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VKM Report 2022: 10

Risk-benefit assessment of sunscreen

Opinion of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food, and Cosmetics of the Norwegian Scientific Committee for Food and Environment

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Preparation of the opinion

The Norwegian Scientific Committee for Food and Environment (Vitenskapskomiteen for mat og miljø, VKM) appointed a project group to draft the opinion. Two referees commented on and reviewed the draft opinion. The Committee, by the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food, and Cosmetics, assessed and approved the final opinion.

Authors of the opinion

The authors have contributed to the opinion in a way that fulfils the authorship principles of VKM. The principles reflect the collaborative nature of the work, and the authors have contributed as members of the project group and/or the VKM Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food, and Cosmetics.

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VKM would like to thank Dr. Javier Pineda for helping to make the data files and R-code used for the exposure assessment ready for publication.

VKM would like to thank the referees Professor Franz Trautinger (Karl Landsteiner University of Health Sciences) and Dr Reginald Edward FitzGerald (University of Basel) for their valuable comments through critical review of the draft opinion. VKM emphasises that the referees are not responsible for the content of the final opinion. In accordance with VKM's routines for approval of a risk assessment (VKM, 2018), VKM received their comments before evaluation and approval, and before the opinion was finalised for publication.

Competence of VKM experts

Persons working for VKM, either as appointed members of the Committee or as external experts, do this by virtue of their scientific expertise, not as representatives for their employers or third party interests. The Civil Services Act instructions on legal competence apply for all work prepared by VKM.

Table of Contents

Abbreviations and definitions

Abbreviations

Abs %	percentage dermal absorption of UV filter
$Abs_{UV\ filter}$	the dermal absorption value for a UV filter
ADME	absorption, distribution, metabolism, excretion
$amt_{Sunscreen}$	the amount of sunscreen used per day
BCC	basal cell carcinoma
BEMT	Bis-ethyl-hexyloxyphenol methoxyphenyl triazine
BMDBM	Butyl methoxydibenzoyl methane
C	UV filter concentration
CAS	Chemical Abstracts Service
CET	Central European Time
Ci	curie
CI	confidence interval
CIE	International Commission on Illumination
CosIng	European Commission Cosmetic Ingredients Database
COADEX	C, current relevance; O, old or past relevance; A, actively sensitized; D, relevance not known; E, exposed; X, the positive test is due to cross-reaction with another allergen (see COADEX under "Definitions").
Danish EPA	The Danish Environmental Protection Agency
DNEL	derived no-effect level
EC	European Commission
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority

EHS	2-Ethylhexyl salicylate
EHT	Ethylhexyl triazone
EU	European Union
F	female
GLP	good laboratory practice
H/A	hydroalcoholic
HR	hazard ratio
IARC	International Agency for Research on Cancer
ICDRG	International Contact Dermatitis Research Group
LD50	lethal dose 50%
LN	lognormal distribution
LOAEL	lowest observed adverse effect level
M	male
MC	Monte-Carlo
NOAEL	no observed adverse effect level
NP-TiO_2	titanium dioxide (nano)
NSAID	non-steroidal anti-inflammatory drug
NTP	National Toxicology Program
OC	octocrylene
OECD	Organisation for Economic Co-operation and Development
OHAT	Office of Health Assessment and Translation
OR	odds ratio
O/W	oil-in-water
PEG	polyethylene glycol
PLE	polymorphic light eruption

PoD	point of departure
PPT	photopatch test
r	random sampling from individual data
RCT	randomised controlled trial
Rf	retention factor
RoB	risk of bias
RR	rate ratio
SC	*stratum corneum*
SCC	squamous cell carcinoma
SCCS	Scientific Committee on Consumer Safety
SD	standard deviation
SED	in the context of solar radiation exposure: standard erythema dose
SPF	sunscreen protection factor
TG	standardised test guideline
UDS	unscheduled DNA synthesis test
UF	uncertainty factor
UV-A/UVA	ultraviolet radiation A
UV-B/UVB	ultraviolet radiation B
UVR	ultraviolet radiation (UV is commonly used instead of UVR)
WHO	World Health Organization
$w_{Sunscreen}$	weight of sunscreen applied
W/O	water-in-oil
WoE	weight of evidence

Definitions

Absorption, distribution, metabolism and elimination (ADME)
The four key processes which describe how drugs and chemicals get into the body, what happens to them while they are there, and how they are eliminated (EFSA Glossary).

Adverse effect
An effect is considered "adverse" when leading to a change in the morphology, physiology, growth, development, reproduction, or life span of an organism, system, or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences" (WHO, 2004).

Beneficial effect
An effect is considered "beneficial" if it has the probability to be linked to a positive (health) effect (*e.g.* increase the resilience of the organism to a certain challenge) and/or the probability to be linked to a reduction of an adverse health effect in an organism, system or (sub)population, in reaction to exposure to an agent (EFSA Scientific Committee, 2010).

In this risk-benefit assessment, beneficial and protective effects are synonyms and used interchangeably. The expressions are used to describe effects of a sunscreen that reduce the dose of solar UVR to skin cells and thereby reduce the induced adverse health effects caused by the irradiation.

COADEX
A clinical relevance system for reactions used in (photo-)patch testing: C, current relevance—the patient has been exposed to allergen during the current episode of dermatitis and improves when the exposure ceases; O, old or past relevance—past episode of dermatitis from exposure to allergen; A, actively sensitized—patient presents with a sensitization (late) reaction; D, relevance not known—not sure if the exposure is current or old; E, exposed—a history of exposure but not resulting in dermatitis; and X, the positive test is due to cross-reaction with another allergen (Kerr et al., 2012).

Certainty of evidence
The certainty (or quality) of evidence is the extent to which we can be confident that what the research tells us about a particular treatment effect is likely to be accurate. Concerns about factors such as bias can reduce the certainty of the evidence. Evidence may be of high certainty; moderate certainty; low certainty or very-low certainty (Cochrane Glossary, 2020).

Derived no-effect level (DNEL)
The level of chemical exposure above which humans should not be exposed.

Dermal exposure
"Dermal exposure is a complex process of contact between a relevant substance and the skin over a period of time" (IPCS, 2014).

External exposure
The amount of a substance reaching the physical barriers of the body.

Internal exposure
The total amount of a substance which is systemically available**.**

No observed adverse effect level (NOAEL)
The largest concentration or amount of a substance tested at which no detectable adverse effects occur in an exposed population.

Optical radiation
Ultraviolet, visible and infrared electromagnetic radiation. Solar radiation includes all three radiation wavelength ranges which at the earth's surface are approximately 290-400 nm, 380-780 nm, and 780-3000 nm, respectively.

Point of departure (PoD)
The point on a dose–response curve established from experimental data used to derive a safe level (EFSA Glossary). The PoD may be derived *e.g.* from the no-observed-adverse-effect level (NOAEL) or by using the benchmark dose (BMD) method. A PoD is also known as a reference point.

Protective effect
See "beneficial effect"

Risk of bias
Internal validity. "The assessment of whether the design and conduct of the study compromised the credibility of the link between exposure and outcome" (Higgins and Green, 2011; OHAT 2015)

Risk-benefit assessment
"In the risk-benefit assessment, the probability of an adverse health effect or harm (both incidence and severity) as a consequence of exposure can be weighed against the probability of benefit, if both are known to be possible" (EFSA Scientific Committee, 2010). The proposed procedure for a risk-benefit assessment is as follows:

Risk assessment	**Benefit assessment**
Hazard identification	Identification of positive health effect or reduced adverse effect.
Hazard characterisation (dose-response assessment)	Characterisation (dose-response assessment) of positive health effect or reduced adverse effect.
Exposure assessment	Exposure assessment
Risk characterisation	Benefit characterisation

In this assessment, the term "health protective effect" (of the sunscreen and UV filters) is substituted for "positive health effect" and "reduced adverse effect".

Sunscreen protection factor (SPF)
The ratio between the minimal erythema dose on skin protected by the product and the minimal erythema dose on unprotected skin, determined *in vivo*. The sunscreen (of any preparation) is applied to a test area on the back of volunteers in amounts of 2 mg/cm^2. After a drying time of 15 to 30 minutes irradiation is performed with a xenon lamp according to certain specifications. Erythema is recorded 20 ± 4 hours after exposure. Due to the reproducibility it is technically difficult to measure a layer thickness less than 2 mg/cm^2. The in vivo method evaluates protection against the short-term effects of UVB-radiation (VKM, 2007).

Sunscreen (topical)
"Any preparation (such as creams, oils, gels, sprays) intended to be placed in contact with the human skin with a view exclusively or mainly to protecting [*sic*] it from UV radiation by absorbing, scattering or reflecting radiation" (Commission Recommendation (2006/647/EC)). Note that sprays and products intended for the lips are not included in this risk-benefit assessment.

UV filters
Substances which are exclusively or mainly intended to protect the skin against certain UV radiation by absorbing, reflecting or scattering UV radiation (Commission Recommendation (2006/647/EC).

UV-A
Ultraviolet radiation A. Denotes electromagnetic wavelengths in the range 315 - 400 nm (CIE, 2011). In this assessment the term "UVA" is also used

UV-B
Ultraviolet radiation B. Denotes electromagnetic wavelengths in the range 280 - 315 nm (CIE, 2011). In this assessment the term "UVB" is also used.

UVR
Optical radiation for which the wavelengths are shorter than those for visible radiation. Wavelength range: 100 - 400 nm (CIE, 2011). Ultraviolet radiation is divided in the three bands ultraviolet radiation A (UV-A, 315-400 nm), ultraviolet radiation B (UV-B, 280-315 nm) and ultraviolet radiation C (UV-C, 100-280 nm) (CIE, 2011). In this assessment the term "UV" is also used.

Weight of evidence
See "certainty of evidence".

Short summary

VKM has performed a risk-benefit assessment of sunscreen use and six UV filters. This task was undertaken on the initiative of a VKM Panel in response to the apparent paradox between the need for protective measures, such as use of sunscreens, to reduce Norway's high incidence and mortality of skin cancer and a consumer concern for the safety of sunscreens. Concerns include safety of ingredients and sunscreens' effect on vitamin D synthesis. Sunscreen products are legally regulated as cosmetic products in the EU, and only approved UV filters up to a maximum determined concentration are allowed in the ready-for-use preparation.

VKM used a systematic approach to assess risks and benefits of sunscreen use and risks of six selected UV filters: bis-ethyl-hexyloxyphenol methoxyphenyl triazine (BEMT), butyl methoxydibenzoyl methane (BMDBM), 2-ethylhexyl salicylate (EHS), ethylhexyl triazone (EHT), octocrylene (OC), and titanium dioxide in nanoform (NP-TiO_2). These UV filters are among the most frequently used in sunscreens on the Norwegian market. Sunscreen sprays and lip products were not included. Scientific publications and reports up to 2020 were retrieved to assess adverse and protective effects of sunscreen and adverse effects of UV filters. We assessed risk of bias in the studies and evidence for health outcomes with the aid of validity tools, and estimated exposure to each UV filter using probabilistic methods.

The evidence showed that sunscreens were beneficial in protecting against certain skin cancers. Insufficient evidence precluded determination of the hazard associated with sunscreen use.

The UV filters occurred in concentrations similar to or below the limits set in the EU cosmetics regulative. VKM considered that little to no hazard was associated with use of the six evaluated UV filters.

VKM concludes that the risks related to use of the six evaluated UV filters are negligible since the real-life use of these UV filters is several-fold lower than the amounts that may cause any adverse health effect. The evidence for harmful health effects of sunscreens is insufficient to determine risk. Sunscreen use protects against certain skin cancers and is beneficial for the general Norwegian population.

Kort sammendrag (norsk)

VKM har utført en nytte- og risikovurdering av solkrembruk og seks UV-filtre på initiativ fra en av faggruppene i VKM. Bakgrunnen er det tilsynelatende paradokset mellom behovet for beskyttelsestiltak, som bruk av solkremer, for å redusere Norges høye forekomst og dødelighet av hudkreft på den ene siden, og forbrukerbekymring om trygghet ved solkremer på den andre. Slike bekymringer kan dreie seg om hvorvidt ingrediensene i solkrem er trygge, eller om man får dannet mindre D-vitamin når man bruker solkrem. Solkremprodukter er lovregulert som kosmetiske produkter i EU, og det er bare godkjente UV-filtre opp til en bestemt maksimumkonsentrasjon som er tillatt.

VKM søkte etter og hentet ut vitenskapelige publikasjoner og rapporter frem til 2020 for å vurdere uønskede og beskyttende effekter av solkrembruk og uønskede effekter av UV-filtre. Seks UV-filtre ble valgt ut: bis-etyl-heksyloksyfenol metoksyfenyltriazin (BEMT), butylmetoksydibenzoylmetan (BMDBM), 2-etylheksylsalisylat (EHS), etylheksyltriazon (EHT), oktokrylen (OC) og titandioksid på nanoform (NP-TiO_2). Disse UV-filtrene er blant de mest brukte i solkremer som selges på det norske markedet. Spray- og leppeprodukter ble utelatt. Vi vurderte risiko for skjevhet (bias) i studiene og kvaliteten på dokumentasjonen for helseutfall på en systematisk måte ved hjelp av validitetsverktøy. Eksponering for hvert UV-filter beregnet vi ved hjelp av probabilistiske metoder.

Vi fant evidens for at bruk av solkrem beskytter mot visse hudkreftformer. Derimot var dokumentasjonen ikke tilstrekkelig til at vi kunne bestemme faren ved solkrembruk.

UV-filtrene forekom i konsentrasjoner tilsvarende eller under grensene som er satt i EUs kosmetikkforskrift. VKM mener at faren forbundet med bruk av de seks vurderte UV-filtrene er ubetydelig.

VKM konkluderer med at risikoen knyttet til bruk av de seks evaluerte UV-filtrene er ubetydelig, siden den daglige bruken av disse UV-filtrene er flere ganger lavere enn mengdene som kan forårsake skadelig helseeffekt. Dokumentasjonen var ikke tilstrekklig, verken i mengde eller kvalitet, til å fastslå at det er risiko for skadelige helseeffekter av solkrembruk. Bruk av solkrem beskytter mot visse hudkreftformer og er gunstig for den generelle norske befolkningen.

Extended summary

Background

In Norway, the incidence of skin cancer is among the highest worldwide, and the incidence rate of melanoma increased by >50% during the period 2000-2020.

Recommendations for ultraviolet radiation (UVR) protection includes sunscreen use in addition to restricting the midday time spent in the sun, seeking shade and wearing clothing.

However, there are concerns whether sunscreens and their specific ingredients pose a risk to human health. The concerns include effects such as contact dermatitis and endocrine disruptive effects, assumed to be caused directly by sunscreen ingredients, and effects such as reduction of vitamin D synthesis, which may be caused indirectly by attenuation of UVR to the skin.

