for oxybenzone. This values was calculated from a dermal absorption value of 3.1% obtained following application of a 6% formulation of oxybenzone to pig ear skin in *vitro* 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).

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Clinical trials indicated that oxybenzone could be systemically absorbed. The plasma concentration of oxybenzone in sunscreens (spray) exceeded 0.5 ng/mL on single application and remained above this threshold until 23 hours after application. The systemic exposure of oxybenzone remained above 0.5 ng/mL in more than 50% of participants for up to 21 days. The continued presence of sunscreen active ingredients in skin at days 21 and the long terminal half-life (> 48 hours) suggest absorption through skin is the rate-limiting step. Intravenous studies are required to determine their elimination rate constants.

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Oxybenzone was found to be of low acute oral and dermal toxicity and did not cause skin or eye irritation (rabbits) or skin sensitisation (guinea pigs and mice). However, 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).

Repeat-dose studies with oxybenzone were conducted in mice and rats following oral and dermal administration. After repeated oral administration of oxybenzone in rats and mice, decreased bodyweight gain and reduced food consumption were observed. Effects on the kidney (decreased weight and renal tubule histopathology) and the liver (increased weight and adaptive changes in histopathology) with associated changes in clinical chemistry parameters were also observed. There were no treatment-related findings following dermal administration except for increases in liver weight with no associated histopathology or clinical pathology. The NOAEL (oral) was established at 6250 ppm (429/393 mg/kg bw/day in males/females) in rats and 6250 ppm (1068/1425 mg/kg bw/day in males/females) in mice. The NOAEL for repeat-dose dermal toxicity was established at 200 mg/kg bw/day in rats and 364 mg/kg bw/day in mice. In reproductive and developmental toxicity studies in rats, decreased normalised anogenital distance was observed in male pups of treated dams, at PND 23. Impairment of spermatocyte development in testes of male offspring and delayed follicular development in females was also observed indicating a potential endocrine disrupting effects. A NOAEL for these effects was established at 67.9 mg/kg bw/day (Nakamura *et al.*, 2015).

The findings from the genotoxicity studies with oxybenzone were found to be equivocal. Two-year carcinogenicity studies with oxybenzone were performed in mice and rats. An increased incidence of brain and spinal cord malignant meningiomas in males and thyroid C-cell adenomas and uterine stromal polyps in females were observed in rats, with no dose-response

relationship. These findings in rats were also considered to be equivocal evidence of carcinogenicity. There was no evidence of carcinogenic activity in male or female mice.

Public exposure to oxybenzone would be expected to be widespread and frequent through a daily use of sunscreen products containing oxybenzone typically at concentrations up to 10%. The SCCS (2021c) determined a dermal absorption of 9.9% [mean (3.1%) + 2 SD (2*3.4%)] for the use of oxybenzone as a UV filter, at an oxybenzone concentration 6% for the calculation of SED and the MoS for sunscreen products. .

The MoS was calculated using an SED of 2.1 for whole body sunscreen exposure. This was calculated based on:

| | |
|---|---|
| A - Applied dose of sunscreen | = 18000 mg/day (whole body application) |
| C – concentration of product | = 6% |
| DA – dermal absorption | = 9.9% |
| BW – mean Australian adult bodyweight | = 50 kg |

Thus, the SED = A x C x DA x BW = 18000 x 0.06 x 0.099 / 50 = 2.1

The margin of safety (MoS) for oxybenzone through typical consumer use of sunscreen products was calculated using a NOAEL of 67.9 mg/kg bw/day derived from a pre- and post-natal developmental toxicity study in rats (Nakamura *et al.* 2015, detailed above) and an SED of 2.1. **The MoS was determined to be 32 (NOAEL/SED = 67.9/2.1 = 32).**

A similar MoS was determined in the study by Hojerova *et al.* (2017), for three realistic exposure scenarios. MoS of 48, 34 and 34 for oxybenzone in the sunscreen applied on the whole-body were calculated, indicating that there would be some concerns regarding the safety for consumers (MoS<100).

**Phenylbenzimidazole sulfonic acid**

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The safety of phenylbenzimidazole sulfonic acid (PBSA) was assessed based on the publicly available safety data from scientific literature, and the SCCP opinion (SCCP, 2006b).

PBSA was rapidly absorbed following oral administration in pregnant rats. The amount of absorption from the gastrointestinal tract was estimated to be 3 – 4%. There was no indication of accumulation in any of the organs investigated and PBSA did not cross the blood/brain barrier. PBSA was mainly excreted though urine and faeces in male rats and via the faeces in pregnant female rats following oral administration. No data were available on the metabolism of PBSA.

PBSA was found to be of low acute toxicity in rats and mice (IP $LD_{50}$ 1000 – 1500 mg/kg/day and the dermal $LD_{50}$ is >3000 mg/kg bw in rats whereas oral $LD_{50}$ in mice is >5000 mg/kg bw). There was no information available for acute inhalational toxicity. PBSA was not a skin or eye irritant in rabbits and did not cause skin sensitisation in guinea pigs. The NOAEL in a 13-week oral study in rats was established at 1000 mg/kg/day, the highest dose tested.

PBSA was not found to be genotoxic *in vitro* (Ames test and chromosome aberration test in human peripheral blood lymphocytes). No information was available for mutagenicity/genotoxicity *in vivo*. No carcinogenicity data on PBSA were available.

No treatment-related findings were noted in a pre-natal developmental toxicity study in rats treated with PBSA from gestation day 6 to 15 at doses up to 1000 mg/kg/day. The NOAEL for maternal and fetal toxicity was 1000 mg/kg/day. PBSA did not cross the blood brain barrier or the placenta following oral administration in rats.

The potential systemic exposure and the MoS for typical consumer use of sunscreen products was calculated as follows (SCCP 2006b):

The margin of safety (MoS) was determined to be **267** (NOAEL/SED = 40/0.150 = 267) based on the following parameters:

| | |
|---|---|
| A - Maximum absorption through the skin (µg/cm²) | = 0.416 µg/cm² |
| SAS – mean adult skin surface area (cm²) | = 17500 cm² |
| Dermal absorption per treatment (SAS x A x 0.001) | = 7.488 mg |
| Australian body weight of an adult | = 50 kg |
| SED - Systemic exposure dose (SAS x A x 0.001/50) | = 0.150 mg/kg |
| NOAEL (from 90-day oral rat study) | = 40 mg/kg bw |

(SCCP 2006b) ;(*) value comply with the SCCS 2016 (Appendix 5.3)

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### 1.3. POTENTIAL ENDOCRINE DISRUPTION OF ACTIVE INGREDIENTS IN SUNSCREENS

In the light of the recent regulations in Europe, several studies have been conducted to investigate the endocrine disruption potential of most of these ingredients. Since the FDA released its draft proposal (FDA, 2019), several studies published in 2020 support previous findings that oxybenzone can act as an endocrine disruptor and may increase the risk of breast cancer and endometriosis (Kariagina 2020, Santamaria 2020).

A systemic review on oxybenzone and octinoxate suggest that current evidence is not sufficient to support the causal relationship between the elevated systemic level of oxybenzone and octinoxate and adverse health outcomes (Suh 2020). There are either contradictory findings among different studies or insufficient number of studies to corroborate the observed association. To accurately evaluate the long-term risk of exposure to oxybenzone and octinoxate from sunscreen, a well-designed longitudinal randomized controlled trial needs to be conducted.

Most current SCCS opinions have evaluated the most current data on endocrine disruption potential for these ingredients.

For ethylhexyl triazone, the only information on reproductive toxicity or endocrine disrupting potential was from short SCCS opinion (Hojerová *et al.* 2017). Therefore, further information would be required for the endocrine disruption potential of ethylhexyl triazone. The available data (evaluated in SCCS opinions) on avobenzone, homosalate, octocrylene, octinoxate and oxybenzone indicate potential endocrine effects, however, they are not adequate to regard them as an endocrine disrupting ingredient, or to derive a toxicological point of departure based on endocrine disrupting properties for use in human health risk assessments.

### 1.4. SAFETY IN PAEDIATRIC POPULATION

No nonclinical information was available for the safety of these ingredients in the paediatric population. Compared to adults, the higher body surface area to volume ratio of children and the unique microstructure of immature skin suggest that children, especially infants, may absorb a greater fraction of topically applied ingredients (Stamatas *et al.* 2010). In addition, the capacity to metabolize and excrete absorbed ingredients by young children and infants may not be at the same level of maturity as in adults. Therefore, this puts them at risk of higher systemic levels and consequently, side effects and toxicities not seen in adults (Stamatas *et al.* 2010).

It is noted (OECD 2019) that the US EPA's exposure factors handbook incorporates child-specific information with regard to exposure assessment (US EPA, 2011). Together with the US EPA's child-specific exposure scenarios examples (US EPA, 2014), the handbook offers general children's activity patterns and exposure factors from a number of published studies, along with approaches in order to address different exposure routes and dose estimates in some specific contexts (US EPA, 2011; US EPA, 2014).

This needs further investigation.

## EVALUATION OF AVAILABLE INFORMATION

### 2. INTRODUCTION

#### 2.1. BACKGROUND

The ARTG currently (Aug 2021) lists 31 active ingredients approved for use in sunscreens in Australia. The safety of these ingredients on the ARTG has been addressed by various means, including grandfathering; assessment of toxicological data; and by reference to overseas regulatory reports. The TGA has been monitoring the emerging scientific literature in this area and working cooperatively with international agencies to monitor these issues to ensure that appropriate action is undertaken if any unacceptable risks are identified.

In 2019, the 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 which 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 FDA proposed rule in 2019 elaborating the requirement for testing and labeling 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. It dictated that if an adequately conducted MUsT demonstrates a steady-state blood level of an ingredient under 0.5 ng/mL, and an adequately conducted toxicological study does not raise any other safety concerns, then studies on systemic carcinogenicity and developmental and reproductive toxicity may not be required. The 0.5 ng/mL limit was selected because it represents approximately the highest plasma concentration under which the risk of carcinogenicity of any unknown compound would be below 1/100,000 following a single dose (FDA, 2019c).

Given the greater use of sunscreens in Australia from a higher frequency of use and longer-term use by the population as whole; and the current interest by the US FDA in the ongoing safety of sunscreen active ingredients, the TGA has begun an audit of its safety data holdings to better understand the safety profile of these ingredients. As part of this audit, a literature review was conducted of the scientific information available for seven active ingredients for use in sunscreens where safety data have not been available in the past to the TGA (avobenzone, ethylhexyl triazone, homosalate, octocrylene, octinoxate, oxybenzone and phenylbenzimidazole sulfonic acid). These ingredients have been widely used in sunscreen products in Australia.

#### 2.2. METHOD OF DATA SEARCH

The review is intended to provide an overview of the available safety information for avobenzone, ethylhexyl triazone (EHT), homosalate, octinoxate, octocrylene, oxybenzone and phenylbenzimidazole sulfonic acid (PBSA) to provide the calculation of the margin of Safety (MoS) and an input to the risk assessment. Keywords included either the chemical name, AAN or the INCI names, and "sunscreen" were used as the search items. Publications in last ten years were searched (2008-2020). See the appendix 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.

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- Opinions from the Scientific Committee on Consumer Safety (SCCS, previously known as SCC/SCCP) where available.[4]
- 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 disruptive properties of ingredients may give rise to a concern for human health. The evaluation of endocrine disruptive properties was described collectively. Of note, all articles dealing with environmental effects of the ingredients were excluded.

## 2.3. CHEMISTRY

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 2-1 Chemical and Physical Properties of the active ingredients under review**

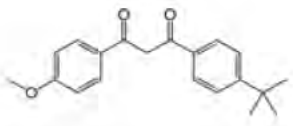
| Active ingredient (*absorption spectrum*) | CAS no. | Chemical name | Molecular formula | Physical properties | | | Other names |
|---|---|---|---|---|---|---|---|
| | | | | Water solubility | Mol. Weight g/mol | Log $P_{ow}$ | |
| Avobenzone (BMDM or BMDBM)<br>*UVA* | 70356-09-1 | 1,3-Propanedione, 1-[4-(1,1-dimethylethyl)phenyl]-3-(4-methoxyphenyl)- | $C_{20}H_{22}O_3$ | 0.01 mg/L | 310.4 | 4.5-6.1 | Butyl methoxydibenzoylmethane, Eusolex® 020, Parsol® 1789, 4-tert-butyl-4'methoxydibenzoyl methane, BMDBM |
| Ethylhexyl triazone (EHT)<br>*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 | 15.5 | Uvinul T150, (octyl triazone) |
| Homosalate<br>*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 | 4.7 | Benzoic Acid, 2-Hydroxy-, 3,3,5-Trimethylcyclohexyl Ester Cyclohexanol, 3,3,5-trimethyl-, salicylate. |

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

| Active ingredient (*absorption spectrum*) | CAS no. | Chemical name | Molecular formula | Physical properties | | | Other names |
|---|---|---|---|---|---|---|---|
| | | | | Water solubility | Mol. Weight g/mol | Log $P_{ow}$ | |
| | | | | | | | Homomethyl salicylate<br><br>Salicylic acid, 3,3,5-trimethylcyclohexyl ester<br><br>Caswell No. 482B, Neo Heliopan® HMS, CCRIS 4885, Filtersol "A" |
| Octinoxate (OMC or EHMC)<br><br>*UVB* | 5466-77-3 | 2-Ethylhexyl 4-methoxycinnamate | $C_{18}H_{26}O_3$ | 0.1 g/100 mL at 27°C | 290.4 | 5.9 | EHMC or octyl-methoxycinnamate (OMC) |
| Octocrylene (OC)<br><br>*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 | 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)<br><br>*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 | >3.7 | Benzophenone-3 |
| Phenylbenzimidazole sulfonic acid (PBSA)<br><br>*UVB* | 27503-81-7 | 2-Phenylbenzimidazole-5-sulfonic acid | $C_{13}H_{10}N_2O_3S$ | > 30% | 274.3 | -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 2-2 Molecular structure of the active ingredients under review**

| Active ingredient | Structure |
|---|---|
| Avobenzone |  |

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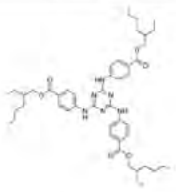
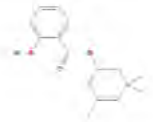
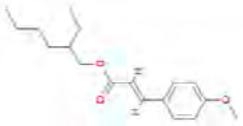
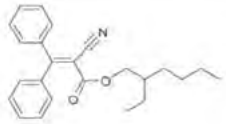
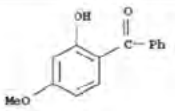
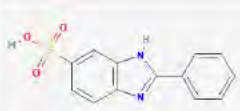
| Active ingredient | Structure |
|---|---|
| Ethylhexyl triazone |  |
| Homosalate |  |
| Octinoxate |  |
| Octocrylene |  |
| Oxybenzone |  |
| Phenylbenzimidazole sulfonic acid |  |

## 2.4. USE

Typically, 2 mg/cm² of sunscreen is recommended to use [the dosage used during the determination of the SPF value corresponding to the application of 6 teaspoons of a lotion (approx. 36 g) for the whole body of an average adult person](EC, 2006; FDA, 2016; TGA, 2016).

The following ingredients are currently approved in Australia for use as active ingredients in sunscreens for dermal application (see the table below), not to be used in topical products for eyes,

with appropriate safety warnings in the labelling (TGA, 2020). It is noted that the FDA regulates sunscreens as over the counter (OTC) drugs rather than as cosmetics whereas it is regulated as cosmetics in EU.

| Active ingredient | Maximum % approved | | | | |
|---|---|---|---|---|---|
| | Australia | EU | USA | Canada | Japan |
| Avobenzone | 5 | 5 | 3 | 3 | 10 |
| Ethylhexyl triazone† | 5 | 5 | Not approved | Not approved | 5 |
| Homosalate | 15 | 10 | 15 | 15 | 10 |
| Octinoxate* | 10 | 10 | 7.5 | | 10 |
| Octocrylene** | 10 | 10 | 10 | | Not approved |
| Oxybenzone*,Δ | 10 | 6 | 6 | 6 | |
| Phenylbenzimidazole sulfonic acid γ | 4 | 8 | NA | | |

* In the USA, Hawaii became the first state to pass the law banning sales of sunscreens containing oxybenzone and octinoxate from January 2021;
**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);
†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).

## 3. PHARMACOKINETICS

~~3.~~ The main safety concerns for these active ingredients arise from the knowledge gap around the toxicokinetic data/pharmacokinetics data. Cutaneous permeation is a critical parameter in the kinetics of these active ingredients. Although most organic UV filters are quite lipophilic, *in vitro* cell permeation studies were also conducted 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 is noted. In the absence of adequate or reliable dermal absorption data, a 10% dermal absorption was assumed for SED calculation in the worst-case scenario and MoS value was estimated according to guidelines applicable for the European Union (SCCS 2016). The dermal absorption value used in the recent SCCS opinions for the relevant active ingredients were used in the estimation of SED, followed by MoS in this review. Selected articles reporting biomonitoring studies of organic UV filters were reviewed, and relevant information is presented in an extensive review by Huang *et al.* (2021).

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### 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), in the 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), there was no indication of systemic bioavailability following dermal exposure.

- *In vitro* studies with isolated pig skin (DSM, 1982) using $^{14}C$-labelled BMBDM 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 (DSM, 1986).

- In an *In vitro* study (DSM, 1982) with $^{14}C$-labelled BMDBM 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.

- A human *in vivo* study (DSM, 1980) also indicate a very low level of systemic penetration of BMDBM 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.[5] 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.

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 human (See Section 2.1).

**In the absence of further kinetic data for avobenzone, based on the data from the *in vitro* study using isolated human abdominal cadaver skin (DSM, 1982), a 7.3% dermal absorption of avobenzone was assumed for Systemic Exposure Dose (SED) calculation in the worst-case scenario.**

**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.

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.

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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

[5] The dose was applied to a small square of gauze (10 cm²) taped to the skin.

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% similar to the recovery (85- 115%) allowed by the SCCS (2016). The SED after the sunscreen application at 1 mg/cm² for 6 h (i) on the face; (ii) on the 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.

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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 10 % dermal absorption was assumed for SED calculation in the worst-case scenario and MoS value was estimated according to guidelines ~~applicable for the European Union~~(SCCS 2016).

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**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 in human skin (range: 0.9-2.0%) (CTFA, 2005).

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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 Section 2.1). 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 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*.

The SCCS report stated that a conclusion on the dermal absorption percentage could not be drawn from the human studies. Therefore, the risk assessment takes account of the dermal absorption value from the skin penetration study using human skin described in the SCCS report (SCCS, 2020). The maximal absorption value observed in the donor with highest absorption values (2%) was used in the MoS calculation in the SCCS report (2020).[6] Identical value was taken for the MoS calculation in this review.

**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 and reproductive/developmental toxicity studies (SCCS, 2021a; ECHA,

[6] June 2021 SCCS opinion for homosalate uses a different dermal absorption value for 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) and a standard sunscreen formulation containing 10% homosalate. This gives even a lower MoS for homosalate for a 60 kg human.

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 was 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).

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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 3-1 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 8-10% octocrylene 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 dermatomed human skin (344 ± 61 µm) in static diffusion cells at a dose of 3 mg/cm² 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 medium. After 24 hours of dosing, octocrylene bioavailability (epidermis, dermis and receptor medium) 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/cm²) 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 medium 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 medium) 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 low dermal absorption rate (≤ 0.25%).

A recent *in vitro* study (Fabian & Landsiedel 2020) with a formulation (10% octocrylene) applied at a dose of 3 mg formulation/cm² on dermatomed 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/cm² (~ 0.15% of the applied dose) consistent with previous findings. The dermal absorption of 0.97 µg/cm² (Fabian & Landsiedel 2020) was considered a worst-case scenario and was used in the calculation of SED followed by MoS determination in the SCCS (2021a). This value was also used in the SED and MoS calculation in this report given it is from the most recent study providing human dermal absorption value.

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**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). [¹⁴C]-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, showing that measuring octinoxate alone could not comprehensively evaluate the human exposure to octinoxate.

Dermal penetration was observed to be dependent on the vehicles, 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/cm²-h (Touitou & Godin, 2008). An accumulation of ~9% of octinoxate in epidermis and ~2-3% in dermis were observed following application of 2mg/cm² and 0.5 mg/cm² 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.

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An *in vitro* absorption study with sunscreen (O/W, oil-in-water 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/cm² after 6-h exposure to the epidermis of frozen-stored skin is 2.7 + 0.6 µg/cm² whereas 1.7 µg/cm² octinoxate was distributed to epidermis after following 18-h permeation (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. No octinoxate was determined in receptor fluid (Klimova *et al.* 2015). The distribution value of 1.7 µg/cm² following 6-h skin exposure + 18-h free permeation after an application of oil-in-water emulsion containing 10% octinoxate was used in the SED calculation in this review.

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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 depends on both lipid lipophilicity and structure and on 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/cm² of cream formulation with 10% octinoxate. Octinoxate was also detected in urine (5 and 8 ng/mL in female and male 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 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, the dermal absorption of 1.77 µg/cm² was considered a worst-case scenario and was used in the calculation of SED (Klimova *et al.* 2015).

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**OXYBENZONE**

Oxybenzone is expected to be rapidly absorbed after oral, intravenous, or topical skin administration 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.

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).

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 in piglets, the elimination half-lives of oxybenzone was approximately 7.14 and 8.04 h (SCCS 2021c).

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%, with this -value used to determine MoS for oxybenzone. 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 to calculate the MoS for oxybenzone in the absence of adequately information from *in vivo* studies.

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**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 $at_{½}$ 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 (2006) to determine the margin of safety for PBSA (SCCP, 2006b).

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### 3.1. 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[7]), 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).

Similar findings were observed in a follow up study with six active ingredients (avobenzone, oxybenzone, octocrylene, homosalate, octisalate[8], 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 - 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 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, %) |
|---|---|

[7] 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.

[8] 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.

| | 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 3-2~~Table 3-2~~). 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.

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**Table 3-2 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

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## 4. 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 are therefore reliant on the accuracy of various published safety assessment reviews (reviews by SCCS/SCC/SCCP, NICNAS, ECHA etc. see in bibliography, p 5653).

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### 4.1. ACUTE TOXICITY

Avobenzone, eithylhexyl triazone, homosalate, oxybenzone, octocrylene, PBSA and octinoxate displayted 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 4-1. Summary of acute toxicity studies for sunscreen ingredients**

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

### 4.2. 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 4-2. Summary of skin and eye irritation studies for sunscreen ingredients**

| Study | Avobenzone (ECHA (2021a; DEPA 2015) | Ethylhexyl triazone (ECHA (2021b; DEPA 2015 | Homosalate (SCCS 2021; 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) |

### 4.3. SENSITISATION

None of the ingredients examined were skin sensitisers in *in vivo* studies in animals (see below).

**Table 4-3. Summary of skin sensitisation studies for sunscreen ingredients**

| Avobenzone (ECHA 2021a; DEPA 2015) | Ethylhexyl triazone (ECHA (2021b; DEPA 2015 | Homosalate (SCCS 2021; 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)<br>Not sensitizing (at 15%, HRIPT) | Not sensitizing (GPMT) | Not sensitizing (GPMT)<br>Moderate sensitising in a LLNA (not properly conducted) | Not sensitizing (GPMT)<br>Not sensitising (LLNA) | Not sensitizing (GPMT) |

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

### 4.4. REPEAT DOSE TOXICITY

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

**Table 4-4. Repeat-dose toxicity studies for sunscreen ingredients**

| Active ingredient | Study details[Δ] | 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.<br>No effect on the body weight and food consumption.<br>↓ RBC in ♀ rats at 1000 mg/kg bw/day.<br>No findings in eyes. No treatment-related necropsy findings.<br>Treatment-related ↑ liver weights at 1000 mg/kg bw/day in ♂ and at 200, 450, and 1000 mg/kg bw/day in ♀ |

| Active ingredient | Study details[Δ] | Major findings |
|---|---|---|
| | | compared to control. All effects were fully reversed after a treatment-free period of 4 weeks.<br>Hypertrophic hepatic parenchyma cells in ♀ at 1000 mg/kg bw/day.<br>**NOAEL: 450 mg/kg bw/day**<br>*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.<br>↑ dose dependent severe dermal reactions ≥ 30 mg/kg/day, more persistent at 100 mg/kg bw/day.<br>↑ Incidence of epidermal thickening in both vehicle control and treatment groups compared to the untreated control group.<br>NOAEL: 360 mg/kg bw/day (based on systemic effects).<br>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<br><br>Study BASF 50S0227/92059 | No treatment-related mortality.<br>No treatment-related clinical signs.<br>Body weight gain: ↓ at HD in both sexes along with decreased food consumption<br>Haematology: RBC affected (↓MCV, ↓MCH, ↓MCHC) at HD in both sexes<br>Organ weights (bodyweight-relative): ↑ absolute and relative weight of liver at 340 and 1085 mg/kg bw/day<br>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<br>NOAEL: 175 mg/kg bw/day |
| | Rabbits (NZW), $n$ = 5/sex/dose 0, 130, 264, 534 mg/kg bw/day (dermal)<br>5 days/week; 13 weeks<br><br>(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.<br>No evidence for haematological or macroscopic and histopathological abnormalities<br>No effects were reported on testicular and epididymal morphology as well as on sperm count and motility<br>NOAEL: 534 mg/kg bw/day (systemic toxicity)<br>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<br><br>Rats (Wistar), $n$ = 5/sex/dose 72, 215, 720 mg/kg bw/day PO (Subset A)<br>63, 188, 630 mg/kg bw/day PO (Subset B)<br><br>28 days (Subset A)<br>14 days (Subset B) | No treatment-related mortality<br>No treatment-related clinical signs.<br>Body weight gain: ↓ at HD in both subsets<br>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<br>Organ weights (bodyweight-relative): ↑ absolute and relative weight of liver at high doses in both sexes in both subsets<br>Histopathology: minimal follicular cell hypertrophy/hyperplasia of the thyroid gland at high doses in both sexes in both subsets<br>NOAEL: 188-215 mg/kg/day |

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| 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.<br>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.<br>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<br>↑ (non-significant) serum alanine phosphatase (SAP) levels and ↑ relative liver weight at HD. Liver effects were not observable upon microscopic examination.<br>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.<br>Dose dependent low-grade epidermal proliferation at all doses (more prominent in ♂).<br>The chemical was considered as a low-grade irritant under the conditions of this study (OECD TG 410)<br>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<br>Lethargy, hunched posture, hair loss, soiled coats, emaciation, increased respiration, swelling of the conjunctivae, and reproductive effects (retardation of testicular growth) at HD.<br>Haematological changes including ↑ neutrophils and urea nitrogen, and ↓ lymphocytes and alkaline phosphatase activity at HD.<br>Dermal irritation effects (erythema, oedema, desquamation, cracking and atonia) were observed at all doses but were more severe at the HD.<br>Histopathology of the skin sites showed an epidermal proliferative response with low grade inflammatory reaction (dose dependent).<br>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.<br>↑ Liver-weight without histological correlates among treated female animals could not be interpreted as being treatment-related<br>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<br>No treatment-related effects on organs<br>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<br>Bodyweight gain: ↓ in ♂at HD.<br>Organ weight: ↑ liver weights (♂ & ♀) from LD, associated histopathology observed at 2041 mg/kg bw/day; ↓ kidney weight in ♂ from 8648 mg/kg bw/day.<br>NOAEL: 992 (♂)/1050 (♀) mg/kg/day |
| | Mice (B6C3F1; *n* = 10/sex), doses: 0, 0, 3125, 6250, 12500, 25000, 50000 ppm (equivalent to 554, | Mortality: none |

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| Active ingredient | Study details[Δ] | Major findings |
|---|---|---|
| | 1246, 2860, 6780, 16238 mg/kg bw/day), 90 days (diet) | Bodyweight: ↓ BW gain in ♂ & ♀ from 6780 mg/kg bw/day<br>Organ weights: ↑ liver weight from 1246 mg/kg bw/day with histopathology from 6780 mg/kg bw/day. Renal histopathology at HD in ♂.<br>Reproductive parameters: ↓ sperm density and ↑ abnormal sperm in ♂ and ↑ oestrus cycle length in ♀ at HD<br>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<br>Bodyweight gain: ↓ in ♂ at HD.<br>Organ weight: ↑ liver (♂ & ♀) and kidney (♂) weights from LD, associated histopathology observed at 576 mg/kg bw/day in liver and at HD in kidney .<br>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.<br>Clinical signs: coloured urine from LD.<br>Bodyweights: ↓ BW gain in ♂ & ♀ from 1702 mg/kg bw/day.<br>Clinical pathology: serum protein levels from 411 mg/kg bw/day, ↑ platelet counts from 1702 mg/kg bw/day<br>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.<br>Reproductive parameters: ↓ sperm motility in ♂ and ↑ oestrus cycle length in ♀ at HD.<br>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<br>Organ weights: ↑ liver weight from 196 mg/kg bw/day.<br>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.<br>Organ weights: ↑ kidney weight in ♂ at all doses<br>Reproductive parameters: ↓ epididymal sperm density in ♂ at all doses.<br>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<br>Organ weights: ↑ liver weight in ♀ from 27.7 mg/kg bw/day, ↑ kidney weight in ♀ at HD<br>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).<br>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.<br>Clinical pathology: ↓ reticulocyte counts from LD, ↑ platelet counts from 50 mg/kg bw/day, ↑ whole blood cell count produced by lymphocytosis at HD.<br>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.<br>NOAEL: 1000 mg/kg bw/day |

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| Active ingredient | Study details[Δ] | Major findings |
|---|---|---|
| Homosalate (SCCS 2021; ECHA 2021c) | Rats, n=5/sex/dose, 0, 100, 300, 1000 mg/kg bw/day, 2 weeks (gavage) | Mortality: none<br>Clinical signs: none treatment related<br>Body weight gain: ↓ at HD in ♂ along with decreased food consumption<br>Haematology: none treatment related<br>Serum chemistry: ↑ Triglycerides in both sexes at HD ↑APTT in ♂ at MD<br>NOAEL: > 300 mg/kg bw/day ♂<br>NOAEL: >1000 mg/kg bw/day ♀ |
| | Repeat dose/ reproduction/ developments study<br><br>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<br>*Clinical signs:* none treatment-related<br>*Body weight gain:* ↓ at 750 mg/kg bw/day in ♂ and ♀<br>*Haematology:* none treatment-related<br>*Serum chemistry:* ↑ Albumin and ↓ Globulin in ♂ at 300 mg/kg bw/day<br>*Urinalysis:* not conducted<br>*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.<br>*Gross pathology:* no treatment-related findings<br>*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). *<br>Minimal/mild hypertrophy of hepatocytes (1/5 ♂) at 120 mg/kg bw/day, and almost every ♂ and ♀ from 300 mg/kg bw/day.<br>Hypertrophy of the follicular epithelium of thyroid gland in ♂ at 750 mg/kg bw/day and in ♀ from 300 mg/kg bw/day.<br>↓ Cortical lymphocytes in males from 300 mg/kg bw/day and in ♀ at 750 mg/kg bw/day<br>*NOAEL:* ** mg/kg bw/day<br>*The REACH registrants considered this as manifestations of hyaline droplet nephropathy without giving further evidence.<br>**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

## 4.5. 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 4-5. Summary of genotoxicity studies with sunscreen ingredients**

| Avobenzone (ECHA (2021a; DEPA 2015) | Ethylhexyl triazone (ECHA (2021b; DEPA 2015 | Homosalate (SCCS 2021; ECHA 2021c) | Octinoxate (ECHA 2021e) | Octocrylene (SCCS, 2021a; ECHA 2021d) | Oxybenzone (SCCP 2006a; 2021c) | PBSA (SCCP 2006b) |
|---|---|---|---|---|---|---|
| In vitro<br>Negative<br>AMES test and gene mutation study V79 Chinese hamster cells<br><br>In vivo<br>Negative<br>Bone marrow polychromatic erythrocytes (mice) | In vitro<br>Negative<br>AMES test, Chinese hamster lung fibroblasts for chromosome aberration, Chinese hamster ovary (CHO) cells, in vivo chromosome aberration test | In vitro<br>Negative<br>AMES test and gene mutation study in V79 Chinese hamster cells<br><br>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<br>Negative<br>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)<br><br>In vivo<br>Negative<br>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<br>Negative<br>AMES test, gene mutation test, cytogenicity test in mammalian cells, chromosome aberrations tests<br><br>In vivo<br>Negative<br>Cytogenicity test in mice ECHA 2020, SCCS 2021 | In vitro<br>Negative<br>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<br><br>In vivo<br>Negative<br>micronucleus test (mice), chromosome aberration test (rats), Drosophila (SMART)† | In vitro<br>Negative<br>AMES test and chromosome aberration test in human peripheral blood lymphocytes<br><br>In vivo<br>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.