Aim

With this risk-benefit assessment, VKM aimed to identify and compare risks and benefits caused by use of sunscreen products and selected UV filters (Figure 1). In this assessment, protection means reduction in adverse health effects caused by solar UVR.

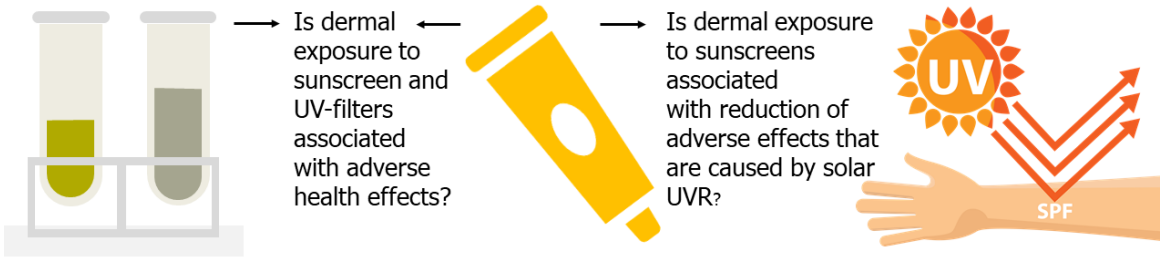


Figure 1. The aim of the risk-benefit assessment.

Sunscreen products and sunscreen ingredients included for assessment

Both sunscreen products and sunscreen ingredients were included in this risk-benefit assessment. VKM delimited the inclusion of sunscreen products to those primarily intended

for UVR protection; thus, *e.g.* make-up with UV filters were not included. Furthermore, products which can cause inhalation or oral absorption of ingredients were not included, *i.e.* sunscreen sprays and sunscreen lip products.

The evaluation of sunscreen ingredients was restricted to UV filters due to their role as active substances in attenuation of UVR. Six of the most frequently used UV filters in sunscreens on the Norwegian market were selected. Other sunscreen ingredients, *e.g.* preservatives, emulsifiers, emollients, thickeners, film formers and fragrances were not included. Such ingredients are present in a variety of other frequently used personal care products, and VKM considered sunscreens not to be the main source of exposure to these substances. An overview of the six selected UV filters is given in Table 1. All UV filters were organic except titanium dioxide in nanoform (NP-TiO_2; inorganic).

Table 1. The UV filters included in the risk-benefit assessment.

UV filter	Abbreviation	Cas no.
Bis-ethyl-hexyloxyphenol methoxyphenyl triazine	BEMT	187393-00-6
Butyl methoxydibenzoyl methane	BMDBM	70356-09-1
2-Ethylhexyl salicylate	EHS	118-60-5
Ethylhexyl triazone	EHT	88122-99-0
Octocrylene	OC	6197-30- 4
Titanium dioxide nanoparticles (NP)	NP-TiO_2	13463-67-7; 1317-70-0; 1317-80-2

The risk-benefit assessment

An overview of the steps in the risk-benefit assessment is given in Figure 2. To identify possible adverse and health protective effects, systematic literature reviews were performed including literature searches in several relevant databases, critical appraisal of the studies, and a narrative evidence synthesis. Systematic literature searches were performed to identify concentrations of UV filters in commercially available sunscreens, and the quality of the measurement methods was evaluated. Data on patterns of sunscreen use and skin (dermal) absorption were identified from several sources, including literature searches. Only data considered to be above a predefined quality level were included in this risk-benefit assessment.

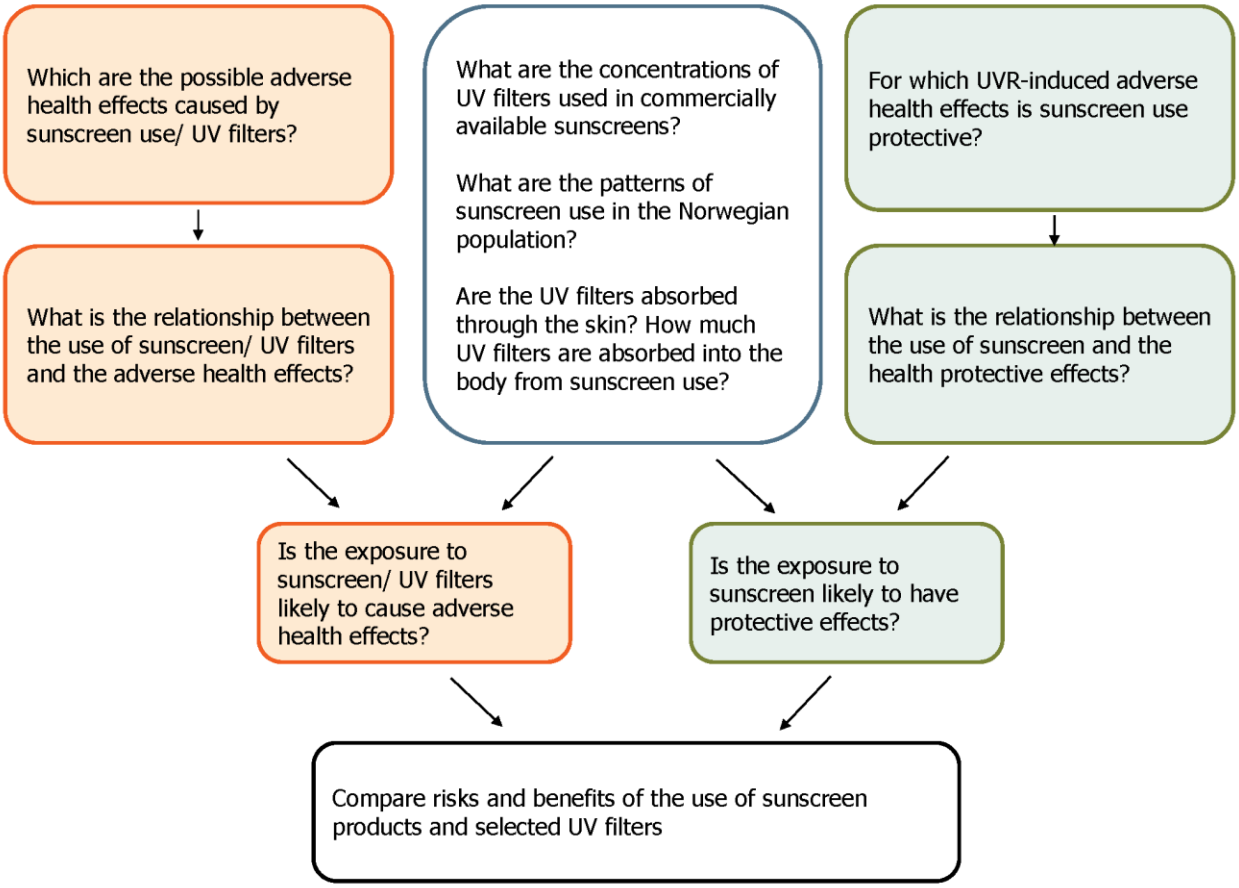


Figure 2. The steps in the risk-benefit assessment.

Exposure assessment

Chronic, daily exposure to each of the six selected UV filters was estimated as shown in Figure 3. To obtain as realistic exposure estimates as possible and to include the variability in the parameters, a probabilistic approach was used. The data on UV filter concentration, percentage dermal absorption and amount applied per day were scrutinised for quality in advance. The dermal absorption of NP-TiO_2 was negligible.

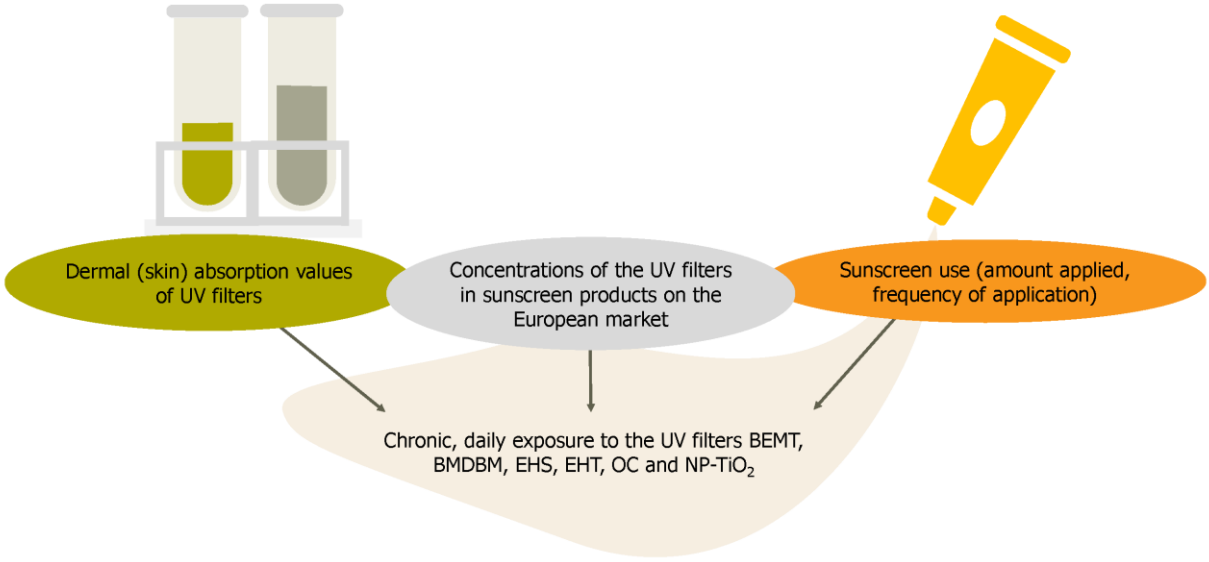


Figure 3. An overview of the parameters included in the probabilistic exposure estimation.

Hazard identification and characterisation

Identification of possible adverse health effects related to sunscreen use and the six selected UV filters was based on human and animal data.

Possible adverse effects addressed in studies on sunscreen use included a correlation between sunscreen use and increase in melanoma and between sunscreen use and reduced vitamin D synthesis. The possible adverse effects addressed in studies on the six UV filters included both systemic toxicity and local effects. Systemic toxicity was acute, subacute, subchronic and chronic toxicity, genotoxicity and carcinogenicity, and reproductive and developmental toxicity. Local effects were skin irritation and skin sensitisation.

The following hazard conclusions were identified by VKM:

- The overall confidence in the evidence for an association between sunscreen use and increase in melanoma was very low. Thus, there was insufficient evidence available to assess whether the exposure to sunscreen use was associated with increased development of melanoma. The hazard could not be classified.
- The overall confidence in the evidence for an association between sunscreen use and reduction in vitamin D synthesis was low. Thus, there was insufficient evidence available to assess whether the exposure to sunscreen use was associated with reduced vitamin D synthesis. The hazard could not be classified.
- Regarding systemic toxicity, the hazard conclusions are given as the derived no effect level (DNEL) for the critical endpoint for each UV filter. The DNEL is the level of chemical exposure above which humans should not be exposed and is derived by dividing the no effect level by the overall uncertainty in the no effect level.

- Regarding local effects, the hazard conclusion for the six selected UV filters is "Not identified as a hazard to humans". The hazard conclusions for local effects are not given as DNELs.

Risk characterisation

The possible risk related to sunscreen use and increase in melanoma or reduced vitamin D synthesis was not determined due to insufficient evidence.

Regarding local toxicity, the six UV filters were not identified as hazards to humans. VKM considered the risk for skin irritation or skin sensitisation for the general population to be negligible.

To characterise the risk related to systemic toxicity for the UV filters, the ratio of the exposure to the DNEL was calculated for each of the organic UV-filters. A risk characterisation ratio <1 was considered not to represent a risk for adverse health effects, whereas a ratio ≥1 might represent a risk for adverse health effects. The risk characterisation ratios for BEMT, BMDBM, EHS, EHT and OC were <1. As the dermal absorption of NP-TiO_2 was considered to be negligible, NP-TiO_2 was regarded not to induce systemic toxicity. Therefore, the risk associated with NP-TiO_2 was considered to be negligible.

VKM concludes that the risk for adverse health effects of the evaluated UV filters is negligible.

Identification and characterisation of protective health effects

Human data were used to identify possible protective health effects related to sunscreen use.

The possible health protective effects addressed in the included literature were prevention of the outcomes melanoma, actinic keratosis, basal cell carcinoma, squamous cell carcinoma, and immunosuppression. An overall hazard conclusion was made for the health outcomes related to skin cancer.

The following conclusions on health protective effects were identified by VKM:

- There was low confidence in the body of evidence for an association between sunscreen use and immunosuppression.
- There was moderate confidence in the evidence for no association between sunscreen use and basal cell carcinoma.
- There was low confidence in the body of evidence for a protective association between sunscreen use and melanoma.
- There was moderate confidence in the body of evidence for a protective effect of sunscreen against actinic keratosis and squamous cell carcinoma.

- Overall, for the health outcome skin (pre-) cancers, sunscreen use is presumed to protect against certain skin (pre-)cancers. The protection is larger for squamous cell carcinoma and actinic keratosis than for melanoma.

Benefit characterisation

Immunosuppression, assessed as depletion of Langerhans cells, was considered to be an insufficient marker on its own and was, therefore, not evaluated for health benefits.

Sunscreen use is presumably beneficial as protection against certain skin (pre-)cancers. The benefit is larger for squamous cell carcinoma and actinic keratosis than for melanoma. There is probably no benefit of sunscreen in protection against basal cell carcinoma.

Data on sunscreen (*e.g.* amount, thickness) and UV exposure associated with protective effects of sunscreen use were not quantified in this risk-benefit assessment. However, amounts of sunscreen use as reported in data from Denmark and other European countries were assumed to be representative for the Norwegian conditions.

Risk and benefit conclusion

VKM concludes that the risks related to use of the six evaluated UV filters are negligible since the real-life user-amounts of these UV filters are several-fold lower than the amounts that may cause any adverse health effect. The evidence for harmful health effects of sunscreens is insufficient to determine the risk. Sunscreen use protects against certain skin cancers and is beneficial for the general Norwegian population.

Key words: Bis-ethylhexyloxyphenol methoxyphenyl triazine, butyl methoxydibenzoyl-methane, 2-ethylhexyl salicylate, ethylhexyl triazone, Norwegian Scientific Committee for Food and Environment, octocrylene, risk-benefit assessment, sunscreen, titanium dioxide, UV filter, VKM.