### 4.6. CARCINOGENICITY

A summary of carcinogenicity studies for each sunscreen ingredient is shown in the table below. No carcinogenicity data is available for avobenzone, octinoxate, octocrylene, ethyl hexyl triazone, 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).

**Table 4-6. Summary of carcinogenicity studies with sunscreen ingredients**

| Active ingredient | Study details | Major findings |
|---|---|---|
| Avobenzone | – | No data |
| Octinoxate | – | No data |
| Octocrylene | – | No data |
| Ethyl hexyl triazone | – | No data |
| Homosalate | – | 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 ♂/♀)<br><br>Rats (SD; *n*=10/sex/group), 0, 1000, 3000, 10000 ppm (equivalent to 58/60, 168/180, 585/632 mg/kg bw/day in ♂/♀)<br>Two years (beginning on GD6 in ♀) | Mice: ↑ lesions in the bone marrow, spleen, and kidney of both sexes and in the liver in ♂<br><br>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.<br>These findings are considered equivocal evidence of carcinogenicity. |
| PBSA | – | No data |

### 4.7. REPRODUCTIVE AND DEVELOPMENTAL STUDIES

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

**Table 4-7. 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.<br>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.<br>↓ 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.<br>In the offspring, ↓ lactation weight gain and organ weights, and slightly delayed sexual maturation (vaginal opening and preputial separation) at HD.<br>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.<br>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. |
| Octocrylene (SCCS, 2021a; ECHA 2021d) | Extended one generation reproductive toxicity study (EOGRTS), GLP<br>Rat (Wistar); Dose: (diets) 55, 153, 534 mg/kg bw/day ♂<br>58, 163, 550 mg/kg bw/day ♀<br><br>*n*= 27 or 28 /sex /dose<br>F1: Cohort 1A: 19/sex/ dose<br>Cohort 1B: 25/sex/dose<br>Cohort 2A: 10/sex/ dose<br>Cohort 2B: 10/sex/dose<br><br>♂: 10-week premating period, during mating up to the day of sacrifice (~ 13 weeks)<br>♀: P: 10-week premating period, termination on LD 21<br>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)<br>F2: until weaning (indirectly)<br>(ECHA, 2021d; SCCS, 2021a) | ↓ number of implantation sites and consequently a lower number of pups at HD<br>↓ bodyweight of pups at HD<br>No effects on male fertility and male and female reproductive parameters such as oestrus cycle, epididymal and testicular sperm parameters at all doses.<br>No effects on sexual and neurodevelopmental parameters in pups.<br>Based on effects on parental and pup body weights, a lower number of implantation sites and lower number of pups delivered.<br>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<br>GD6–GD15; termination on GD21 | F0:<br>Transient salivation at HD.<br>↑ relative liver weight at MD and HD<br>F1:<br>No treatment related effects.<br>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<br>Odio *et al.* (1994) | No treatment related adverse effects.<br>NOEL: 1000 mg/kg bw/day (mice) |

| Active ingredient | Study details | Major findings |
|---|---|---|
| | Rabbit (NZW): $n$ = 17 ♀/dose<br>Dose: 0, 65, 267 mg/kg bw/day,<br>(Dermal, open, clipped area on the back), dosing GD6–GD18; termination on GD21<br>Odio *et al.* (1994) | No treatment related adverse effects.<br>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.<br>Maternal NOAEL = 1000 mg/kg bw/day;<br>Developmental NOAEL = 1000 mg/kg bw/day |
| Homosalate (SCCS 2021; 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).<br>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):<br>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.<br>↓ 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).<br>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;<br>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.<br>In mice, there were no effects on reproductive organ weight, cauda epidiymal sperm concentration, sperm parameters, testicular spermatid concentration or testicular histology.<br>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 was 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 |

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| Active ingredient | Study details | Major findings |
|---|---|---|
| | | 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 dDecrease 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 207.167.9 mg/kg bw/day. |
| 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-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 rise concerns about potential prenatal exposure and developmental toxicity of UV filters.

### 4.8. ENDOCRINE DISRUPTION

Endocrine-disrupting chemicals (EDCs) are exogenous chemicals that interfere with hormone action, thereby 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[9] 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[10] were also investigated for androgen receptor (AR) agonism/antagonism in vitro,*

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

*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 disruptors 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 disrupting effects of the commonly used UV filters) from the Wang review is provided in the Appendix.

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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".*

In the light of increased safety concerns regarding the ED 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 ED 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 EDCs based on hormone actions and EDC 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 has 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 evidences above are given below.

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***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)[11] and to act as an antagonist of androgen receptor (AR)(CASE Ultra and Leadscope),[11][12]

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The SCCS (2020) conclusion was based on a Risk Management Options Analysis (RMOA) 2016 by ANSES[12]. 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.

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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."*

[11] 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.

[12] French Agency for Food, Environmental and Occupational Health & Safety (ANSES)

The SCCS opinion also recommended that homosalate be permitted as an ingredient in cosmetics at no more than 1.4%, due to concerns that it behaves as an endocrine disrupter (SCCS, 2020).

**Octocrylene**

The endocrine disruption 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 disruption 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**

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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 feedbacks.

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. Currently a public call by the European Commission for data on the ED potential of octinoxate is in place (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.

### 4.9. OTHER STUDIES

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The photo-allergic potential of avobenzone has been extensively reviewed in several publications (Nash & 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 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 Draize repeated insult patch test was carried out at a concentration of 2% 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.

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Oxybenzone was tested for photobinding to human serum albumin and histidine photo-oxidation potential in a newly proposed mechanistic *in vitro* test for the discrimination of the photo-allergic and photo-irritants. Oxybenzone revealed no phototoxic and no photo-allergic potential (SCCP 2006a).

10% ethylhexyl triazone 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%) were 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 & 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 & 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 & 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 given below. However, this is not reviewed in this discuss elaborately as similar mechanisms apply on endocrine disruption potential of these ingredients (Ruszkiewcz *et al.*, 2017)

| 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 | Decreased hypothalamic release of LHRH. Increased GABA release in |

| | | | |
|---|---|---|---|
| | | immature rats; 60 min; 0.263µM | 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. |
| Benzophenone-3 or oxybenzone | Danio rerio | 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. |
| | Sprague-Dawley rats | Dermal application; 30 days; 5 mg/kg/day | No changes in behavioural tests (locomotor and motor co-ordination). |
| | Rat primary cortical astorcytes and neurones | 1–7 days; 1–10 µg/mL | Decreased cell viability of neurons but not of astrocytes. |
| | SH-SY5Y neuroblastoma cell line | 72 h; $10^{-8}$–$10^{-4}$M | Decreased cell viability and increased caspase-3 activity. |
| Octocyrylene | Danio rerio | Waterborne; 14 days; 22–383 µg/L | Impaired expression of genes related with development and metabolism in the brain. |

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.

# 5. APPENDIX

## 5.1. SEARCH STRATEGY

### *Search criteria (word input)*

Keywords included either the chemical name, AAN or the INCI names, and "sunscreen" were used as the search items. Publications in last ten years were searched (2008-2020). 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

Didn't find anything relevant.

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

- Coslng 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/

***Example of the search strategy for avobenzone***

Search for: remove duplicates from 141 [67 or 140], results: 163

| Embase, Ovid MEDLINE(R) | | | |
|---|---|---|---|
| **#** | **Search Statement** | **Results** | **Annotation** |
| 1 | exp avobenzone/ or Avobenzone.mp. | 914 | |
| 2 | 70356-09-1.rn. | 629 | |
| 3 | Butyl methoxydibenzoylmethane.mp. | 189 | |
| 4 | Butyl methoxy dibenzoylmethane.mp. | 19 | |
| 5 | 4-tert-butyl-4-methoxy dibenzoylmethane.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy] | 14 | |
| 6 | Avobenzona.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy] | 3 | |
| 7 | Avobenzonum.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy] | 0 | |
| 8 | 1 or 2 or 3 or 4 or 5 or 6 or 7 | 995 | |
| 9 | exp drug carcinogenicity/ | 835 | |
| 10 | exp carcinogenicity/ | 31868 | |

| | | | |
|---|---|---|---|
| 11 | exp carcinogen/ | 148982 | |
| 12 | exp Carcinogens/ | 286093 | |
| 13 | exp Carcinogenicity Tests/ | 6877 | |
| 14 | exp Mutagens/ | 108755 | |
| 15 | exp mutagenicity tests/ | 60479 | |
| 16 | exp genotoxicity/ | 33452 | |
| 17 | exp Neoplasms/ | 7761161 | |
| 18 | ((Dermal or systemic) adj2 carcinog*).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 411 | |
| 19 | Carcinog*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 539368 | |
| 20 | 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 | 8168404 | |
| 21 | 8 and 20 | 176 | |
| 22 | limit 21 to yr="2010 -Current" | 83 | |
| 23 | limit 22 to animals | 7 | |
| 24 | limit 22 to animal studies [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained] | 16 | |
| 25 | ("in vitro" or "cell cultur*" or "tissue cultur*").mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 4180142 | |
| 26 | 22 and 25 | 15 | |
| 27 | 23 or 24 or 26 | 25 | |
| 28 | remove duplicates from 27 | 22 | Carcinogenicity |
| 29 | exp drug toxicity/ | 242986 | |
| 30 | exp reproductive toxicity/ | 11312 | |
| 31 | exp toxicity/ | 680419 | |
| 32 | exp toxicity testing/ | 45674 | |
| 33 | exp acute toxicity/ | 20152 | |
| 34 | exp developmental toxicity/ | 3060 | |
| 35 | exp Toxicity Tests/ | 157598 | |
| 36 | exp Toxicology/ | 84344 | |
| 37 | exp teratogens/ | 56503 | |
| 38 | exp teratogen/ | 28428 | |
| 39 | exp teratogenesis/ | 11684 | |
| 40 | exp teratogenicity/ | 17251 | |
| 41 | ((Development* or reproduct*) adj3 toxic*).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 36335 | |
| 42 | 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 | 1069060 | |
| 43 | 8 and 42 | 108 | |
| 44 | limit 43 to yr="2010 -Current" | 47 | |
| 45 | limit 44 to animals | 7 | |
| 46 | limit 44 to animal studies [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained] | 11 | |

| | | | |
|---|---|---|---|
| 47 | 25 and 44 | 16 | |
| 48 | 45 or 46 or 47 | 23 | |
| 49 | remove duplicates from 48 | 21 | Toxicity |
| 50 | exp toxicokinetics/ | 12513 | |
| 51 | Toxicokinetic*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 18322 | |
| 52 | 50 or 51 | 18322 | |
| 53 | 8 and 52 | 1 | toxicokinetics |
| 54 | exp endocrine function/ | 484253 | |
| 55 | exp endocrine disease/ | 2973497 | |
| 56 | exp endocrine system/ | 1216506 | |
| 57 | exp Endocrine Disruptors/ | 16224 | |
| 58 | (("long term" or endocrin*) adj3 effect*).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 195242 | |
| 59 | 54 or 55 or 56 or 57 or 58 | 4241536 | |
| 60 | 8 and 59 | 34 | |
| 61 | limit 60 to animals | 4 | |
| 62 | limit 60 to animal studies [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained] | 8 | |
| 63 | 60 and 25 | 11 | |
| 64 | 61 or 62 or 63 | 15 | |
| 65 | remove duplicates from 64 | 11 | endocrine effects |
| 66 | 28 or 49 or 53 or 65 | 48 | |
| 67 | remove duplicates from 66 | 47 | non clinical combined |
| 68 | exp contact dermatitis/ | 53966 | |
| 69 | exp skin allergy/ | 20467 | |
| 70 | exp skin toxicity/ | 22884 | |
| 71 | exp skin irritation/ | 13378 | |
| 72 | exp skin sensitization/ | 5437 | |
| 73 | exp sensitization/ | 71113 | |
| 74 | exp photodermatosis/ | 9330 | |
| 75 | exp application site reaction/ | 4811 | |
| 76 | exp application site inflammation/ | 89 | |
| 77 | exp Skin Irritancy Tests/ | 46387 | |
| 78 | exp Skin Tests/ | 132447 | |
| 79 | exp skin pruritus/ | 3400 | |
| 80 | exp pruritus/ | 105892 | |
| 81 | exp allergic rash/ | 305 | |
| 82 | exp contact allergy/ | 8227 | |
| 83 | exp contact dermatitis/ | 53966 | |
| 84 | exp drug hypersensitivity/ | 102543 | |

| | | | |
|---|---|---|---|
| 85 | exp allergy/ | 413969 | |
| 86 | exp Hypersensitivity/ | 943748 | |
| 87 | exp Allergens/ | 110041 | |
| 88 | ((dermal or skin) adj3 (sensiti* or irritat*)).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 38460 | |
| 89 | 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 | 1247473 | |
| 90 | 8 and 89 | 296 | |
| 91 | limit 90 to human | 255 | |
| 92 | limit 91 to yr="2010 -Current" | 110 | |
| 93 | limit 92 to english language | 108 | |
| 94 | limit 93 to (conference abstract or conference paper or "conference review" or editorial or letter or note) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained] | 21 | |
| 95 | 93 not 94 | 87 | skin irritation |
| 96 | exp phototoxicity/ | 8810 | |
| 97 | exp photoallergy/ | 2680 | |
| 98 | (phototox* or photoalle*).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 18852 | |
| 99 | 96 or 97 or 98 | 18852 | |
| 100 | 8 and 99 | 163 | |
| 101 | limit 100 to english language | 148 | |
| 102 | limit 101 to human | 122 | |
| 103 | limit 102 to yr="2010 -Current" | 55 | |
| 104 | limit 103 to (conference abstract or conference paper or "conference review" or editorial or letter or note) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained] | 8 | |
| 105 | 103 not 104 | 47 | |
| 106 | remove duplicates from 105 | 39 | phototoxicity |
| 107 | exp drug bioavailability/ | 65733 | |
| 108 | exp bioavailability/ | 153820 | |
| 109 | exp drug absorption/ | 82919 | |
| 110 | exp pharmacokinetics/ | 1036741 | |
| 111 | exp Skin Absorption/ | 18649 | |
| 112 | exp Biological Availability/ | 153820 | |
| 113 | exp Absorption, Physiological/ | 133321 | |
| 114 | (absorp* or absorb*).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 1037779 | |
| 115 | (penetration or penetrate or permeability).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 555651 | |
| 116 | (penetration or penetrate or permeability).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 555651 | |
| 117 | bioavail*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 227239 | |

| | | | |
|---|---|---|---|
| 118 | 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 | 2405762 | |
| 119 | 8 and 118 | 390 | |
| 120 | 107 or 108 or 109 or 111 or 112 or 113 or 117 | 429161 | |
| 121 | 8 and 120 | 148 | |
| 122 | limit 121 to english language | 141 | |
| 123 | limit 122 to human | 86 | |
| 124 | limit 123 to yr="2010 -Current" | 45 | |
| 125 | limit 119 to english language | 376 | |
| 126 | limit 125 to human | 207 | |
| 127 | limit 126 to yr="2010 -Current" | 106 | |
| 128 | limit 127 to (conference abstract or conference paper or "conference review" or editorial or letter or note) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained] | 15 | |
| 129 | 127 not 128 | 91 | |
| 130 | remove duplicates from 129 | 72 | bioavailability absorption |
| 131 | (safe or safety or "side effect" or "side effects" or adverse).mp. or exp adverse drug reaction/ or exp drug-related side effects/ or exp drug safety/ or toxic*.mp. or hazard*.mp. | 8304938 | |
| 132 | 8 and 131 | 406 | |
| 133 | limit 132 to english language | 389 | |
| 134 | limit 133 to human | 281 | |
| 135 | limit 134 to yr="2010 -Current" | 130 | |
| 136 | limit 135 to (conference abstract or conference paper or "conference review" or editorial or letter or note) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained] | 14 | |
| 137 | 135 not 136 | 116 | |
| 138 | remove duplicates from 137 | 91 | general safety |
| 139 | 95 or 106 or 130 or 138 | 153 | |
| 140 | remove duplicates from 139 | 139 | clinical search |
| 141 | 67 or 140 | 173 | |
| 142 | remove duplicates from 141 | 163 | **Final clinical and non-clinical combined** |

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## 5.2. TABLE 2: LISTING ENDOCRINE DISRUPTING EFFECTS OF COMMONLY USED UV FILTERS

Table 2

Endocrine disrupting effects of the 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 minnows; Reduce of the uterine weight in immature Long-Evans rats |
| | Androgenic disrupting effects | Antagonists of human AR transactivation; Repression of 4,5-dihydrotestosterone-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; Induction of proliferation of MCF-7 cell; Induction of pS2 protein in MCF-7 cells; Reduce of the uterine weight in rats; Induction of VTG in fish |
| | 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 progesterone 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; Reduce of the uterine weight in rats; Induction of VTG in fish |
| | Disrupting effects toward thyroid hormone receptor | Decrease of T4 level; 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; Reduce of the 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

### 5.3. TABLE 3: MEAN EXPOSED SKIN SURFACE AREA PER PRODUCT TYPE AND FREQUENCY OF APPLICATION PER PRODUCT TYPE (BREMMER *ET AL.*, 2006)

| Product type | Skin surface area involved (RIVM) | | Frequency of application |
|---|---|---|---|
| | Surface area ($cm^2$) | Parameters (if specified) | |
| **Bathing, showering** | | | |
| Shower gel | 17500 | total body area | 1.43/day |
| Hand wash soap | 860 | area hands | 10/day |
| Bath oil, salts, etc. | 16340 | area body - area head | 1/day |
| **Hair care** | | | |
| Shampoo | 1440 | area hands | 1/day |
| | | + 1/2 area head | |
| Hair conditioner | 1440 | area hands + 1/2 area head | 0.28/day |
| Hair styling products | 1010 | 1/2 area hands + 1/2 area head | *1.14/day* |
| Semi-permanent hair dyes (and lotions) | 580 | 1/2 area head | 1/week (20 min.) |
| Oxidative/permanent hair dyes | 580 | 1/2 area head | 1/month (30 min.) |
| **Skin care** | | | |
| Body lotion | 15670 | area body - area headfemale | *2.28/day* |
| Face cream | 565 | 1/2 area head female | *2.14/day* |
| Neck | 320 | | |
| Back of neck | 80 | | |
| Hand cream | 860 | area hands | 2/day |
| **Make-up** | | | |
| Liquid foundation | 565 | 1/2 area head female | 1/day |
| Make-up remover | 565 | 1/2 area head female | 1/day |
| Eye shadow | 24 | | 2/day |
| Mascara | 1.6 | | 2/day |
| Eyeliner | 3.2 | | 2/day |
| Lipstick, lip salve | 4.8 | | *2/day* |
| **Deodorant/antiperspirant** | | | |
| Deodorant aerosol spray and non-spray | 200 | both axillae | *2/day* |
| **Fragrances** | | | |
| Eau de toilette spray | 200 | | 1/day |
| Perfume spray | 100 | | 1/day |
| **Men's cosmetics** | | | |
| Shaving cream | 305 | 1/4 area head male | 1/day |
| Aftershave | 305 | 1/4 area head male | 1/day |
| **Sun care cosmetics** | | | |

| | | | |
|---|---|---|---|
| **Sunscreen lotion / cream** | **17500** | **total body area** | **2/day** |

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Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

# Literature Review

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

June 2022

TGA Health Safety Regulation

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## EXECUTIVE SUMMARY

The TGA has completed a literature review investigating the safety of the following seven sunscreen active ingredients available for use in Australia:

- Butyl methoxydibenzoylmethane (avobenzone)
- ethylhexyl triazone
- homosalate
- octocrylene
- octinoxate
- oxybenzone
- phenylbenzimidazole sulfonic acid

The purpose of this review was to identify any significant data gaps related to safety for these ingredients used in listed medicines (sunscreen products) so that appropriate risk management approaches could be considered 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 higher number of sunscreen products marketed in Australia, and safety signals reported in media and overseas. The review utilised available national and international safety assessment reports and peer reviewed publications.

The two main issues considered in this review was the evidence for the ability of these ingredients to penetrate the skin to reach viable cells systemically, and the potential toxicity exerted by them. Based on the data available, a Margin of Safety (MoS) was determined for each of the ingredients using SCCS Guidelines[1]. The MoS was calculated based on the current permitted concentrations for sunscreens that can be listed on the Australian Register of Therapeutic Goods. However, it is noted that the concentrations of these actives in products appear in a number of cases to be less than the permitted amounts; and that some products contain a combination of the active ingredients.

Based on the limited data that were~~as~~ available and MoS determined as per the SCCS guidelines:

- avobenzone, ethylhexyl triazone, octocrylene, octinoxate and phenylbenzimidazole sulfonic acid are unlikely to cause any significant systemic toxicity.
- **homosalate and oxybenzone** when used at the maximum ~~permitted dose~~recommended application in Australia had an unacceptable MoS of less than 100. The calculation was based on available dermal absorption data and data from a combined repeated dose toxicity study with the reproduction/developmental toxicity and pre- and post-natal developmental toxicity study for homosalate and oxybenzone, respectively.

The systemic absorption of avobenzone, homosalate, octocrylene, octinoxate and oxybenzone was noted in a limited number of clinical trials reported overseas based on current use scenarios in the relevant countries where the tests were conducted. The available information on these ingredients indicate potential endocrine effects, however, the data are not adequate to derive a conclusion. Further data on the endocrine disrupting potential of these chemicals are warranted.

Please see Annex 1 for alternate estimations of safe concentrations of the above active ingredients in sunscreens.

The limitations of this literature review are:

a) The No Observed ~~A~~adverse E~~e~~ffects L~~l~~evels (NOAELs) were collected from published international safety assessment reports. Actual firsthand evaluation of the data, study quality, compliance was not possible.
b) Additional studies would be required to fully evaluate the pharmacokinetics of these ingredients.

[1] Risk assessments were conducted as per the SCCS 2016, 2018, and 2021 guidelines. A copy of the 2021 guidelines is available at https://health.ec.europa.eu/system/files/2021-04/sccs_o_250_0.pdf

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c) Due to a lack of specific data and guidelines for the determination of the MoS in paediatric populations, the safety of these ingredients is uncertain when used on infants and children.
d) Due to a lack of specific data and guidelines for the determination of the MoS in pregnant and lactating women, the safety of these ingredients is uncertain when used in this population.
e) The SCCS guidelines suggests the European estimate was based on application to the total body twice a day (twice being the 90th percentile), factoring in how it is generally applied by consumers in the EU and not the recommended dosage. There is a lack of information surrounding the typical use patterns of sunscreens in Australia. Therefore, the Australia recommended directions for use, or Australian use data were not considered in these exposure assessments. Further consideration of Australia specific calculations are available in Annex 1.
f) The directions for use are not consistent across different sunscreen products (e.g. lip balm only products, roll on products, spray) and primary sunscreens (e.g. sports products, swimming products, toddler products) impacting the Systemic Exposure Dose (SED) calculation.
g) Formulation-specific effects was not considered in the review. Active sunscreen ingredients are normally formulated with other ingredients that could lead to increased transdermal permeability and systemic exposure.
h) Consumer products other than sunscreens that contain the same active ingredients were not considered in this review for any exposure modelling. This is beyond the scope of the literature review which was solely focussed on sunscreen active ingredients given the safety signals noted by the FDA and the available safety data.

This review highlights the data gaps associated with the safety and exposure estimates for some of these ingredients, leading to unacceptable MoS in some cases. Further data are required to bridge these gaps.

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## 1. ASSESSMENT

Maintaining public confidence in the safety and effectiveness of sunscreens is an important part of the TGA's role in regulation of therapeutic sunscreens. Recent concerns about the skin absorption of active ingredients in sunscreens have arisen in part by the FDA's proposed changes in the regulation of sunscreen ingredients (US FDA 2019b). The proposed changes state that the FDA considers that a sunscreen active ingredient is safe and effective, if it demonstrates a steady-state blood level of an ingredient under 0.5 ng/mL, and an adequately conducted toxicological study does not raise any other safety concerns (US FDA 2019b). The FDA published two studies looking at the dermal absorption of the most common active ingredients in sunscreens (Matta *et al.,* 2020; 2019). Both studies demonstrated that the ingredients were absorbed in significant quantities and that they can remain in plasma for an extended time after the last application.

In response to the findings from the FDA and given the greater use of sunscreens in Australia (frequency and longer-term use), the TGA undertook its own targeted review to understand the safety profile of the active ingredients approved for use in sunscreens in Australia.[2] A targeted safety assessment of seven ingredients (avobenzone, ethylhexyl triazone, homosalate, octocrylene, octinoxate, oxybenzone and phenylbenzimidazole sulfonic acid) was undertaken, considering the highest reported use of the sunscreen products in Australia containing these active ingredients (Appendix 3.4) and international safety signals (FDA, 2019b).

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Assessments and guidelines from the Scientific Committee on Consumer Safety (SCCS) were used to support the safety of these sunscreen ingredients, given the SCCS is approved as a comparable overseas body (COB) for use in pre-market evaluations for listed medicine ingredients (e.g. sunscreens).[3] The safety assessment of the selected ingredients was based on information provided in the newest opinions from the SCCS where available, and information identified from a literature search in PubMed and an open search for information on specific endpoints from published reports from the internet. Review articles and documents focusing on the individual toxicological endpoints were featured in the hazard assessment where no recent SCCS opinions were available. EU Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) registration dossiers for individual ingredients published by European Chemicals Agency (ECHA) and risk assessment by national regulatory agencies (i.e., AICIS) were also considered if available.

Exposure to these selected ingredients from other products that were not sunscreens (e.g. cosmetics) or metabolites of these ingredients or impurities, or use in specific populations (paediatric or pregnant/lactating women), - has also not been considered in this review. Given the directions for use are not consistent across different sunscreen products (e.g. lip balm only products, roll on products, spray) and primary sunscreens (e.g. sports products, swimming products, toddler products), only the amount of sunscreen lotions/creams applied per day (18 g/day; per SCCS guidelines) were considered for the SED calculation.

During 2020-21, the European Commission published opinions (preliminary and/or final) on the safety of oxybenzone, homosalate and octocrylene. Risk assessments were conducted based on available information, and a Margin of Safety (MoS) determined for each ingredient as per relevant guidelines (SCC, 2000; SCCS, 2016; SCCS, 2021d). The opinions found that the levels of oxybenzone and homosalate were not safe and proposed a concentration limit of 2.2% and 1.4% (0.5% in the final opinion) for oxybenzone and homosalate, respectively when used in sunscreens.

The TGA literature review follows a similar approach of risk assessment based on a MoS determination as per the SCCS guidelines while recognising limited available data. Further randomized controlled trials may need to be conducted to accurately evaluate the long-term risk of

[2] Permissible sunscreen ingredients are included in a legislative instrument: see the Therapeutic Goods (Permissible Ingredients) Determination (No. 2) 2022 (legislation.gov.au)

[3] Comparable overseas bodies (COBs) for complementary medicines | Therapeutic Goods Administration (TGA)

exposure to these active ingredients when used in sunscreens. However, this is subject to ethical considerations.

### 1.1. MARGIN OF SAFETY

As per the *SCCNFP's notes of guidance for the testing of cosmetic ingredients and their safety evaluation, 9th-11th revision* (SCCS, 2016, 2018 and 2021), the risk assessment of active ingredients in sunscreens can be conducted by calculating the MoS using uncertainty factors. MoS can be extrapolated from animals to humans to predict the potential risk in human. Usually, a MoS > 100 would indicate that the ingredient is safe under the proposed use conditions. MoS is the ratio between a NOAEL and a Systemic Exposure Dose (SED).

$$MoS = \frac{NOAEL(mg/kg\ bw/d)}{SED(mg/kg\ bw/d)}$$

The SED of a cosmetic substance is the amount expected to enter the blood stream (and therefore be systemically available) per kg body weight and per day. It is expressed in mg/kg body weight (bw)/day. For this definition, the human body weight of 60 kg is commonly accepted; however, the TGA usually considers a more conservative approach to calculate the SED, with a typical body weight for adults of 50 kg. *ICH guideline Q3C (R8) on impurities: guideline for residual solvents* also advocates using '*...an arbitrary adult human body weight for either sex of 50 kg.*' as a way of providing an additional safety factor in permissible daily exposure (PDE) calculations.[4]

SED can be calculated using either of the following two formulas depending on the method of reporting for the dermal absorption value as per SCCS notes of guidance (2016, 2018 and SCCS 2021d).

*Option 1: Dermal absorption reported as a percentage of the amount of substance applied in in vitro studies:*

The percentage of dermal absorption is expected to be calculated from *in vitro* studies with doses, concentrations and amounts mimicking, but not exceeding the intended use conditions. Otherwise, the studies may result in an underestimation of the penetration.

| Description | Parameter |
|---|---|
| Amount of sunscreen applied daily | Q (mg/day) |
| Concentration of ingredient in finished product | C (%) |
| Total amount of active ingredient applied | Qi = Q x C (mg/day) |
| Absorption of active ingredient | $DA_p$(%) |
| Total amount absorbed | Abs =Qi x $DA_p$ × 0.01 × 0.01 mg/day |

SED= Abs/body weight (50 kg)[5], based upon the amount applied and the frequency of application, for sunscreen lotion, an application of 18 g/d is used in the MoS calculation (SCCS, 2016, 2018, 2021d) (See section 2.4:Use).

[4] ICH guideline Q3C (R8) on impurities: guideline for residual solvents

[5] TGA usually consider a more conservative approach to calculate the SED, with a typical body weight for adults of 50 kg.

Note: In the case that the molecular weight (MW) > 500 Da and the log $P_{ow}$ (octanol-water partition coefficient) is less than -1 or higher than 4, the value of 10% dermal absorption may be considered appropriate to use in the absence of empirical data.

*Option 2: Dermal absorption of test substance reported in µg/cm²*

For calculating the SED, the skin surface to be treated with the finished cosmetic product containing the substance under study has to be taken into account, as well as its frequency of application per day. All other variables should have been taken into consideration in the proper design of the dermal absorption study itself (SCCS, 2016).

$$SED = \frac{DA_a\ (\mu g/cm^2) \times SSA\ (cm^2) \times F\ (day^{-1})}{50\ kg} \times 10^{-3}$$

$DA_a$ (µg/cm²) = Dermal Absorption reported as amount/cm², resulting from an assay under in-use mimicking conditions

SSA (cm²) = Skin Surface Area expected to be treated with the finished cosmetic product (See Table 3 in appendix)

F ($day^{-1}$) = Frequency of application of the finished product (F ≥ 1)

Although dermal data is expected to reflect real time exposure and toxicity following application of sunscreens, in the absence of dermal toxicity data, oral toxicity data were considered in the MoS determination using a conservative approach given oral toxicity data may reflect systemic toxicity in worst case scenario.

### 1.2. RISK ASSESSMENT OF THE ACTIVE INGREDIENTS IN SUNSCREENS

**Butyl methoxydibenzoylmethane (avobenzone)**

Butyl methoxydibenzoylmethane is approved in Australia for use as an active ingredient in sunscreens at a maximum concentration of 5% for dermal application, not to be used in topical products for eyes, with appropriate safety warnings on the label (e.g. 'Wear protective clothing - hats and eyewear when exposed to the sun' [or words to this effect]).[6]

This review is based on the international safety assessment reports (ECHA, 2021a; DEPA, 2015) and available peer reviewed publications investigating the safety and toxicokinetics of avobenzone.

The ECHA dossier suggested low percutaneous absorption of avobenzone. Potential systemic availability of avobenzone or metabolites at a high oral dosage was suggested from the oral toxicity studies in rats with up to 3 months exposure. Low systemic exposure from dermal contact was also noted in the ECHA dossier and insignificant inhalation exposure was assumed due to the low vapour pressure. In a study with pigskin (2% and 7.5% avobenzone containing formulations), about 95% of avobenzone remained on the skin surface, 1-2 % were in the stratum corneum, 1 - 3.4% in the skin and only ≤0.5% was found to pass the skin (ECHA 2021A). In an *in vitro* dermal absorption study with human skin (2% avobenzone in water-oil cream) dermal absorption increased with exposure time from 0.3% to 7.3% (this value is used in the MoS calculation, see below) after 18 hours (DSM, 1982). In a recent study (Montenegro *et al.* 2018) to investigate the effects of the vehicle and repeated applications of sunscreens on skin permeation, the skin permeation was demonstrated to

[6] Therapeutic Goods (Permissible Ingredients) Determination (No. 3) 2022

be very poor after single or repeated applications leading to a MoS above the accepted safety limit (>100).

Nonetheless, recent randomised clinical trials indicate that avobenzone could be systemically absorbed (Matta *et al.*, 2020; 2019). The systemic exposure of avobenzone in all product types (spray, lotion, aerosol spray) exceeded 0.5 ng/mL on single application and remained above the threshold until 23 hours after application, and up to 7 days in more than 50% of participants. The long terminal half-life typically exceeded 48 hours and the ingredient remained detectable through to day 21, suggesting absorption through the skin is the rate-limiting step. However, further studies are required to determine other kinetic parameters e.g. elimination rate constants.

The available information reported for avobenzone indicate it has low acute toxicity (rats) and it is not an irritant to skin (very slight irritation at 10%) and eye (≤ 20%) in rabbits. No treatment-related effects were seen in guinea pig studies investigating irritation, sensitization, phototoxicity, and photoallergenicity potential. The ingredient was not found to be genotoxic, mutagenic, photo mutagenic or teratogenic in animals. Clinical data have shown the ingredient to be a rare allergen and/or photoallergen. *Based on a 13-week oral repeated dose toxicity study in rats, the NOAEL of avobenzone was considered to be 450 mg/kg bw/day and used for the MoS calculation given the longer duration of the study and a better reflection of systemic toxicity using a conservative approach.* Dose related local dermal effects like erythema and oedema were seen in a 28 day dermal repeat dose study in rabbits with no systemic effects, therefore the NOAEL was not used in the calculation of the MoS. In this study, the systemic NOAEL was determined to be 360 mg/kg/day bw (18% avobenzone) whereas the LOAEL (dermal) was 30 mg/kg/day bw (1.5% avobenzone) based on topical local effects. A NOAEL (oral) for maternal, developmental and embryotoxicity of 1,000 mg/kg bw/day was determined in rats.

Assuming the mean average body weight of 50 kg for Australian public, the SED is determined 1.3 mg/kg bw/day resulting in a MoS of 346 (see below).

| Description | Parameter | Sunscreen |
|---|---|---|
| Amount of sunscreen applied daily | Q (mg/day) | 18000 |
| Concentration of ingredient in finished product | C (%) | 5 |
| Total amount of active ingredient applied | Qi = Q x C (mg/day) | 90000 |
| Absorption of active ingredient | $DA_p$ (%) | 7.3 |
| Total amount absorbed | Abs =Qi x $DA_p$ × 0.01 × 0.01 mg/day | 65.7 |
| **SED** | ABs/body weight (50 kg) | 1.3 |

~~No Observed Adverse Effect Level (~~NOAEL~~)~~ = 450 mg/kg bw/day

**MoS = NOAEL/SED = 346 (>100)**

The Danish Environmental Protection Agency (DEPA, 2015) calculated the MoS with the maximum allowed concentration of 5% and determined a MoS around 300 for sunscreens containing avobenzone applied on people with mean average weight of 60 kg. They also concluded that avobenzone did not pose a risk to consumers based on the REACH registration dossier assuming 36 g was applied daily (MoS ≥ 100). In 2013, publicly available data on endocrine disruptive properties of the substance were collected and evaluated by the Danish Centre on Endocrine Disruptors which concluded that there was not enough data to conclude whether the substance had endocrine disruptive properties or not.

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Based on the information available, the MoS was determined to be more than 100 and no immediate systemic safety concerns were evident with the use of avobenzone at 5% in sunscreens with an

estimated usage of 18 g per day. However, the risk of endocrine disruption has not been sufficiently addressed.

**Ethylhexyl triazone (EHT)**

Ethylhexyl triazone is approved in Australia for use as an active ingredient in sunscreens at a maximum concentration of 5% for dermal application, not to be used in topical products for eyes, with appropriate sunscreen safety warnings on the label (e.g. Wear protective clothing - hats and eyewear when exposed to the sun' [or words to this effect])[7].

The summary is primarily based on the REACH dossier (ECHA, 2021b) and published peer reviewed articles.

The ECHA registration dossier indicated the dermal uptake of ethylhexyl triazone was negligible or low (maximum uptake of 1.3%). Recent *in vitro* experiments with a static skin diffusion cell design under real life conditions indicated that 18.3 ± 2.5 µg/cm² of ethylhexyl triazone was found in the stratum corneum, whereas no ethylhexyl triazone was determined in the receptor fluid following the application of a sunscreen with 5% ethylhexyl triazone on the intact human skin at the dose of 1mg/cm² for 6 h (Hojerová *et al.* 2017). 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. Higher ethylhexyl triazone absorption was noted on shaved skin.

Undiluted ethylhexyl triazone is not expected to be a skin or eye irritant. There are no data for respiratory irritation. It was not found to be sensitising in guinea pigs. The NOAELs were determined 1000 mg/kg/day and ≤ 1275 mg/kg/day in two 90-day oral repeat dose studies in rats. Ethylhexyl triazone was not found to be genotoxic in *in vivo* and *in vitro* studies. No carcinogenicity data were available, and no adverse effects were reported in a pre-natal developmental study (maternal and developmental NOAEL 1000 mg/kg/day bw).

Because no dermal repeated-dose toxicity study for ethylhexyl triazone was available from the literature, and in accordance with the guidance provided in SCCS (2016), the lower NOAEL value (1000 mg/kg bw/day) from oral repeated dose toxicity studies in rats was used in the MoS determination.

In the absence of an appropriate dermal absorption value for ethylhexyl triazone, a 50% dermal absorption was assumed for SED calculation in the worst-case scenario using option 1 (SCCS 2021) considering physiochemical properties (molecular weight > 500 and a $logP_{ow}$ > 4).

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| Description | Parameter | Sunscreen |
|---|---|---|
| Amount of sunscreen applied daily | Q (mg/day) | 18000 |
| Concentration of ingredient in finished product | C (%) | 5 |
| Total amount of active ingredient applied | Qi = Q x C (mg/day) | 90000 |
| Absorption of active ingredient | $DA_p$ (%) | 50 |
| Total amount absorbed | Abs =Qi x $DA_p$ × 0.01 × 0.01 mg/day | 450 |
| SED | Abs/body weight (50 kg) | 9 |

~~No Observed Adverse Effect Level (~~NOAEL~~)~~ = 1000 mg/kg bw/day

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Therefore, the MoS was determined = NOAEL/SED= 1000/9 = 111 (> 100)

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There are no immediate systemic safety concerns with the use of this ingredient in sunscreens in the current use scenarios. However, the primary data and analysis have not been subject to scrutiny by the evaluator.

**Homosalate**

Homosalate is approved in Australia for use as an active ingredient in sunscreens, and excipient in topical medicines, at a maximum concentration of 15% for dermal application, not to be used in topical products for eyes, with appropriate safety warnings on the label if used in sunscreens (e.g. Wear protective clothing - hats and eyewear when exposed to the sun' [or words to this effect])[8].

This review is based on the published literature, ECHA dossier and SCCS opinions (ECHA, 2021c; SCCS, 2020). The SCCS has published their opinion on homosalate in 2007, and recently extended their preliminary opinion based on new information of homosalate in 2020 (SCCS, 2020).[9]

Animal studies and studies with human skin showed that homosalate could penetrate the skin. Evidence from *in vitro* experiments indicates that about 1.1% of the applied dose was absorbed in human skin (range: 0.9-2.0%)(CTFA, 2005). The maximal absorption value observed in the donor with highest absorption values (2%) was taken for MoS calculation.[10]

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 Section 2.1).

Homosalate was found to be systemically absorbed in recent randomised clinical trials (Matta *et al.,* 2020, 2021). The systemic exposure of homosalate in sunscreens (spray) exceeded 0.5 ng/mL on single application and repeated applications (in > 50% of participants up to 21 days). The continued presence of homosalate at skin up to 21 days and long terminal half-life (> 48 hours) suggest skin absorption of homosalate (Matta *et al.,* 2020). Intravenous studies would be required to determine elimination rate constants. Homosalate was also detected in human milk samples after topical application in human volunteers (Schlumpf *et al.* 2010). Given homosalate systemic exposure was noted in clinical trials, the clinical relevance of the presence of homosalate in human milk after topical application raises safety concerns around the use of products containing homosalate warranting further investigation.

*In vitro*, homosalate was hydrolysed into salicylic acid and 3,3,5-trimethylcyclohexano associated with conjugation and hydroxylation of intact homosalate.

Based on publicly available safety information from animal studies, homosalate was found to be of low acute oral and dermal toxicity, not a skin or eye irritant (at 10%) and with no sensitising potential. Undiluted homosalate was also found to be a non-irritant in a human epidermis skin test with no sensitising potential at 15% in a human repeat patch test.

A general toxicity NOAEL of 300 mg/kg bw/day was established in a combined repeat dose and reproductive/developmental screening study in rats based on mortality in female rats at the highest dose. However, treatment-related effects were observed in kidneys, liver, thyroid and thymus in male rats at 60 mg/kg bw/day. Therefore, the SCCS concluded that this dose should be considered the LOAEL. The SCCS also states that technical errors might have contributed to the effects observed, influencing the reliability of the study. A NOAEL of > 300 mg/kg bw/day in males and >1000 mg/kg

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[9] The final opinion was published in June 2021, after this review was drafted.

[10] A 5% dermal absorption value was used in the final SCCS opinion on homosalate (June 2021) resulting in a MoS value of 6. This does not change the safety assessment of homosalate as the current MoS is not acceptable (< 100).

bw/day in females was established in a two-week study in rats. Both these studies indicate that the treatment-related effects were more adverse in males. The human relevance of this species-specific effect is uncertain.

While two recent studies indicated that there was a genotoxic potential for homosalate, the studies were found inadequate due to methodological errors (Yazar *et al.* 2018; 2019). No carcinogenicity data were available. A combined repeated dose and reproductive/developmental screening study in rats by gavage up to 750 mg/kg bw/day was recently reported (SCCS, 2020; ECHA, 2018). The SCCS noted that the occurrence of constant lighting (illumination) during the conduct of the study significantly affected the reliability of this study, especially for developmental/reproductive effects. In addition, the low number of pregnancies per group questions the validity of the data on the development of offspring in this study. Homosalate was found to adversely affect the survival, proliferation, and invasiveness of human trophoblast cells which highly associated with the development of human placenta during early pregnancy and, as such, may pose a threat to pregnant women (Yang *et al.* 2018).

Therefore, further studies (e.g. a sub-chronic toxicity study, a prenatal developmental toxicity study, an extended one-generation reproductive toxicity study, and the identification of degradation products) would be required to fully allay concerns related to homosalate exposure and reproductive and developmental concerns.

The SED for homosalate when used as a UV filter in cosmetic products, was calculated using a dermal absorption value of 2% derived from an *in vitro* dermal penetration study using viable human skin (SCCS 2020).

| Description | Parameter | Sunscreen |
|---|---|---|
| Amount of sunscreen applied daily | Q (mg/day) | 18000 |
| Concentration of ingredient in finished product | C (%) | 15 |
| Total amount of active ingredient applied | Qi = Q x C (mg/day) | 270000 |
| Absorption of active ingredient | $DA_p$ (%) | 2 |
| Total amount absorbed | Abs =Qi x $DA_p$ × 0.01 × 0.01 mg/day | 54 |
| SED | Abs/body weight (50 kg) | 1.08 |

As point of departure for risk assessment, a LOAEL of 60 mg/kg bw/day was used, based on a combined repeated dose toxicity study with the Reproduction/Developmental Toxicity Screening Test. Since the point of departure was based on a LOAEL, an additional uncertainty factor of 3 was added. Furthermore, due to lack of information on oral bioavailability, 50% of the administered dose was used as the default oral absorption value, resulting in an adjusted NOAEL of 10 mg/kg bw/day.

Therefore, **MoS = NOAEL/SED = 10/1.08 = 9.25**

The SCCS (2020) report takes into account the 10% concentration of the active approved in EU and 60 kg adult body weight to calculate the margin of safety. This gives rise to a **MoS of 17** (Systemic exposure dose (SED) A x 1000 mg/kg x C/100 x $DA_p$ /100/60 = 0.6 mg/kg; ~~Margin of Safety (~~MoS~~)~~: adjusted NOAEL/SED = 10/0.6 = **17.0**; *In order to derive at MoS of 100, the SED should be maximally 0.1 mg/kg meaning that A x 1000 mg/kg x C/100 x $DA_p$ /100/60 = 0.1.* )

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The SCCS concluded:

> *"On the basis of safety assessment of homosalate, and considering the concerns related to potential endocrine disrupting properties, the SCCS has concluded that homosalate is not safe when used as a UV-filter in cosmetic products at concentrations of up to 10%.*

*In the SCCS's opinion, the use of homosalate as a UV filter in cosmetic products is safe for the consumer up to a maximum concentration of 1.4% homosalate in the final product.*
*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."*

There are immediate systemic safety concerns with the use of this ingredient in sunscreens at 15% based on available information as per the SCCS guidelines. However, the primary data and analysis have not been subject to scrutiny by the evaluator.

**Octocrylene**

Octocrylene is approved in Australia for use as an active ingredient in sunscreens at a maximum concentration of 10% for dermal application, not to be used in topical products for eyes, with appropriate safety warnings on the label (e.g. Wear protective clothing - hats and eyewear when exposed to the sun' [or words to this effect])[11].

This review aims to present the main safety data on octocrylene from the ECHA website (ECHA, 2020), as well as those reported in the SCCS opinions (SCCS, 2021a) and scientific articles from peer-reviewed journals. In a recently published SCCS opinion on the safety of octocrylene (SCCS, 2021a), the SCCS considered that octocrylene was safe at concentrations of up to 10% when used individually or together as a UV-filter in cosmetic products, i.e. in sunscreen cream/lotion, sunscreen pump spray, face cream, hand cream and lipstick (SCCS, 2021a). However, a lower concentration of octocrylene (9%) is considered safe in sunscreen propellant spray when the sunscreen propellent spray is used along with face cream, hand cream, and lipstick (containing 10% octocrylene).

Extensive studies were available investigating octocrylene pharmacokinetics, and these have been summarised in Section 2.5.

Octocrylene is a lipophilic substance, and it is reported to be metabolised to a variety of metabolites where 2-cyano-3,3-diphenylacrylic acid (CDAA) is the main metabolite. Information was lacking on whether the most significant toxic agent was octocrylene or its metabolites. Considering the relatively long half-life of both octocrylene and CDAA in plasma and the low elimination rate of CDAA in urine, an accumulation of octocrylene and CDAA in the human body following repeated dermal applications would be expected.

The higher maximum observed concentration of CDAA (1351.7 ng/mL) *vs* octocrylene (25.0 ng/mL) also suggested that measuring only unmetabolized octocrylene might underestimate total systemic absorption and thereby influencing the safety assessment of octocrylene. It was also noted that ~~In addition, it was noted that higher~~ absolute concentrations of octocrylene ~~were observed from exposure to "real-life" conditions~~ was found much higher in studies conducted under experimental "real-life" conditions compared to studies "indoor maximal use conditions" suggesting ~~indicating~~ peak plasma concentrations may be even higher in real-world usage conditions.

Systemic absorption of octocrylene was demonstrated in recent randomised clinical trials following dermal application. The plasma concentration of octocrylene from sunscreens exceeded 0.5 ng/mL on single application (until 23 hours after application) whereas the systemic exposure to octocrylene

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remained above the threshold of 0.5 ng/mL in plasma in more than 50% of participants for up to 10 days. The continued presence of octocrylene in skin at days 10 and its long terminal half-life suggested absorption through skin was the rate-limiting step. Intravenous studies with octocrylene would be required to determine elimination rate constants.

The SCCS determined that the SEDs for dermal exposures to octocrylene from sunscreen cream/lotion were 0.566 mg/kg bw/day. SEDs for inhalation exposures to sunscreen sprays were 0.176 and 0.002 mg/kg bw/day for propellant and pump spray, respectively (Matta *et al.,* 2019, 2020).

As tabulated in Section 2.7, Toxicity, octocrylene was found to be of low acute toxicity. Octocrylene was not an eye or skin irritant based on available data. It was found to not sensitising in a Guinea Pig Maximization Test (GPMT). Octocrylene was found to be a moderate skin sensitiser and a skin photosensitiser [local lymph nose assay (LLNA) with 1- 30% octocrylene, EC3: 7.7% and human patch studies with 10% octocrylene]. However, the LLNA study was not considered properly conducted and the occurrence of photoallergy to octocrylene was suspected to be related to a previous photoallergy to topical ketoprofen. Photoallergic contact dermatitis to octocrylene has been found to be much more frequent in adults than in children whereas contact allergy cases to octocrylene have been reported more in children compared to adults. This is likely due to the immaturity of the skin epidermal barrier and the prevalence of atopic dermatitis in young children as the study authors suggested (Gilaberte & Carrascosa, 2014). Therefore, the potential skin sensitisation effects of octocrylene at 10% concentration can not be ruled out.

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No systemic effects were reported in rabbits after dermal exposure to octocrylene at 534 mg/kg bw/day. After oral exposure, effects on liver and thyroid were reported in a study in rats (males) at 340 and 1085 mg/ kg bw/day. These effects on liver and thyroid were investigated in an additional mechanistic study which showed that effects on thyroid were indirect and probably due to hepatic enzyme induction potential of octocrylene. Recently reported repeat dose toxicity studies with octocrylene (SCCS, 2021a; ECHA, 2020) do not alter the previously established NOAEL of 175 mg/kg bw/day, noted in a previous SCCS report for octocrylene.

Octocrylene is not expected to be genotoxic based on available genotoxicity data (Section 2.7.5). No carcinogenicity data were available. Based on the effects on parental and pup body weights, a lower number of implantation sites and lower number of pups in the extended one generation reproductive toxicity study (EOGRTS), a NOAEL was established at 153/163 mg/kg/day for parental systemic toxicity, fertility/reproduction performance, and general and sexual development. No neuro-/developmental effects were observed at the highest dose level tested (534/550 mg/kg/day). A monitoring study revealed that during the periods of pregnancy and lactation, > 78% of the women used some cosmetic product containing UV filters and UV filters were detected in 82.5% of human milk samples (Schlumpf *et al.* 2010, 2008). Octocrylene (OC) was one of the most frequently used UV filters and most frequently detected in milk samples (i.e. 27.50 ± 22.15 ng/g of lipids) (Schlumpf *et al.* 2010, 2008). Use of UV filters and concentration in human milk were significantly correlated. The results indicate transdermal passage of UV filters and potential placental transfer of octocrylene. Given the effect of octocrylene in pregnant and lactating mothers is unknown, warranting further investigation.

Public exposure to octocrylene would be expected to be widespread and frequent through a daily use of sunscreen products containing ingredient typically at concentrations up to 10 %.

Given dermal absorption value of 0.97 µg/cm$^2$ was available from experimental data for octocrylene, option 2 was used for systemic exposure dose (SED) calculation to estimate the MoS. The SED was determined to be 0.339 mg/kg bw/day for octocrylene in sunscreen (for a 60 kg bw person) in the SCCS opinion (SCCS 2021a) (dermal absorption value of 0.97 µg/cm$^2$ from Fabian & Landsiedel, 2020; octocrylene concentration of 10%). The NOAEL of 153 mg/kg bw/day based on the EOGRTS is

used for the calculation of MoS. Based on an oral bioavailability of 50% (Bury *et al.*, 2019), an adjusted NOAEL of 76.5 mg/kg bw/day was determined. Details of the calculation of SED is in SCCS 2021a. The MoS was calculated as:

**MoS = NOAEL/SED = 76.5/0.339**

**= 225 (≥ 100).**

Assuming a body weight of 50 kg for an Australian adult, the SED was determined to be 0.679 mg/kg bw/day resulting in a **MoS of 112.** This value is slightly above the accepted safety threshold. There are no immediate systemic safety concerns with the use of this ingredient in sunscreens at 10% based on available information as per the SCCS guidelines. The primary data and analysis have not been subject to scrutiny by the evaluator. In addition, t~~T~~he potential skin sensitisation effects of octocrylene at 10% concentration cannot be ruled out and further definitive study data would be required. ~~However, the primary data and analysis have not been subject to scrutiny by the evaluator.~~

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**Octinoxate**

Octyl methoxycinnamate (octinoxate) is approved in Australia for use as an active ingredient in sunscreens at a maximum concentration of 10% for dermal application, not to be used in topical products for eyes, with appropriate safety warnings on the label (e.g. Wear protective clothing - hats and eyewear when exposed to the sun' [or words to this effect])[12].

This review was based on the safety data from the ECHA website, the SCCS opinion (SCC, 2000), NICNAS Human Health Tier II Assessment Report, and scientific articles from peer-reviewed journals (NICNAS 2017, currently known as AICIS; ECHA 2021e).

Available *in vitro* and *in vivo* studies indicate octinoxate exhibits poor penetration into the skin. Systemic absorption of octinoxate was also demonstrated in recent randomised clinical trials (Matta *et al.*, 2020). However, elimination rate constant was not determined due to the absence of intravenous studies.

Octinoxate was found to be of low and moderate acute oral toxicity in mice and rats, respectively. Based on the limited data available, the chemical is not considered to be a skin irritant or an eye irritant. The chemical is not considered to be a skin sensitiser in humans. There is potential for photosensitivity following UV exposure, but the results are inconclusive.

No systemic effects were reported in a 13-week dermal repeat dose study in rats administered up to 534 mg/kg/day. The NOAEL was determined 450 mg/kg/day in a 13-week oral repeat dose study. Based on the available studies, the chemical was not considered to cause serious damage to health from repeated dermal exposure.

Octinoxate is not expected to have genotoxic potential, however, the lack of studies with isomers *cis* and *trans* was noted.

No carcinogenicity study was conducted as per ICH guidelines. The chemical has not been shown to be a tumour initiator in photocarcinogenesis studies in mice. No genotoxic potential was observed. Quantitative Structure-Activity Relationship (QSAR) modelling gave an alert for potential non-genotoxic carcinogenicity, but no details are available (OECD QSAR Toolbox ver.3.2).

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The SCC and NICNAS report stated that "*based on the available data, the chemical is not considered to be reproductively or developmentally toxic at doses relevant to human exposure*". A NOAEL of 450 mg/kg bw/day was established for fertility and reproduction parameters, and for systemic parental and developmental toxicity (Schneider *et al.* 2005).

A study (Axelstad *et al.* 2011) to investigate the effect of octinoxate treatment (500-1000 mg/kg/day, oral) on the endocrinological and neurological development of rat offspring indicated decreased motor activity in female offspring and increased spatial learning in male offspring (transient effects on thyroid axis, and in oestrogen level were also observed). The effects were observed at a much higher doses compared to clinical doses (Axelstad *et al.* 2011).

The value of 1.77 µg/cm² following 6-h pig-ear skin exposure + 18-h free permeation after an application of oil-in-water emulsion sunscreen dose (0.5 mg/cm²) containing 10% octinoxate was used in the SED calculation using option 2 in this review as per the SCCS opinion (Klimova *et al.* 2015).

The parameters used were:

- DA (µg/cm²) = dermal absorption reported as amount/ cm²: 1.77 µg/cm²
- SSA (cm²) = Skin surface area expected to be treated: 17500 cm² *
- F (day⁻¹) = frequency of application of the finished product: 2 *
- Body weight = default human body weight: 50 kg

(*) value complies with the SCCS 2016 (Appendix ~~5.3~~3.3)

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SED= 1.24 mg/kg/day

For the calculation of MoS the NOAEL that correspond to the worst-case scenario (rat, 13 week oral study), 450 mg/kg was selected.

**MoS = NOAEL/SED= 450/1.24 = 363 ≥ 100.**

There are no immediate systemic safety concerns with the use of this ingredient in sunscreens at 10% based on available information as per the SCCS guidelines. However, the primary data and analysis have not been subject to scrutiny by the evaluator.

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**Oxybenzone**

~~Oxybenzone~~Oxybenzone is approved in Australia for use as an active ingredient in sunscreens at a maximum concentration of 10% for dermal application, not to be used in topical products for eyes, with appropriate safety warnings on the label (e.g. Wear protective clothing - hats and eyewear when exposed to the sun' [or words to this effect])[13].

This review was based on peer-reviewed publications and the SCCS opinion on benzophenone-3 (2021c; SCCP, 2006a; SCCP, 2008).

Oxybenzone was shown to be rapidly absorbed after oral, intravenous, or topical skin administration and widely distributed in animals, 2,4-diOH BP (BP-1) was the major metabolite of oxybenzone in rats and humans. Oxybenzone was primarily excreted though urine.

A number of *in vitro* and *in vivo* dermal absorption studies have been evaluated by the SCCS. A dermal absorption value of 9.9% was used to calculate the MoS for oxybenzone. This value was

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calculated from a dermal absorption value of 3.1% obtained following application of a 6% formulation of oxybenzone to pig ear skin in *vitro* 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).

Clinical trials indicated that oxybenzone could be systemically absorbed. The plasma concentration of oxybenzone in sunscreens (spray) exceeded 0.5 ng/mL on single application and remained above this threshold until 23 hours after application. The systemic exposure of oxybenzone remained above 0.5 ng/mL in more than 50% of participants for up to 21 days. ~~The authors concluded that the~~The continued presence of sunscreen active ingredients in skin at days 21 and the long terminal half-life (> 48 hours) suggest absorption through skin is the rate-limiting step; hence, intravenous studies are required to determine their elimination rate constants.

Oxybenzone was found to be of low acute oral and dermal toxicity and did not cause skin or eye irritation (rabbits) or skin sensitisation (guinea pigs and mice). However, 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).

Repeat-dose studies with oxybenzone were conducted in mice and rats following oral and dermal administration. After repeated oral administration of oxybenzone in rats and mice, decreased bodyweight gain and reduced food consumption were observed. Effects on the kidney (decreased weight and renal tubule histopathology) and the liver (increased weight and adaptive changes in histopathology) with associated changes in clinical chemistry parameters were also observed. There were no treatment-related findings following dermal administration except for increases in liver weight with no associated histopathology or clinical pathology. The NOAEL (oral) was established at 6250 ppm (429/393 mg/kg bw/day in males/females) in rats and 6250 ppm (1068/1425 mg/kg bw/day in males/females) in mice. The NOAEL for repeat-dose dermal toxicity was established at 200 mg/kg bw/day in rats and 364 mg/kg bw/day in mice. In reproductive and developmental toxicity studies in rats, decreased normalised anogenital distance was observed in male pups of treated dams, at PND 23. Impairment of spermatocyte development in testes of male offspring and delayed follicular development in females was also observed indicating a potential endocrine disrupting effect. A NOAEL for these effects was established at 67.9 mg/kg bw/day (Nakamura *et al.*, 2015).

The findings from the genotoxicity studies with oxybenzone were found to be equivocal. Two-year carcinogenicity studies with oxybenzone were performed in mice and rats. An increased incidence of brain and spinal cord malignant meningiomas in males and thyroid C-cell adenomas and uterine stromal polyps in females were observed in rats, with no dose-response relationship. These findings in rats were also considered to be equivocal evidence of carcinogenicity. There was no direct evidence of carcinogenic activity in male or female mice other than lesions in bone marrow, spleen, kidney and liver.

The SCCS (2021c) determined a dermal absorption of 9.9% [mean (3.1%) + 2 SD (2*3.4%)] for the use of oxybenzone as a UV filter, at an oxybenzone concentration 6% for the calculation of SED and the MoS for sunscreen products.

The SED was calculated

| Description | Parameter | Sunscreen |
|---|---|---|
| Amount of sunscreen applied daily | Q (mg/day) | 18000 |
| Concentration of ingredient in finished product | C (%) | 6 |
| Total amount of active ingredient applied | Qi = Q x C (mg/day) | 108000 |
| Absorption of active ingredient | $DA_P$ (%) | 9.9 |
| Total amount absorbed | Abs =Qi x $DA_P$ × 0.01 × 0.01 mg/day | 106.9 |
| **SED** | Abs/body weight (50 kg) | 2.1 |

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The margin of safety (MoS) for oxybenzone through typical consumer use of sunscreen products was calculated using a NOAEL of 67.9 mg/kg bw/day derived from a pre- and post-natal developmental toxicity study in rats (Nakamura *et al.* 2015, detailed above) and an SED of 2.1.

**The MoS was determined to be 32 (NOAEL/SED = 67.9/2.1 = 32).**

A similar MoS was determined in the study by Hojerova *et al.* (2017), for three realistic exposure scenarios. MoS of 48, 34 and 34 for oxybenzone in the sunscreen applied on the whole-body were calculated, raising safety concerns for consumers in the current use scenarios (MoS < 100).

There are systemic safety concerns with the use of this ingredient in sunscreens at 10% based on available information as per the SCCS guidelines. The potential photoallergic effects of oxybenzone at 10% concentration cannot be ruled out. However, the primary data and analysis have not been subject to scrutiny by the evaluator.

**Phenylbenzimidazole sulfonic acid**

Phenylbenzimidazole sulfonic acid is approved in Australia for use as an active ingredient in sunscreens at a maximum concentration of 4% for dermal application, not to be used in topical products for eyes, with appropriate sunscreen safety warnings on the label (e.g. Wear protective clothing - hats and eyewear when exposed to the sun' [or words to this effect])[14].

The safety of phenylbenzimidazole sulfonic acid (PBSA) was assessed based on the publicly available safety data from scientific literature, and the SCCP opinion (SCCP, 2006b).

PBSA was rapidly absorbed following oral administration in pregnant rats. The amount of absorption from the gastrointestinal tract was estimated to be 3 – 4%. There was no indication of accumulation in any of the organs investigated and PBSA did not cross the blood/brain barrier. PBSA was mainly excreted though urine and faeces in male rats and via the faeces in pregnant female rats following oral administration. No data were available on the metabolism of PBSA.

PBSA was found to be of low acute toxicity in rats and mice (IP $LD_{50}$ 1000 – 1500 mg/kg/day and the dermal $LD_{50}$ is >3000 mg/kg bw in rats whereas oral $LD_{50}$ in mice is >5000 mg/kg bw). There was no information available for acute inhalational toxicity. PBSA was not a skin or eye irritant in rabbits and did not cause skin sensitisation in guinea pigs. The NOAEL in a 13-week oral study in rats was established at 1000 mg/kg/day, the highest dose tested.

PBSA was not found to be genotoxic *in vitro* (Ames test and chromosome aberration test in human peripheral blood lymphocytes). No information was available for mutagenicity/genotoxicity *in vivo*. No carcinogenicity data on PBSA were available.

No treatment-related findings were noted in a pre-natal developmental toxicity study in rats treated with PBSA from gestation day 6 to 15 at doses up to 1000 mg/kg/day. The NOAEL for maternal and fetal toxicity was 1000 mg/kg/day. PBSA did not cross the blood brain barrier or the placenta following oral administration in rats.