Utvidet sammendrag (norsk)

Bakgrunn

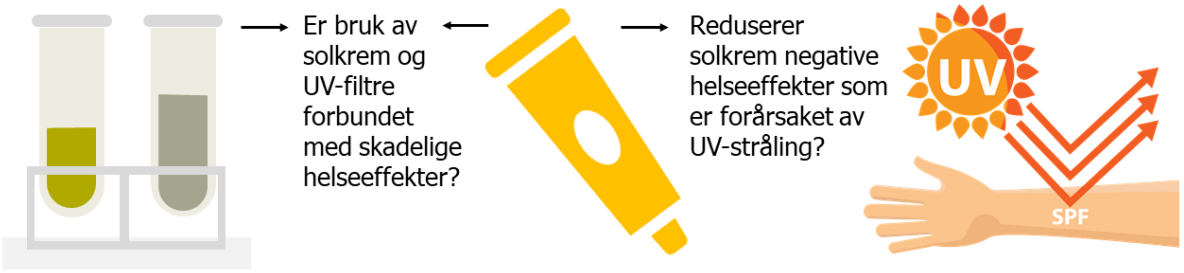
Forekomsten av hudkreft i Norge er blant den høyeste i verden, og forekomsten av melanom økte med >50 % i perioden 2000-2020.

Anbefalinger for beskyttelse mot ultrafiolett stråling (UVR) inkluderer bruk av solkrem i tillegg til å begrense oppholdstid i solen, søke skygge og bruke klær.

Det diskuteres om solkrem og enkelte av ingrediensene kan føre til negative helseeffekter. Dette gjelder for eksempel hormonforstyrrende effekter og redusert dannelse av vitamin D.

Hensikt

Målet med denne nytte- og risikovurderingen var å sammenligne nytte ved å bruke solkrem med risiko fra solkremprodukter og utvalgte UV-filtre (Figur 1). Med nytte mener vi reduksjon i negative helseeffekter fra UV-stråler.



Figur 1. Hensikten med nytte- og risikovurderingen.

Solkrem og solkremingredienser

Både solkremprodukter og noen utvalgte solkremingredienser er inkludert i denne vurderingen. Solkremproduktene ble avgrenset til produkter hvis hovedfunksjon er å beskytte mot UV-stråler; produkter som for eksempel sminke med UV-filtre er derfor ikke inkludert. Solkrem i spray-form og solkremer for lepper er ikke med, fordi disse også kan føre til opptak av ingredienser, henholdsvis via lunger og mage-tarmkanalen.

Av de ingrediensene som benyttes i solkremer, ble kun UV-filtre inkludert, da det er denne ingredienstypen som har som oppgave å beskytte huden mot UV-stråler. Seks UV-filtre som er mye brukt i solkremer på det norske markedet, er tatt med (se tabell 1). Alle UV-filtrene

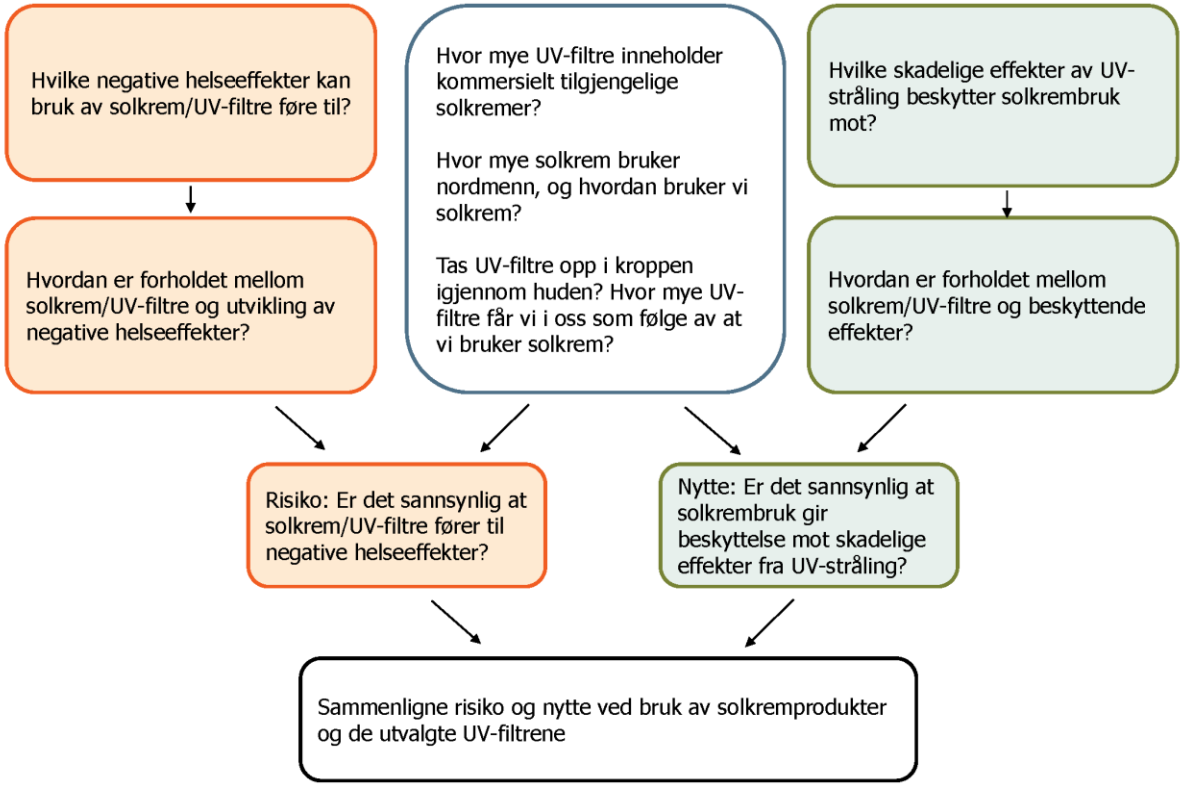
er organiske, bortsett fra titandioksid i nanoform (NP-TiO_2; uorganisk). Ingredienstyper som for eksempel konserveringsmidler, emulgatorer, mykgjøringsmidler, fortykningsmidler, filmdannere og duftstoffer ble ikke tatt med siden disse ingrediensene finnes i en rekke andre kroppspleieprodukter, og det antas at disse produktene utgjør en viktigere kilde til eksponering enn solkremer.

Tabell 1. UV-filtrene som er med i denne vurderingen.

Navn på UV filter	Forkortelse	CAS-nummer
Bis-ethyl-hexyloxyphenol methoxyphenyl triazine	BEMT	187393-00-6
Butyl methoxydibenzoyl methane	BMDBM	70356-09-1
2-Ethylhexyl salicylate	EHS	118-60-5
Ethylhexyl triazone	EHT	88122-99-0
Octocrylene	OC	6197-30- 4
Titanium dioxide nanoparticles (NP)	NP-TiO_2	13463-67-7; 1317-70-0; 1317-80-2

Nytte- og risikovurdering

Trinnene i nytte- og risikovurderingen er vist i figur 2.

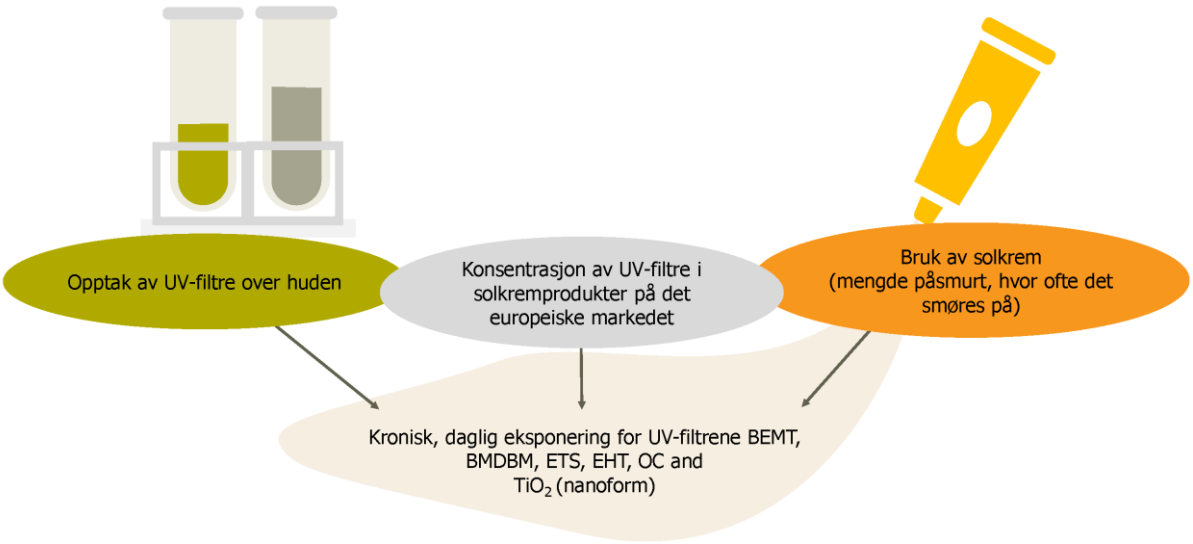


Figur 2. Trinnene i nytte- og risikovurderingen.

VKM har oppsummert forskning på mulige negative og beskyttende effekter av solkrem/UV-filtre på en systematisk måte. Det betyr at vi har brukt en eksplisitt framgangsmåte i formuleringen av spørsmål som skal besvares, i søk etter litteratur, og til å vurdere og sammenstille kunnskapen. Vi inkluderte kun data som ble vurdert til å være av tilstrekkelig kvalitet (et forhåndsdefinert kvalitetsnivå).

Beregne eksponering

VKM beregnet kronisk, daglig eksponering for hvert av de seks utvalgte UV-filtrene slik det er vist i figur 3. For å få et mest mulig realistisk estimat, og for å inkludere variasjonen i parameterne, ble det brukt en probabilistisk metode. Opptak av NP-TiO_2 over hud ble ansett å være ubetydelig.



Figur 3. Parameterne som er inkludert i eksponeringsberegningene.

Identifisering og karakterisering av fare

VKM brukte data fra humane studier og fra dyrestudier til å identifisere mulige negative helseeffekter knyttet til bruk av solkrem og de seks UV-filtrene. I humane studier på effekter av solkrem ble det undersøkt om det er en sammenheng mellom bruk av solkrem og henholdsvis en økt forekomst av melanom og redusert produksjon av vitamin D. I studiene av de seks UV-filtrene ble det sett på systemisk toksisitet og lokale effekter. Systemisk toksisitet inkluderte akutt, subakutt, subkroniske og kronisk toksisitet, gentoksisitet og karsinogenese, og reproduksjons- og utviklingstoksisitet. De lokale effektene omfattet hudirritasjon og hudsensibilisering.

VKM konkluderte følgende om fare:

- Tiltroen til dokumentasjonen for at det er en sammenheng mellom bruk av solkrem og økning i melanom var svært lav.
- Tiltroen til dokumentasjonen for at det er en sammenheng mellom bruk av solkrem og redusert vitamin D-produksjon var lav.
- For de systemiske effektene av de ulike UV-filtrene ble det utledet et null-effekt-nivå (DNEL; derived no effect level) ut ifra det kritiske endepunktet som er vist i dyrestudier. DNEL angir det høyeste nivået for eksponering av et stoff som mennesker ikke bør utsettes for. DNEL fastsettes ved at en verdi for eksponering som ikke gir negativ effekt, deles på usikkerheten i denne verdien.
- De seks UV-filtrene utgjør ingen fare for negative lokale effekter. Det fastsettes ikke DNEL for lokale effekter.

Karakterisering av risiko

På grunn av at det ikke var god nok dokumentasjon for å vurdere om bruk av solkrem var assosiert med økt utvikling av melanom og redusert vitamin D-produksjon, var det ikke mulig å si noe om en eventuell risiko.

Siden det ble konkludert at de seks UV-filtrene ikke utgjør noen fare for negative lokale effekter, konkluderte VKM med at risikoen for hudirritasjon og hudsensibilisering er ubetydelig for den generelle befolkningen.

For å karakterisere risikoen knyttet til systemisk toksisitet for UV-filtrene, ble ratioen mellom eksponeringen for UV-filtrene og DNEL beregnet. En ratio <1 ble ansett å ikke representere en risiko for negative helseeffekter, mens en ratio≥ 1 kan representere en risiko for negative helseeffekter. For BEMT, BMDBM, EHS, EHT og OC var ratioen<1. Siden opptak av NP-TiO_2 over hud antas å være ubetydelig, anses NP-TiO_2 å ikke føre til systemisk toksisitet.

VKM konkluderer med at risikoen for negative helseeffekter av de seks UV-filtrene er ubetydelig.

Identifisering og karakterisering av beskyttende helseeffekter

VKM brukte data fra humane studier til å identifisere mulige beskyttende helseeffekter knyttet til bruk av solkrem. I studiene ble det undersøkt om det er en sammenheng mellom bruk av solkrem og beskyttelse mot henholdsvis melanom, aktinisk keratose, basalcellekarsinom, plateepitelkarsinom og immunsuppresjon.

VKM konkluderte følgende om beskyttende effekter:

- Tiltroen til evidensen for en sammenheng mellom bruk av solkrem og immunsuppresjon er lav.
- Det er ikke tilstrekkelig evidens tilgjengelig for å vurdere om bruk av solkrem beskytter mot basalcellekarsinom.

- Tiltroen til evidensen for en sammenheng mellom bruk av solkrem og redusert forekomst av melanom er lav.
- Tiltroen til evidensen for en sammenheng mellom bruk av solkrem redusert forekomst av aktinisk keratose og plateepitelkarsinom er moderat.
- Samlet sett, for helseutfallet hudkreft, antas bruk av solkrem å beskytte mot visse typer. Beskyttelsen er større for plateepitelkarsinom og aktinisk keratose enn for melanom.

Karakterisering av nytte

VKM vurderte at markøren som var studert for å se om solkrem beskytter mot immunsuppresjon er utilstrekkelig, og det ble derfor ikke vurdert om solkrem beskytter mot immunsuppresjon.

Bruk av solkrem antas å være gunstig som beskyttelse mot visse typer hudkreft. Fordelen er større for plateepitelkarsinom og aktinisk keratose enn for melanom. Det er ikke sannsynlig at solkrem beskytter mot basalcellekarsinom.

Risiko- og nyttekonklusjon

VKM konkluderer med at risikoen knyttet til påsmøring av de seks UV-filtrene på huden er ubetydelig, siden den reelle mengden vi smører på oss av disse UV-filtrene er flere ganger lavere enn mengdene som kan forårsake negative helseeffekter. Det ble ikke vurdert om bruk av solkrem kan utgjøre en risiko på grunn av manglende evidens. Bruk av solkrem beskytter mot visse hudkreftformer og er derfor gunstig for den generelle norske befolkningen.