The SED was calculated based on the following parameters obtained from SCCP, 2006b:

A - Maximum absorption through the skin (µg/cm²) = 0.416 µg/cm²

[14] Therapeutic Goods (Permissible Ingredients) Determination (No. 3) 2022

| | |
|---|---|
| SAS – mean adult skin surface area (cm²) | = 17500 cm²* |
| Dermal absorption per treatment (SAS x A x 0.001) | = 7.28 mg |
| Australian body weight of an adult | = 50 kg |
| SED - Systemic exposure dose (7.28/50) | = 0.150 mg/kg |
| NOAEL (from 90-day oral rat study) | = 40 mg/kg bw[Δ] |

The ~~margin of safety (~~MoS~~)~~ was determined to be 267 (NOAEL/SED = 40/0.150 = 267).

[Δ]~~(~~SCCP, 2006b, SCCP 2006 opinion factored in 4% absorption to determine this value of 40 mg/kg bw. ~~; if~~ no factor is considered, the MoS would be 6667~~)~~; (*) value complies with the SCCS 2016 (Appendix 3.3)

There are no immediate systemic safety concerns with the use of this ingredient in sunscreens at 4% based on available information as per the SCCS guidelines (MoS 267 > 100). However, the primary data and analysis have not been subject to scrutiny by the evaluator.

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### 1.3. POTENTIAL ENDOCRINE DISRUPTION OF ACTIVE INGREDIENTS IN SUNSCREENS

In light of the recent regulations in Europe, several studies have been conducted to investigate the endocrine disruption potential of most of these ingredients. Since the FDA released its draft proposal (FDA, 2019b), several studies published in 2020 support previous findings that oxybenzone can act as an endocrine disruptor and may increase the risk of breast cancer and endometriosis (Kariagina 2020, Santamaria 2020).

A systematic review on oxybenzone and octinoxate suggest that current evidence is not sufficient to support the causal relationship between the elevated systemic level of oxybenzone and octinoxate and adverse health outcomes (Suh 2020). There are either contradictory findings among different studies or insufficient number of studies to corroborate the observed association. To accurately evaluate the long-term risk of exposure to oxybenzone and octinoxate from sunscreen, a well-designed longitudinal randomized controlled trial needs to be conducted, which is not feasible from an ethical point of view.

Most current SCCS opinions have evaluated the most current data on endocrine disruption potential for these ingredients.

For ethylhexyl triazone, the only information on reproductive toxicity or endocrine disrupting potential was from short SCCS opinion (Hojerová *et al.* 2017). Therefore, further information would be required for the endocrine disruption potential of ethylhexyl triazone. The available data (evaluated in SCCS opinions) on avobenzone, homosalate, octocrylene, octinoxate and oxybenzone indicate potential endocrine effects, however, they are not adequate to regard them as an endocrine disrupting ingredient, or to derive a toxicological point of departure based on endocrine disrupting properties for use in human health risk assessments.

### 1.4. SAFETY IN PAEDIATRIC POPULATION

No nonclinical information was available for the safety of these ingredients in the paediatric population. Compared to adults, the higher body surface area to volume ratio of children and the unique microstructure of immature skin suggest that children, especially infants, may absorb a greater fraction of topically applied ingredients (Stamatas *et al.* 2010). In addition, the capacity to metabolize and excrete absorbed ingredients by young children and infants may not be at the same level of maturity as in adults. ~~The c~~Children may also be exposed to these ingredients or their metabolites through breast milk noting the information above suggests many UV filters are excreted in breastmilk. Therefore, this puts them at risk of higher systemic levels and consequently, side effects and toxicities not seen in adults (Stamatas *et al.* 2010).

Section 3.6.10 of the SCCS Guideline (2021) (SCCS, 2021d) discusses the factors influencing the risk assessment of ingredients when used in babies and children's products. Risk assessment in the specific case of "children" has been discussed for parabens as preservatives in cosmetic products (SCCS/1446/11) and for phenoxyethanol (SCCS/1575/16).

It is noted that the US EPA's exposure factors handbook incorporates child-specific information with regard to exposure assessment (OECD 2019, US EPA, 2011). Together with the US EPA's child-specific exposure scenarios examples (US EPA, 2014), the handbook offers general children's activity patterns and exposure factors from a number of published studies, along with approaches in order to address different exposure routes and dose estimates in some specific contexts (US EPA, 2011; US EPA, 2014). In the Australian context, the risk assessment of ingredients used in sunscreen products for children is difficult given there are~~is~~ no Australian ~~proper~~ sunscreen use data. This needs further investigation.

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## 2. EVALUATION OF AVAILABLE INFORMATION

### 2.1. INTRODUCTION

Since 1991, the *Therapeutic Goods Act 1989* has been the principal legislation regulating the use of therapeutic goods in Australia. Products that were already commercially available in Australia at the time the regulatory framework was enacted were transferred directly onto the ARTG without an individual, detailed evaluation. Similarly, ingredients that were commonly being used in lower risk complementary medicines that were already commercially available in Australia at the time were permitted for use in listed medicines. These ingredients make up the majority of ingredients that are currently permitted for use in listed medicines.

The Therapeutic Goods (Permissible Ingredients) Determination (No. 3) 2022 currently lists 31 active ingredients approved for use in sunscreens 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.

The TGA has been monitoring the emerging scientific literature ~~on this the area~~ of the safety of sunscreens and working cooperatively with international agencies to monitor these issues to ensure that appropriate action is undertaken if any unacceptable risks are identified.

The TGA seeks to promote high standards of therapeutic product vigilance for the protection of the health and safety of Australians. It does this by monitoring the continuing safety, quality and efficacy of therapeutic goods in the market through therapeutic product vigilance activities. The TGA's strong pharmacovigilance program also involves the assessment of adverse events that are reported to the TGA by consumers, health professionals, the pharmaceutical industry, international medicines regulators or by the medical and scientific experts ~~on TGA advisory committees~~. Information on the TGA's approach to managing compliance risk is available via the following link to the TGA website: http://www.tga.gov.au/about/compliance.htm https://www.tga.gov.au/hubs/compliance-and-enforcement/compliance-management

Post-market monitoring of listed medicines also includes environmental scanning such as collection and review of scientific and medical literature, media reports and regulatory news to identify safety issues that require further investigation.

In 2019, the 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 which 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 an 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]). ~~Cinoxate, dioxybenzone,~~ Eensulizole, homosalate, octinoxate, octisalate, octocrylene, oxybenzone, avobenzone are currently used in Australian products.

The FDA proposed rule also dictated that if an adequately conducted MUsT demonstrates a steady-state blood level of an ingredient under 0.5 ng/mL, and an adequately conducted toxicological study

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does not raise any other safety concerns, then studies on systemic carcinogenicity and developmental and reproductive toxicity may not be required. The 0.5 ng/mL limit was selected because it represents approximately the highest plasma concentration under which the risk of carcinogenicity of any unknown compound would be below 1/100,000 following a single dose (FDA, 2019c).

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. This document reviews the margin of safety of the ingredients as per the SCCS guidelines given most of the data were extracted from current SCCS opinions on the ingredients. Annex 1 discusses the risk assessment using alternative exposure estimates.

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 (Appendix 3.4). 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 Expert Panel, 2019) reached the conclusion that octisalate is safe as 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). ~~The nonclinical data for octisalate was also submitted to the TGA for a safety assessment when used as an excipient at 8.5% (R10/104098).~~ As such, the literature review was not conducted for octisalate (octyl salicylate)~~, given the availability of a TGA nonclinical safety assessment report for this chemical.~~

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A literature review 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 (Appendix 3.4). The review is intended to provide an overview of the publicly available safety information for these ingredients, calculate the margin of Safety (MoS) as per SCCS guidelines using the concentration of the ingredient approved in Australia, and provide information needed to assess the suitability of these ingredients for use in sunscreens.

### 2.2. METHOD OF DATA SEARCH

The literature review was conducted using keywords like either the chemical name, AAN or the INCI names, and "sunscreen" as the search items. Publications in last ten years were searched (2008-2020). See the Appendix 3.1 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 SCC/SCCP) where available.[15]
- Information identified through literature search in PubMed and on the internet where a newer SCCS opinion was~~is~~ not available.

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

- 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 disruptive properties of ingredients may give rise to a concern for human health. The evaluation of endocrine disruptive properties is described collectively. All articles dealing with environmental effects of the ingredients have been excluded.

## 2.3. CHEMISTRY

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).

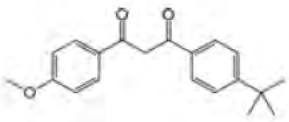
**Table 2-1 Chemical and Physical Properties of the active ingredients under review**

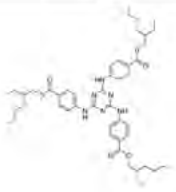
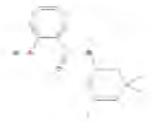
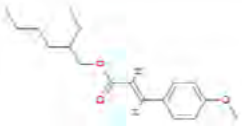
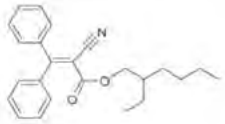
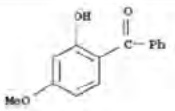
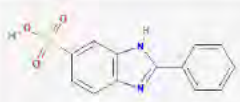
| Active ingredient (*absorption spectrum*) | CAS no. | Chemical name | Molecular formula | Physical properties | | | Other names |
|---|---|---|---|---|---|---|---|
| | | | | Water solubility | Mol. Wt g/mol | Log $P_{ow}$ | |
| Avobenzone (BMDM or BMDBM)<br><br>*UVA* | 70356-09-1 | 1,3-Propanedione, 1-[4-(1,1-dimethylethyl)phenyl]-3-(4-methoxyphenyl)- | $C_{20}H_{22}O_3$ | 0.01 mg/L | 310.4 | 4.5-6.1 | Butyl methoxydibenzoylmethane, Eusolex® 020, Parsol® 1789, 4-tert-butyl-4'methoxydibenzoyl methane, BMDBM |
| Ethylhexyl triazone (EHT)<br><br>*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 | 15.5 | Uvinul T150, (octyl triazone) |
| Homosalate<br><br>*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 | 4.7 | Benzoic Acid, 2-Hydroxy-, 3,3,5-Trimethylcyclohexyl Ester Cyclohexanol, 3,3,5-trimethyl-, salicylate.<br><br>Homomethyl salicylate<br><br>Salicylic acid, 3,3,5-trimethylcyclohexyl ester<br><br>Caswell No. 482B, Neo Heliopan® HMS, CCRIS 4885, Filtersol "A" |

| Active ingredient (*absorption spectrum*) | CAS no. | Chemical name | Molecular formula | Physical properties | | | Other names |
|---|---|---|---|---|---|---|---|
| | | | | Water solubility | Mol. Wt g/mol | Log $P_{ow}$ | |
| Octinoxate (OMC or EHMC)<br>*UVB* | 5466-77-3 | 2-Ethylhexyl 4-methoxycinnamate | $C_{18}H_{26}O_3$ | 0.1 g/100 mL at 27°C | 290.4 | 5.9 | EHMC or octyl-methoxycinnamate (OMC) |
| Octocrylene (OC)<br>*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 | 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)<br>*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 | 228.22 | >3.7 | Benzophenone-3 |
| Phenylbenzimidazole sulfonic acid (PBSA)<br>*UVB* | 27503-81-7 | 2-Phenylbenzimidazole-5-sulfonic acid | $C_{13}H_{10}N_2O_3S$ | > 30% | 274.3 | -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 2-2 Molecular structure of the active ingredients under review**

| Active ingredient | Structure |
|---|---|
| Avobenzone |  |

| Active ingredient | Structure |
|---|---|
| Ethylhexyl triazone |  |
| Homosalate |  |
| Octinoxate |  |
| Octocrylene |  |
| Oxybenzone |  |
| Phenylbenzimidazole sulfonic acid |  |

### 2.4. USE

The following ingredients are currently approved in Australia for use as active ingredients in 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 (TGA, 2020). It is noted that the FDA regulates sunscreens as over the counter (OTC) drugs rather than as cosmetics whereas they are regulated as cosmetics in EU.

| Active ingredient | Maximum % approved | | | | |
|---|---|---|---|---|---|
| | Australia | EU | USA | Canada[16] | Japan[17] |
| Avobenzone | 5 | 5 | 3 | 3 | 10 |
| Ethylhexyl triazone† | 5 | 5 | Not approved | Not approved | 5 |
| Homosalate | 15 | 10 | 15 | 15 | 10 (restricted in all types of cosmetics) |
| Octinoxate* | 10 | 10 | 7.5 | 7.5 | 10 |
| Octocrylene** | 10 | 10 | 10 | 10 | 10 (restricted in all types of cosmetics) |
| Oxybenzone*,Δ | 10 | 6 | 6 | 6 | |
| Phenylbenzimidazole sulfonic acid γ | 4 | 8 | NA | 4 | 3 (cosmetics not used for mucosa and to be/not to be washed away) |

* In the USA, Hawaii became the first state to pass the law banning sales of sunscreens containing oxybenzone and octinoxate from January 2021;
**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);
†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).

There are discrepancies between direction of use of sunscreen and real time use of sunscreens. For sunscreen lotion, an amount of 18.0 g/day is used in the MoS calculation in the safety evaluation carried out by the SCCS but is not meant as a recommended amount to be applied by the consumer (SCCNFP/0321/02).[18] To reach a comparable level as indicated by the Sun Protection Factor (SPF), sunscreen products have to be applied in quantities similar to the ones used for SPF testing, i.e. 2 mg/cm² (total amount of approx. 36 grams) for the body of an average adult person (60 kg in EU settings). The quantity of 2 mg/cm², however, is the amount necessary to obtain reproducible SPF results under laboratory conditions. It is higher than the amount usually applied by consumers. This

[16] http://webprod.hc-sc.gc.ca/nhpid-bdipsn/atReq.do?atid=sunscreen-ecransolaire&lang=eng
[17] (https://www.mhlw.go.jp/english/dl/cosmetics.pdf
[18] https://ec.europa.eu/health/system/files/2021-04/sccs_o_250_0.pdf

observation has been reported frequently: when consumers use their own sun products (lotions, gels, creams, sprays) and apply the products on the whole body surface, values for use of products between of 0.39-1 mg/cm$^2$ depending on the study protocol used, the location on the body measured and several other factors. When the product is applied only to the face, then the amount applied might be higher than 2 mg/cm$^2$ (Gomez-Berrada et al., 2017). The amount used by the SCCS in safety calculations reflects actual consumer use and takes the whole body area (17500 cm$^2$) into account. The average exposed skin area of sunscreen users according to the recent report of the Danish authorities is 14,700 cm$^2$. The use of 18g/d sunscreen corresponds with the values reported by Biesterbos et al. (Biesterbos et al., 2013), who found a mean use amount of 9.2 g/application, derived on the basis of pictures. If two applications are considered, this is about 18 g/d. Unpublished data by von Goetz (von Goetz, 2018) from a small-scale pilot study with weighing also provided a mean of 9 g for whole-body application (5 applications by 2 persons).

~~Whereas~~ In Australia, the Cancer Council Australia (CCA, 2017) recommends a teaspoon (5 mL) for the face, neck and ears; a teaspoon for each arm and leg; and a teaspoon each for the front and back of the body at least every 2 hours. This amounts to 35 mL per application and, if an individual were to spend 8 hours (i.e. application frequency of 4 times/day) ~~a day~~ in the sun, the recommended daily dose would equate to 140 mL of dermally applied sunscreen. ~~And then t~~The density of the substance also needs to be accounted for to arrive at a total amount of sunscreen used in mg/day. The TGA notes that the claimed sun protection factor (SPF) must be established by testing according to the method described in AS/NZS Standard for sunscreen products. This testing method is undertaken using an application of 2 mg/cm$^2$. ~~While, however although~~ this quantity~~amount~~ is needed to achieve the expected sun protection. this ~~amount~~ may not reflect current ~~be applied by consumers in~~ practice. As such, without Australian specific use data, and in the context of the literature review, the TGA has ~~considered~~utilised the SCCS exposure calculations when reviewing the SCCS opinions. ~~This is likely to be a worst-case scenario, and not anticipated to be applied every day at this rate for extended periods~~seems a huge amount to be applied every day. ~~Without Australian specific use data, and I~~in the ~~context of this literature review, the TGA has considered the SCCS exposure calculations when reviewing the SCCS opinions. Without Australian specific use data, this appears to be the best available exposure model.~~ However, where an acute toxicity exposure risk is identified, then a calculation based on either a single application of 35 mL or a total daily exposure of 140 mL ~~exposure~~ may be ~~applied~~necessary. ~~on a case by case basis.~~ Further exposure assessment calculations are considered in Annex~~ppendix~~ 1.

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## 2.5. PHARMACOKINETICS

The main safety concerns for these active ingredients arise from the knowledge gap around the toxicokinetic data/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 is noted. In the absence of adequate or reliable dermal absorption data, a ~~10~~50% dermal absorption was assumed for SED calculation in the worst-case scenario and MoS value was estimated according to guidelines applicable for the European Union (SCCS ~~2016~~2021). Please note, although dermal data is expected to reflect real time exposure and toxicity following application of sunscreens, in the absence of dermal toxicity data, oral toxicity data were considered in the MoS determination using a conservative approach given oral toxicity data may reflect system~~at~~ic toxicity in worst case scenario.

The dermal absorption value used in the recent SCCS opinions for the relevant active ingredients were used in the estimation of SED, followed by MoS determination in this review.

### 2.5.1. 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~~ 21-day dermal rabbit toxicity study (Keller, 1980), in the 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), there was no indication of systemic bioavailability following dermal exposure.

- *In vitro* studies with isolated pig skin using $^{14}$C-labelled BMBDM 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 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 indicates a very low level of systemic penetration of BMDBM 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.[19] 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 human (See Section 2.1).

In the absence of further kinetic data for avobenzone, 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 for Systemic Exposure Dose (SED) calculation in the worst-case scenario. **Please note, this applies to intact skin, not on lips/sensitive areas/children with higher skin surface/kg ratio.**

### 2.5.2. 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 (Mol weight > 500 Dalton and Log $P_{oW}$ > 4; Table 2.1)

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

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% similar to the recovery (85- 115%) allowed by the SCCS (2016). The SED after the sunscreen application at 1 mg/cm$^2$ for 6 h (i) on the face; (ii) on the 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.

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 50% dermal absorption was assumed for SED calculation in the worst-case scenario and MoS value was estimated according to guidelines (SCCS 2016). **Please note, the 10% dermal absorption applies to intact skin, not on lips/sensitive areas/children with higher skin surface/kg ratio.**

### 2.5.3. 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 in 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 Section 2.1). 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 lactating 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 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*.

The SCCS report stated that a conclusion on the dermal absorption percentage could not be drawn from the human studies. Therefore, the risk assessment takes account of the dermal absorption value from the skin penetration study using human skin described in the SCCS report (SCCS, 2020).

The maximal absorption value observed in the donor with highest absorption values (2%) was used in the MoS calculation in the SCCS report (2020).[20] Identical value was taken for the MoS calculation in this review. **Please note, this applies to intact skin, not on lips/sensitive areas/children with higher skin surface/kg ratio.**

### 2.5.4. Octocrylene

Octocrylene is expected to be absorbed in the gastrointestinal 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 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. 2CDAA 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.

**Table 2-3~~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 8-10% octocrylene in *in vitro* studies, poor skin penetration (< 5%) of octocrylene was observed with majority remaining in the stratum corneum (Freitas *et al.* 2015;

[20] June 2021 SCCS opinion for homosalate uses a different dermal absorption value for 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) and a standard sunscreen formulation containing 10% homosalate. This gives even a lower MoS for homosalate for a 60 kg human.

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 dermatomed 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 medium. After 24 hours of dosing, octocrylene bioavailability (epidermis, dermis and receptor medium) was estimated to be ~ 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 medium 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 medium) 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 low dermal absorption rate (≤ 0.25%).

A recent *in vitro* study (Fabian & Landsiedel 2020) with a formulation (10% octocrylene) applied at a dose of 3 mg formulation/cm$^2$ on dermatomed 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 & Landsiedel 2020) was considered a worst-case scenario and was used in the calculation of SED followed by MoS determination in the SCCS (2021a). **Please note, this applies to intact skin, not on lips/sensitive areas/children with higher skin surface/kg ratio.** This value was also used in the SED and MoS calculation in this report given it is from the most recent study providing human dermal absorption value.

### 2.5.5. 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, showing that measuring octinoxate alone could not comprehensively evaluate the human exposure to octinoxate.

Dermal penetration was observed to be dependent on the vehicles, 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 & Godin, 2008). An accumulation of ~9% of octinoxate in epidermis and ~2-3% in dermis were observed following application of 2mg/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 of long skin exposure), a more realistic 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 being release in the later time, the dermal absorption was evaluated at the end of the exposure period immediately after washing off a sunscreen) and following next 18-h permeation.

The dermal absorption was obtained by the sum of the filter absorbed in the dermis and the RF (which was considered systemically available), corrected by the fresh/frozen –stored skin permeability coefficient. **The dermal absorption value of 1.77 µg/cm$^2$ following 6-h skin exposure + 18-h free permeation after an application of oil-in-water emulsion containing 10% octinoxate was used in the SED calculation in this review.** Please note, this applies to intact skin, not on lips/sensitive areas/children with higher skin surface/kg ratio. 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 depends on both lipid lipophilicity and structure and on 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 female and male 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 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, the dermal absorption of 1.77 µg/cm$^2$ was considered a worst-case scenario and was used in the calculation of SED (Klimova *et al.* 2015). **Please note, this applies to intact skin, not on lips/sensitive areas/children with higher skin surface/kg ratio.**

### 2.5.6. Oxybenzone

Oxybenzone is expected to be rapidly absorbed after oral, intravenous, or topical skin administration 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.

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).

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 in piglets, the elimination half-lives of oxybenzone was approximately 7.14 and 8.04 h (SCCS 2021c).

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%, with this value used to determine MoS for oxybenzone. **Please note, this applies to intact skin, not on lips/sensitive areas/children with higher skin surface/kg ratio.** 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 to calculate the MoS for oxybenzone in the absence of adequately information from *in vivo* studies.

### 2.5.7. 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 (2006) to determine the margin of safety for PBSA (SCCP, 2006b). **Please note, this applies to intact skin, not on lips/sensitive areas/children with higher skin surface/kg ratio.**

### 2.6. 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$^2$ [21]on 75% of body surface area. The sunscreen products were spray 1 (3% avobenzone/ 6% oxybenzone/2.35 % octocrylene/ 0% ecamsule[22]), 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).

Similar findings were observed in a follow up study with six active ingredients (avobenzone, oxybenzone, octocrylene, homosalate, octisalate[23], 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 - 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 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 | Non-aerosol 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) |

[21] If we use 140 ml as recommended by Cancer Council Australia, and assuming skin surface area of 17500 cm$^2$, this will be equiv. to ~8 mg/cm$^2$, depending on density of the substance.

[22] 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.

[23] 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.

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 2-4~~Table 3-2~~). 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 2-4~~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

## 2.7. 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 are therefore reliant on the accuracy of various published safety assessment reviews (reviews by SCCS/SCC/SCCP, NICNAS, ECHA etc. see in bibliography, p 6152~~52~~).

### 2.7.1. 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 4-1. Summary of acute toxicity studies for sunscreen ingredients**

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

### 2.7.2. 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 4-2. Summary of skin and eye irritation studies for sunscreen ingredients**

| Study | Avobenzone (ECHA (2021a; DEPA 2015) | Ethylhexyl triazone (ECHA (2021b; DEPA 2015 | Homosalate (SCCS 2021; 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) |

### 2.7.3. 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 4-3. Summary of skin sensitisation studies for sunscreen ingredients**

| Avobenzone (ECHA 2021a; DEPA 2015) | Ethylhexyl triazone (ECHA (2021b; DEPA 2015 | Homosalate (SCCS 2021; 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)<br>Not sensitizing (at 15%, HRIPT) | Not sensitizing (GPMT) | Not sensitizing (GPMT)<br>Moderate sensitising in a LLNA (not properly conducted) | Not sensitizing (GPMT)<br>Not sensitising (LLNA) | Not sensitizing (GPMT) |

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

### 2.7.4. Repeat dose toxicity

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

**Table 4-4. Repeat-dose toxicity studies for sunscreen ingredients**

| Active ingredient | Study details[Δ] | 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.<br>No effect on the body weight and food consumption.<br>↓ RBC in ♀ rats at 1000 mg/kg bw/day.<br>No findings in eyes. No treatment-related necropsy findings.<br>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.<br>Hypertrophic hepatic parenchyma cells in ♀ at 1000 mg/kg bw/day.<br>**NOAEL: 450 mg/kg bw/day**<br>*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.<br>↑ dose dependent severe dermal reactions ≥ 30 mg/kg/day, more persistent at 100 mg/kg bw/day.<br>↑ Incidence of epidermal thickening in both vehicle control and treatment groups compared to the untreated control group.<br>NOAEL: 360 mg/kg bw/day (based on systemic effects).<br>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<br><br>Study BASF 50S0227/92059 | No treatment-related mortality.<br>No treatment-related clinical signs.<br>Body weight gain: ↓ at HD in both sexes along with decreased food consumption<br>Haematology: RBC affected (↓MCV, ↓MCH, ↓MCHC) at HD in both sexes<br>Organ weights (bodyweight-relative): ↑ absolute and relative weight of liver at 340 and 1085 mg/kg bw/day<br>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<br>NOAEL: 175 mg/kg bw/day |
| | Rabbits (NZW), *n* = 5/sex/dose<br>0, 130, 264, 534 mg/kg bw/day (dermal)<br>5 days/week; 13 weeks<br><br>(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.<br>No evidence for haematological or macroscopic and histopathological abnormalities<br>No effects were reported on testicular and epididymal morphology as well as on sperm count and motility<br>NOAEL: 534 mg/kg bw/day (systemic toxicity)<br>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<br><br>Rats (Wistar), *n* = 5/sex/dose<br>72, 215, 720 mg/kg bw/day PO (Subset A)<br>63, 188, 630 mg/kg bw/day PO (Subset B)<br><br>28 days (Subset A)<br>14 days (Subset B) | No treatment-related mortality<br>No treatment-related clinical signs.<br>Body weight gain: ↓ at HD in both subsets<br>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<br>Organ weights (bodyweight-relative): ↑ absolute and relative weight of liver at high doses in both sexes in both subsets<br>Histopathology: minimal follicular cell hypertrophy/hyperplasia of the thyroid gland at high doses in both sexes in both subsets<br>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.<br>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.<br>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<br>↑ (non-significant) serum alanine phosphatase (SAP) levels and ↑ relative liver weight at HD. Liver effects were not observable upon microscopic examination.<br>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.<br>Dose dependent low-grade epidermal proliferation at all doses (more prominent in ♂).<br>The chemical was considered as a low-grade irritant under the conditions of this study (OECD TG 410)<br>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<br>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.<br>Dermal irritation effects (erythema, oedema, desquamation, cracking and atonia) were observed at all doses but were more severe at the HD.<br>Histopathology of the skin sites showed an epidermal proliferative response with low grade inflammatory reaction (dose dependent).<br>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.<br>↑ Liver-weight without histological correlates among treated female animals could not be interpreted as being treatment-related<br>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<br>No treatment-related effects on organs<br>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<br>Bodyweight gain: ↓ in ♂at HD.<br>Organ weight: ↑ liver weights (♂ & ♀) from LD, associated histopathology observed at 2041 mg/kg bw/day; ↓ kidney weight in ♂ from 8648 mg/kg bw/day.<br>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<br>Bodyweight: ↓ BW gain in ♂ & ♀ from 6780 mg/kg bw/day<br>Organ weights: ↑ liver weight from 1246 mg/kg bw/day with histopathology from 6780 mg/kg bw/day. Renal histopathology at HD in ♂.<br>Reproductive parameters: ↓ sperm density and ↑ abnormal sperm in ♂ and ↑ oestrus cycle length in ♀ at HD<br>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<br>Bodyweight gain: ↓ in ♂at HD.<br>Organ weight: ↑ liver (♂ & ♀) and kidney (♂) weights from LD, associated histopathology observed at 576 mg/kg bw/day in liver and at HD in kidney .<br>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.<br>Clinical signs: coloured urine from LD.<br>Bodyweights: ↓ BW gain in ♂ & ♀ from 1702 mg/kg bw/day.<br>Clinical pathology: serum protein levels from 411 mg/kg bw/day. ↑ platelet counts from 1702 mg/kg bw/day<br>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.<br>Reproductive parameters: ↓ sperm motility in ♂ and ↑ oestrus cycle length in ♀ at HD.<br>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 | Mortality: none<br>Organ weights: ↑ liver weight from 196 mg/kg bw/day. |

| Active ingredient | Study details[Δ] | Major findings |
|---|---|---|
| | mg/mouse in acetone or lotion* (equivalent to 24.8, 48.4, 100, 196, 388 mg/kg bw/day), 14 days (dermal) | 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.<br>Organ weights: ↑ kidney weight in ♂ at all doses<br>Reproductive parameters: ↓ epididymal sperm density in ♂ at all doses.<br>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<br>Organ weights: ↑ liver weight in ♀ from 27.7 mg/kg bw/day, ↑ kidney weight in ♀ at HD<br>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).<br>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.<br>Clinical pathology: ↓ reticulocyte counts from LD, ↑ platelet counts from 50 mg/kg bw/day, ↑ whole blood cell count produced by lymphocytosis at HD.<br>NOAEL: 200 mg/kg bw/day |
| PBSA<br>(SCCP 2006b) | Rats (Wistar; *n* = 15/sex/group)<br>Doses: 0, 100, 330 and 1000 mg/kg bw, ~~13 weeks~~90 days (oral) | No treatment-related effects.<br>NOAEL: 1000 mg/kg bw/day |
| Homosalate<br>(SCCS 2021; ECHA 2021c) | Rats, n=5/sex/dose, 0, 100, 300, 1000 mg/kg bw/day, 2 weeks (gavage) | Mortality: none<br>Clinical signs: none treatment related<br>Body weight gain: ↓ at HD in ♂ along with decreased food consumption<br>Haematology: none treatment related<br>Serum chemistry: ↑ Triglycerides in both sexes at HD ↑APTT in ♂ at MD<br>NOAEL: > 300 mg/kg bw/day ♂<br>NOAEL: >1000 mg/kg bw/day ♀ |
| | Repeat dose/ reproduction/ developments study<br><br>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<br>*Clinical signs:* none treatment-related<br>*Body weight gain:* ↓ at 750 mg/kg bw/day in ♂ and ♀<br>*Haematology:* none treatment-related<br>*Serum chemistry:* ↑ Albumin and ↓ Globulin in ♂ at 300 mg/kg bw/day<br>*Urinalysis:* not conducted<br>*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.<br>*Gross pathology:* no treatment-related findings<br>*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). *<br>Minimal/mild hypertrophy of hepatocytes (1/5 ♂) at 120 mg/kg bw/day, and almost every ♂ and ♀ from 300 mg/kg bw/day.<br>Hypertrophy of the follicular epithelium of thyroid gland in ♂ at 750 mg/kg bw/day and in ♀ from 300 mg/kg bw/day.<br>↓ Cortical lymphocytes in males from 300 mg/kg bw/day and in ♀ at 750 mg/kg bw/day |

| Active ingredient | Study details[Δ] | Major findings |
|---|---|---|
| | | *NOAEL:* ** mg/kg bw/day<br>*The REACH registrants considered this as manifestations of hyaline droplet nephropathy without giving further evidence.<br>**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

### 2.7.5. 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 it induced DNA damage in the Comet assay in isolated human peripheral lymphocytes and in the micronucleus assay *in vivo*.