1 Introduction

In 2020, melanoma and non-melanoma skin cancers were the 19th and fourth most commonly occurring cancers, respectively, in men and women globally (Sung et al., 2021). In Norway, the incidence of skin cancer is among the highest worldwide (Bray et al., 2018). The incidence rate of melanoma, the most severe form of skin cancers, increased by more than 50% during the period 2000-2020 (Cancer Registry of Norway, 2021). The mortality rate in Norway due to malignant melanoma, is the highest in Europe (Sacchetto et al., 2018).

About 2300 new cases of malignant melanoma and 3000 new squamous cell carcinomas were diagnosed in Norway in 2020. (Cancer Registry of Norway, 2021). Basal cell carcinomas are not publicly registered in Norway, but the incidence is estimated to be 20000-25000 per year (The Norwegian Cancer Society, 2022). About 90% of skin cancers are expected to result from exposure to ultraviolet radiation (UVR).

One of the protection measures against skin cancers is the use of sunscreen (WHO.org, The Norwegian Cancer Society, 2022). Sunscreens are legally regulated as cosmetic products in the EU (Regulation (EC) No 1223/2009). Only UV filters included in the positive list of approved filters in Annex VI to the Cosmetics Regulation may be used in cosmetics up to the maximum allowed concentration (Regulation (EC) No 1223/2009). Currently, the positive list consists of 32 entries (European Commission, 2009). The Cosmetics Regulation (Regulation (EC) No 1223/2009) specifies that all sunscreen products must be safe under normal and reasonably foreseeable use conditions.

Concerns are occasionally raised whether exposure to sunscreens and their specific ingredients pose a risk to human health as well as to the environmental. These concerns may come from the public, consumer organisations, or researchers. Health concerns addressed are *e.g.* contact dermatitis and endocrine disruptive effects, caused by direct exposure to ingredients in sunscreens or in combination with UVR. Another potential adverse effect of sunscreen use is reduced vitamin D synthesis, which may result indirectly by attenuation of UVR to the skin.

On this background, VKM wants to contribute to a clarification of risk and benefit of the use of sunscreens. A scoping review of systematic reviews on environmental effects of sunscreens was published 2020 (VKM et al., 2020b) and a revised protocol for the current risk-benefit assessment was published 2020 (VKM et al., 2020a). The VKM used methodological tools for systematic reviews to ensure quality, transparency, reproducibility and objectivity as described in Chapter 5, 6 and 7. In line with this view, scripts made to obtain exposure estimates, and the data used for the exposure estimates, are published together with the assessment.

1.1 Ultraviolet radiation (UVR)

Ultraviolet radiation (UVR) covers the electromagnetic wavelength range of 100–400 nm, and is divided in the three bands ultraviolet radiation A (UV-A, 315-400 nm), ultraviolet radiation B (UV-B, 280-315 nm) and ultraviolet radiation C (UV-C, 100-280 nm) (CIE, 2011). UVR comes naturally from the sun, but is also generated by artificial lamp sources such as halogen and xenon lamps, fluorescent tubes and light emitting diodes to be used *e.g.* in sunbeds, medical treatments apparatus and a diversity of instruments. The UVR part of the solar energy that reaches the Earth's surface comprises about 5-6%. UVA irradiation is 10 to 100 times more abundant than UVB (Moan, 2006). Typically, in the middle of the day, the available UVR consists of about 95% UVA and 5% UVB. Wavelengths shorter than about 280 nm are absorbed mainly by stratospheric ozone; thus, all the UV-C and approximately 90% of the UV-B radiation are removed (IARC, 2012). The radiant energy of solar UVR, especially that of UV-B, depends on the solar elevation and varies with season, time of day and latitude (WHO, 2016). The radiant energy emitted from the Sun or an artificial source and received on a surface is measured in irradiance (W/cm^2). The product of irradiance and irradiation time (s) gives the radiant exposure (J/cm^2), often referred to as the popularised term "UV dose" in this assessment.

1.1.1 UVR-induced effects

UVB is about 1000 times more efficient than UVA in inducing biological adverse effects such as sunburn and DNA damage. Whether health effects are induced by UVR and to which extent, depend on the irradiance, exposure duration and, indirectly, the radiant exposure, as well as the frequency and mode of exposure, *i.e.* whether the irradiation is received continuously or intermittently. Among the factors that determine individual sensitivity to UVR are skin characteristics, *e.g.* degree and type of pigmentation, immunology, and genetics.

Most UVB is absorbed by and can damage and cause reddening (erythema) and sunburn of the epidermis, the outermost skin layer. This layer includes the outer multi-layered squamous cell epithelium (*stratum corneum*). The deepest layer of epidermis is the basal cell layer (*stratum basale*) from which the cells divide and are pushed outward while maturing and being keratinised. Keratinocytes comprise more than 90% of epidermal cells. Also residing in epidemis are the antigen-presenting macrophages Langerhans cells. Melanocytes in the basal layer produce the brownish-black pigment melanin, which reside in the keratinocytes as melanosomes. The UV-visible absorption of melanin decreases with increasing wavelength. Another UVB absorbing substance in epidermis, predominantly in the *stratum corneum*, is urocanic acid. The cis-isomer of urocanic acid is associated with suppression of induction of immunity in skin (Dahl et al., 2010). An advantageous effect of UVB exposure is the synthesis of vitamin D following absorption of 7-dehydrocholesterol in keratinocytes in the epidermis. Of the incident radiation on skin, about 10% of UVB and 50% of UVA reaches the basal layer of the epithelium. UVA can reach the dermis, the vascularised

layer below the epidermis, and damage collagen and elastic fibres, a process called photoaging.

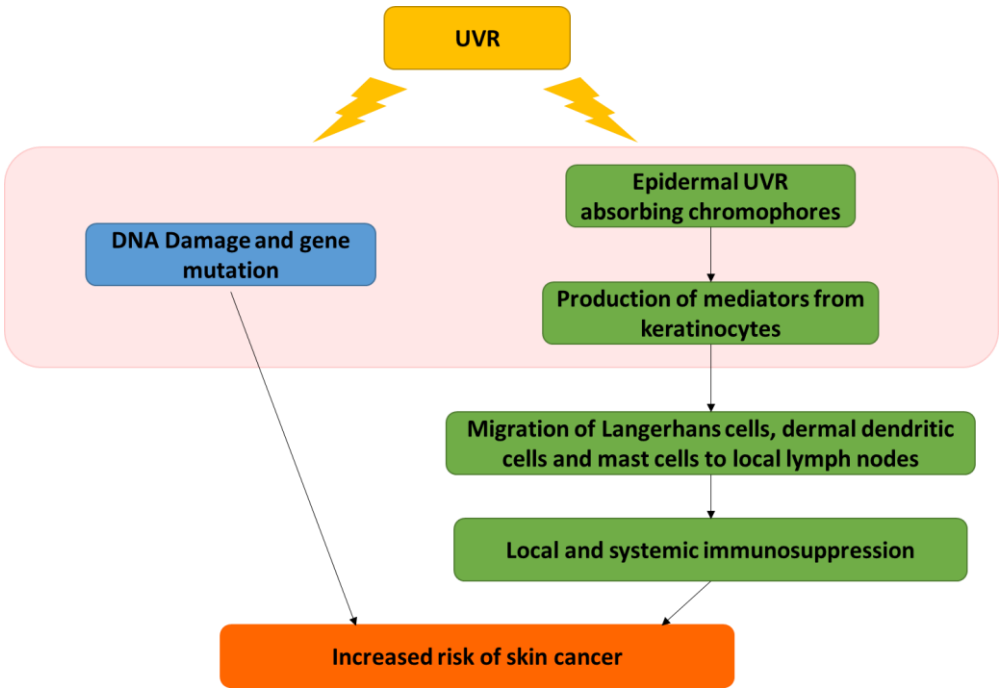


Figure 1.1.1-1. Schematic illustration of the major steps leading to increased risk of skin cancer by immunosuppression induced by UVR exposure. UVR can cause direct DNA damage but also lead to immunosuppression creating a favourable environment for tumor development. Initially, energy of UVR is absorbed by epidermal chromophores and components of keratinocytes. UVR induced responses of keratinocytes may initiate several pathways leading to immunosuppression, including formation of platelet activating factor (PAF) and PAF-like lipids, production of cytokines, chemokines and surface markers. These mediators may then signal migration of Langerhans cells to the draining nodes where they cause an activation of T regulatory cells. UVR exposure may also stimulates dermal dendritic cells to migrate to the draining lymph nodes where UVR-induced activation of the aryl hydrocarbon receptor (AhR) may cause a switch from a stimulatory into a regulatory phenotype of these cells supporting a generation of T regulatory cells. Thus, UVR leads to a greater number of T regulatory cells and fewer effector T cells in the skin, shifting the balance from T cell-mediated immunity to immunosuppression. With regard to systemically immunosuppression, dermal mast cells are important mediators. Other important mediators of immunosuppression are neuropeptide release from keratinocytes, complement activation, activation of monocytes, macrophages, B regulatory cells and natural killer (NK) T cells (Hart and Norval, 2018; Yu et al., 2014). The figure is modified from Hart and Norval (2018).

Aside from the DNA-protective effects of melanin and urocanic acid, thickening of the epidermis following UV exposure protects the skin against further exposure. Furthermore, several DNA-repair mechanisms in epidermal cells prevent mutations and development of skin cancers. The most common skin cancers are the non-melanoma (keratinocyte) skin cancers basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) that originate in basal cells and squamous cells, respectively, and malignant melanoma which originates in melanocytes. A direct link between UVR and carcinogenicity has been made, and the

International Agency for Research on Cancer (IARC) has classified UVR as carcinogenic to humans (Wild et al., 2020).

The median age for diagnosis of malignant melanoma in Norway was 66 years in the time period 2016-2020. This cancer is the second most frequently occurring in the age group 25-49 years (Cancer Registry of Norway, 2021). The latency time for onset has been reported to be 10-50 years (Rushton and J Hutchings, 2017). Most of the patients being diagnosed with squamous cell carcinoma are above 60 years of age. The median age at diagnosis was 79 years for the non-melanoma skin cancers in the years 2016-2020 (Cancer Registry of Norway, 2021). The latency time from UV damage to onset of basal cell carcinoma is 20-50 years (Pollock et al., 2008).

1.2 UVR skin protection

Solar UV protection recommendations of WHO are to limit sun exposure in the midday sun, seeking shade, wearing protective clothing, and lastly, to use a sunscreen of sun protection factor (SPF) 15+. Sunscreens are considered necessary for UV-exposed parts like the hands and face. It should never be used to prolong the duration of sun exposure (WHO, 2022). The Norwegian Cancer Society mirrors these recommendations: In addition to restricting the midday time spent in the sun, the protective measures are shade, clothing and use of sunscreen SPF 30+ (Norwegian Cancer Society, 2022).

Sunscreens are formulated products to be applied on the skin to protect against adverse effects of UVR. The protective effect is due to UV filters that act by absorbing, scattering or reflecting UVR. The SPF gives an indication of the effectiveness of the sunscreen (ISO, 2022). According to the ISO standard for sun protection test methods, the SPF "is a ratio calculated from the energies required to induce a minimum erythemal response with and without sunscreen product applied to the skin of human test subjects. It uses ultraviolet radiation usually from an artificial source." (ISO, 2022). The EU Commission Recommendation (2006) includes minimum degrees of protection to consider a sunscreen effective and sets requirements for products to be marketed as sunscreens: SPF must be at least 6 against UVB, and the UVA protection factor must be 1/3 of the SPF. In addition, the so-called "critical wavelength", *i.e* the wavelength below which the area under the absorbance curve represents 90% of the total area under the curve in the UV region (290-400 nm), must be at least 370 nm (FDA, 2022). UV filters are commonly divided into organic (carbon-based or "chemical") and inorganic (mineral-based or "physical") filters. The main protection mechanism for both is absorption rather than reflection and scattering. Both filter types can protect against UVA and UVB radiation (BASF, 2022), but not all filters protect against the full solar UV range. Sunscreen products may contain combinations of several organic and/or inorganic filters.

In countries where solar UVB exposure is sufficient to contribute to vitamin D synthesis in humans throughout the year and the diet contributes sparingly to the vitamin, the UVB radiation may be a major contributor to a satisfactory vitamin D status. In Norway with

latitudes between 58 and 71°N, the UV exposure is inadequate for efficient vitamin D synthesis (Brustad and Meyer, 2014) for about 5 -7 months of the year, depending on latitude. The population is therefore dependent on vitamin D in the diet and supplements when needed. The relevance of and interest in vitamin D has been the subject of debate among researchers for decades (Amrein et al. 2020), probably contributing to high public interest. Consequently, with the focus of avoiding vitamin D deficiency a concern has arisen about the potential of sunscreens to reduce the synthesis following absorption of UVB in skin. Studies report that sunscreen both may prevent vitamin D synthesis (Shahriari et al., 2010) and the opposite (Young et al., 2019).

1.3 Risk-benefit assessment

An overview of the steps included in a risk-benefit assessment is shown in Figure 1.3-1. In this risk-benefit assessment, the term "health protective effect" is used instead of "positive health effect" or "reduced adverse health effect".

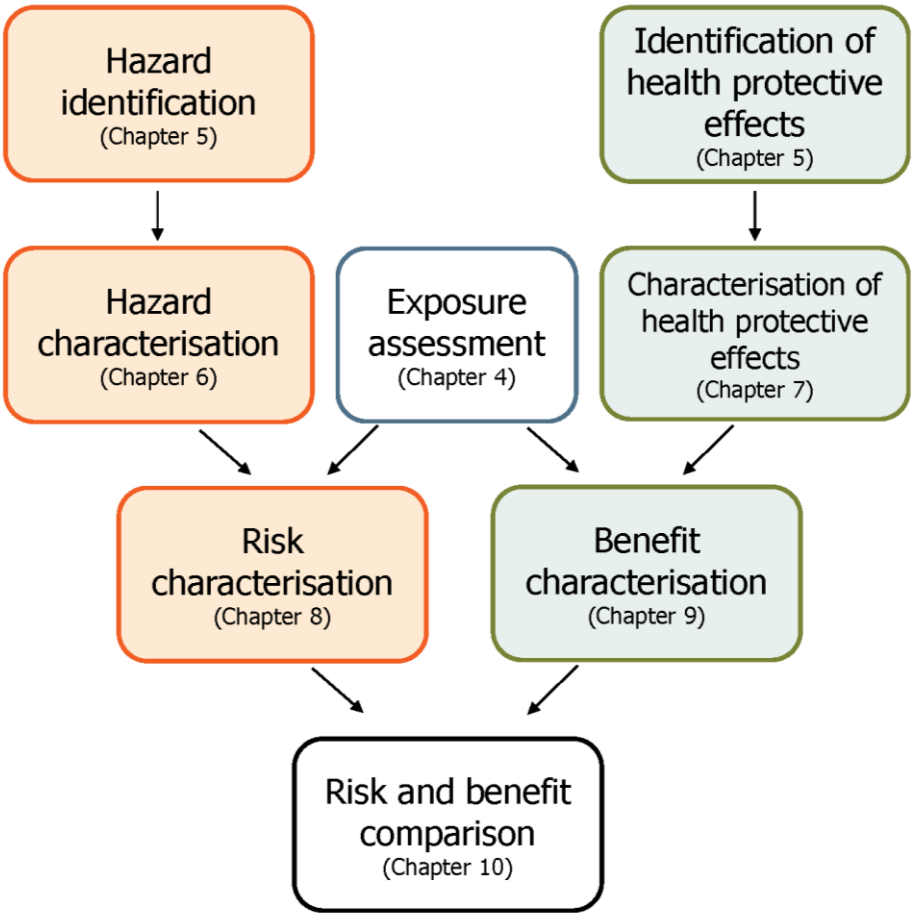


Figure 1.3-1. The individual steps in a risk-benefit assessment modified from EFSA Scientific Committee (2010).The hazard assessment was performed for sunscreen products and six selected UV filters, whereas the assessment of health protective effects was performed for sunscreen products.