**Table 4-5. Summary of genotoxicity studies with sunscreen ingredients**

| Avobenzone (ECHA (2021a; DEPA 2015) | Ethylhexyl triazone (ECHA (2021b; DEPA 2015 | Homosalate (SCCS 2021; ECHA 2021c) | Octinoxate (ECHA 2021e) | Octocrylene (SCCS, 2021a; ECHA 2021d) | Oxybenzone (SCCP 2006a; 2021c) | PBSA (SCCP 2006b) |
|---|---|---|---|---|---|---|
| In vitro<br>Negative<br>AMES test and gene mutation study V79 Chinese hamster cells<br><br>In vivo<br>Negative<br>Bone marrow polychromatic erythrocytes (mice) | In vitro<br>Negative<br>AMES test, Chinese hamster lung fibroblasts for chromosome aberration, Chinese hamster ovary (CHO) cells, in vivo chromosome aberration test | In vitro<br>Negative<br>AMES test and gene mutation study in V79 Chinese hamster cells<br><br>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 | In vitro<br>Negative<br>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)<br><br>In vivo<br>Negative<br>Chromosomal aberrations in micronucleus assay in bone marrow polychromatic erythrocytes, Cell gene mutation assay (V79, ± | In vitro<br>Negative<br>AMES test, gene mutation test, cytogenicity test in mammalian cells, chromosome aberrations tests<br><br>In vivo<br>Negative<br>Cytogenicity test in mice<br>ECHA 2020, SCCS 2021 | In vitro<br>Negative<br>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<br><br>In vivo<br>Negative<br>micronucleus test (mice), chromosome aberration test (rats), Drosophila (SMART)† | In vitro<br>Negative<br>AMES test and chromosome aberration test in human peripheral blood lymphocytes<br><br>In vivo<br>No data |

| Avobenzone (ECHA (2021a; DEPA 2015) | Ethylhexyl triazone (ECHA (2021b; DEPA 2015 | Homosalate (SCCS 2021; ECHA 2021c) | Octinoxate (ECHA 2021e) | Octocrylene (SCCS, 2021a; ECHA 2021d) | Oxybenzone (SCCP 2006a; 2021c) | PBSA (SCCP 2006b) |
|---|---|---|---|---|---|---|
| | | al. 2018; 2019). | S9) showed a very slight increase in mutant colonies (up to 20 mg/mL) | | | |

† 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.

### 2.7.6. Carcinogenicity

A summary of carcinogenicity studies for each sunscreen ingredient is shown in the table below. No carcinogenicity data is available for avobenzone, octinoxate, octocrylene, ethyl hexyl triazone, 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).

**Table 4-6. Summary of carcinogenicity studies with sunscreen ingredients**

| Active ingredient | Study details | Major findings |
|---|---|---|
| Avobenzone | – | No data |
| Octinoxate | – | No data |
| Octocrylene | – | No data |
| Ethyl hexyl triazone | – | No data |
| Homosalate | – | 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 ♂/♀)<br><br>Rats (SD; *n*=10/sex/group), 0, 1000, 3000, 10000 ppm (equivalent to 58/60, 168/180, 585/632 mg/kg bw/day in ♂/♀)<br>Two years (beginning on GD6 in ♀) | Mice: ↑ lesions in the bone marrow, spleen, and kidney of both sexes and in the liver in ♂<br><br>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.<br>These findings are considered equivocal evidence of carcinogenicity. |
| PBSA | – | No data |

### 2.7.7. Reproductive and developmental studies

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

**Table 4-7. 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.<br>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.<br>↓ 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.<br>In the offspring, ↓ lactation weight gain and organ weights, and slightly delayed sexual maturation (vaginal opening and preputial separation) at HD.<br>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.<br>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. |
| Octocrylene (SCCS, 2021a; ECHA 2021d) | Extended one generation reproductive toxicity study (EOGRTS), GLP<br>Rat (Wistar); Dose: (diets) 55, 153, 534 mg/kg bw/day ♂<br>58, 163, 550 mg/kg bw/day ♀<br><br>*n*= 27 or 28 /sex /dose<br>F1: Cohort 1A: 19/sex/ dose<br>Cohort 1B: 25/sex/dose<br>Cohort 2A: 10/sex/ dose<br>Cohort 2B: 10/sex/dose<br><br>♂: 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<br>↓ bodyweight of pups at HD<br>No effects on male fertility and male and female reproductive parameters such as oestrus cycle, epididymal and testicular sperm parameters at all doses.<br>No effects on sexual and neurodevelopmental parameters in pups.<br>Based on effects on parental and pup body weights, a lower number of implantation sites and lower number of pups delivered.<br>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<br>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)<br>F2: until weaning (indirectly)<br>(ECHA, 2021d; SCCS, 2021a) | |
| | Pregnant rats (Wistar); *n* = 25/♀/dose, Dose: 0, 100, 400, 1000 mg/kg bw/day PO<br>GD6–GD15; termination on GD21 | F0:<br>Transient salivation at HD.<br>↑ relative liver weight at MD and HD<br>F1:<br>No treatment related effects.<br>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<br>Odio *et al.* (1994) | No treatment related adverse effects.<br>NOEL: 1000 mg/kg bw/day (mice) |
| | Rabbit (NZW); *n* = 17 ♀/dose<br>Dose: 0, 65, 267 mg/kg bw/day, (Dermal, open, clipped area on the back), dosing GD6–GD18; termination on GD21<br>Odio *et al.* (1994) | No treatment related adverse effects.<br>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.<br>Maternal NOAEL = 1000 mg/kg bw/day;<br>Developmental NOAEL = 1000 mg/kg bw/day |
| Homosalate (SCCS 2021; 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).<br>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):<br>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.<br>↓ 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;<br>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.<br>In mice, there were no effects on reproductive organ weight, cauda epididymal sperm concentration, sperm parameters, testicular spermatid concentration or testicular histology.<br>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 was 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)<br>Reproductive toxicity study in rats (SD; *n*=7-8 mated ♀);<br>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.<br>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 207.167.9 mg/kg bw/day. |
| 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.<br>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-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.

### 2.7.8. Endocrine disruption

Endocrine-disrupting chemicals (EDCs) are exogenous chemicals that interfere with hormone action, thereby 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[24] 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[25] 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 disruptors 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 disrupting 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:

[24] EHT was included in these 14 ingredients
[25] Homosalate and avobenzone were included

> *"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".*

In light of increased safety concerns regarding the Endocrine Disruption (ED) 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 ED 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 EDCs based on hormone actions and EDC 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 has 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)[26] and to act as an antagonist of androgen receptor (AR)(CASE Ultra and Leadscope),~~2613~~

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[26] QSAR software for modelling and predicting toxicity of chemicals. CASE Ultra has both methodologies (statistics based

The SCCS (2020) conclusion was based on a Risk Management Options Analysis (RMOA) 2016 by ANSES[27]. 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 disruption 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 disruption 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].

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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.

[27] French Agency for Food, Environmental and Occupational Health & Safety (ANSES)

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 feedbacks.

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. Currently a public call by the European Commission for data on the ED potential of octinoxate is in place (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.

### 2.8. OTHER STUDIES

The photo-allergic potential of avobenzone has been extensively reviewed in several publications (Nash & 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 Draize repeated insult patch test 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).

10% ethylhexyl triazone 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%) were 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 & 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 & 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 & 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 given below. However, this is not reviewed in this discuss elaborately as similar mechanisms apply on endocrine disruption potential of these ingredients (Ruszkiewcz *et al.*, 2017).

| 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. |
| Benzophenone-3 or oxybenzone | Danio rerio | 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. |
| | 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. |
| | SH-SY5Y neuroblastoma cell line | 72 h; $10^{-8}$–$10^{-4}$M | Decreased cell viability and increased caspase-3 activity. |
| Octocrylene | Danio rerio | Waterborne; 14 days; 22–383 µg/L | Impaired expression of genes related with development and metabolism in the brain. |

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.

# 3. APPENDIX

## 3.1. SEARCH STRATEGY

### *Search criteria (word input)*

Keywords included either the chemical name, AAN or the INCI names, and "sunscreen" were used as the search items. Publications in last ten years were searched (2008-2020). 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
- Coslng 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/

***Example of the search strategy for avobenzone***

Search for: remove duplicates from 141 [67 or 140], results: 163

| Embase, Ovid MEDLINE(R) | | | |
|---|---|---|---|
| **#** | **Search Statement** | **Results** | **Annotation** |
| 1 | exp avobenzone/ or Avobenzone.mp. | 914 | |
| 2 | 70356-09-1.rn. | 629 | |
| 3 | Butyl methoxydibenzoylmethane.mp. | 189 | |
| 4 | Butyl methoxy dibenzoylmethane.mp. | 19 | |
| 5 | 4-tert-butyl-4-methoxy dibenzoylmethane.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy] | 14 | |
| 6 | Avobenzona.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy] | 3 | |
| 7 | Avobenzonum.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy] | 0 | |
| 8 | 1 or 2 or 3 or 4 or 5 or 6 or 7 | 995 | |
| 9 | exp drug carcinogenicity/ | 835 | |
| 10 | exp carcinogenicity/ | 31868 | |
| 11 | exp carcinogen/ | 148982 | |

| | | | |
|---|---|---|---|
| 12 | exp Carcinogens/ | 286093 | |
| 13 | exp Carcinogenicity Tests/ | 6877 | |
| 14 | exp Mutagens/ | 108755 | |
| 15 | exp mutagenicity tests/ | 60479 | |
| 16 | exp genotoxicity/ | 33452 | |
| 17 | exp Neoplasms/ | 7761161 | |
| 18 | ((Dermal or systemic) adj2 carcinog*).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 411 | |
| 19 | Carcinog*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 539368 | |
| 20 | 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 | 8168404 | |
| 21 | 8 and 20 | 176 | |
| 22 | limit 21 to yr="2010 -Current" | 83 | |
| 23 | limit 22 to animals | 7 | |
| 24 | limit 22 to animal studies [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained] | 16 | |
| 25 | ("in vitro" or "cell cultur*" or "tissue cultur*").mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 4180142 | |
| 26 | 22 and 25 | 15 | |
| 27 | 23 or 24 or 26 | 25 | |
| 28 | remove duplicates from 27 | 22 | Carcinogenicity |
| 29 | exp drug toxicity/ | 242986 | |
| 30 | exp reproductive toxicity/ | 11312 | |
| 31 | exp toxicity/ | 680419 | |
| 32 | exp toxicity testing/ | 45674 | |
| 33 | exp acute toxicity/ | 20152 | |
| 34 | exp developmental toxicity/ | 3060 | |
| 35 | exp Toxicity Tests/ | 157598 | |
| 36 | exp Toxicology/ | 84344 | |
| 37 | exp teratogens/ | 56503 | |
| 38 | exp teratogen/ | 28428 | |
| 39 | exp teratogenesis/ | 11684 | |
| 40 | exp teratogenicity/ | 17251 | |
| 41 | ((Development* or reproduct*) adj3 toxic*).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 36335 | |
| 42 | 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 | 1069060 | |
| 43 | 8 and 42 | 108 | |
| 44 | limit 43 to yr="2010 -Current" | 47 | |
| 45 | limit 44 to animals | 7 | |
| 46 | limit 44 to animal studies [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained] | 11 | |
| 47 | 25 and 44 | 16 | |

| | | | |
|---|---|---|---|
| 48 | 45 or 46 or 47 | 23 | |
| 49 | remove duplicates from 48 | 21 | Toxicity |
| 50 | exp toxicokinetics/ | 12513 | |
| 51 | Toxicokinetic*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 18322 | |
| 52 | 50 or 51 | 18322 | |
| 53 | 8 and 52 | 1 | toxicokinetics |
| 54 | exp endocrine function/ | 484253 | |
| 55 | exp endocrine disease/ | 2973497 | |
| 56 | exp endocrine system/ | 1216506 | |
| 57 | exp Endocrine Disruptors/ | 16224 | |
| 58 | (("long term" or endocrin*) adj3 effect*).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 195242 | |
| 59 | 54 or 55 or 56 or 57 or 58 | 4241536 | |
| 60 | 8 and 59 | 34 | |
| 61 | limit 60 to animals | 4 | |
| 62 | limit 60 to animal studies [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained] | 8 | |
| 63 | 60 and 25 | 11 | |
| 64 | 61 or 62 or 63 | 15 | |
| 65 | remove duplicates from 64 | 11 | endocrine effects |
| 66 | 28 or 49 or 53 or 65 | 48 | |
| 67 | remove duplicates from 66 | 47 | non clinical combined |
| 68 | exp contact dermatitis/ | 53966 | |
| 69 | exp skin allergy/ | 20467 | |
| 70 | exp skin toxicity/ | 22884 | |
| 71 | exp skin irritation/ | 13378 | |
| 72 | exp skin sensitization/ | 5437 | |
| 73 | exp sensitization/ | 71113 | |
| 74 | exp photodermatosis/ | 9330 | |
| 75 | exp application site reaction/ | 4811 | |
| 76 | exp application site inflammation/ | 89 | |
| 77 | exp Skin Irritancy Tests/ | 46387 | |
| 78 | exp Skin Tests/ | 132447 | |
| 79 | exp skin pruritus/ | 3400 | |
| 80 | exp pruritus/ | 105892 | |
| 81 | exp allergic rash/ | 305 | |
| 82 | exp contact allergy/ | 8227 | |
| 83 | exp contact dermatitis/ | 53966 | |
| 84 | exp drug hypersensitivity/ | 102543 | |
| 85 | exp allergy/ | 413969 | |

| | | | |
|---|---|---|---|
| 86 | exp Hypersensitivity/ | 943748 | |
| 87 | exp Allergens/ | 110041 | |
| 88 | ((dermal or skin) adj3 (sensiti* or irritat*)).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 38460 | |
| 89 | 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 | 1247473 | |
| 90 | 8 and 89 | 296 | |
| 91 | limit 90 to human | 255 | |
| 92 | limit 91 to yr="2010 -Current" | 110 | |
| 93 | limit 92 to english language | 108 | |
| 94 | limit 93 to (conference abstract or conference paper or "conference review" or editorial or letter or note) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained] | 21 | |
| 95 | 93 not 94 | 87 | skin irritation |
| 96 | exp phototoxicity/ | 8810 | |
| 97 | exp photoallergy/ | 2680 | |
| 98 | (phototox* or photoalle*).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 18852 | |
| 99 | 96 or 97 or 98 | 18852 | |
| 100 | 8 and 99 | 163 | |
| 101 | limit 100 to english language | 148 | |
| 102 | limit 101 to human | 122 | |
| 103 | limit 102 to yr="2010 -Current" | 55 | |
| 104 | limit 103 to (conference abstract or conference paper or "conference review" or editorial or letter or note) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained] | 8 | |
| 105 | 103 not 104 | 47 | |
| 106 | remove duplicates from 105 | 39 | phototoxicity |
| 107 | exp drug bioavailability/ | 65733 | |
| 108 | exp bioavailability/ | 153820 | |
| 109 | exp drug absorption/ | 82919 | |
| 110 | exp pharmacokinetics/ | 1036741 | |
| 111 | exp Skin Absorption/ | 18649 | |
| 112 | exp Biological Availability/ | 153820 | |
| 113 | exp Absorption, Physiological/ | 133321 | |
| 114 | (absorp* or absorb*).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 1037779 | |
| 115 | (penetration or penetrate or permeability).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 555651 | |
| 116 | (penetration or penetrate or permeability).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 555651 | |
| 117 | bioavail*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 227239 | |
| 118 | 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 | 2405762 | |

| | | | |
|---|---|---|---|
| 119 | 8 and 118 | 390 | |
| 120 | 107 or 108 or 109 or 111 or 112 or 113 or 117 | 429161 | |
| 121 | 8 and 120 | 148 | |
| 122 | limit 121 to english language | 141 | |
| 123 | limit 122 to human | 86 | |
| 124 | limit 123 to yr="2010 -Current" | 45 | |
| 125 | limit 119 to english language | 376 | |
| 126 | limit 125 to human | 207 | |
| 127 | limit 126 to yr="2010 -Current" | 106 | |
| 128 | limit 127 to (conference abstract or conference paper or "conference review" or editorial or letter or note) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained] | 15 | |
| 129 | 127 not 128 | 91 | |
| 130 | remove duplicates from 129 | 72 | bioavailability absorption |
| 131 | (safe or safety or "side effect" or "side effects" or adverse).mp. or exp adverse drug reaction/ or exp drug-related side effects/ or exp drug safety/ or toxic*.mp. or hazard*.mp. | 8304938 | |
| 132 | 8 and 131 | 406 | |
| 133 | limit 132 to english language | 389 | |
| 134 | limit 133 to human | 281 | |
| 135 | limit 134 to yr="2010 -Current" | 130 | |
| 136 | limit 135 to (conference abstract or conference paper or "conference review" or editorial or letter or note) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained] | 14 | |
| 137 | 135 not 136 | 116 | |
| 138 | remove duplicates from 137 | 91 | general safety |
| 139 | 95 or 106 or 130 or 138 | 153 | |
| 140 | remove duplicates from 139 | 139 | clinical search |
| 141 | 67 or 140 | 173 | |
| 142 | remove duplicates from 141 | 163 | **Final clinical and non-clinical combined** |

## 3.2. TABLE 2: LISTING ENDOCRINE DISRUPTING EFFECTS OF COMMONLY USED UV FILTERS

Table 2

Endocrine disrupting effects of the 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 minnows; Reduce of the uterine weight in immature Long-Evans rats |
| | Androgenic disrupting effects | Antagonists of human AR transactivation; Repression of 4,5-dihydrotestosterone-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; Induction of proliferation of MCF-7 cell; Induction of pS2 protein in MCF-7 cells; Reduce of the uterine weight in rats; Induction of VTG in fish |
| | 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 progesterone 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; Reduce of the uterine weight in rats; Induction of VTG in fish |
| | Disrupting effects toward thyroid hormone receptor | Decrease of T4 level; 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; Reduce of the 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

### 3.3. TABLE 3: MEAN EXPOSED SKIN SURFACE AREA PER PRODUCT TYPE AND FREQUENCY OF APPLICATION PER PRODUCT TYPE (BREMMER *ET AL.*, 2006)

| Product type | Skin surface area involved (RIVM) | | Frequency of application |
|---|---|---|---|
| | Surface area ($cm^2$) | Parameters (if specified) | |
| **Bathing, showering** | | | |
| Shower gel | 17500 | total body area | 1.43/day |
| Hand wash soap | 860 | area hands | 10/day |
| Bath oil, salts, etc. | 16340 | area body - area head | 1/day |
| **Hair care** | | | |
| Shampoo | 1440 | area hands | 1/day |
| | | + 1/2 area head | |
| Hair conditioner | 1440 | area hands + 1/2 area head | 0.28/day |
| Hair styling products | 1010 | 1/2 area hands + 1/2 area head | *1.14/day* |
| Semi-permanent hair dyes (and lotions) | 580 | 1/2 area head | 1/week (20 min.) |
| Oxidative/permanent hair dyes | 580 | 1/2 area head | 1/month (30 min.) |
| **Skin care** | | | |
| Body lotion | 15670 | area body - area head female | *2.28/day* |
| Face cream | 565 | 1/2 area head female | *2.14/day* |
| Neck | 320 | | |
| Back of neck | 80 | | |
| Hand cream | 860 | area hands | 2/day |
| **Make-up** | | | |
| Liquid foundation | 565 | 1/2 area head female | 1/day |
| Make-up remover | 565 | 1/2 area head female | 1/day |
| Eye shadow | 24 | | 2/day |
| Mascara | 1.6 | | 2/day |
| Eyeliner | 3.2 | | 2/day |
| Lipstick, lip salve | 4.8 | | *2/day* |
| **Deodorant/antiperspirant** | | | |
| Deodorant aerosol spray and non-spray | 200 | both axillae | *2/day* |
| **Fragrances** | | | |
| Eau de toilette spray | 200 | | 1/day |
| Perfume spray | 100 | | 1/day |
| **Men's cosmetics** | | | |
| Shaving cream | 305 | 1/4 area head male | 1/day |
| Aftershave | 305 | 1/4 area head male | 1/day |
| **Sun care cosmetics** | | | |
| **Sunscreen lotion / cream** | **17500** | **total body area** | **2/day** |

### 3.4. Reported use of active ingredients in sunscreen products marketed in Australia

s47C

The following table reflects the Reporter analysis for listed sunscreens in Australia (760 products on ***13/2/20***) and the 31 ingredients approved for use as active ingredients in these products. The 12 ingredients categorised III in the FDA proposed rule are highlighted in bold font. Please note that approximately 70% of sunscreen products contain avobenzone and/or octocrylene.

| Active ingredient (AAN) | No. of listed sunscreens |
|---|---|
| 4-methylbenzylidene camphor | 244 |
| **Avobenzone (butyl methoxydibenzoylmethane)** | **541** |
| Bemotrizinol | 128 |
| Benzylidene camphor sulfonic acid | 0 |
| Camphor benzalkonium methosulfate | 0 |
| **Cinoxate** | 0 |
| Diethylamino hydroxybenzoyl hexyl benzoate | 90 |
| **Dioxybenzone** | 0 |
| Disodium phenyl dibenzimidazole tetrasulfonate | 0 |
| Drometrizole trisiloxane | 20 |
| Ecamsule | 17 |
| **Ensulizole (phenylbenzimidazole sulfonic acid)** | **100** |
| Ethylhexyl triazone | **113** |
| **Homosalate** | **303** |
| Isoamyl methoxycinnamate | 0 |
| **Meradimate (menthyl anthranilate)** | 0 |
| Methylene bis-benzotriazolyl tetramethylbutylphenol | 32 |
| **Octinoxate (octyl methoxycinnamate)** | **134** |
| **Octisalate (octyl salicylate)** | **296** |
| **Octocrylene** | **522** |
| **Oxybenzone** | **126** |
| PABA (amino benzoic acid) | 0 |
| **Padimate o** | 0 |
| Peg-25 paba | 0 |
| Polysilicone-15 | 2 |
| **Sulisobenzone** | 0 |
| sulisobenzone sodium | 0 |
| Titanium dioxide | 78 |
| Tris-biphenyl triazine | 0 |
| Trolamine salicylate | 0 |
| Zinc oxide | 229 |

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Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

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# Literature Review

## Avobenzone, ethylhexyl triazone, homosalate, octocrylene, octinoxate, oxybenzone and phenylbenzimidazole sulfonic acid

January 2022

TGA Health Safety Regulation

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**EXECUTIVE SUMMARY**

- The literature review of seven active ingredients (avobenzone, ethylhexyl triazone, homosalate, octocrylene, octinoxate, oxybenzone and phenylbenzimidazole sulfonic acid) was based on the national and international safety assessment reports and available peer reviewed publications investigating the safety and toxicokinetics of the ingredients, where available.
- These ingredients were selected for this targeted priority review considering the status of the availability of nonclinical safety data to TGA and their reported use in higher number of sunscreen products marketed in Australia in addition to the safety signals reported in media and overseas.
- 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. Based on the data available for these ingredients, a Margin of Safety (MoS) was determined for each of the ingredients as per relevant guidelines.
- The systemic absorption of avobenzone, homosalate, octocrylene, octinoxate and oxybenzone was noted in a limited number of clinical trials.
- Based on the limited data that was available, avobenzone, ethylhexyl triazone, octocrylene, octinoxate and phenylbenzimidazole sulfonic acid are unlikely to cause any significant systemic toxicity (Margin of Safety (MoS) >100). However, the MoS was less than 100 for **homosalate and oxybenzone** when used as active ingredients in sunscreens in the current use scenario. The calculation was based on available dermal absorption data and data from a combined repeated dose toxicity study with the reproduction/developmental toxicity and pre- and post-natal developmental toxicity study for homosalate and oxybenzone, respectively.
- The available information on avobenzone, homosalate, octocrylene, octinoxate and oxybenzone indicate potential endocrine effects, however, the data are not adequate to derive a conclusion. Further data on the endocrine disrupting potential of these chemicals are warranted.
- The following challenges were identified during the literature review.
    a) The NOAELs were collected from published international safety assessment reports. Actual firsthand evaluation of the data, study quality, compliance was not possible.
    b) Additional clinical studies would be required to fully evaluate the pharmacokinetics of the active ingredients.
    c) Due to a lack of specific data and guidelines for the determination of the MoS in paediatric populations, the safety of these ingredients is uncertain when used on infants and children.
    d) International safety assessments were conducted considering the use pattern of sunscreens within specific countries and regulatory framework. There is a lack of information surrounding the typical use patterns (frequency of use, duration of use, how much is applied etc.) of sunscreens in Australia.

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## 1. ASSESSMENT

Maintaining public confidence in the safety and effectiveness of sunscreens is an important part of the TGA's role in therapeutic sunscreen regulation. Concerns about the safety of sunscreens expressed in the media and by consumer groups could lead to a loss of public confidence in this key component of Australia's skin cancer-prevention strategy.

Recent concerns about the skin absorption of active ingredients in sunscreens have arisen in part by the FDA's proposed changes in the regulation of sunscreen ingredients (US FDA 2019). The proposed changes state that the FDA considers that a sunscreen active ingredient is safe and effective, if it demonstrates a steady-state blood level of an ingredient under 0.5 ng/mL, and an adequately conducted toxicological study does not raise any other safety concerns (US FDA 2019). The FDA published two studies in 2019 and 2020 looking at the dermal absorption of the most common active ingredients in sunscreens (Matta *et al.,* 2020; 2019). Both studies demonstrated that the studied sunscreen active ingredients were absorbed in appreciable quantities and that active ingredients can remain in plasma for an extended time after the last application.

In response to the findings from the FDA and given the greater use of sunscreens in Australia from a higher frequency of use and longer-term use by the population as whole, the TGA is undertaking its own audit to understand the safety profile of the active ingredients approved for use in sunscreens in Australia. An audit to review the safety information of ingredients currently approved by TGA as actives in sunscreens revealed safety data for existing 'grandfathered' ingredients were limited. Subsequently, following consideration of the highest reported use of the sunscreen products in Australia containing these active ingredients (Appendix 5.4) and international safety signals (FDA, 2019) related to these ingredients, a targeted safety assessment of seven ingredients (avobenzone, ethylhexyl triazone, homosalate, octocrylene, octinoxate, oxybenzone and phenylbenzimidazole sulfonic acid) was undertaken by the TGA.

The safety assessment of the selected ingredients was based on information provided in the newest opinions from the Scientific Committee on Consumer Safety (SCCS) where available, and information identified from a literature search in PubMed and an open search for information on specific endpoints from published reports from the internet. Review articles and documents focusing on the individual toxicological endpoints were featured in the hazard assessment where no recent SCCS opinions were available. REACH registration dossiers for individual ingredients published by ECHA and risk assessment by national regulatory agencies (i.e., AICIS) were also considered if available. Exposure to these selected ingredients from other products than sunscreens has not been considered. Exposure to metabolites of these ingredients or impurities present in these ingredients has not been considered for safety assessment in this review.

Within 2020-21, the European Commission has published opinions (preliminary and/or final) on the safety of oxybenzone, homosalate and octocrylene. Based on the available information, risk assessments of each of these ingredients were conducted and a Margin of Safety (MoS) determined for each of the ingredients as per relevant guidelines (SCC, 2000; SCCS, 2016). It found that the levels of oxybenzone and homosalate were not safe in the current use scenarios and proposed a concentration limit of 2.2% and 1.4% (0.5% in the final opinion) for oxybenzone and homosalate, respectively when used in sunscreens.

The TGA literature review follows a similar approach of risk assessment based on a MoS determination while recognising limited available data (2008-2020). It is noted that current evidence may not be sufficient to support the causal relationship between the elevated systemic level of the ingredients and adverse health outcomes. To accurately evaluate the long-term risk of exposure to these active ingredients from sunscreen, further randomized controlled trial may need to be conducted.

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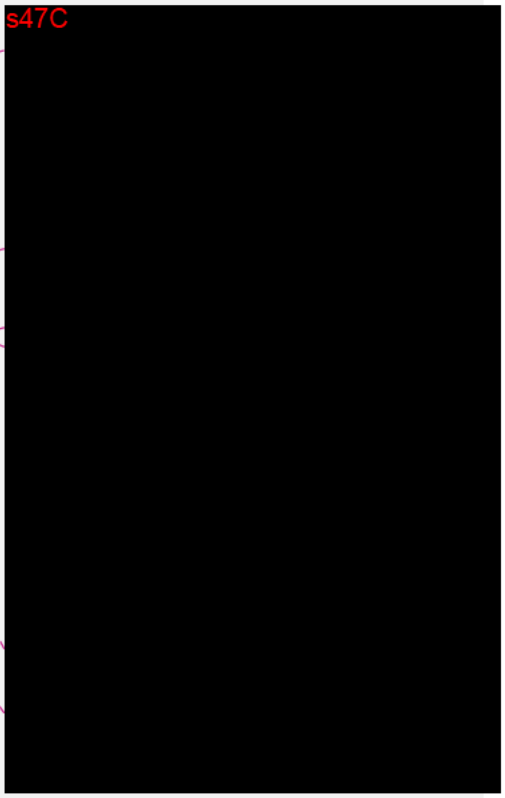

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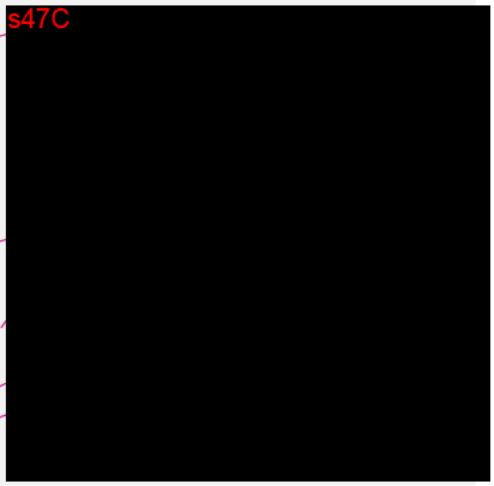

### 1.1. MARGIN OF SAFETY

As per the *SCCNFP's notes of guidance for the testing of cosmetic ingredients and their safety evaluation, 9th revision* (SCCS, 2016), the risk assessment of active ingredients in sunscreens can be conducted by calculating the MoS using uncertainty factors. MoS can be extrapolated from animals to humans to predict the potential risk in human. Usually, a MoS > 100 would indicate that the ingredient is safe under the proposed use conditions. MoS is the ratio between a NOAEL and a Systemic Exposure Dose (SED).

$$MoS = \frac{NOAEL(mg/kg\ bw/d)}{SED(mg/kg\ bw/d)}$$

The SED of a cosmetic substance is the amount expected to enter the blood stream (and therefore be systemically available) per kg body weight and per day. It is expressed in mg/kg body weight (bw)/day. For this definition, the human body weight of 60 kg is commonly accepted; however, the TGA usually consider a more conservative approach to calculate the SED, with a typical body weight for adults of 50 kg. ICH guideline Q3C (R8) on impurities: guideline for residual solvents also advocates using '*...an arbitrary adult human body weight for either sex of 50 kg.*' as a way of providing an additional safety factor in PDE calculations.[1]

SED can be calculated using either of the following two formulas depending on the method of reporting for the dermal absorption value.

*Option 1: Dermal absorption reported as a percentage of the amount of substance applied in in vitro studies:*

The percentage of dermal absorption is expected to be calculated from *in vitro* studies with doses, concentrations and amounts mimicking, but not exceeding the intended use conditions. Otherwise, the studies may result in an underestimation of the penetration.

$SED = A\ (mg/kg\ bw/day) \times C\ (\%)/100 \times DA_p(\%)/100$

A= Estimated daily exposure to a cosmetic product per kg body weight[2], based upon the amount applied and the frequency of application, For sunscreen lotion, an application of 18 g/d is used in the MoS calculation (SCCS, 2016, also Appendix 5.3) C (%) = concentration of the ingredient under study in the finished product on the application site

DA= Dermal Absorption expressed as a percentage of the test dose assumed to be applied in real-life conditions.

Note: In the case that the molecular weight (MW) > 500 Da and the log $P_{ow}$ (octanol-water partition coefficient) is less than -1 or higher than 4, the value of 10% dermal absorption may be considered appropriate to use in the absence of empirical data.