2 Aim, limitations, selection of ingredients, and research questions

2.1 Aim

As outlined in the protocol (VKM et al., 2020) for this risk-benefit assessment of sunscreens, we aim to identify and compare adverse health effects caused by sunscreen products and their ingredients with protective effects (*i.e.* reduction in solar UVR-induced adverse health effects) of sunscreen products. Thus, protective effects are not evaluated on an ingredient basis. More specifically, we will:

- Estimate the exposure to sunscreen ingredients when used as solar UVR protection
- Identify and characterise adverse health effects related to use of sunscreen products and selected ingredients
- Identify and characterise the protective effects related to use of sunscreen products.
- Characterise health risks related to sunscreen products and selected ingredients when used as protection against solar UVR
- Characterise health benefits related to sunscreen products when used as protection against solar UVR
- Compare risks and benefits of sunscreen products when used as protection against solar UVR
- Identify and describe main knowledge gaps that may have an impact on the conclusions

2.2 Delimitations

The protocol (VKM et al., 2020) outlined that both commercially available sunscreen products as such and sunscreen ingredients were to be included in the risk-benefit assessment. However, VKM restricted the inclusion of sunscreen ingredients to UV filters only. The rationale for the choice was due to their role as active substances in attenuation of UVR. In contrast, other ingredients of sunscreens, *e.g.* preservatives, emulsifiers, emollients, thickeners, film formers and fragrances, are present also in a variety of other personal care products. To delimit the assessment to dermal exposure, VKM excluded commercially available sunscreen sprays, which would also include exposure assessment by the inhalation route, and sunscreen products intended for the lips only, which would include assessment by the oral route. We also excluded cosmetics which was not primarily intended for UV protection, but which, nonetheless, contained UV filters.

The adverse effects induced by UVR affect individuals to different degrees and represent different levels of importance for human health. Consequently, VKM ranked the importance of such health effects and included those considered to be "critical" and "important, but not critical", according to an evaluation tool, in the current assessment (Chapter 5).

Data on UV filter concentrations in sunscreens for each of the six selected filters were restricted to sunscreen products on the European market. This restriction was applied to ensure the relevance of the data for sunscreen products on the Norwegian market. However, this may imply that the assessment is less relevant for persons using sunscreen products on the market outside Europe. Tanning behaviour related to use of sunscreens was outside the scope of this risk-benefit assessment.

2.3 Selection of sunscreen ingredients

The most frequently used UV filters on the Norwegian market was assessed in the present opinion. The filters were identified by inspecting the ingredient lists of commercial sunscreen products available online and in physical stores from June to December 2017. One particular brand could have different types of sunscreen products with several different SPFs and combinations of UV filters. In such cases, all sunscreen formulations and types relevant for inclusion and all SPFs of that particular brand, were included. The list of ingredients of cosmetics with a sun protection factor (SPF), but which were not defined as sunscreens, *e.g.* SPF <6, were not checked for the presence of UV filters. Following identification of ingredients in 47 sunscreens, we included the five most frequently occurring organic UV filters. One inorganic UV filter was included to cover both types of filters (Table 2.2-1). These filters were also among the most frequently occurring in sunscreen products described in a Danish report (Mikkelsen et al., 2015). The selected filters are among the allowed substances in the EU regulation Annex VI (Regulation (EC) No 1223/2009). They represent both UVR absorption ranges: mostly UVA (BMDBM); mostly UVB (EHS, EHT, OC); and UVA and UVB combined (BEMT, NP-TiO_2). An overview of names and identifiers, physical and chemical properties is provided in the Appendix (Chapter 15).

Table 2.2-1. UV filters selected for inclusion in the current risk-benefit assessment.

Chemical name of UV filter	Abbreviation	CAS number	Maximum allowed concentration in ready for use preparation*
Bis-ethyl-hexyloxyphenol methoxyphenyl triazine	BEMT	187393-00-6	10%
Butyl methoxydibenzoyl methane	BMDBM	70356-09-1	5%
2-Ethylhexyl salicylate	EHS	118-60-5	5%
Ethylhexyl triazone	EHT	88122-99-0	5%
Octocrylene	OC	6197-30- 4	10%
Titanium dioxide (nano)	NP-TiO_2	13463-67-7; 1317-70-0; 1317-80-2	25%**

*According to Annex VI in the Cosmetics Regulation (EC) No 1223/2009

**In case of combined use of titanium dioxide and titanium dioxide (nano), the sum shall not exceed the limit of 25%.

2.4 Research questions

The questions addressed in the hazard identification and characterisation steps of the assessment are presented in Table 2.4-1.

Table 2.4-1. Questions addressed in the hazard identification and characterisation steps.

Hazard	No	Questions
Identification	1	Is exposure to sunscreen and UV filters, combined or not with UVR, associated with adverse health effects?
Characterisation	2	What are the dose-response relationships between exposure to sunscreen and UV filters, combined or not with UVR, and the adverse effects?
	3	Can a PoD* be identified for UV filters?

*PoD (point of departure): The point on a dose–response curve established from experimental data used to derive a safe level (EFSA Glossary).

The questions addressed with regard to identification and characterisation of the protective ability of sunscreen use against UVR-induced adverse effects (Chapter 5 and 7) are presented in Table 2.4-2.

Table 2.4-2. Question addressed in the identification and characterisation steps of UVR protective effects.

Benefit (protective effects)	No.	Question
Identification	1	Is dermal exposure to sunscreens associated with reduction of adverse effects that are caused by solar UVR?
Characterisation	2	What are the relationships between sunscreen use and reduction of adverse effects caused by solar UVR?

The questions addressed in the exposure assessment are presented in Table 2.4-3.

Table 2.4-3. Questions addressed in the exposure assessment.

	No	Questions
Occurrence	1	What are the concentrations of the included UV filters used in sunscreens?
Use	2	What are the patterns of use of sunscreen in the Norwegian population (amount used, frequency of use, choice of sun protection factor)?
Exposure	3	What is the dermal absorption of the selected UV filters?
	4	What is the internal exposure to UV filters?

2.5 Overview of the exposure assessment and the identification and characterisation of health protective and adverse health effects

2.5 Overview of the exposure assessment and the identification and characterisation of health protective and adverse health effects

The research questions addressed and methods used to answer them in the exposure assessment (Chapter 4) is given in Figure 2.5-1.

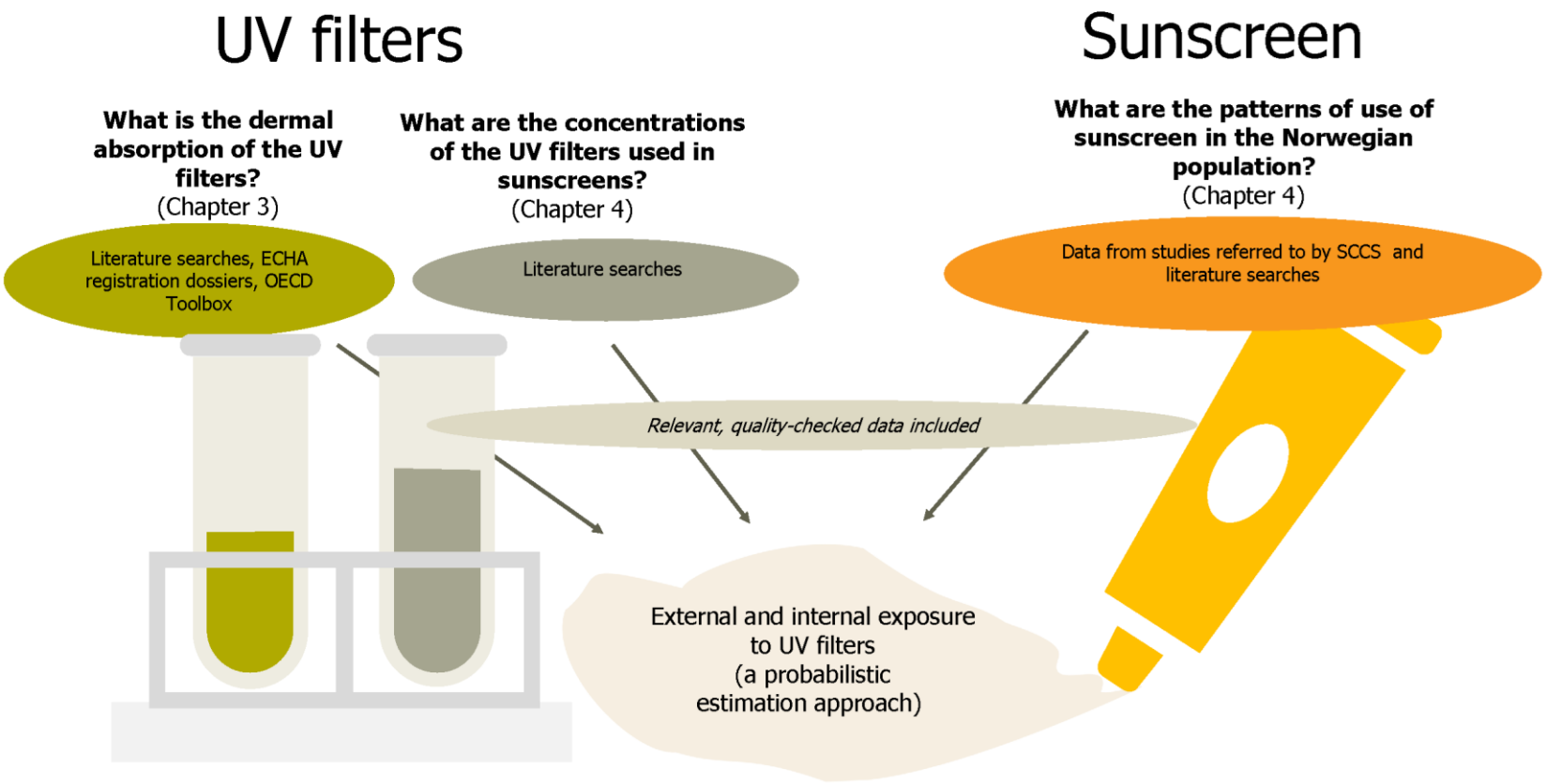


Figure 2.5-1. An overview of the exposure assessment (Chapter 4). SCCS: Scientific Committee for Consumer Safety.

An overview of the research questions addressed and answered, as well asassessment methods in the identification and characterisation of health protective and adverse health effects (Chapter 5, 6 and 7) is given in Figure 2.5-2.

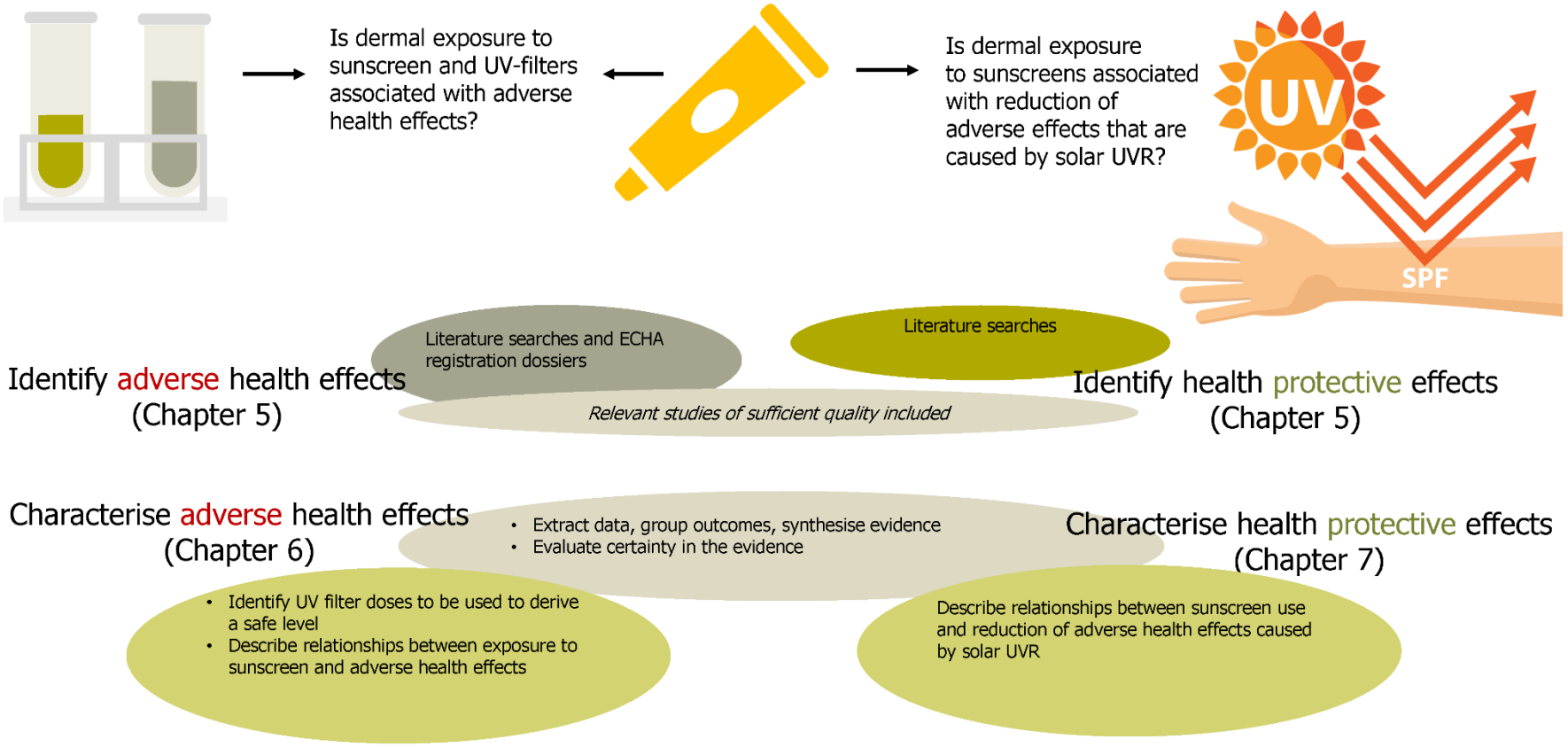


Figure 2.5-2. The identification (Chapter 5) and characterisation of hazard (Chapter 6) and health protective effects (Chapter 7).