*Option 2: Dermal absorption of test substance reported in µg/cm²*

For calculating the SED, the skin surface envisaged to be treated with the finished cosmetic product containing the substance under study has to be taken into account, as well as its

[redacted]

[1] ICH guideline Q3C (R8) on impurities: guideline for residual solvents

[2] TGA usually consider a more conservative approach to calculate the SED, with a typical body weight for adults of 50 kg.

frequency of application per day. All other variables should have been taken into consideration in the proper design of the dermal absorption study itself (SCCS, 2016).

$$SED = \frac{DA_a\ (\mu g/cm^2) \times SSA\ (cm^2) \times F\ (day^{-1})}{50\ kg^2} \times 10^{-3}$$

$DA_a$ ($\mu g/cm^2$) = Dermal Absorption reported as amount/$cm^2$, resulting from an assay under in-use mimicking conditions

SSA ($cm^2$) = Skin Surface Area expected to be treated with the finished cosmetic product (See Table 3 in appendix)

F ($day^{-1}$) = Frequency of application of the finished product ($F \geq 1$)

Please note, although dermal data is expected to reflect real time exposure and toxicity following application of sunscreens, in the absence of dermal toxicity data, oral toxicity data were considered in the MoS determination using a conservative approach given oral toxicity data may reflect systematic toxicity in worst case scenario.

### 1.2. RISK ASSESSMENT OF THE ACTIVE INGREDIENTS IN SUNSCREENS

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[redacted]

**Avobenzone**

This review is based on the international safety assessment reports for avobenzone (SCC; 2000; ECHA, 2021a; DEPA, 2015) and available peer reviewed publications investigating the safety and toxicokinetics of avobenzone.

The ECHA dossier suggested low percutaneous absorption of avobenzone. Potential systemic availability of avobenzone or metabolites at a high oral dosage was suggested from the oral toxicity studies in rats with up to 3 months exposure. Low systemic exposure from dermal contact was also noted in the ECHA dossier and insignificant inhalation exposure was assumed due to the low vapour pressure. In a study with pigskin (2% and 7.5% avobenzone containing formulations), about 95 % of avobenzone remained on the skin surface, 1-2 % were in the stratum corneum, 1 - 3.4 % in the skin and only ≤0.5 % was found to pass the skin (ECHA 2021A). In an *in vitro* dermal absorption study with human skin (2% avobenzone in water-oil cream) dermal absorption increased with exposure time from 0.3% to 7.3% (this value is used in the MoS calculation, see below) after 18 hours (DSM, 1982). In a recent study (Montenegro *et al.* 2018) to investigate the effects of the vehicle and repeated applications of sunscreens on skin permeation, the skin permeation was demonstrated to be very poor after single or repeated applications leading to a MoS above the accepted safety limit (>100).

Nonetheless, recent randomised clinical trials indicate that avobenzone could be systemically absorbed (Matta *et al.*, 2020; 2019). The systemic exposure of avobenzone in all product types (spray, lotion, aerosol spray) exceeded 0.5 ng/mL on single application and remained above the threshold until 23 hours after application, and up to 7 days in more than 50% of participants. The long terminal half-life typically exceeded 48 hours and the ingredient remained detectable through to day 21, suggesting absorption through the skin is the rate-limiting step. However, further studies are required to determine other kinetic parameters e.g. elimination rate constants.

The available information reported for avobenzone indicate it has low acute toxicity (rats) and it is not an irritant to skin (very slight irritation at 10%) and eye (≤ 20%) in rabbits. No treatment-related effects were seen in guinea pig studies investigating irritation, sensitization, phototoxicity, and photoallergenicity potential. The ingredient was not found to be genotoxic, mutagenic, photo mutagenic or teratogenic in animals. Clinical data have shown the ingredient to be a rare allergen

and/or photoallergen. Based on a 13-week oral repeated dose toxicity study in rats, the NOAEL of avobenzone was considered to be 450 mg/kg bw/day and used for the MoS calculation given the longer duration of the study and a better reflection of systemic toxicity using a conservative approach. Dose related local dermal effects like erythema and oedema were seen in a 28 day dermal repeat dose study in rabbits with no systemic effects, therefore the NOAEL was not used in the calculation of the MoS. In this study, the systemic NOAEL was determined to be 360 mg/kg/day bw (18% avobenzone) whereas the LOAEL (dermal) was 30 mg/kg/day bw (1.5% avobenzone) based on topical local effects. A NOAEL (oral) for maternal, developmental and embryotoxicity of 1,000 mg/kg bw/day was determined in rats.

The Danish EPA (DEPA, 2015) calculated the MoS with the maximum allowed concentration of 5% and determined a MoS around 300 for sunscreens containing avobenzone applied on people with mean average weight of 60 kg. Assuming the mean average body weight of 50 kg for Australian public, the SED is determined 1.3 mg/kg bw/day resulting in a MoS of 346 (see below).

| Description | Parameter | Sunscreen |
|---|---|---|
| Amount of sunscreen applied daily | Q (mg/day) | 18000 |
| Concentration of ingredient in finished product | C (%) | 5 |
| Total amount of active ingredient applied | Qi = Q x C (mg/day) | 90000 |
| Absorption of active ingredient | Dap (%) | 7.3 |
| Total amount absorbed | Abs =Qi x Dap × 0.01 × 0.01 mg/day | 65.7 |
| **SED** | ABs/body weight (50 kg) | 1.3 |

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No Observed Adverse Effect Level (NOAEL) = 450 mg/kg bw/day

**MoS= NOAEL/SED= 346**

The Danish EPA (DEPA, 2015) also concluded that avobenzone did not pose a risk to consumers based on the REACH registration dossier assuming 36 g was applied daily (MoS ≥ 100). In 2013, publicly available data on endocrine disruptive properties of the substance were collected and evaluated by the Danish Centre on Endocrine Disruptors which concluded that there was not enough data to conclude whether the substance had endocrine disruptive properties or not.

Based on the information available and MoS determined to be more than 100, there are no immediate systemic safety concerns with the use of avobenzone at 5% in sunscreens. However, the primary data and analysis have not been subject to scrutiny by the evaluator.

**Ethylhexyl triazone (EHT)**

The summary is primarily based on the REACH dossier (ECHA, 2021b) and published peer reviewed articles.

The ECHA registration dossier indicated the dermal uptake of ethylhexyl triazone was negligible or low (maximum uptake of 1.3%). Recent *in vitro* experiments with a static skin diffusion cell design under real life conditions indicated that 18.3 ± 2.5 µg/cm² of ethylhexyl triazone was found in the stratum corneum, whereas no ethylhexyl triazone was determined in the receptor fluid following the application of a sunscreen with 5% ethylhexyl triazone on the intact human skin at the dose of 1mg/cm² for 6 h (Hojerová *et al.* 2017). 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. Higher ethylhexyl triazone absorption was noted on shaved skin.

Undiluted ethylhexyl triazone is not expected to be a skin or eye irritant. There are no data for respiratory irritation. It was not found to be sensitising in guinea pigs. The NOAELs were determined 1000 mg/kg/day and ≤ 1275 mg/kg/day in two 90 day oral repeat dose studies in rats, respectively. Ethylhexyl triazone was not found to be genotoxic in *in vivo* and *in vitro* studies. No carcinogenicity data were available, and no adverse effects were reported in a pre-natal developmental study (maternal and developmental NOAEL 1000 mg/kg/day bw).

Because no dermal repeated-dose toxicity study for ethylhexyl triazone was available from the literature, and in accordance with the guidance provided in SCCS (2016), the NOAEL value (1000 mg/kg bw/day) from oral repeated dose toxicity studies in rats was used in the MoS determination.

Public exposure to ethylhexyl triazone is expected to be widespread and frequent through a daily use of listed products containing the ingredient at concentrations up to 5% (approved on TGA permitted list).[3] In the absence of an appropriate dermal absorption value for ethylhexyl triazone, a 10% dermal absorption was assumed for SED calculation in the worst case scenario using option 1 (Section 1.1, Page **Error! Bookmark not defined.**) considering physiochemical properties (molecular weight > 500 and a log$P_{ow}$ > 4).

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[redacted]

| Description | Parameter | Sunscreen |
|---|---|---|
| Amount of sunscreen applied daily | Q (mg/day) | 18000 |
| Concentration of ingredient in finished product | C (%) | 5 |
| Total amount of active ingredient applied | Qi = Q x C (mg/day) | 90000 |
| Absorption of active ingredient | Dap (%) | 10 |
| Total amount absorbed | Abs =Qi x Dap × 0.01 × 0.01 mg/day | 90 |
| SED | ABs/body weight (50 kg) | 1.8 |

No Observed Adverse Effect Level (NOAEL) = 1000 mg/kg bw/day

Therefore, the MoS was determined = NOAEL/SED= 1000/1.8 = **555** (> 100)

**Homosalate**

This review is based on the published literature, ECHA dossier and SCCS opinions (ECHA, 2021c; SCCS, 2020). The SCCS has published their opinion on homosalate in 2007, and recently extended their preliminary opinion based on new information of homosalate in 2020 (SCCS, 2020).[4]

Animal studies and studies with human skin showed that homosalate could penetrate the skin. Evidence from *in vitro* experiments indicates that about 1.1% of the applied dose was absorbed in human skin (range: 0.9-2.0%)(CTFA, 2005). The maximal absorption value observed in the donor with highest absorption values (2%) was taken for MoS calculation.[5]

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 Section 2.1). Homosalate was also detected in human milk samples after topical application in human volunteers (Schlumpf *et al.* 2010).

Homosalate was found to be systemically absorbed in recent randomised clinical trials (Matta *et al.*, 2020, 2021). The systemic exposure of homosalate in sunscreens (spray) exceeded 0.5 ng/mL on single application and repeated applications (in > 50% of participants up to 21 days). The continued

[3] Therapeutic Goods (Permissible Ingredients) Determination (No. 2) 2021
[4] The final opinion was published in June 2021, after this review was drafted.
[5] A 5% dermal absorption value was used in the final SCCS opinion on homosalate (June 2021) resulting in a MoS value of 6. This does not change the safety assessment of homosalate as the current MoS is not acceptable (< 100).

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presence of homosalate at skin up to 21 days and long terminal half-life (> 48 hours) suggest skin absorption of homosalate (Matta *et al.,* 2020). Intravenous studies would be required to determine elimination rate constants.

*In vitro,* homosalate was hydrolysed into salicylic acid and 3,3,5-trimethylcyclohexano associated with conjugation and hydroxylation of intact homosalate.

Based on available safety information from animal studies, homosalate was found to be of low acute oral and dermal toxicity, not a skin or eye irritant (at 10%) and with no sensitising potential. Undiluted homosalate was also found to be a non-irritant in a human epidermis skin test with no sensitising potential at 15% in a human repeat patch test.

A general toxicity NOAEL of 300 mg/kg bw/day was established in a combined repeat dose and reproductive/developmental screening study in rats based on mortality in female rats at the highest dose. However, treatment-related effects were observed in kidneys, liver, thyroid and thymus in male rats at 60 mg/kg bw/day. Therefore, the SCCS concluded that this dose should be considered LOAEL. The SCCS also states that technical errors might have contributed to the effects observed, influencing the reliability of the study. A NOAEL of > 300 mg/kg bw/day in males and >1000 mg/kg bw/day in females was established in a two-week study in rats. Both these studies indicate that the treatment-related effects were more adverse in males. The human relevance of this species-specific effect is uncertain.

Homosalate was not found to be genotoxic in a standard battery of tests. While two recent studies indicated that there was a genotoxic potential for homosalate, the studies were found inadequate due to methodological errors (Yazar *et al.* 2018; 2019). No carcinogenicity data were available. A combined repeated dose and reproductive/developmental screening study in rats by gavage up to 750 mg/kg bw/day was recently reported (SCCS, 2020; ECHA, 2018). The SCCS noted that the occurrence of constant lighting (illumination) during the conduct of the study significantly affected the reliability of this study, especially for developmental/reproductive effects. In addition, the low number of pregnancies per group questions the validity of the data on the development of offspring in this study. Homosalate was found to adversely affect the survival, proliferation, and invasiveness of human trophoblast cells which highly associated with the development of human placenta during early pregnancy and, as such, may pose a threat to pregnant women (Yang *et al.* 2018).

Therefore, further studies (e.g. a sub-chronic toxicity study, a prenatal developmental toxicity study, an extended one-generation reproductive toxicity study, and the identification of degradation products) would be required to fully allay concerns related to homosalate exposure and reproductive and developmental concerns.

The SED for homosalate when used as a UV filter in cosmetic products, was calculated using a dermal absorption value of 2% derived from an *in vitro* dermal penetration study using viable human skin and a standard sunscreen formulation containing 10% homosalate.

The SCCS (2020) report takes into account the following consideration to calculate the margin of safety:

> *As point of departure for risk assessment, a LOAEL of 60 mg/kg bw/day was used, based on a combined repeated dose toxicity study with the Reproduction/Developmental Toxicity Screening Test. Since the point of departure was based on a LOAEL, an additional uncertainty factor of 3 was added. Furthermore, due to lack of information on oral bioavailability, 50% of the administered dose was used as the default oral absorption value, resulting in an adjusted NOAEL of 10 mg/kg bw/day.*

- *Amount of sunscreen applied A (g/d) = 18*
- *Concentration in the finished product C (%) = 10 %*

- *Dermal Absorption $DA_p$ (%) = 2 %*
- *Typical bodyweight of human = 60 kg*

*Systemic exposure dose (SED) A x 1000 mg/kg x C/100 x Dap/100/60 = 0.6 mg/kg*

*LOAEL = 60 mg/kg; NOAEL/LOAEL adjustment 20 mg/kg*

*Bioavailability 50% = 10 mg*

*Margin of Safety (MoS): adjusted NOAEL/SED = 10/0.6 = **17.0***

*In order to derive at MoS of 100, the SED should be maximally 0.1 mg/kg meaning that*

*A x 1000 mg/kg x C/100 x Dap/100/60 = 0.1.*

With the above values, C is 1.666, meaning the safe level is maximally 1.7 % homosalate in sunscreen.

TGA usually consider a more conservative approach to calculate the SED, with a typical body weight for adults of 50 kg, using this parameter the MoS obtained (~14.0) is similar to the result calculated in SCCS report **(MoS = 17).**

s47C [redacted]

The SCCS concluded:

> *"On the basis of safety assessment of homosalate, and considering the concerns related to potential endocrine disrupting properties, the SCCS has concluded that homosalate is not safe when used as a UV-filter in cosmetic products at concentrations of up to 10%.*
>
> *In the SCCS's opinion, the use of homosalate as a UV filter in cosmetic products is safe for the consumer up to a maximum concentration of 1.4% homosalate in the final product.*
> *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**

This review aims to present review the main safety data on octocrylene from the ECHA website (ECHA, 2020), as well as those reported in the SCCS opinions (SCCS, 2021a) and scientific articles from peer-reviewed journals. In a recently published SCCS opinion on the safety of octocrylene (SCCS, 2021a), the SCCS considered that octocrylene was safe at concentrations of up to 10% when used individually or together as a UV-filter in cosmetic products, i.e. in sunscreen cream/lotion, sunscreen pump spray, face cream, hand cream and lipstick (SCCS, 2021a). However, a lower concentration of octocrylene (9%) is considered safe in sunscreen propellant spray when the sunscreen propellent spray is used along with face cream, hand cream, and lipstick (containing 10% octocrylene).

s47C [redacted]

Extensive studies were available investigating octocrylene pharmacokinetics, and these have been summarised in Section 3 (Page 23).

Octocrylene is a lipophilic substance, and it is reported to be metabolised to a variety of metabolites where CDAA is the main metabolite. Information was lacking on whether the most significant toxic

agent was octocrylene or its metabolites. Considering the relatively long half-life of both octocrylene and CDAA in plasma and the low elimination rate of CDAA in urine, an accumulation of octocrylene and CDAA in the human body following repeated dermal applications would be expected.

The higher maximum observed concentration of CDAA (1351.7 ng/mL) *vs* octocrylene (25.0 ng/mL) also suggested that measuring only unmetabolized octocrylene might underestimate total systemic absorption and thereby influencing the safety assessment of octocrylene. In addition, it was noted that higher absolute concentrations of octocrylene were observed from exposure to "real-life" conditions compared to "indoor maximal use conditions", indicating peak plasma concentrations may be even higher in real-world usage conditions.

Systemic absorption of octocrylene was demonstrated in recent randomised clinical trials following dermal application. The plasma concentration of octocrylene from sunscreens exceeded 0.5 ng/mL on single application (until 23 hours after application) whereas the systemic exposure to octocrylene remained above the threshold of 0.5 ng/mL in plasma in more than 50% of participants for up to 10 days. The continued presence of octocrylene in skin at days 10 and its long terminal half-life suggested absorption through skin was the rate-limiting step. Intravenous studies with octocrylene would be required to determine elimination rate constants to the parent. Considering the above, the clinical significance of the systemic exposure and the metabolism of octocrylene in humans requires further investigation.

s47C [redacted]

The SCCS determined that the SEDs for dermal exposures to octocrylene from sunscreen cream/lotion were 0.566 mg/kg bw/day. SEDs for inhalation exposures to sunscreen sprays were 0.176 and 0.002 mg/kg bw/day for propellant and pump spray, respectively (Matta *et al.,* 2019, 2020).

As tabulated in Section 4, Toxicity, octocrylene was found to be of low acute toxicity. Octocrylene was not an eye or skin irritant based on available data. It was found to not sens itising in a Guinea Pig Maximization Test (GPMT). Octocrylene was found to be a moderate skin sensitiser and a skin photosensitiser [local lymph nose assay (LLNA) with 1- 30% octocrylene, EC3: 7.7% and human patch studies with 10% octocrylene]. However, the LLNA study was not considered properly conducted and the occurrence of photoallergy to octocrylene was suspected to be related to a previous photoallergy to topical ketoprofen. Photoallergic contact dermatitis to octocrylene has been found to be much more frequent in adults than in children whereas contact allergy cases to octocrylene have been reported more in children compared to adults. This is likely due to the immaturity of the skin epidermal barrier and the prevalence of atopic dermatitis in young children as the study authors suggested (Gilaberte & Carrascosa, 2014). Considering the information above, octocrylene was considered a skin sensitiser at 10%.

s47C [redacted]

No systemic effects were reported in rabbits after dermal exposure to octocrylene at 534 mg/kg bw/day. After oral exposure, effects on liver and thyroid were reported in a study in rats (males) at 340 and 1085 mg/ kg bw/day. These effects on liver and thyroid were investigated in an additional mechanistic study which showed that effects on thyroid were indirect and probably due to hepatic enzyme induction potential of octocrylene. Recently reported repeat dose toxicity studies with octocrylene (SCCS, 2021a; ECHA, 2020) do not alter the previously established NOAEL of 175 mg/kg bw/day, that was established in a previous SCCS report for octocrylene.

s47C [redacted]

Octocrylene is not expected to be genotoxic. No carcinogenicity data were available. Based on the effects on parental and pup body weights, a lower number of implantation sites and lower number of pups in the extended one generation reproductive toxicity study (EOGRTS), a NOAEL was established at 153/163 mg/kg/day for parental systemic toxicity, fertility/reproduction performance, and general and sexual development. No neuro-/developmental effects were observed at the highest dose level tested (534/550 mg/kg/day). A monitoring study revealed that during the periods of pregnancy and lactation, > 78% of the women used some cosmetic product containing UV filters and

UV filters were detected in 82.5% of human milk samples (Schlumpf *et al.* 2010, 2008). Octocrylene (OC) was one of the most frequently used UV filters and most frequently detected in milk samples (i.e. 27.50 ± 22.15 ng/g of lipids) (Schlumpf *et al.* 2010, 2008). Use of UV filters and concentration in human milk were significantly correlated. The results indicate transdermal passage of UV filters and potential placental transfer of octocrylene.

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[redacted]

Public exposure to octocrylene would be expected to be widespread and frequent through a daily use of sunscreen products containing ingredient typically at concentrations up to 10 %.

As per option 2 for SED calculation (Margin of Safety ), the SED was determined to be 0.339 mg/kg bw/day for octocrylene in sunscreen (for a 60 kg bw person) using the values from SCCS 2021a (dermal absorption value of 0.97 µg/cm² from Fabian & Landsiedel, 2020; octocrylene concentration of 10% ). The NOAEL of 153 mg/kg bw/day based on the EOGRTS is used for the calculation of MOS. Based on an oral bioavailability of 50% (Bury *et al.*, 2019), an adjusted NOAEL of 76.5 mg/kg bw/day was determined. Details of the calculation of systemic exposure dose (SED) is in SCCS 2021a. The MoS was calculated as:

MoS= NOAEL/SED= 76.5/0.339

= **225 (≥ 100).**

Assuming a body weight of 50 kg for an Australian adult, the SED was determined to be 0.679 mg/kg bw/day resulting in a **MoS of 112**. This value slightly above the accepted safety threshold.

**Octinoxate**

This review was based on the safety data from the ECHA website, the SCCS opinion (SCC, 2000), NICNAS Human Health Tier II Assessment Report, and scientific articles from peer-reviewed journals (NICNAS 2017, currently known as AICIS; ECHA 2021e).

Available *in vitro* and *in vivo* studies indicate octinoxate can poorly penetrate the skin. Systemic absorption of octinoxate was also demonstrated in recent randomised clinical trials (Matta *et al.*, 2020). However, elimination rate constant was not determined due to the absence of intravenous studies.

Octinoxate was found to be of low and moderate acute oral toxicity in mice and rats, respectively. Based on the limited data available, the chemical is not considered to be a skin irritant or an eye irritant. The chemical is not considered to be a skin sensitiser in humans. There is potential for photosensitivity following UV exposure, but the results are inconclusive.

No systemic effects were reported in a 13-week dermal repeat dose study in rats administered up to 534 mg/kg/day. The NOAEL was determined 450 mg/kg/day in a 13-week oral repeat dose study. Based on the available studies, the chemical was not considered to cause serious damage to health from repeated dermal exposure.

Octinoxate is not expected to have genotoxic potential, however, the lack of studies with isomers *cis* and *trans* was noted.

No carcinogenicity study was conducted as per ICH guidelines. The chemical has not been shown to be a tumour initiator in photocarcinogenesis studies in mice. No genotoxic potential was observed. Quantitative Structure-Activity Relationship (QSAR) modelling gave an alert for potential non-genotoxic carcinogenicity, but no details are available (OECD QSAR Toolbox ver.3.2).

The SCC and NICNAS report stated that "*based on the available data, the chemical is not considered to be reproductively or developmentally toxic at doses relevant to human exposure*". A NOAEL of 450

mg/kg bw/day was established for fertility and reproduction parameters, and for systemic parental and developmental toxicity (Schneider *et al.* 2005).

A study (Axelstad *et al.* 2011) to investigate the effect of octinoxate treatment (500-1000 mg/kg/day, oral) on the endocrinological and neurological development of rat offspring indicated decreased motor activity in female offspring and increased spatial learning in male offspring (transient effects on thyroid axis, and in oestrogen level were also observed). The effects were observed at a much higher doses compared to clinical doses (Axelstad *et al.* 2011).

The value of 1.77 µg/cm$^2$ following 6-h pig-ear skin exposure + 18-h free permeation after an application of oil-in-water emulsion sunscreen dose (0.5 mg/cm$^2$) containing 10% octinoxate was used in the SED calculation in this review (Klimova *et al.* 2015).

The parameters used were:

- DA (µg/cm$^2$) = dermal absorption reported as amount/ cm$^2$: 1.77 µg/cm$^2$
- SSA (cm$^2$) = Skin surface area expected to be treated: 17500 cm$^2$ *
- F (day$^{-1}$) = frequency of application of the finished product: 2 *
- Body weight = default human body weight: 50 kg

(*) value comply with the SCCS 2016 (Appendix 5.3)

SED= 1.24 mg/kg/day

For the calculation of MoS the NOAEL that correspond to the worst-case scenario (rat, 13 week oral study), 450 mg/kg was selected.

**MoS = NOAEL/SED= 450/1.24= 363 ≥ 100.**

**Oxybenzone**

This review was based on peer-reviewed publications and the SCCS opinion on benzophenone-3 (2021c; SCCP, 2006a; SCCP, 2008).

Oxybenzone was shown to be rapidly absorbed after oral, intravenous, or topical skin administration and widely distributed in animals, 2,4-diOH BP (BP-1) was the major metabolite of oxybenzone in rats and humans. Oxybenzone was primarily excreted though urine.

A number of *in vitro* and *in vivo* dermal absorption studies have been evaluated by the SCCS. A dermal absorption value of 9.9% was used to calculate the MoS for oxybenzone. This value was calculated from a dermal absorption value of 3.1% obtained following application of a 6% formulation of oxybenzone to pig ear skin in *vitro* 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).

Clinical trials indicated that oxybenzone could be systemically absorbed. The plasma concentration of oxybenzone in sunscreens (spray) exceeded 0.5 ng/mL on single application and remained above this threshold until 23 hours after application. The systemic exposure of oxybenzone remained above 0.5 ng/mL in more than 50% of participants for up to 21 days. The authors concluded that the continued presence of sunscreen active ingredients in skin at days 21 and the long terminal half-life (> 48 hours) suggest absorption through skin is the rate-limiting step; hence, intravenous studies are required to determine their elimination rate constants.

Oxybenzone was found to be of low acute oral and dermal toxicity and did not cause skin or eye irritation (rabbits) or skin sensitisation (guinea pigs and mice). However, 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).

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Repeat-dose studies with oxybenzone were conducted in mice and rats following oral and dermal administration. After repeated oral administration of oxybenzone in rats and mice, decreased bodyweight gain and reduced food consumption were observed. Effects on the kidney (decreased weight and renal tubule histopathology) and the liver (increased weight and adaptive changes in histopathology) with associated changes in clinical chemistry parameters were also observed. There were no treatment-related findings following dermal administration except for increases in liver weight with no associated histopathology or clinical pathology. The NOAEL (oral) was established at 6250 ppm (429/393 mg/kg bw/day in males/females) in rats and 6250 ppm (1068/1425 mg/kg bw/day in males/females) in mice. The NOAEL for repeat-dose dermal toxicity was established at 200 mg/kg bw/day in rats and 364 mg/kg bw/day in mice. In reproductive and developmental toxicity studies in rats, decreased normalised anogenital distance was observed in male pups of treated dams, at PND 23. Impairment of spermatocyte development in testes of male offspring and delayed follicular development in females was also observed indicating a potential endocrine disrupting effect. A NOAEL for these effects was established at 67.9 mg/kg bw/day (Nakamura *et al.*, 2015).

The findings from the genotoxicity studies with oxybenzone were found to be equivocal. Two-year carcinogenicity studies with oxybenzone were performed in mice and rats. An increased incidence of brain and spinal cord malignant meningiomas in males and thyroid C-cell adenomas and uterine stromal polyps in females were observed in rats, with no dose-response relationship. These findings in rats were also considered to be equivocal evidence of carcinogenicity. There was no evidence of carcinogenic activity in male or female mice.

Public exposure to oxybenzone would be expected to be widespread and frequent through a daily use of sunscreen products containing oxybenzone typically at concentrations up to 10%. The SCCS (2021c) determined a dermal absorption of 9.9% [mean (3.1%) + 2 SD (2*3.4%)] for the use of oxybenzone as a UV filter, at an oxybenzone concentration 6% for the calculation of SED and the MoS for sunscreen products.

The MoS was calculated using an SED of 2.1 for whole body sunscreen exposure. This was calculated based on:

| | |
|---|---|
| A - Applied dose of sunscreen | = 18000 mg/day (whole body application) |
| C – concentration of product | = 6% |
| DA – dermal absorption | = 9.9% |
| BW – mean Australian adult bodyweight | = 50 kg |

Thus, the SED = A x C x DA x BW = 18000 x 0.06 x 0.099 / 50 = 2.1

The margin of safety (MoS) for oxybenzone through typical consumer use of sunscreen products was calculated using a NOAEL of 67.9 mg/kg bw/day derived from a pre- and post-natal developmental toxicity study in rats (Nakamura *et al.* 2015, detailed above) and an SED of 2.1. **The MoS was determined to be 32 (NOAEL/SED = 67.9/2.1 = 32).**

A similar MoS was determined in the study by Hojerova *et al.* (2017), for three realistic exposure scenarios. MoS of 48, 34 and 34 for oxybenzone in the sunscreen applied on the whole-body were calculated, indicating that there would be some concerns regarding the safety for consumers (MoS<100).

**Phenylbenzimidazole sulfonic acid**

The safety of phenylbenzimidazole sulfonic acid (PBSA) was assessed based on the publicly available safety data from scientific literature, and the SCCP opinion (SCCP, 2006b).

PBSA was rapidly absorbed following oral administration in pregnant rats. The amount of absorption from the gastrointestinal tract was estimated to be 3 – 4%. There was no indication of accumulation in any of the organs investigated and PBSA did not cross the blood/brain barrier. PBSA was mainly excreted though urine and faeces in male rats and via the faeces in pregnant female rats following oral administration. No data were available on the metabolism of PBSA.

PBSA was found to be of low acute toxicity in rats and mice (IP $LD_{50}$ 1000 – 1500 mg/kg/day and the dermal $LD_{50}$ is >3000 mg/kg bw in rats whereas oral $LD_{50}$ in mice is >5000 mg/kg bw). There was no information available for acute inhalational toxicity. PBSA was not a skin or eye irritant in rabbits and did not cause skin sensitisation in guinea pigs. The NOAEL in a 13-week oral study in rats was established at 1000 mg/kg/day, the highest dose tested.

PBSA was not found to be genotoxic *in vitro* (Ames test and chromosome aberration test in human peripheral blood lymphocytes). No information was available for mutagenicity/genotoxicity *in vivo*. No carcinogenicity data on PBSA were available.

No treatment-related findings were noted in a pre-natal developmental toxicity study in rats treated with PBSA from gestation day 6 to 15 at doses up to 1000 mg/kg/day. The NOAEL for maternal and fetal toxicity was 1000 mg/kg/day. PBSA did not cross the blood brain barrier or the placenta following oral administration in rats.

The potential systemic exposure and the MoS for typical consumer use of sunscreen products was calculated as follows (SCCP 2006b):

The margin of safety (MoS) was determined to be **267** (NOAEL/SED = 40/0.150 = 267) based on the following parameters:

| | |
|---|---|
| A - Maximum absorption through the skin (µg/cm²) | = 0.416 µg/cm²[Δ] |
| SAS – mean adult skin surface area (cm²) | = 17500 cm² * |
| Dermal absorption per treatment (SAS x A x 0.001) | = 7.488 mg |
| Australian body weight of an adult | = 50 kg |
| SED - Systemic exposure dose (SAS x A x 0.001/50) | = 0.150 mg/kg |
| NOAEL (from 90-day oral rat study) | = 40 mg/kg bw |

[Δ](SCCP, 2006b); (*) value comply with the SCCS 2016 (Appendix 5.3)

### 1.3. POTENTIAL ENDOCRINE DISRUPTION OF ACTIVE INGREDIENTS IN SUNSCREENS

In the light of the recent regulations in Europe, several studies have been conducted to investigate the endocrine disruption potential of most of these ingredients. Since the FDA released its draft proposal (FDA, 2019), several studies published in 2020 support previous findings that oxybenzone can act as an endocrine disruptor and may increase the risk of breast cancer and endometriosis (Kariagina 2020, Santamaria 2020).

s47C [redacted]

A systemic review on oxybenzone and octinoxate suggest that current evidence is not sufficient to support the causal relationship between the elevated systemic level of oxybenzone and octinoxate and adverse health outcomes (Suh 2020). There are either contradictory findings among different

studies or insufficient number of studies to corroborate the observed association. To accurately evaluate the long-term risk of exposure to oxybenzone and octinoxate from sunscreen, a well-designed longitudinal randomized controlled trial needs to be conducted.

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Most current SCCS opinions have evaluated the most current data on endocrine disruption potential for these ingredients.

For ethylhexyl triazone, the only information on reproductive toxicity or endocrine disrupting potential was from short SCCS opinion (Hojerová *et al.* 2017). Therefore, further information would be required for the endocrine disruption potential of ethylhexyl triazone. The available data (evaluated in SCCS opinions) on avobenzone, homosalate, octocrylene, octinoxate and oxybenzone indicate potential endocrine effects, however, they are not adequate to regard them as an endocrine disrupting ingredient, or to derive a toxicological point of departure based on endocrine disrupting properties for use in human health risk assessments.

### 1.4. SAFETY IN PAEDIATRIC POPULATION

No nonclinical information was available for the safety of these ingredients in the paediatric population. Compared to adults, the higher body surface area to volume ratio of children and the unique microstructure of immature skin suggest that children, especially infants, may absorb a greater fraction of topically applied ingredients (Stamatas *et al.* 2010). In addition, the capacity to metabolize and excrete absorbed ingredients by young children and infants may not be at the same level of maturity as in adults. Therefore, this puts them at risk of higher systemic levels and consequently, side effects and toxicities not seen in adults (Stamatas *et al.* 2010).

It is noted that the US EPA's exposure factors handbook incorporates child-specific information with regard to exposure assessment (OECD 2019, US EPA, 2011). Together with the US EPA's child-specific exposure scenarios examples (US EPA, 2014), the handbook offers general children's activity patterns and exposure factors from a number of published studies, along with approaches in order to address different exposure routes and dose estimates in some specific contexts (US EPA, 2011; US EPA, 2014). This needs further investigation.

## EVALUATION OF AVAILABLE INFORMATION

## 2. INTRODUCTION

### 2.1. BACKGROUND

The ARTG currently (Aug 2021) lists 31 active ingredients approved for use in sunscreens in Australia. The safety of these ingredients on the ARTG has been addressed by various means, including grandfathering; assessment of toxicological data; and by reference to overseas regulatory reports. The TGA has been monitoring the emerging scientific literature in this area and working cooperatively with international agencies to monitor these issues to ensure that appropriate action is undertaken if any unacceptable risks are identified.

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In 2019, the 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 which 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 an 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).

The FDA proposed rule also dictated that if an adequately conducted MUsT demonstrates a steady-state blood level of an ingredient under 0.5 ng/mL, and an adequately conducted toxicological study does not raise any other safety concerns, then studies on systemic carcinogenicity and developmental and reproductive toxicity may not be required. The 0.5 ng/mL limit was selected because it represents approximately the highest plasma concentration under which the risk of carcinogenicity of any unknown compound would be below 1/100,000 following a single dose (FDA, 2019c).

Given the greater use of sunscreens in Australia from a higher frequency of use and longer-term use by the population as whole, and the current interest by the US FDA in the ongoing safety of sunscreen active ingredients, the TGA has begun 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 12 organic filters categorised III (additional data needed) by the FDA proposed rule have been widely used in sunscreen products in Australia (Appendix 5.4). 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 Expert Panel, 2019) reached the conclusion that octisalate is safe as used in cosmetics in the present practices of use 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). The nonclinical data for octisalate was also submitted to the TGA for a safety assessment when used as an excipient in ELLAVIE™(an oestradiol transdermal spray for the treatment of moderate to severe vasomotor symptoms associated with menopause) at 8.5% (R10/104098). Hereby, the literature review was not conducted for octyl salicylate given the availability of a TGA nonclinical safety assessment report for this chemical.

Eventually, a literature review was conducted of 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 where safety data have not been available in the past to the TGA. These ingredients have been widely used in sunscreen products in Australia (Appendix 5.4). The review is intended to provide an overview of the publicly available safety information for these ingredients, to provide the calculation of the margin of Safety (MoS) and an input to the risk assessment.

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[redacted]

### 2.2. METHOD OF DATA SEARCH

The literature review was conducted using keywords like either the chemical name, AAN or the INCI names, and "sunscreen" as the search items. Publications in last ten years were searched (2008-2020). See the Appendix 5.1 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 SCC/SCCP) where available.[6]
- 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 disruptive properties of ingredients may give rise to a concern for human health. The evaluation of endocrine disruptive properties was described collectively. Of note, all articles dealing with environmental effects of the ingredients were excluded.

### 2.3. CHEMISTRY

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).

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

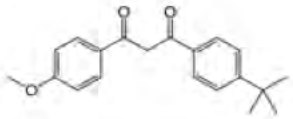
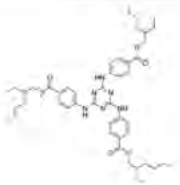
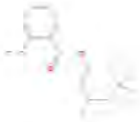
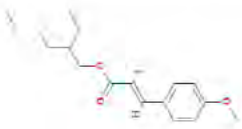
**Table 2-1 Chemical and Physical Properties of the active ingredients under review**

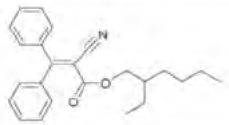
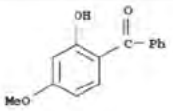
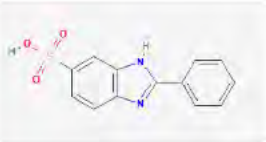
| Active ingredient (*absorption spectrum*) | CAS no. | Chemical name | Molecular formula | Physical properties | | | Other names |
|---|---|---|---|---|---|---|---|
| | | | | Water solubility | Mol. Weight g/mol | Log $P_{ow}$ | |
| Avobenzone (BMDM or BMDBM)<br>*UVA* | 70356-09-1 | 1,3-Propanedione, 1-[4-(1,1-dimethylethyl)phenyl]-3-(4-methoxyphenyl)- | $C_{20}H_{22}O_3$ | 0.01 mg/L | 310.4 | 4.5-6.1 | Butyl methoxydibenzoylmethane, Eusolex® 020, Parsol® 1789, 4-tert-butyl-4'methoxydibenzoyl methane, BMDBM |
| Ethylhexyl triazone (EHT)<br>*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 | 15.5 | Uvinul T150, (octyl triazone) |
| Homosalate<br>*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 | 4.7 | Benzoic Acid, 2-Hydroxy-, 3,3,5-Trimethylcyclohexyl Ester Cyclohexanol, 3,3,5-trimethyl-, salicylate.<br><br>Homomethyl salicylate<br><br>Salicylic acid, 3,3,5-trimethylcyclohexyl ester<br><br>Caswell No. 482B, Neo Heliopan® HMS, CCRIS 4885, Filtersol "A" |
| Octinoxate (OMC or EHMC)<br>*UVB* | 5466-77-3 | 2-Ethylhexyl 4-methoxycinnamate | $C_{18}H_{26}O_3$ | 0.1 g/100 mL at 27°C | 290.4 | 5.9 | EHMC or octyl-methoxycinnamate (OMC) |
| Octocrylene (OC)<br>*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 | 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) | 131-57-7 | 2-benzoyl-5-methoxyphenol; 4-Methoxy-2- | $C_{14}H_{12}O_3$ | 0.0037 g/L at 20°C | 228.3 | >3.7 | Benzophenone-3 |

| Active ingredient (*absorption spectrum*) | CAS no. | Chemical name | Molecular formula | Physical properties | | | Other names |
|---|---|---|---|---|---|---|---|
| | | | | Water solubility | Mol. Weight g/mol | Log $P_{ow}$ | |
| *UVB* | | hydroxybenzophenone | | | | | |
| Phenylbenzimidazole sulfonic acid (PBSA)<br><br>*UVB* | 27503-81-7 | 2-Phenylbenzimidazole-5-sulfonic acid | $C_{13}H_{10}N_2O_3S$ | > 30% | 274.3 | -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 2-2 Molecular structure of the active ingredients under review**

| Active ingredient | Structure |
|---|---|
| Avobenzone |  |
| Ethylhexyl triazone |  |
| Homosalate |  |
| Octinoxate |  |

| Active ingredient | Structure |
|---|---|
| Octocrylene |  |
| Oxybenzone |  |
| Phenylbenzimidazole sulfonic acid |  |

### 2.4. USE

Typically, 2 mg/cm² of sunscreen is recommended to use. The dosage used during the determination of the SPF value corresponding to the application of 6 teaspoons of a lotion (approx. 36 g) for the whole body of an average adult person (EC, 2006; FDA, 2016; TGA, 2016).

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The following ingredients are currently approved in Australia for use as active ingredients in sunscreens for dermal application (see the table below), not to be used in topical products for eyes, with appropriate safety warnings in the labelling (TGA, 2020). It is noted that the FDA regulates sunscreens as over the counter (OTC) drugs rather than as cosmetics whereas it is regulated as cosmetics in EU.

| Active ingredient | Maximum % approved | | | | |
|---|---|---|---|---|---|
| | Australia | EU | USA | Canada | Japan |
| Avobenzone | 5 | 5 | 3 | 3 | 10 |
| Ethylhexyl triazone † | 5 | 5 | Not approved | Not approved | 5 |
| Homosalate | 15 | 10 | 15 | 15 | 10 |
| Octinoxate* | 10 | 10 | 7.5 | | 10 |
| Octocrylene** | 10 | 10 | 10 | | Not approved |
| Oxybenzone*,Δ | 10 | 6 | 6 | 6 | |
| Phenylbenzimidazole sulfonic acid γ | 4 | 8 | NA | | |

* In the USA, Hawaii became the first state to pass the law banning sales of sunscreens containing oxybenzone and octinoxate from January 2021;
**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);
†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).

## 3. PHARMACOKINETICS

The main safety concerns for these active ingredients arise from the knowledge gap around the toxicokinetic data/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 is noted. In the absence of adequate or reliable dermal absorption data, a 10% dermal absorption was assumed for SED calculation in the worst-case scenario and MoS value was estimated according to guidelines applicable for the European Union (SCCS 2016). Please note, although dermal data is expected to reflect real time exposure and toxicity following application of sunscreens, in the absence of dermal toxicity data, oral toxicity data were considered in the MoS determination using a conservative approach given oral toxicity data may reflect systematic toxicity in worst case scenario.

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The dermal absorption value used in the recent SCCS opinions for the relevant active ingredients were used in the estimation of SED, followed by MoS determination in this review.

### 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), in the 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), there was no indication of systemic bioavailability following dermal exposure.

- *In vitro* studies with isolated pig skin using $^{14}$C-labelled BMBDM 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 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 indicates a very low level of systemic penetration of BMDBM 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.[7] 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

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

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 human (See Section 2.1).

**In the absence of further kinetic data for avobenzone, 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 for Systemic Exposure Dose (SED) calculation in the worst-case scenario.**

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**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.

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% similar to the recovery (85- 115%) allowed by the SCCS (2016). The SED after the sunscreen application at 1 mg/cm² for 6 h (i) on the face; (ii) on the 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.

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 10% dermal absorption was assumed for SED calculation in the worst-case scenario and MoS value was estimated according to guidelines (SCCS 2016).

**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 in 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 Section 2.1). 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 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*.

The SCCS report stated that a conclusion on the dermal absorption percentage could not be drawn from the human studies. Therefore, the risk assessment takes account of the dermal absorption value from the skin penetration study using human skin described in the SCCS report (SCCS, 2020). The maximal absorption value observed in the donor with highest absorption values (2%) was used in the MoS calculation in the SCCS report (2020).[8] Identical value was taken for the MoS calculation in this review.

**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 ($4*10^{\wedge-7}$ Pa at 20°C) (ECHA, 2020b).

Octocrylene has been found to induce xenobiotic-metabolising enzymes based on mechanistic studies, oral repeated dose 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 was 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.

[8] June 2021 SCCS opinion for homosalate uses a different dermal absorption value for 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) and a standard sunscreen formulation containing 10% homosalate. This gives even a lower MoS for homosalate for a 60 kg human.

**Table 3-1 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 8-10% octocrylene 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 dermatomed human skin (344 ± 61 µm) in static diffusion cells at a dose of 3 mg/cm² 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 medium. After 24 hours of dosing, octocrylene bioavailability (epidermis, dermis and receptor medium) 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/cm²) 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 medium 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 medium) 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 low dermal absorption rate (≤ 0.25%).

A recent *in vitro* study (Fabian & Landsiedel 2020) with a formulation (10% octocrylene) applied at a dose of 3 mg formulation/cm² on dermatomed 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/cm² (~ 0.15% of the applied dose) consistent with previous findings. The dermal absorption of 0.97 µg/cm² (Fabian & Landsiedel 2020) was considered a worst-case scenario and was used in the calculation of SED followed by MoS determination in the SCCS (2021a). This value was also used in the SED and MoS calculation in this report given it is from the most recent study providing human dermal absorption value.

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**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, showing that measuring octinoxate alone could not comprehensively evaluate the human exposure to octinoxate.

Dermal penetration was observed to be dependent on the vehicles, 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/cm²·h (Touitou & Godin, 2008). An accumulation of ~9% of octinoxate in epidermis and ~2-3% in dermis were observed following application of 2mg/cm² and 0.5 mg/cm² 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/cm² after 6-h exposure to the epidermis of frozen-stored skin was 4.8± 0.7 µg/cm², dermis 1.2 ± 0.1 µg/cm² and undetectable in receptor fluid, whereas 3.4 ± 0.6 µg/cm² , 2.1 ± 0.4 µg/cm² and 0.9 ± 0.1 µg/cm² 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 hs (in contrast of classic studies of long skin exposure), a more realistic dose of sunscreen was used (0.5 mg/cm²). Considering that some chemical substances , instead of passing entirely through the skin, can remain partly in the skin and being release in the later time, the dermal absorption was evaluated at the end of the exposure period immediately after washing off a sunscreen) and following next 18-h permeation.

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The dermal absorption was obtained by the sum of the filter absorbed in the dermis and the RF (which was considered systematically available), corrected by the fresh/frozen –stored skin permeability coefficient. **The dermal absorption value of 1.77 µg/cm² following 6-h skin exposure + 18-h free permeation after an application of oil-in-water emulsion containing 10% octinoxate was used in the SED calculation in this review.** 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 depends on both lipid lipophilicity and structure and on 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/cm² of cream formulation

with 10% octinoxate. Octinoxate was also detected in urine (5 and 8 ng/mL in female and male 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 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, **the dermal absorption of 1.77 µg/cm$^2$ was considered a worst-case scenario and was used in the calculation of SED (**Klimova *et al.* 2015).

**OXYBENZONE**

Oxybenzone is expected to be rapidly absorbed after oral, intravenous, or topical skin administration 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.

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).

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 in piglets, the elimination half-lives of oxybenzone was approximately 7.14 and 8.04 h (SCCS 2021c).

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%, with this value used to determine MoS for oxybenzone. 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 to calculate the MoS for oxybenzone in the absence of adequately 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 $at_{½}$ 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 (2006) to determine the margin of safety for PBSA (SCCP, 2006b).

### 3.1. CLINICAL TRIALS

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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[9]), 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).

Similar findings were observed in a follow up study with six active ingredients (avobenzone, oxybenzone, octocrylene, homosalate, octisalate[10], 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 - 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 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).

[9] 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.

[10] 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 3-2). 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 3-2 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

## 4. 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 are therefore reliant on the accuracy of various published safety assessment reviews (reviews by SCCS/SCC/SCCP, NICNAS, ECHA etc. see in bibliography, p 57).

### 4.1. ACUTE TOXICITY

Avobenzone, eithylhexyl triazone, homosalate, oxybenzone, octocrylene, PBSA and octinoxate displayted 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 4-1. Summary of acute toxicity studies for sunscreen ingredients**

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

### 4.2. 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 4-2. Summary of skin and eye irritation studies for sunscreen ingredients**

| Study | Avobenzone (ECHA (2021a; DEPA 2015) | Ethylhexyl triazone (ECHA (2021b; DEPA 2015 | Homosalate (SCCS 2021; 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) |

### 4.3. SENSITISATION

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None of the ingredients examined were skin sensitisers in *in vivo* studies in animals (see below).

**Table 4-3. Summary of skin sensitisation studies for sunscreen ingredients**

| Avobenzone (ECHA 2021a; DEPA 2015) | Ethylhexyl triazone (ECHA (2021b; DEPA 2015 | Homosalate (SCCS 2021; 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)<br>Not sensitizing (at 15%, HRIPT) | Not sensitizing (GPMT) | Not sensitizing (GPMT)<br>Moderate sensitising in a LLNA (not properly conducted) | Not sensitizing (GPMT)<br>Not sensitising (LLNA) | Not sensitizing (GPMT) |

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

### 4.4. REPEAT DOSE TOXICITY

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

**Table 4-4. Repeat-dose toxicity studies for sunscreen ingredients**

| Active ingredient | Study details[Δ] | 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.<br>No effect on the body weight and food consumption.<br>↓ RBC in ♀ rats at 1000 mg/kg bw/day.<br>No findings in eyes. No treatment-related necropsy findings.<br>Treatment-related ↑ liver weights at 1000 mg/kg bw/day in ♂ and at 200, 450, and 1000 mg/kg bw/day in ♀ |

| Active ingredient | Study details[Δ] | Major findings |
|---|---|---|
| | | compared to control. All effects were fully reversed after a treatment-free period of 4 weeks.<br>Hypertrophic hepatic parenchyma cells in ♀ at 1000 mg/kg bw/day.<br>**NOAEL: 450 mg/kg bw/day**<br>*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.<br>↑ dose dependent severe dermal reactions ≥ 30 mg/kg/day, more persistent at 100 mg/kg bw/day.<br>↑ Incidence of epidermal thickening in both vehicle control and treatment groups compared to the untreated control group.<br>NOAEL: 360 mg/kg bw/day (based on systemic effects).<br>LOAEL: 30 mg/kg/bw/day (dermal) |
| Octocrylene (ECHA 2021d, SCCS 2021a) | Rats (Wistar), $n$ = 10/sex/dose<br>0, 58, 175, 340 and 1085 mg/kg bw/day (diet), 13 weeks<br><br>Study BASF 50S0227/92059 | No treatment-related mortality.<br>No treatment-related clinical signs.<br>Body weight gain: ↓ at HD in both sexes along with decreased food consumption<br>Haematology: RBC affected (↓MCV, ↓MCH, ↓MCHC) at HD in both sexes<br>Organ weights (bodyweight-relative): ↑ absolute and relative weight of liver at 340 and 1085 mg/kg bw/day<br>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<br>NOAEL: 175 mg/kg bw/day |
| | Rabbits (NZW), $n$ = 5/sex/dose<br>0, 130, 264, 534 mg/kg bw/day (dermal)<br>5 days/week; 13 weeks<br><br>(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.<br>No evidence for haematological or macroscopic and histopathological abnormalities<br>No effects were reported on testicular and epididymal morphology as well as on sperm count and motility<br>NOAEL: 534 mg/kg bw/day (systemic toxicity)<br>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<br><br>Rats (Wistar), $n$ = 5/sex/dose<br>72, 215, 720 mg/kg bw/day PO (Subset A)<br>63, 188, 630 mg/kg bw/day PO (Subset B)<br><br>28 days (Subset A)<br>14 days (Subset B) | No treatment-related mortality<br>No treatment-related clinical signs.<br>Body weight gain: ↓ at HD in both subsets<br>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<br>Organ weights (bodyweight-relative): ↑ absolute and relative weight of liver at high doses in both sexes in both subsets<br>Histopathology: minimal follicular cell hypertrophy/hyperplasia of the thyroid gland at high doses in both sexes in both subsets<br>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.<br>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.<br>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<br>↑ (non-significant) serum alanine phosphatase (SAP) levels and ↑ relative liver weight at HD. Liver effects were not observable upon microscopic examination.<br>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.<br>Dose dependent low-grade epidermal proliferation at all doses (more prominent in ♂).<br>The chemical was considered as a low-grade irritant under the conditions of this study (OECD TG 410)<br>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<br>Lethargy, hunched posture, hair loss, soiled coats, emaciation, increased respiration, swelling of the conjunctivae, and reproductive effects (retardation of testicular growth) at HD.<br>Haematological changes including ↑ neutrophils and urea nitrogen, and ↓ lymphocytes and alkaline phosphatase activity at HD.<br>Dermal irritation effects (erythema, oedema, desquamation, cracking and atonia) were observed at all doses but were more severe at the HD.<br>Histopathology of the skin sites showed an epidermal proliferative response with low grade inflammatory reaction (dose dependent).<br>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.<br>↑ Liver-weight without histological correlates among treated female animals could not be interpreted as being treatment-related<br>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<br>No treatment-related effects on organs<br>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<br>Bodyweight gain: ↓ in ♂at HD.<br>Organ weight: ↑ liver weights (♂ & ♀) from LD, associated histopathology observed at 2041 mg/kg bw/day; ↓ kidney weight in ♂ from 8648 mg/kg bw/day.<br>NOAEL: 992 (♂)/1050 (♀) mg/kg/day |
| | Mice (B6C3F1; *n* = 10/sex), doses: 0, 0, 3125, 6250, 12500, 25000, 50000 ppm (equivalent to 554, | Mortality: none |

| Active ingredient | Study details[Δ] | Major findings |
|---|---|---|
| | 1246, 2860, 6780, 16238 mg/kg bw/day), 90 days (diet) | Bodyweight: ↓ BW gain in ♂ & ♀ from 6780 mg/kg bw/day<br>Organ weights: ↑ liver weight from 1246 mg/kg bw/day with histopathology from 6780 mg/kg bw/day. Renal histopathology at HD in ♂.<br>Reproductive parameters: ↓ sperm density and ↑ abnormal sperm in ♂ and ↑ oestrus cycle length in ♀ at HD<br>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<br>Bodyweight gain: ↓ in ♂at HD.<br>Organ weight: ↑ liver (♂ & ♀) and kidney (♂) weights from LD, associated histopathology observed at 576 mg/kg bw/day in liver and at HD in kidney .<br>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.<br>Clinical signs: coloured urine from LD.<br>Bodyweights: ↓ BW gain in ♂ & ♀ from 1702 mg/kg bw/day.<br>Clinical pathology: serum protein levels from 411 mg/kg bw/day, ↑ platelet counts from 1702 mg/kg bw/day<br>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.<br>Reproductive parameters: ↓ sperm motility in ♂ and ↑ oestrus cycle length in ♀ at HD.<br>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<br>Organ weights: ↑ liver weight from 196 mg/kg bw/day.<br>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.<br>Organ weights: ↑ kidney weight in ♂ at all doses<br>Reproductive parameters: ↓ epididymal sperm density in ♂ at all doses.<br>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<br>Organ weights: ↑ liver weight in ♀ from 27.7 mg/kg bw/day, ↑ kidney weight in ♀ at HD<br>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).<br>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.<br>Clinical pathology: ↓ reticulocyte counts from LD, ↑ platelet counts from 50 mg/kg bw/day, ↑ whole blood cell count produced by lymphocytosis at HD.<br>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.<br>NOAEL: 1000 mg/kg bw/day |

| Active ingredient | Study details[Δ] | Major findings |
|---|---|---|
| Homosalate (SCCS 2021; ECHA 2021c) | Rats, n=5/sex/dose, 0, 100, 300, 1000 mg/kg bw/day, 2 weeks (gavage) | Mortality: none<br>Clinical signs: none treatment related<br>Body weight gain: ↓ at HD in ♂ along with decreased food consumption<br>Haematology: none treatment related<br>Serum chemistry: ↑ Triglycerides in both sexes at HD<br>↑APTT in ♂ at MD<br>NOAEL: > 300 mg/kg bw/day ♂<br>NOAEL: >1000 mg/kg bw/day ♀ |
| | Repeat dose/ reproduction/ developments study<br><br>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<br>*Clinical signs:* none treatment-related<br>*Body weight gain:* ↓ at 750 mg/kg bw/day in ♂ and ♀<br>*Haematology:* none treatment-related<br>*Serum chemistry:* ↑ Albumin and ↓ Globulin in ♂ at 300 mg/kg bw/day<br>*Urinalysis:* not conducted<br>*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.<br>*Gross pathology:* no treatment-related findings<br>*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). *<br>Minimal/mild hypertrophy of hepatocytes (1/5 ♂) at 120 mg/kg bw/day, and almost every ♂ and ♀ from 300 mg/kg bw/day.<br>Hypertrophy of the follicular epithelium of thyroid gland in ♂ at 750 mg/kg bw/day and in ♀ from 300 mg/kg bw/day.<br>↓ Cortical lymphocytes in males from 300 mg/kg bw/day and in ♀ at 750 mg/kg bw/day<br>*NOAEL:* ** mg/kg bw/day<br>*The REACH registrants considered this as manifestations of hyaline droplet nephropathy without giving further evidence.<br>**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

### 4.5. 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 4-5. Summary of genotoxicity studies with sunscreen ingredients**

| Avobenzone (ECHA (2021a; DEPA 2015) | Ethylhexyl triazone (ECHA (2021b; DEPA 2015 | Homosalate (SCCS 2021; ECHA 2021c) | Octinoxate (ECHA 2021e) | Octocrylene (SCCS, 2021a; ECHA 2021d) | Oxybenzone (SCCP 2006a; 2021c) | PBSA (SCCP 2006b) |
|---|---|---|---|---|---|---|
| In vitro<br>Negative<br>AMES test and gene mutation study V79 Chinese hamster cells<br><br>In vivo<br>Negative<br>Bone marrow polychromatic erythrocytes (mice) | In vitro<br>Negative<br>AMES test, Chinese hamster lung fibroblasts for chromosome aberration, Chinese hamster ovary (CHO) cells, in vivo chromosome aberration test | In vitro<br>Negative<br>AMES test and gene mutation study in V79 Chinese hamster cells<br><br>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<br>Negative<br>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)<br><br>In vivo<br>Negative<br>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<br>Negative<br>AMES test, gene mutation test, cytogenicity test in mammalian cells, chromosome aberrations tests<br><br>In vivo<br>Negative<br>Cytogenicity test in mice<br>ECHA 2020, SCCS 2021 | In vitro<br>Negative<br>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<br><br>In vivo<br>Negative<br>micronucleus test (mice), chromosome aberration test (rats), Drosophila (SMART)† | In vitro<br>Negative<br>AMES test and chromosome aberration test in human peripheral blood lymphocytes<br><br>In vivo<br>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.

### 4.6. CARCINOGENICITY

A summary of carcinogenicity studies for each sunscreen ingredient is shown in the table below. No carcinogenicity data is available for avobenzone, octinoxate, octocrylene, ethyl hexyl triazone, 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).

**Table 4-6. Summary of carcinogenicity studies with sunscreen ingredients**

| Active ingredient | Study details | Major findings |
|---|---|---|
| Avobenzone | – | No data |
| Octinoxate | – | No data |
| Octocrylene | – | No data |
| Ethyl hexyl triazone | – | No data |
| Homosalate | – | 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 ♂/♀)<br><br>Rats (SD; *n*=10/sex/group), 0, 1000, 3000, 10000 ppm (equivalent to 58/60, 168/180, 585/632 mg/kg bw/day in ♂/♀)<br>Two years (beginning on GD6 in ♀) | Mice: ↑ lesions in the bone marrow, spleen, and kidney of both sexes and in the liver in ♂<br><br>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.<br>These findings are considered equivocal evidence of carcinogenicity. |
| PBSA | – | No data |

### 4.7. REPRODUCTIVE AND DEVELOPMENTAL STUDIES

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

**Table 4-7. 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.<br>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.<br>↓ 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.<br>In the offspring, ↓ lactation weight gain and organ weights, and slightly delayed sexual maturation (vaginal opening and preputial separation) at HD.<br>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.<br>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. |
| Octocrylene (SCCS, 2021a; ECHA 2021d) | Extended one generation reproductive toxicity study (EOGRTS), GLP<br>Rat (Wistar); Dose: (diets) 55, 153, 534 mg/kg bw/day ♂<br>58, 163, 550 mg/kg bw/day ♀<br><br>*n*= 27 or 28 /sex /dose<br>F1: Cohort 1A: 19/sex/ dose<br>Cohort 1B: 25/sex/dose<br>Cohort 2A: 10/sex/ dose<br>Cohort 2B: 10/sex/dose<br><br>♂: 10-week premating period, during mating up to the day of sacrifice (~ 13 weeks)<br>♀: P: 10-week premating period, termination on LD 21<br>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)<br>F2: until weaning (indirectly)<br>(ECHA, 2021d; SCCS, 2021a) | ↓ number of implantation sites and consequently a lower number of pups at HD<br>↓ bodyweight of pups at HD<br>No effects on male fertility and male and female reproductive parameters such as oestrus cycle, epididymal and testicular sperm parameters at all doses.<br>No effects on sexual and neurodevelopmental parameters in pups.<br>Based on effects on parental and pup body weights, a lower number of implantation sites and lower number of pups delivered.<br>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<br>GD6–GD15; termination on GD21 | F0:<br>Transient salivation at HD.<br>↑ relative liver weight at MD and HD<br>F1:<br>No treatment related effects.<br>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<br>Odio *et al.* (1994) | No treatment related adverse effects.<br>NOEL: 1000 mg/kg bw/day (mice) |

| Active ingredient | Study details | Major findings |
|---|---|---|
| | Rabbit (NZW): $n$ = 17 ♀/dose<br>Dose: 0, 65, 267 mg/kg bw/day, (Dermal, open, clipped area on the back), dosing GD6–GD18; termination on GD21<br>Odio *et al.* (1994) | No treatment related adverse effects.<br>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.<br>Maternal NOAEL = 1000 mg/kg bw/day;<br>Developmental NOAEL = 1000 mg/kg bw/day |
| Homosalate (SCCS 2021; 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).<br>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):<br>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.<br>↓ 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).<br>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;<br>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.<br>In mice, there were no effects on reproductive organ weight, cauda epidiymal sperm concentration, sperm parameters, testicular spermatid concentration or testicular histology.<br>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 was 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 |

| Active ingredient | Study details | Major findings |
|---|---|---|
| | | 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 dDecrease 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 207.167.9 mg/kg bw/day. |
| 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-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 rise concerns about potential prenatal exposure and developmental toxicity of UV filters.

### 4.8. ENDOCRINE DISRUPTION

Endocrine-disrupting chemicals (EDCs) are exogenous chemicals that interfere with hormone action, thereby 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[11] 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*

[11] EHT was included in these 14 ingredients

> *in-group E[12] 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 disruptors 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 disrupting 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".*

s47C [redacted]

In the light of increased safety concerns regarding the ED 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 ED 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 EDCs based on hormone actions and EDC 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).

[12] Homosalate and avobenzone were included

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 has 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 evidences 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)[13] and to act as an antagonist of androgen receptor (AR)(CASE Ultra and Leadscope).[13]

The SCCS (2020) conclusion was based on a Risk Management Options Analysis (RMOA) 2016 by ANSES[14]. 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*

[13] 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.
[14] French Agency for Food, Environmental and Occupational Health & Safety (ANSES)

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

The SCCS opinion also recommended that homosalate be permitted as an ingredient in cosmetics at no more than 1.4%, due to concerns that it behaves as an endocrine disrupter (SCCS, 2020).

s47C

[redacted]

**Octocrylene**

The endocrine disruption 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 disruption 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 feedbacks.

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. Currently a public call by the European Commission for data on the ED potential of octinoxate is in place (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.

s47C

[redacted]

### 4.9. OTHER STUDIES

The photo-allergic potential of avobenzone has been extensively reviewed in several publications (Nash & 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 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 Draize repeated insult patch test was carried out at a concentration of 2% 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 newly proposed mechanistic *in vitro* test for the discrimination of the photo-allergic and photo-irritants. Oxybenzone revealed no phototoxic and no photo-allergic potential (SCCP 2006a).

10% ethylhexyl triazone 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%) were 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 & 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 & 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 & 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 given below. However, this is not reviewed in this discuss elaborately as similar mechanisms apply on endocrine disruption potential of these ingredients (Ruszkiewcz *et al.,* 2017).

| 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. |
| Benzophenone-3 or oxybenzone | Danio rerio | 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. |
| | Sprague-Dawley rats | Dermal application; 30 days; 5 mg/kg/day | No changes in behavioural tests (locomotor and motor co-ordination). |
| | Rat primary cortical astorcytes and neurones | 1–7 days; 1–10 µg/mL | Decreased cell viability of neurons but not of astrocytes. |
| | SH-SY5Y neuroblastoma cell line | 72 h; $10^{-8}$–$10^{-4}$M | Decreased cell viability and increased caspase-3 activity. |
| Octocyrylene | Danio rerio | Waterborne; 14 days; 22–383 µg/L | Impaired expression of genes related with development and metabolism in the brain. |

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.