3 Absorption, distribution, metabolism and excretion (ADME)

3.1 BEMT (CAS number 187393-00-6)

A literature search was performed in PubMed to identify relevant studies addressing dermal absorption of BEMT (see Chapter 16.1 for search terms and search strategy). Eight studies were identified in the search. The full-text articles were assessed by one reviewer, and one relevant article on dermal absorption was identified (Souza et al., 2017). Souza used a low concentration of BEMT (4%) compared to the allowed maximum concentration (10%), and the number of replicates was six and not the recommended eight replicates. The dermal absorption was reported to be 9.14±1.86% (mean±SD). An overview of study characteristics is given in Table 3.1-1.

In Souza *et al.* BEMT was not detected in the receptor fluid. The epidermis should, therefore, be excluded from the calculation of the dermal absorption (SCCS, 2021). Since the value for dermal absorption was reported as the amount in dermis and epidermis together and not for the two compartments separately, both compartents is included in the dermal absorption value.

In the registration dossier for BEMT (ECHA, 2021c), two key studies were described. One of the studies was a 13 week *in vivo* dermal absorption study in rats (OECD 427) in which reported dermal absorption values ranging between 0.01 to 0.06%. The other study addressed toxicokinetics following oral intake of BEMT. The ADME data in the ECHA registration dossier for BEMT is presented in Table 3.1-2 (ECHA, 2021c).

The physicochemical properties of BEMT are indicative of very low dermal absorption (molecular weight >500 Da and LogP ≥4), in addition to low solubility), whereas a dermal absorption value of around 9% was reported in Souza *et al.* (2017). Since epidermis is included in this value it most likely represents an overestimate of the dermal absorption of BEMT. Therefore,

Table 3.1-1. Characteristics of the included study of dermal absorption of BEMT identified in the literature search.

Reference/model	Dose/number	BEMT concentration	Exposure period	Mass balance	% dermally absorbed (mean ± SD)	Comment
Souza et al., 2017 ***In vitro,* porcine skin**	2.0 mg/cm^2 n=6	4% (w/w) in a sunscreen formulation	24 h	100.6%	Total dermal absorption: 7.31 ± 1.49 µg/cm^2. This corresponds to: 9.14 ± 1.86%	According to the guideline, 8 replicates from 4 donors should be included

Table 3.1-2 ADME studies of BEMT identified in the ECHA registration dossier; study characteristics and reliability.

Reference	Model/administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
ECHA (2021c)	Rat, oral (gavage) OECD Guideline 417 (Toxicokinetics) GLP compliance: yes Study report, 2002	50 mg/kg bw	Key study 1 - reliable without restrictions	Absorption: negligible (blood samples below limit of detection). Distribution: <0.01% of the dose remained in tissues. No specific target tissue was identified. 0.26% of dose (males) and 0.1% of dose (females) remained in residual carcass. Metabolism: >99.6% of dose were excreted as unchanged test substance. No metabolites were identified, and >99.6% of the dose was excreted as unchanged test substance.

Reference	Model/administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
				Excretion: 94% in faeces and 0.1% in urine (males), 97% in faeces and 0.2% in urine (females).
	Rat, dermal OECD Guideline 427 (Skin Absorption: In Vivo Method) GLP compliance: yes Study report, 2004	Daily: 0, 250, 500, 1000 (without collar), 1000 (with collar) mg/kg bw for 13 weeks.	Key study 1 - reliable without restrictions	The absorption was about 0.01 to 0.06% for 1000 mg/kg bw.

ECHA (2021c) concluded that BEMT has a very low potential for absorption via oral and dermal routes.

3.2 BMDBM (CAS number 70356-09-1)

A literature search was performed in PubMed to identify relevant studies addressing dermal absorption of BMDBM (see Chapter 16.2 for search terms and search strategy). Five studies were identified in the search. The full-text articles were assessed by one reviewer, and two relevant articles on dermal absorption were identified (Chatelain et al., 2003; Montenegro et al., 2013). In addition, two studies in the ECHA reagistration dossier were relevant regarding dermal absorption. An overview of study characteristics is given in Table 3.2-1.

None of the studies fulfilled enough criteria for *in vitro* dermal absorption experiments to be used as a key study (see Table 3.2-1). However, since exposure estimates in the present opinion are based on a distribution of values, it was decided to use the following dermal absorption values for the exposure estimates for MBDBM:

- 0.1% from Chatelain et al.: Values from BMDBM in emulsion, the vehicle most resembling a sunscreen lotion. Longest exposure time
- 0.8% from Montenegro et al.: Mean+2SD of the test items with 0-8-1.5% BMDBM in emulsion
- 1.8% and 4.5% from ECHA supporting study (porcine skin): The mean of the values reported after application of 2 or 7.5% BMDBM in oil-in-water lotion, oil-in-water cream or water-in-oil cream. Mean+2SD for the 2% and 7.5% formulations were used.

- 7.3% from ECHA supporting study (human skin): BMDBM was not detected in the receptor fluid. According to the SCCS Notes of Guidance (SCCS, 2021), in the case of substances with very low dermal absorption and limited permeation, the epidermis may be excluded from the calculations when it is demonstrated that no movement of the chemicals from the skin reservoir to the receptor fluid occurs. Therefore, the mean value without epidermis after 18 hours exposure time were used.

Data on ADME in the registration dossier for BMDBM (ECHA, 2021a) is presented in Table 3.2-2.

Based on data presented in Table 3.2-1 and 3.2-2, the dermal absorption values for BMDBM used in the exposure estimation are 0.1, 0.8, 1.8, 4.5, and 7.3%.

Table 3.2-1. Characteristics of included dermal absorption studies of BMDBM identified in the literature search. (O/W: oil-in-water; W/O: water-in-oil)

Reference/model	Dose/ number	Concentration	Exposure period	Mass balance	% dermally absorbed (mean ± SD)	Comment
Chatelain et al., 2003 ***In vitro*, human skin**	3 mg/cm^2 n=4	2% (w/w) in O/W emulsion or petrolatum jelly	0.5 and 6 h	85-95%	Emulsion: 0.1% Petrolatum: 0.2%	According to the guideline: The exposure period should be 24 h The number of replicates should be 8 from 4 different donors SC not removed from epidermis after the exposure period SD not reported

Reference/model	Dose/ number	Concentration	Exposure period	Mass balance	% dermally absorbed (mean ± SD)	Comment
Montenegro et al. 2013 ***In vitro*, human *Stratum corneum* and epidermis (SCE membranes)**	20 mg/cm^2 n not reported	0.2-1% in 6 O/W emulsions for sun protection 0.2% in 4 oil vehicles	24 h	Not reported	Calculated from µg/cm^2 Emulsion 1: 3.13±0.15 2: 0.81±0.04 3: 0.66±0.04 4: 0.42±0.03 5: 0.67±0.04 6: 0.82±0.04 Oil A: 3.00±0.28 B: 3.40±0.48 C: 2.85±0.33 D: 3.7±0.40	According to the guideline: The number of replicates should be 8 from 4 different donors Mass balance: Not reported Measures of cumulative amount permeated through the SCE membranes
From ECHA (a study from 1982) Supporting study ***In vitro*, human skin**	2.5 mg/cm^2 n=1 per dose and exposure period	2% in W/O cream	1, 6, 18 h		1 hrs: 0.38 6 hrs: 0.66 18 hrs: 10.14 Values without epidermis 1 hrs: 0.20 6 hrs: 0.37 18 hrs: 7.30	According to the guideline: The exposure period should be 24 h The number of replicates should be 8 from 4 different donors Mass balance not reported

Reference/model	Dose/ number	Concentration	Exposure period	Mass balance	% dermally absorbed (mean ± SD)	Comment
From ECHA (a study from 1982) Supporting study ***In vitro*, pig skin**	O/W lotion, O/W cream, W/O cream N=1 per dose and exposure period	2 and 7.5% (0.6-2.25 µg/cm^2=	6 h	95-97%	2% BMDBM in - O/W lotion 0.9 - O/W cream 1.2 - W/O cream 1.5 7.5% BMDBM in • O/W lotion 2.8 • O/W cream 3.5 • W/O cream 3.9	According to the guideline: The exposure period should be 24 h The number of replicates should be 8 from 4 different donors Dermis and epidermis not separated before analysis

Table 3.2-2 ADME studies of BMDBM identified in the ECHA registration dossier; study characteristics and reliability. Ci: curie

Reference	Model/administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
ECHA (2021a)	Gas chromatography, OECD Guideline 107 (Partition Coefficient (n-octanol / water), Shake Flask Method), OECD Guideline 117 (Partition Coefficient (n-octanol / water), HPLC Method), EU Method A.8 (Partition Coefficient)		Key study 1 - reliable without restrictions	The partition coefficient, log Pow, of tert-butyl-4-methoxy-4'-dibenzoylmethane was calculated from the individual solubilities in n-octanol and in water, respectively, to be 6.1.

Reference	Model/administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
	GLP compliance: yes Other result type, 2009			
ECHA (2021a)	Healthy human volunteers, dermal, absorption and excretion study GLP compliance: no Study report, 1980	10% / 25 µCi, 8 h single treatment	Supporting study 2 – reliable with restrictions	High recovery of the dose from the skin, undetectable radioactivity in plasma and faeces and a very low percentage of the applied dose excreted in the urine.
ECHA (2021a)	Skin from miniature swine, dermal OECD 428 skin-*in vitro* GLP compliance: no Study report, 1982	600 and 2250 µg, for 6 h	Supporting study 2 – reliable with restrictions	After 6 h exposure, the majority of the applied dose was recovered (minimum 97.1%). The total penetration rate value was between 0.9% and 3.9%. No significant differences were noted when values of the penetration rate of BMDBM from the 3 vehicles used were compared.
ECHA (2021a)	Human cadaver abdominal skin samples GLP compliance: no Study report, 1982	100 µg, 1, 6, and 18 h	Supporting study 2 – reliable with restrictions	Uniform skin penetration into the epidermis and the upper corium to about 600 - 800 µm, the concentration increased as a function of time. Further penetration into the deeper layers was very slowly. No radioactivity detected in the penetration chamber water at any time.

Additional information on oral absorption from the ECHA registration dossier (ECHA, 2021a): "A systemic biological effect involving the liver was seen in the oral 13 week rat study (DSM,1983) at the high dose of 1000 mg/kg bw/day. This indirectly indicates there is bioavailability of parent or of metabolites following oral intake at high dosage but gives no indication of the amount absorbed."

3.3 EHS (CAS number 118-60-5)

A literature search was performed in PubMed to identify relevant studies addressing dermal absorption of EHS (see Chapter 16.3 for search terms and search strategy). Eight studies were identified in the search, the full-text articles were assessed by one reviewer, and two relevant articles on dermal absorption were identified (Chatelain et al., 2003; Walters et al., 1997. An overview of study characteristics is given in Table 3.3-1. Data on absorption in the ECHA registration dossier for EHS is presented in Table 3.3-2 (ECHA, 2021b). Information in Walters et al. (1997) and the key study (see Table 3.3-1) in the ECHA registration dossier are based on the same experiment.

None of the studies fulfilled enough criteria for *in vitro* dermal absorption experiments to be used as a key study. However, since exposure estimates in the present opinion are based on a distribution of values, it was decided to use the following dermal absorption values for the exposure estimates for EHS:

- 0.2% from Chaterlaine et al.: Values from EHS in emulsion, the vehicle most resembling a sunscreen lotion. Longest exposure time
- 1.0% from Walters et al.: Mean+2SD of EHS in emulsion, the vehicle most resembling a sunscreen lotion. Both finite and infinite doses
- 3% from ECHA's endpoint summary for toxicokinetics, metabolism and distribution (ECHA, 20121).

Table 3.3-1. Characteristics of included dermal absorption studies of EHS identified in the literature search. H/A formulation: hydroalcoholic formulation; O/W: oil-in-water; SC: *stratum corneum*

Reference/model	Dose/ number	Concentration	Exposure period	Mass balance	% dermally absorbed (mean ± SD)	Comment
Chatelain et al., 2003 ***In vitro*, human skin**	3 mg/cm^2 N=4	5% in O/W emulsion or petrolatum jelly	0.5 and 6 h	85-95%	Emulsion: 0.2% ± NR Petrolatum: 0.5 hr: 0.2% ± NR 6 hrs: 0.3% ± NR	According to the guideline: The exposure period should be 24 h

Reference/model	Dose/ number	Concentration	Exposure period	Mass balance	% dermally absorbed (mean ± SD)	Comment
						The number of replicates should be 8 from 4 different donors SC not removed from epidermis after the exposure period SD not reported
Walters et al., 1997 ***In vitro*, human *Stratum corneum* and epidermis (SCE membranes)**	Finite dose: 5.4 mg/cm^2 (O/W) 5.1 µl/cm^2 (H/A) Infinite dose 117 mg/cm^2 (O/W) 100 µl/cm^2 (H/A)	5% in O/W emulsion or H/A formulation	48 h	Finite dose: 55 and 70% Infinite dose: 46 and 83%	Finite dose: • O/W: 0.65 ± 0.16% • H/A: 0.59 ± 0.09% Infinite dose: • O/W: 0.47 ± 0.22% • H/A: 0.23 ± 0.05%	According to the guideline: The exposure period should be 24 h The mass balance too low* (requirement: 85-115%) SC not removed from epidermis after the exposure period

*Based on the background of a test with better washing procedure, the authors states that it is likely that the poor recovery was the results of incomplete recovery from the donor side of the system and that the % absorbed EHS would not have been affected by the low recovery in the main experiments.

Table 3.3-2 Absorption studies of EHS identified in the ECHA registration dossier; study characteristics and reliability.

Reference	Model/administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
ECHA (2021b)	Human skin OECD Guideline 428 (Skin Absorption: *In vitro* Method) GLP compliance: yes Study report, 1993	• Dose: 51.58 ± 0.36 µg/cm^2 • Dose: 527.54 ± 13.91 µg/cm^2 • Dose: 51.58 ± 0.25 µg/cm^2 • Dose: 11.28 ± 2.55 µg/cm^2 • Dose: 1.65 ± 0.39 µg/cm^2 48 h	Key study 2 - reliable with restrictions	• Absorption: > 0.49 - < 0.81 % • Absorption: > 0.25 - < 0.69 % • Absorption: > 0.5 - < 0.68 % • Absorption: > 0.18 - < 0.28 % • Absorption: > 0.91 - < 1.37 %
ECHA (2021b)	Human skin OECD Guideline 428 (Skin Absorption: *In vitro* Method) GLP compliance: no Publication, 1996	2.26 and 2.52 mg/cm², for 2 min, 30 min, 2 hours and 6 hours, applying 3% in o/w emulsion or 3% in in petroleum jelly	Supporting study 2 - reliable with restrictions	• Absorption for 2.26 mg/cm^2, 3% in o/w emulsion, for 2 min: 0.94% • Absorption for 2.26 mg/cm^2, 3% in o/w emulsion, for 30 min: 2.13% • Absorption for 2.26 mg/cm^2, 3% in o/w emulsion, for 2 h: 1.54% • Absorption for 2.26 mg/cm^2, 3% in o/w emulsion, for 6 h: 7.29% • Absorption for 2.52 mg/cm^2, 3% in petroleum jelly, for 2 min: 1.81% • Absorption for 2.26 mg/cm^2, 3% in petroleum jelly, for 30 min: 0.6% • Absorption for 2.26 mg/cm^2, 3% in petroleum jelly, for 2 h: 1.97%

Reference	Model/administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
				• Absorption for 2.26 mg/cm^2, 3% in petroleum jelly, for 6 h: 1.96%

Additional information on oral absorption from the ECHA registration dossier (ECHA, 2021b): "It is concluded that the absorption of 2-ethylhexyl salicylate via the dermal route is very low (3%), while it is well absorbed via the oral route (100% absorption assumed)."

3.4 EHT (CAS number 88122-99-0)

A literature search was performed in PubMed to identify relevant studies addressing dermal absorption of EHT (see Chapter 164 for search terms and search strategy). Eight studies were identified in the search, the full-text articles were assessed by one reviewer, and three relevant articles on dermal absorption were identified (Pottard et al. 1999; Hojerova et al., 2017; Souza et al., 2017). An overview of study characteristics is given in Table 3.4-1. The studies fulfilled many of the criteria for *in vitro* dermal absorption experiments, and we therefore decided to use the the mean +1 SD as dermal absorption values for the exposure estimates for EHT:

- 0.1% from Pottard et al.: EHT was not be detected in the receptor fluid. According to the SCCS Notes of Guidance (SCCS, 2021), in the case of substances with very low dermal absorption and limited permeation, the epidermis may be excluded from the calculations when it is demonstrated that no movement of the chemicals from the skin reservoir to the receptor fluid occurs. Therefore, the mean value without epidermis after 16 hours exposure time were used.
- 4.1 % from Souza et al.
- 6.5% from Hojerova et al.: Based on two applications of EHT in emulsion
- 10.4% from Hojerova et al.: Based on one application of EHT in emulsion

According to the key information in the ECHA registration dossier (ECHA, 2021f) "no specific toxicokinetic data are available, however it can be predicted that the substance will have low oral and dermal bioavailability ". Two of the studies retrieved from the literatur search (Hojerova et al. and Souza et al.) concluded that EHT can be dermally absorbed to a greater extent than reported by Pottard et al. It should be noted that EHT was not detected in the receptor fluid in Hojerova et al. and Souza et al. The epidermis could, therefore, be excluded from the calculation of the dermal absorption. Because the value for dermal absorption in these studies was reported as the amount in dermis and epidermis together and not for the two compartments separately, both compartents are included in the abovementioned dermal absorption values. However, since the quality of the studies was comparable, fulfilled several of the criteria for *in vitro* dermal absorption studies and the reported values covered a relatively large range (4.1-10.4%), VKM decided to use all the values in the exposure estimates for EHT.

Table 3.4-1. Characteristics of included dermal absorption studies of EHT identified in the literature search.

Reference/model	Dose/ number	Concentration	Exposure period	Mass balance	% dermally absorbed (mean ± SD)	Comment
Pottard 1999 ***In vitro*, human skin**	3 mg/cm^2 N=7	4%	16 h	97%	0.1 ± 0.1 (epidermis) 0.03 ± 0.05 µg/cm^2 Corresponding to: 0.08 ± 0.08% 0.03 ± 0.04%	According to the guideline: The exposure period should be 24 h The number of replicates should be 8 from 4 different donors
Hojerova 2017 ***In vitro*, porcine ear skin**	1x1 mg/cm^2 N=6	5 in W/O emulsion	6 h	88%	3.9 ± 1.3 µg/cm^2 Corresponding to: 7.8 ± 2.6%	According to the guideline: The exposure period should be 24 h

Reference/model	Dose/ number	Concentration	Exposure period	Mass balance	% dermally absorbed (mean ± SD)	Comment
						The number of replicates should be 8 from 4 different donors Dermis and epidermis not separated before analysis
Hojerova 2017 ***In vitro*, porcine ear skin**	1 mg/cm^2, applied twice, 3 h between the applications N=6	5 in W/O emulsion	6 h	88%	5.3 ± 1.2 µg/cm^2 Corresponding to: 5.3 ± 1.2%	According to the guideline: The exposure period should be 24 h The number of replicates should be 8 from 4 different donors
Souza 2017 ***In vitro*, porcine ear skin**	4% 2 mg/cm^2 N=6		24 h	98%	2.69 ± 0.56 µg/cm^2 Corresponding to: 3.36 ± 0.70%	According to the guideline: The number of replicates should be 8 from 4 different donors Dermis and epidermis not separated before analysis

3.5 OC (CAS number 197-30-4)

According to SCCS (2021), the mean dermal absorption of octocrylene is 0.45 ± 0.52 µg/cm^2 corresponding to 0.15 ± 0.18%. To screen for dermal adsorption factors for OC, its SMILES code (as obtained from PubChem) was submitted to an OECD QSAR Toolbox (vers. 4.3.1, 2019) chemical database search. This search returned a value of approximately 0.1% (ratio) which was stated to be based on two literature sources namely, Potard et al. (1999) and (2000), and was linked to one ECHA registration dossier (ECHA (2021d). Based on these data, the following mean absorption values are used for the exposure estimation: 0.1 and 0.33% (mean + 1SD).

Additional information on oral absorption from the ECHA registration dossier (ECHA, 2021d): "No key study for the toxicokinetics of octocrilene is available. Based on its physicochemical properties, such as poor water solubility (40 µg/L at 20°C) and high logPow (6.1), octocrilene is a lipophilic compound, which is likely to be absorbed in the GI tract by micellular solubilization. Oral repeated dose and reproductive/developmental toxicity studies showed evident systemic effects, that can be based on systemically available octocrilene, which further confirms its oral absorption capabilities."

3.6 NP-TiO_2 (CAS number 13463-67-7/ 1317-70-0/ 1317-80-2)

According to key information in the ECHA registration dossier (ECHA, 2021e), "no substantial accumulation of titanium was observed in tissues following oral administration of titanium dioxide. Titanium dioxide has been shown not to penetrate human skin to any appreciable degree, so that the dermal absorption of titanium dioxide through human skin is considered negligible."

As there is evidence of no absorption through the skin (ECHA, 2021e; SCCS, 2013) the dermal absorption of NP-TiO_2 is considered to be negligible, and systemic exposure resulting from dermal application of sunscreen is not estimated.

3.7 Summary: dermal adsorption values for the UV-filters

The following dermal absorption values are used in the

- BMDBM: 0.1, 0.8, 1.8, 4.5, and 7.3%
- EHS: 0.2, 1, and 3 %
- EHT: 0.1, 4.1, 6.5, and 10.4%
- OC: 0.1 and 0.33%
- NP-TiO_2: 0%

4 Exposure assessment

4.1 Identification of concentration data for UV filters

Literature searches (Chapter 4.1.1) were performed to retrieve studies relevant for answering research question 1 in Table 2.4-3. A research librarian was involved in the planning and conduction of the search. The publication selection (Chapter 4.1.2) was performed by pairs of reviewers. To ensure calibration, all reviewers screened a sample of the retrieved titles and abstracts and checked consistent application of the inclusion criteria. Publications that passed the screening were evaluated in fulltext. A similar between-reviewer calibration process was performed before pairs of reviewers independently evaluated the publications based on the eligibility criteria. To ensure that the eligible publications retrieved from the literature searches were of sufficient quality, the methods used for the UV filter analyses were evaluated (Chapter 4.1.3). Studies applying analytical methods considered not to be of sufficient quality were excluded. Relevant data were extracted in an Excel sheet used for the exposure estimation. One reviewer extracted data and another independently checked the data extraction for accuracy and completeness. An overall summary of the literature searches is given in Chapter 4.1.5.

4.1.1 Literature search

Literature searches in the electronic databases from MEDLINE (Ovid), Embase, Web of Science, Cochrane Database of Systematic Reviews, CRD (the Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED) and HTA) and Epistemonikos were performed on 16 March, 2020. For search terms and search strategy, see Appendix II Chapter 18. An experienced research librarian was involved in the planning and conducted the search.

The identified records were imported into EndNote (Thomson Reuters, version X9), duplicates were removed, and the records were imported into Rayyan (Ouzzani et al., 2016) for the study selection.

4.1.2 Publication selection

The study selection was based on the predefined eligibility criteria (Table 4.1.2-1).

Table 4.1.2-1. Eligibility criteria.

Literature screening (question 1)		
Study design	In	Analytical studies on concentrations of UV filters. Biomonitoring studies on concentration of UV filters in blood and/or urine samples.

Literature screening (question 1)		
Analytical method	In	All methods
Outcome of interest	In	Concentration data and biomonitoring data for UV filters.
	Out	Concentration data for UV filters in other cosmetics than sunscreens and in sunscreen lipsticks/aerosol can sprays. Studies reporting exclusively on toxicity or preventive/beneficial effects.
Language of the full text	In	Danish, English, German, Norwegian, and Swedish
Publication type	In	Scientific publications, reports and risk assessments

First, titles and abstracts of 877 records were screened and then 104 full-text articles were assessed. One study was excluded as full-text was not available (Westgate and Sherma, 2000). Forty publications fulfilled the eligibility criteria. Twelve studies addressed biomonitoring, whereas 28 studies included analysis of UV filter concentration in sunscreen.

4.1.3 Methodological quality

The quality of the method used in the analysis of the concentration of UV filters was evaluated for the 28 studies fulfilling the eligibility criteria. The evaluation included scoring of the sample extraction method, analytical method, and the validation of the method and the data presentation according to a scale of scores from 1 to 5, where 1 and 5 represent the lowest and highest quality, respectively (Table 4.1.3-1). To obtain the total score, the individual element scores were weighted as follows: 0.2 each from sample extraction and instrumental analysis and 0.6 from validation and data presentation.

Table 4.1.3-1. Table for quality evaluation of the analytical method used.

Questions to evaluate for methodological quality	Element score	Weighting factor
• **How appropriate was the solvent used for the extraction method?**	1 - 5	0.2
• **Which analytical method was used?**	1 - 5	0.2
• **Which validation method was used, and was LOD/LOQ, internal/external calibration, number of samples described?**	1 - 5	0.6
Weighted total score	1.0 - 5.0	

Only studies with a total score of ≥ 3.5 were included for the exposure assessment. A total of 25 studies received a total score of ≥3.5 (Table 4.1.3-2). Three studies were excluded due to a total score <3.5 (Chapter 18.3).

Table 4.1.3-2. Scoring of methodological quality – included studies. Questions: see Table 4.1.3-1

Reference	Question 1	Question 2	Question 3	Total score	UV filter analysed
(Benitez-Martinez et al., 2016)	3.5	3.5	4.0	3.8	NP-TiO_2
(Bocca et al., 2018)	4.0	4.0	4.5	4.3	NP-TiO_2
(Botta et al., 2011)	4.0	4.0	3.5	3.7	NP-TiO_2
(Chang et al., 2015)	3.0	4.0	4.0	3.8	BMDBM, EHS, OC
(Chisvert et al., 2001a)	3.0	4.0	4.0	3.8	BMDBM, EHS
(Chisvert et al., 2001b)	3.0	4.0	4.0	3.8	EHS
(Dan et al., 2015)	4.0	4.5	4.5	4.4	NP-TiO_2
(De Orsi et al., 2006)	4.5	4.0	5.0	4.0	BEMT, BMDBM, EHT, OC
(Ding et al., 2018)	4.5	4.8	4.0	4.3	EHS, OC
(Dutra et al., 2004)	Data reported by the industry				EHS
(Ferreira et al., 2013)	3.8	4.0	4.0	4.0	OC
(Junior et al., 2012)	3.5	3.8	4.0	3.9	OC
(Kavitha and Lakshmi, 2017)	4.0	3.5	4.0	3.9	BMDBM
(Kedor-Hackmann et al., 2006)	4.5	4.5	4.75	4.7	BMDBM, EHS
(Liu and Wu, 2011)	4.8	4.8	4.8	4.8	EHS*
(Menneveux et al., 2015)	3.5	4.0	3.5	3.6	NP-TiO_2
(Muller et al., 2018)	4.0	4.25	3.5	3.8	NP-TiO_2
(Nischwitz and Goenaga-Infante, 2012)	4.0	4.25	4.0	4.1	NP-TiO_2
(Peruchi and Rath, 2012)	4.0	4.0	3.8	3.9	BMDBM, EHS, OC*
(Philippe et al., 2018)	4.0	4.0	3.25	3.6	NP-TiO_2
(Rastogi, 2002)	4.0	4.0	4.0	4.0	BMDBM, EHS, OC
(Simeoni et al., 2005)	4.0	3.8	3.3	3.5	BMDBM
(Vosough et al., 2017)	4.0	4.0	4.5	4.3	BMDBM, OC
(Yang et al., 2011)	3.3	3.5	4.0	3.8	EHS
(Yousef Agha et al., 2013)	3.8	4.0	4.0	4.0	EHS, OC

*Not included in the database as only minimum and maximum values were reported.

4.1.4 Data extraction and database

The project group jointly developed an Excel file for extracted data, which is available upon here. The availability of concentration data was variable, with 5, 68, 30, 1, 58 and 39 reported concentrations analysed in sunscreens for BEMT, BMDBM, EHS, EHT, OC and NP-TiO_2, respectively. The concentrations ranged from 10-71 mg/g for BEMT, 0 to 63 mg/g for BMDBM, 0 to 52 mg/g for EHS, 21-21 for EHT mg/g, 0 to 108 mg/g for OC, and 0-213 mg/g for NP-TiO_2.