# 5. APPENDIX

## 5.1. SEARCH STRATEGY

### *Search criteria (word input)*

Keywords included either the chemical name, AAN or the INCI names, and "sunscreen" were used as the search items. Publications in last ten years were searched (2008-2020). 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
- Coslng 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/

***Example of the search strategy for avobenzone***

Search for: remove duplicates from 141 [67 or 140], results: 163

| Embase, Ovid MEDLINE(R) | | | |
|---|---|---|---|
| **#** | **Search Statement** | **Results** | **Annotation** |
| 1 | exp avobenzone/ or Avobenzone.mp. | 914 | |
| 2 | 70356-09-1.rn. | 629 | |
| 3 | Butyl methoxydibenzoylmethane.mp. | 189 | |
| 4 | Butyl methoxy dibenzoylmethane.mp. | 19 | |
| 5 | 4-tert-butyl-4-methoxy dibenzoylmethane.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy] | 14 | |
| 6 | Avobenzona.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy] | 3 | |
| 7 | Avobenzonum.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy] | 0 | |
| 8 | 1 or 2 or 3 or 4 or 5 or 6 or 7 | 995 | |
| 9 | exp drug carcinogenicity/ | 835 | |
| 10 | exp carcinogenicity/ | 31868 | |
| 11 | exp carcinogen/ | 148982 | |

| | | | |
|---|---|---|---|
| 12 | exp Carcinogens/ | 286093 | |
| 13 | exp Carcinogenicity Tests/ | 6877 | |
| 14 | exp Mutagens/ | 108755 | |
| 15 | exp mutagenicity tests/ | 60479 | |
| 16 | exp genotoxicity/ | 33452 | |
| 17 | exp Neoplasms/ | 7761161 | |
| 18 | ((Dermal or systemic) adj2 carcinog*).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 411 | |
| 19 | Carcinog*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 539368 | |
| 20 | 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 | 8168404 | |
| 21 | 8 and 20 | 176 | |
| 22 | limit 21 to yr="2010 -Current" | 83 | |
| 23 | limit 22 to animals | 7 | |
| 24 | limit 22 to animal studies [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained] | 16 | |
| 25 | ("in vitro" or "cell cultur*" or "tissue cultur*").mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 4180142 | |
| 26 | 22 and 25 | 15 | |
| 27 | 23 or 24 or 26 | 25 | |
| 28 | remove duplicates from 27 | 22 | Carcinogenicity |
| 29 | exp drug toxicity/ | 242986 | |
| 30 | exp reproductive toxicity/ | 11312 | |
| 31 | exp toxicity/ | 680419 | |
| 32 | exp toxicity testing/ | 45674 | |
| 33 | exp acute toxicity/ | 20152 | |
| 34 | exp developmental toxicity/ | 3060 | |
| 35 | exp Toxicity Tests/ | 157598 | |
| 36 | exp Toxicology/ | 84344 | |
| 37 | exp teratogens/ | 56503 | |
| 38 | exp teratogen/ | 28428 | |
| 39 | exp teratogenesis/ | 11684 | |
| 40 | exp teratogenicity/ | 17251 | |
| 41 | ((Development* or reproduct*) adj3 toxic*).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 36335 | |
| 42 | 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 | 1069060 | |
| 43 | 8 and 42 | 108 | |
| 44 | limit 43 to yr="2010 -Current" | 47 | |
| 45 | limit 44 to animals | 7 | |
| 46 | limit 44 to animal studies [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained] | 11 | |
| 47 | 25 and 44 | 16 | |

| | | | |
|---|---|---|---|
| 48 | 45 or 46 or 47 | 23 | |
| 49 | remove duplicates from 48 | 21 | Toxicity |
| 50 | exp toxicokinetics/ | 12513 | |
| 51 | Toxicokinetic*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 18322 | |
| 52 | 50 or 51 | 18322 | |
| 53 | 8 and 52 | 1 | toxicokinetics |
| 54 | exp endocrine function/ | 484253 | |
| 55 | exp endocrine disease/ | 2973497 | |
| 56 | exp endocrine system/ | 1216506 | |
| 57 | exp Endocrine Disruptors/ | 16224 | |
| 58 | (("long term" or endocrin*) adj3 effect*).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 195242 | |
| 59 | 54 or 55 or 56 or 57 or 58 | 4241536 | |
| 60 | 8 and 59 | 34 | |
| 61 | limit 60 to animals | 4 | |
| 62 | limit 60 to animal studies [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained] | 8 | |
| 63 | 60 and 25 | 11 | |
| 64 | 61 or 62 or 63 | 15 | |
| 65 | remove duplicates from 64 | 11 | endocrine effects |
| 66 | 28 or 49 or 53 or 65 | 48 | |
| 67 | remove duplicates from 66 | 47 | non clinical combined |
| 68 | exp contact dermatitis/ | 53966 | |
| 69 | exp skin allergy/ | 20467 | |
| 70 | exp skin toxicity/ | 22884 | |
| 71 | exp skin irritation/ | 13378 | |
| 72 | exp skin sensitization/ | 5437 | |
| 73 | exp sensitization/ | 71113 | |
| 74 | exp photodermatosis/ | 9330 | |
| 75 | exp application site reaction/ | 4811 | |
| 76 | exp application site inflammation/ | 89 | |
| 77 | exp Skin Irritancy Tests/ | 46387 | |
| 78 | exp Skin Tests/ | 132447 | |
| 79 | exp skin pruritus/ | 3400 | |
| 80 | exp pruritus/ | 105892 | |
| 81 | exp allergic rash/ | 305 | |
| 82 | exp contact allergy/ | 8227 | |
| 83 | exp contact dermatitis/ | 53966 | |
| 84 | exp drug hypersensitivity/ | 102543 | |
| 85 | exp allergy/ | 413969 | |

| | | | |
|---|---|---|---|
| 86 | exp Hypersensitivity/ | 943748 | |
| 87 | exp Allergens/ | 110041 | |
| 88 | ((dermal or skin) adj3 (sensiti* or irritat*)).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 38460 | |
| 89 | 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 | 1247473 | |
| 90 | 8 and 89 | 296 | |
| 91 | limit 90 to human | 255 | |
| 92 | limit 91 to yr="2010 -Current" | 110 | |
| 93 | limit 92 to english language | 108 | |
| 94 | limit 93 to (conference abstract or conference paper or "conference review" or editorial or letter or note) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained] | 21 | |
| 95 | 93 not 94 | 87 | skin irritation |
| 96 | exp phototoxicity/ | 8810 | |
| 97 | exp photoallergy/ | 2680 | |
| 98 | (phototox* or photoalle*).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 18852 | |
| 99 | 96 or 97 or 98 | 18852 | |
| 100 | 8 and 99 | 163 | |
| 101 | limit 100 to english language | 148 | |
| 102 | limit 101 to human | 122 | |
| 103 | limit 102 to yr="2010 -Current" | 55 | |
| 104 | limit 103 to (conference abstract or conference paper or "conference review" or editorial or letter or note) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained] | 8 | |
| 105 | 103 not 104 | 47 | |
| 106 | remove duplicates from 105 | 39 | phototoxicity |
| 107 | exp drug bioavailability/ | 65733 | |
| 108 | exp bioavailability/ | 153820 | |
| 109 | exp drug absorption/ | 82919 | |
| 110 | exp pharmacokinetics/ | 1036741 | |
| 111 | exp Skin Absorption/ | 18649 | |
| 112 | exp Biological Availability/ | 153820 | |
| 113 | exp Absorption, Physiological/ | 133321 | |
| 114 | (absorp* or absorb*).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 1037779 | |
| 115 | (penetration or penetrate or permeability).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 555651 | |
| 116 | (penetration or penetrate or permeability).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 555651 | |
| 117 | bioavail*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 227239 | |
| 118 | 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 | 2405762 | |

| | | | |
|---|---|---|---|
| 119 | 8 and 118 | 390 | |
| 120 | 107 or 108 or 109 or 111 or 112 or 113 or 117 | 429161 | |
| 121 | 8 and 120 | 148 | |
| 122 | limit 121 to english language | 141 | |
| 123 | limit 122 to human | 86 | |
| 124 | limit 123 to yr="2010 -Current" | 45 | |
| 125 | limit 119 to english language | 376 | |
| 126 | limit 125 to human | 207 | |
| 127 | limit 126 to yr="2010 -Current" | 106 | |
| 128 | limit 127 to (conference abstract or conference paper or "conference review" or editorial or letter or note) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained] | 15 | |
| 129 | 127 not 128 | 91 | |
| 130 | remove duplicates from 129 | 72 | bioavailability absorption |
| 131 | (safe or safety or "side effect" or "side effects" or adverse).mp. or exp adverse drug reaction/ or exp drug-related side effects/ or exp drug safety/ or toxic*.mp. or hazard*.mp. | 8304938 | |
| 132 | 8 and 131 | 406 | |
| 133 | limit 132 to english language | 389 | |
| 134 | limit 133 to human | 281 | |
| 135 | limit 134 to yr="2010 -Current" | 130 | |
| 136 | limit 135 to (conference abstract or conference paper or "conference review" or editorial or letter or note) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained] | 14 | |
| 137 | 135 not 136 | 116 | |
| 138 | remove duplicates from 137 | 91 | general safety |
| 139 | 95 or 106 or 130 or 138 | 153 | |
| 140 | remove duplicates from 139 | 139 | clinical search |
| 141 | 67 or 140 | 173 | |
| 142 | remove duplicates from 141 | 163 | **Final clinical and non-clinical combined** |

## 5.2. TABLE 2: LISTING ENDOCRINE DISRUPTING EFFECTS OF COMMONLY USED UV FILTERS

Table 2

Endocrine disrupting effects of the 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 minnows; Reduce of the uterine weight in immature Long-Evans rats |
| | Androgenic disrupting effects | Antagonists of human AR transactivation; Repression of 4,5-dihydrotestosterone-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; Induction of proliferation of MCF-7 cell; Induction of pS2 protein in MCF-7 cells; Reduce of the uterine weight in rats; Induction of VTG in fish |
| | 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 progesterone 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; Reduce of the uterine weight in rats; Induction of VTG in fish |
| | Disrupting effects toward thyroid hormone receptor | Decrease of T4 level; 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; Reduce of the 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

### 5.3. TABLE 3: MEAN EXPOSED SKIN SURFACE AREA PER PRODUCT TYPE AND FREQUENCY OF APPLICATION PER PRODUCT TYPE (BREMMER *ET AL.*, 2006)

| Product type | Skin surface area involved (RIVM) | | Frequency of application |
|---|---|---|---|
| | Surface area ($cm^2$) | Parameters (if specified) | |
| **Bathing, showering** | | | |
| Shower gel | 17500 | total body area | 1.43/day |
| Hand wash soap | 860 | area hands | 10/day |
| Bath oil, salts, etc. | 16340 | area body - area head | 1/day |
| **Hair care** | | | |
| Shampoo | 1440 | area hands | 1/day |
| | | + 1/2 area head | |
| Hair conditioner | 1440 | area hands + 1/2 area head | 0.28/day |
| Hair styling products | 1010 | 1/2 area hands + 1/2 area head | *1.14/day* |
| Semi-permanent hair dyes (and lotions) | 580 | 1/2 area head | 1/week (20 min.) |
| Oxidative/permanent hair dyes | 580 | 1/2 area head | 1/month (30 min.) |
| **Skin care** | | | |
| Body lotion | 15670 | area body - area head female | *2.28/day* |
| Face cream | 565 | 1/2 area head female | *2.14/day* |
| Neck | 320 | | |
| Back of neck | 80 | | |
| Hand cream | 860 | area hands | 2/day |
| **Make-up** | | | |
| Liquid foundation | 565 | 1/2 area head female | 1/day |
| Make-up remover | 565 | 1/2 area head female | 1/day |
| Eye shadow | 24 | | 2/day |
| Mascara | 1.6 | | 2/day |
| Eyeliner | 3.2 | | 2/day |
| Lipstick, lip salve | 4.8 | | *2/day* |
| **Deodorant/antiperspirant** | | | |
| Deodorant aerosol spray and non-spray | 200 | both axillae | *2/day* |
| **Fragrances** | | | |
| Eau de toilette spray | 200 | | 1/day |
| Perfume spray | 100 | | 1/day |
| **Men's cosmetics** | | | |
| Shaving cream | 305 | 1/4 area head male | 1/day |
| Aftershave | 305 | 1/4 area head male | 1/day |
| **Sun care cosmetics** | | | |
| **Sunscreen lotion / cream** | **17500** | **total body area** | **2/day** |

### 5.4. REPORTED USE OF ACTIVE INGREDIENTS IN SUNSCREEN PRODUCTS MARKETED IN AUSTRALIA

The following table reflects the Reporter analysis for listed sunscreens in Australia (760 products on ***13/2/20***) and the 31 ingredients approved for use as active ingredients in these products. The 12 ingredients categorised III in the FDA proposed rule are highlighted in bold font. Please note that products which contain avobenzone and/or octocrylene make up approximately 70% of the entire Australian market of sunscreens.

| Active ingredient (AAN) | No. of listed sunscreens |
|---|---|
| 4-methylbenzylidene camphor | 244 |
| **Avobenzone (butyl methoxydibenzoylmethane)** | **541** |
| Bemotrizinol | 128 |
| Benzylidene camphor sulfonic acid | 0 |
| Camphor benzalkonium methosulfate | 0 |
| **Cinoxate** | 0 |
| Diethylamino hydroxybenzoyl hexyl benzoate | 90 |
| **Dioxybenzone** | 0 |
| Disodium phenyl dibenzimidazole tetrasulfonate | 0 |
| Drometrizole trisiloxane | 20 |
| Ecamsule | 17 |
| **Ensulizole (phenylbenzimidazole sulfonic acid)** | **100** |
| Ethylhexyl triazone | **113** |
| **Homosalate** | **303** |
| Isoamyl methoxycinnamate | 0 |
| **Meradimate (menthyl anthranilate)** | 0 |
| Methylene bis-benzotriazolyl tetramethylbutylphenol | 32 |
| **Octinoxate (octyl methoxycinnamate)** | **134** |
| **Octisalate (octyl salicylate)** | **296** |
| **Octocrylene** | **522** |
| **Oxybenzone** | **126** |
| PABA (amino benzoic acid) | 0 |
| **Padimate o** | 0 |
| Peg-25 paba | 0 |
| Polysilicone-15 | 2 |
| **Sulisobenzone** | 0 |
| sulisobenzone sodium | 0 |
| Titanium dioxide | 78 |
| Tris-biphenyl triazine | 0 |
| Trolamine salicylate | 0 |
| Zinc oxide | 229 |

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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).

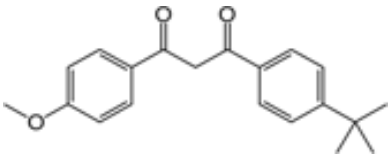
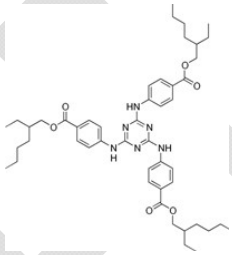
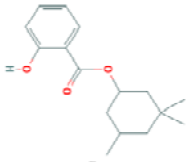
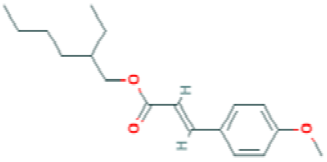
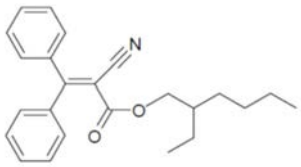
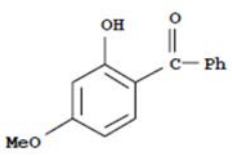
**Table 0-1 Chemical and Physical Properties of the active ingredients under review**

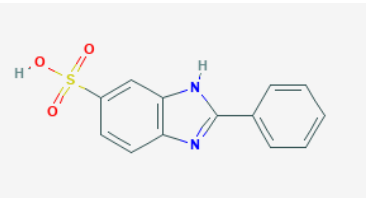
| Active ingredient (*absorption spectrum*) | CAS no. | Chemical name | Molecular formula | Physical properties | | | | Other names |
|---|---|---|---|---|---|---|---|---|
| | | | | Water solubility | MW g/mol | Density | Log $P_{ow}$ | |
| Avobenzone (BMDM or BMDBM)<br><br>*UVA* | 70356-09-1 | 1,3-Propanedione, 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'methoxydibenzoyl methane, BMDBM |
| Ethylhexyl triazone (EHT)<br><br>*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) |
| Homosalate<br><br>*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, |

| 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.<br><br>Homomethyl salicylate<br><br>Salicylic acid, 3,3,5-trimethylcyclohexyl ester<br><br>Caswell No. 482B, Neo Heliopan® HMS, CCRIS 4885, Filtersol ''A'' |
| Octinoxate (OMC or EHMC)<br><br>*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)<br><br>*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)<br><br>*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)<br><br>*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 |  |
| 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$^{\Delta}$ | 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 $^{\gamma}$ | 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/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 x$10^{-7}$ 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 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/cm²** 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.

[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)<br>Dermal, inconclusive* | Oral > 5000 mg/kg bw (rats) | Oral > 5000 mg/kg (rats)<br>Dermal > 5000 mg/kg bw (rabbits) | Oral >8 g/kg (mice)<br>>20 mL/kg (20.0 mg/kg) (rats)<br>Dermal >126.5 mg/kg (rats)<br>Inhalation LC50 >0.511 mg/L (rats) | Oral > 5000 mg/kg bw (rats)<br>Dermal > 2000 mg/kg bw (rats) | Oral > 6000 mg/kg bw (rats)<br>Dermal > 16000 mg/kg bw (rabbits) | Oral<br>>5000 mg/kg bw (mice)<br>>1600 mg/kg bw (rats)<br>Dermal >3000 mg/kg bw (rats)<br>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)<br>Not sensitizing (at 15%, HRIPT) | Not sensitizing (GPMT) | Not sensitizing (GPMT)<br>Moderate sensitising in a LLNA (not properly conducted) | Not sensitizing (GPMT)<br>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[Δ] | 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.<br>No effect on the body weight and food consumption.<br>↓ RBC in ♀ rats at 1000 mg/kg bw/day.<br>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.<br>Hypertrophic hepatic parenchyma cells in ♀ at 1000 mg/kg bw/day.<br>**NOAEL: 450 mg/kg bw/day**<br>*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.<br>↑ dose dependent severe dermal reactions ≥ 30 mg/kg/day, more persistent at 100 mg/kg bw/day.<br>↑ Incidence of epidermal thickening in both vehicle control and treatment groups compared to the untreated control group.<br>NOAEL: 360 mg/kg bw/day (based on systemic effects).<br>LOAEL: 30 mg/kg/bw/day (dermal) |
| Octocrylene (ECHA 2021d; SCCS 2021a) | Rats (Wistar), *n* = 10/sex/dose<br>0, 58, 175, 340 and 1085 mg/kg bw/day (diet), 13 weeks<br><br>Study BASF 50S0227/92059 | No treatment-related mortality.<br>No treatment-related clinical signs.<br>Body weight gain: ↓ at HD in both sexes along with decreased food consumption<br>Haematology: RBC affected (↓MCV, ↓MCH, ↓MCHC) at HD in both sexes<br>Organ weights (bodyweight-relative): ↑ absolute and relative weight of liver at 340 and 1085 mg/kg bw/day<br>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<br>NOAEL: 175 mg/kg bw/day |
| | Rabbits (NZW), *n* = 5/sex/dose<br>0, 130, 264, 534 mg/kg bw/day (dermal)<br>5 days/week; 13 weeks<br><br>(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.<br>No evidence for haematological or macroscopic and histopathological abnormalities<br>No effects were reported on testicular and epididymal morphology as well as on sperm count and motility<br>NOAEL: 534 mg/kg bw/day (systemic toxicity)<br>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<br><br>Rats (Wistar), *n* = 5/sex/dose<br>72, 215, 720 mg/kg bw/day PO (Subset A)<br>63, 188, 630 mg/kg bw/day PO (Subset B)<br><br>28 days (Subset A)<br>14 days (Subset B) | No treatment-related mortality<br>No treatment-related clinical signs.<br>Body weight gain: ↓ at HD in both subsets<br>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<br>Organ weights (bodyweight-relative): ↑ absolute and relative weight of liver at high doses in both sexes in both subsets<br>Histopathology: minimal follicular cell hypertrophy/hyperplasia of the thyroid gland at high doses in both sexes in both subsets<br>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.<br>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.<br>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<br>↑ (non-significant) serum alanine phosphatase (SAP) levels and ↑ relative liver weight at HD. Liver effects were not observable upon microscopic examination.<br>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.<br>Dose dependent low-grade epidermal proliferation at all doses (more prominent in ♂).<br>The chemical was considered as a low-grade irritant under the conditions of this study (OECD TG 410)<br>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<br>Lethargy, hunched posture, hair loss, soiled coats, emaciation, increased respiration, swelling of the conjunctivae, and reproductive effects (retardation of testicular growth) at HD.<br>Haematological changes including ↑ neutrophils and urea nitrogen, and ↓ lymphocytes and alkaline phosphatase activity at HD.<br>Dermal irritation effects (erythema, oedema, desquamation, cracking and atonia) were observed at all doses but were more severe at the HD.<br>Histopathology of the skin sites showed an epidermal proliferative response with low grade inflammatory reaction (dose dependent).<br>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.<br>↑ Liver-weight without histological correlates among treated female animals could not be interpreted as being treatment-related.<br>**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<br>No treatment-related effects on organs<br>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<br>Bodyweight gain: ↓ in ♂at HD.<br>Organ weight: ↑ liver weights (♂ & ♀) from LD, associated histopathology observed at 2041 mg/kg bw/day; ↓ kidney weight in ♂ from 8648 mg/kg bw/day.<br>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<br>Bodyweight: ↓ BW gain in ♂ & ♀ from 6780 mg/kg bw/day<br>Organ weights: ↑ liver weight from 1246 mg/kg bw/day with histopathology from 6780 mg/kg bw/day. Renal histopathology at HD in ♂.<br>Reproductive parameters: ↓ sperm density and ↑ abnormal sperm in ♂ and ↑ oestrus cycle length in ♀ at HD<br>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<br>Bodyweight gain: ↓ in ♂at HD.<br>Organ weight: ↑ liver (♂ & ♀) and kidney (♂) weights from LD, associated histopathology observed at 576 mg/kg bw/day in liver and at HD in kidney .<br>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.<br>Clinical signs: coloured urine from LD.<br>Bodyweights: ↓ BW gain in ♂ & ♀ from 1702 mg/kg bw/day.<br>Clinical pathology: serum protein levels from 411 mg/kg bw/day, ↑ platelet counts from 1702 mg/kg bw/day<br>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.<br>Reproductive parameters: ↓ sperm motility in ♂ and ↑ oestrus cycle length in ♀ at HD.<br>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<br>Organ weights: ↑ liver weight from 196 mg/kg bw/day.<br>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.<br>Organ weights: ↑ kidney weight in ♂ at all doses<br>Reproductive parameters: ↓ epididymal sperm density in ♂ at all doses.<br>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<br>Organ weights: ↑ liver weight in ♀ from 27.7 mg/kg bw/day, ↑ kidney weight in ♀ at HD<br>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).<br>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.<br>Clinical pathology: ↓ reticulocyte counts from LD, ↑ platelet counts from 50 mg/kg bw/day, ↑ whole blood cell count produced by lymphocytosis at HD.<br>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<br>Clinical signs: none treatment related<br>Body weight gain: ↓ at HD in ♂ along with decreased food consumption<br>Haematology: none treatment related<br>Serum chemistry: ↑ Triglycerides in both sexes at HD ↑APTT in ♂ at MD<br>NOAEL: > 300 mg/kg bw/day ♂<br>NOAEL: >1000 mg/kg bw/day ♀ |
| | Repeat dose/ reproduction/ developments study<br><br>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<br>*Clinical signs:* none treatment-related<br>*Body weight gain:* ↓ at 750 mg/kg bw/day in ♂ and ♀<br>*Haematology:* none treatment-related<br>*Serum chemistry:* ↑ Albumin and ↓ Globulin in ♂ at 300 mg/kg bw/day<br>*Urinalysis:* not conducted<br>*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.<br>*Gross pathology:* no treatment-related findings<br>*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). *<br>Minimal/mild hypertrophy of hepatocytes (1/5 ♂) at 120 mg/kg bw/day, and almost every ♂ and ♀ from 300 mg/kg bw/day.<br>Hypertrophy of the follicular epithelium of thyroid gland in ♂ at 750 mg/kg bw/day and in ♀ from 300 mg/kg bw/day.<br>↓ Cortical lymphocytes in males from 300 mg/kg bw/day and in ♀ at 750 mg/kg bw/day<br>*NOAEL:* ** mg/kg bw/day<br>*The REACH registrants considered this as manifestations of hyaline droplet nephropathy without giving further evidence.<br>**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*<br>Negative<br>AMES test and gene mutation study V79 Chinese hamster cells<br><br>In vivo<br>Negative<br>Bone marrow polychromatic erythrocytes (mice) | *In vitro*<br>Negative<br>AMES test, Chinese hamster lung fibroblasts for chromosome aberration, Chinese hamster ovary (CHO) cells, in vivo chromosome aberration test | *In vitro*<br>Negative<br>AMES test and gene mutation study in V79 Chinese hamster cells<br><br>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*<br>Negative<br>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)<br><br>In vivo<br>Negative<br>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*<br>Negative<br>AMES test, gene mutation test, cytogenicity test in mammalian cells, chromosome aberrations tests<br><br>In vivo<br>Negative<br>Cytogenicity test in mice (ECHA 2020, SCCS 2021a) | *In vitro*<br>Negative<br>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<br><br>In vivo<br>Negative<br>micronucleus test (mice), chromosome aberration test (rats), Drosophila (SMART)† | *In vitro*<br>Negative<br>AMES test and chromosome aberration test in human peripheral blood lymphocytes<br><br>In vivo<br>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 ♂/♀)<br><br>Rats (SD; *n*=10/sex/group), 0, 1000, 3000, 10000 ppm (equivalent to 58/60, 168/180, 585/632 mg/kg bw/day in ♂/♀)<br>Two years (beginning on GD6 in ♀) | Mice: ↑ lesions in the bone marrow, spleen, and kidney of both sexes and in the liver in ♂<br><br>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.<br>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.<br>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.<br>↓ 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.<br>In the offspring, ↓ lactation weight gain and organ weights, and slightly delayed sexual maturation (vaginal opening and preputial separation) at HD.<br>**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.<br>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)<br>Modified one-generation study<br>Rats (SD); *n*=26/dose; exposure through feed and/or lactation<br>1000, 3000, 6000 ppm (equivalent to 70 to 87, 207-418 , 419-842 mg/kg/day)<br>$F_0$ dams: GD6 - LD 28<br>$F_1$ 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.<br>$F_2$ 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.<br>Equivocal evidence of developmental toxicity was observed:<br>↓ Mean pup body weight ($F_1$) at HD<br>↑ Vaginal opening ($F_1$) from MD<br>↑ Balanopreputial separation ($F_1$) at HD<br><br>NOAEL: 6000 ppm for parental systemic toxicity, fertility and reproduction performance<br>NOAEL: 1000 ppm for developmental toxicity |
| Octocrylene (SCCS 2021a; ECHA 2021d) | Extended one generation reproductive toxicity study (EOGRTS), GLP<br>Rat (Wistar); Dose: (diets) 55, 153, 534 mg/kg bw/day ♂<br>58, 163, 550 mg/kg bw/day ♀<br><br>*n*= 27 or 28 /sex /dose<br>F1: Cohort 1A: 19/sex/ dose<br>Cohort 1B: 25/sex/dose<br>Cohort 2A: 10/sex/ dose<br>Cohort 2B: 10/sex/dose<br><br>♂: 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<br>↓ bodyweight of pups at HD<br>No effects on male fertility and male and female reproductive parameters such as oestrus cycle, epididymal and testicular sperm parameters at all doses.<br>No effects on sexual and neurodevelopmental parameters in pups.<br>Based on effects on parental and pup body weights, a lower number of implantation sites and lower number of pups delivered.<br>**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<br>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)<br>F2: until weaning (indirectly)<br>(ECHA 2021d; SCCS 2021a) | |
| | Pregnant rats (Wistar); *n* = 25/♀/dose, Dose: 0, 100, 400, 1000 mg/kg bw/day PO<br>GD6–GD15; termination on GD21 | F0:<br>Transient salivation at HD.<br>↑ relative liver weight at MD and HD<br>F1:<br>No treatment related effects.<br>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<br>Odio *et al*. (1994) | No treatment related adverse effects.<br>NOEL: 1000 mg/kg bw/day (mice) |
| | Rabbit (NZW); *n* = 17 ♀/dose<br>Dose: 0, 65, 267 mg/kg bw/day, (Dermal, open, clipped area on the back), dosing GD6–GD18; termination on GD21<br>Odio *et al*. (1994) | No treatment related adverse effects.<br>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.<br>Maternal NOAEL = 1000 mg/kg bw/day;<br>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).<br>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):<br>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.<br>↓ 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;<br>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.<br>In mice, there were no effects on reproductive organ weight, cauda epididymal sperm concentration, sperm parameters, testicular spermatid concentration or testicular histology.<br>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)<br>Reproductive toxicity study in rats (SD; *n*=7-8 mated ♀);<br>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.<br>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)<br>Reproductive toxicity study in mice (ICR; *n*=13-15 mated ♀)<br>Doses: 0, 0.1, 10, 1000 mg/kg/day PO<br>Treatment from GD1-GD13 | No adverse effect on maternal body weight and the relative weights of the liver, brain and the uterus<br>Slight ↑ rate of fetal loss at HD; ↑ placental thrombosis and necrosis from LD (severity not assessed) |
| | NTP-DART-05 (2022a)<br>Modified one-generation study<br>Rats (SD; mated ♀; *n*= 25/dose)<br>Doses: 0, 3000,10000, 30000 ppm; exposure through feed and/or lactation<br>(equivalent of 205 to 426, 697 to 1621, and 2,644 to 5944 mg/kg/day respectively)<br>$F_0$ GD6 - LD28<br>$F_1$ 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.<br>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.<br>The relationship of the ↑ occurrence of diaphragmatic and hepatodiaphragmatic hernias in $F_1$ adults and $F_2$ pups from MD is unclear.<br>Exposure to oxybenzone was associated with ↑ nonneoplastic kidney lesions in the $F_0$, $F_1$, and $F_2$ generations at HD<br>Exposure to oxybenzone was not associated with signals consistent with alterations in estrogenic, androgenic, or antiandrogenic action.<br><br>NOAEL: 3000 ppm |

| Active ingredient | Study details | Major findings |
|---|---|---|
| | continued until necropsy on PND96, PND120 or PND150<br>$F_2$ offspring were exposed in utero, during lactation and postweaning until necropsy on GD21 or PND28. | |
| PBSA<br>(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.<br>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/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<br>Increased reactivity to the contractile agents – serotonin, histamine and KCl<br>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<br>(Xu *et al.* 2021) | Waterborne; 0.056 -38 µg/L 42 days post fertilization | Decreased female to male ratio from 2.3 µg/L<br>Increased expression of estrogen receptors *esr2a* and *vtg2 i*n the brain and hepatic *vtg2* at HD |
| | Zebrafish<br>(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<br>(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<br>(Meng *et al.* 2021) | 96 h incubation; hatching rates of zebrafish (50-250uM)<br>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 )<br>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<br>(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<br>(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<br>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 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
- Coslng 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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