4.1.5 Summary: concentration data for UV filters

Concentration data for the six selected UV filters in sunscreens were obtained from literature searches, and were restricted to include sunscreen products on the European market to ensure the relevance of the data for the Norwegian population. The availability of concentration data was variable, with only one analysed concentration in sunscreen for EHT and 68 reported concentrations analysed in sunscreens for BMDBM. The maximum concentrations reported were 71 mg/g for BEMT, 63 mg/g for BMDBM, 52 mg/g for EHS, 21 for EHT mg/g, 108 mg/g for OC, and 213 mg/g for NP-TiO_2. In the exposure estimation, a random sampling from the concentration data was done.

An overview of the study selection and the evaluation of the methodological quality of the analyses are given in Figure 4.1.5-1. An overview of the UV filters analysed in these studies is given in Table 4.1.5-1.

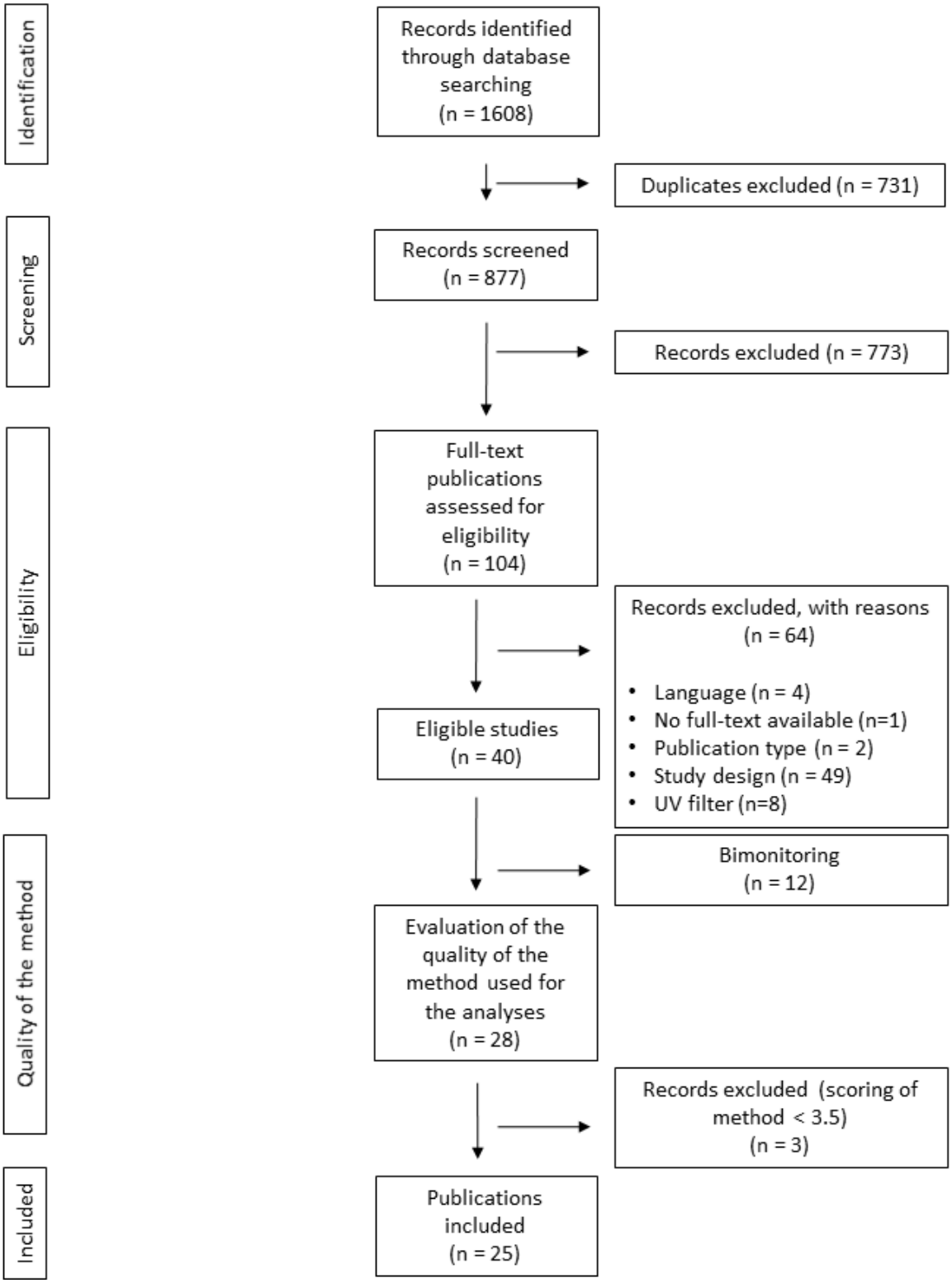


Figure 4.1.5-1. Flowchart for the selection of eligible studies of sufficient quality and reporting concentration data for the UV filters (modified from Moher et al. (2009)).

Table 4.1.5-1. UV filters and the studies reporting concentration data. *Concentration data for TiO_2 are not used, as only NP-TiO_2 is included in this assessment.

UV filter	Reference
BEMT	De Orsi et al. (2006)
BMDBM	Chang et al. (2015); Chisvert et al. (2001a); De Orsi et al. (2006); Kavitha and Lakshmi (2017); Kedor-Hackmann et al. (2006); Peruchi and Rath (2012); Rastogi (2002); Simeoni et al. ((2005); Vosough et al. (2017)
EHS	Chang et al. (2015); Chisvert et al. (2001a); Chisvert et al. (2001b); Ding et al. (2018); Dutra et al. (2004); Kedor-Hackmann et al. (2006); Liu and Wu (2011); Rastogi (2002); Yang et al. (2011)
EHT	Sobanska and Pyzowski (2012b)
OC	Chang et al. (2015); De Orsi et al. (2006); Ding et al. (2018); Ferreira et al. (2013); Junior et al. (2012); Junior et al. (2012); Liu and Wu (2011); Peruchi and Rath (2012); Quinones et al. (2016); Rastogi (2002); Vosough et al. (2017)
NP-TiO_2	Benitez-Martinez et al. (2016); Bocca et al. (2018); Botta et al. (2011); Dan et al. (2015); Menneveux et al. (2015); Muller et al. (2018); Nischwitz and Goenaga-Infante (2012); Philippe et al. (2018)

4.2 Data on dermal absorption

The dermal absorption data (presented in Table 4.4-1) were used for the UV filters BEMT, BMDBM, EHS, EHT and OC in the exposure assessment. For a more detailed description of the selection of dermal absorption values, see Chapter 3. The dermal absorption data were obtained from studies where the quality was evaluated as adequate based on existing guidelines for *in vitro* dermal absorption and the SCCS Notes of Guidance (SCCS, 2021). The absorption values reported for each filter in these studies were considered to be of sufficient quality. Instead of applying the more conservative approach using the highest reported value for dermal absorption, the selected absorption values were used probabilistically in the exposure assessment. Dermal absorption values for NP-TiO_2 are considered to be negligible. (ECHA, 2021e; SCCS, 2013)(Chapter 3). In the exposure estimate, a random sampling from the absorption values was used.

4.2.1 Dermal application: External and internal expsoure

In the exposure assessment, first the external exposure dose on the skin is calculated (*i.e.*, the dose that is available for dermal absorption). The external exposure can further be used to calculate internal (or systemic) exposure which corresponds to the internal dose (Figure 4.3). For the calculation of the internal exposure dose, absorption specific to the dermal route has to be taken into account. Local effects, like skin/eye irritation, skin sensitisation or sun-induced skin reactions are mostly dependent on the amount of substance acting on the skin and require comparison to a local external dose. Systemic effects, however, require

comparison to an internal (systemic) exposure dose (SCCS, 2021).

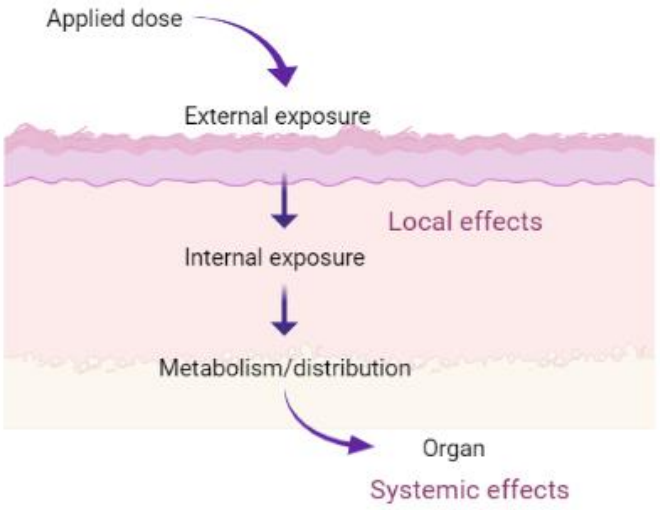


Figure 4.2.1-1. Schematic illustration of the processes of dermal absorption and the sites of local and systemic effects following application of a chemical substance to the skin surface (Ill. B. Granum, 2022, created in BioRender.com).

4.3 Data on amount of sunscreen used

Data on the amount of sunscreen used was obtained from the literature. No data on the amount of sunscreen used by the Norwegian population were identified. The data used were obtained from surveys in Denmark and other European countries, and were assumed to be representative for the Norwegian population. Seven publications describing the amount of sunscreen used in a population were found in the literature search (Autier, 2001; Biesterbos et al., 2013; Dupuy et al., 2005; Ficheux et al., 2016; Gomez-Berrada et al., 2017; Gomez-Berrada et al., 2018; The Danish Environmental Protection Agency, 2016). Only studies that clearly described the method used and reported the amount of sunscreen use as g/use or mg or g/day as individual data or summary data were included in the amount data used for the exposure assessment. Studies describing only the amount used for spray sunscreen were excluded, since spray sunscreen is not included in this risk-benefit assessment. The three studies fulfilling the criteria were from Autier (2001); Ficheux et al. (2016); The Danish Environmental Protection Agency (2016).

The study from The Danish Environmental Protection Agency (EPA) (2016) collected data during the period June-August 2016, between the time points 10:30 and 15:15 (CET). Sunscreen tubes were weighed before and after use. The study reported both individual and summary data. We defined the weight of sunscreen reported per day as daily use (g/day). Since the skin surface area was not reported, we assumed it to be the total body surface area. The information on surface area is not used directly in the exposure assessment.

Table 4.3-1. Summary of sunscreen amount data from EPA (2016).

Participants	n	Quantity used per application, mean (g/use)	Quantity used per application, SD (g/use)
Women, 18-73 years	76	8.08	4.48
Men, 19-69 years	23	10.47	4.33

The individual data on the amount of sunscreen used were directly and probabilistically incorporated into the exposure assessment. These data were shown to have a lognormal distribution, and this information was used to extract individual data from the studies by Autier et al. (2001) and Ficheux et al. (2016) (see below).

In a study by Autier et al. (2001), a total of 148 students aged 18-24 years were randomised into groups receiving sunscreens of SPF10 or SPF30. Eighty-six subjects (sex not given) were recruited in 1997 and 61 subjects in 1998. Of these, 85% contributed with data, resulting in a total sample size of n=124. Sunscreen tubes were distributed in June and collected and weighed in September/October the same year. The two SPFs were not used in the exposure estimations, only the amount data per SPF group.

Due to limited information on sample size in the SPF groups per year, we made an approximation of the group sample size based on the total numbers of subjects reported for SPF groups and participation per year.

Table 4.3-2. Summary of sunscreen amount data from Autier et al. (2001). SPF: Sun protection factor (not used for exposure estimates).

Data extraction						**Input data for sampling**		
Year	n	SPF group	Overall quantity used, mean (g)	Overall quantity used, SD (g)	Number of days used	n[a]	g/day, mean[b]	g/day, SD[b]
1997	69	10	71	41	9	36	7.9	4.6
1997		30	72	59	9	33	8.0	6.6
1998	55	10	67	32	8	29	8.4	4.0
1998		30	77	43	8	26	9.6	5.4

[a]Estimated sample size based on data from Table 1 in Autier et al. (2001): 22+42=64 subjects received SPF10 (52%) and 18+42=60 received SPF30. The numbers of participating subjects were 26+43=69 and 14+41=55, in 1997 and in 1998, respectively. We assumed that 69*0.52= 36 participants in 1997 received SPF10 and 69-36=33 received SPF30. In 1998, the corresponding numbers were 55*0.52=29 and 26 for SPF10 and SPF30, respectively.
[b]Estimated quantity used daily, calculated as overall quantity divided by number of days used.

Data on use of sunscreen, for girls 4-14 years and women and men 15+ years were extracted from Ficheux et al. (2016; Table 3 and Table 6, respectively). The amount used was measured by weighing the sunscreen tube before and after use.

We estimated quantity of daily use (g/day) from the reported quantity used per application. This quantity was multiplied by two to take reapplication into consideration. The skin surface areas were not included in the exposure estimates.

Table 4.3-3. Summary of sunscreen amount data from Ficheux et al. (2016). N.a.: not applicable

Data extraction				Input data for sampling		
	Sunscreen skin surface area (cm^2)	Quantity used per application, mean (g/use)	Quantity used per application, SD (g/use)	n	g/day, mean[a]	g/day, SD[a]
Girls, 4-14 years	n.a.	6.3	5.4	16	12.6	10.8
Women, 15+ years	<4000	2.5	3	38	5	6
	4000-14000	6.9	7	33	13.8	14
	>14500	15.7	9.1	58	31.4	18.2
Men, 15+ years	<4000	3.5	2.1	6	7	4.2
	4000-14000	9.9	5.3	10	19.8	10.6
	>14500	18.2	14.5	31	36.4	29

[a] Estimated quantity used daily, calculated from quantity used per application multiplied by two to estimate daily use.

4.3.1 Simulation of individual data

Based on the fact that individual data reported by EPA (2016) have a lognormal distribution, the summary data from Autier et al. (2001) (mean and SD) were used to sample n individual data from a lognormal distribution using Equations 1 and 2. The equations 1 and 2 descibes the location (Loc) and shape parameters, respectively, which define the lognormal (ln) distribution based on mean and SD from the original data. Using the programming language R (version 4.0.4) and the function rlnorm, individual data can be simulated based on the Loc and shape parameters calculated from that dataset. The rlnorm function returns simulated data in its original form.

$$Loc = \ln\left(mean^2 / \sqrt{sd^2 + mean^2}\right)$$ **Equation 1**

$$\text{shape} = \sqrt{\log\left(1 + \frac{sd^2}{mean^2}\right)}$$ **Equation 2**

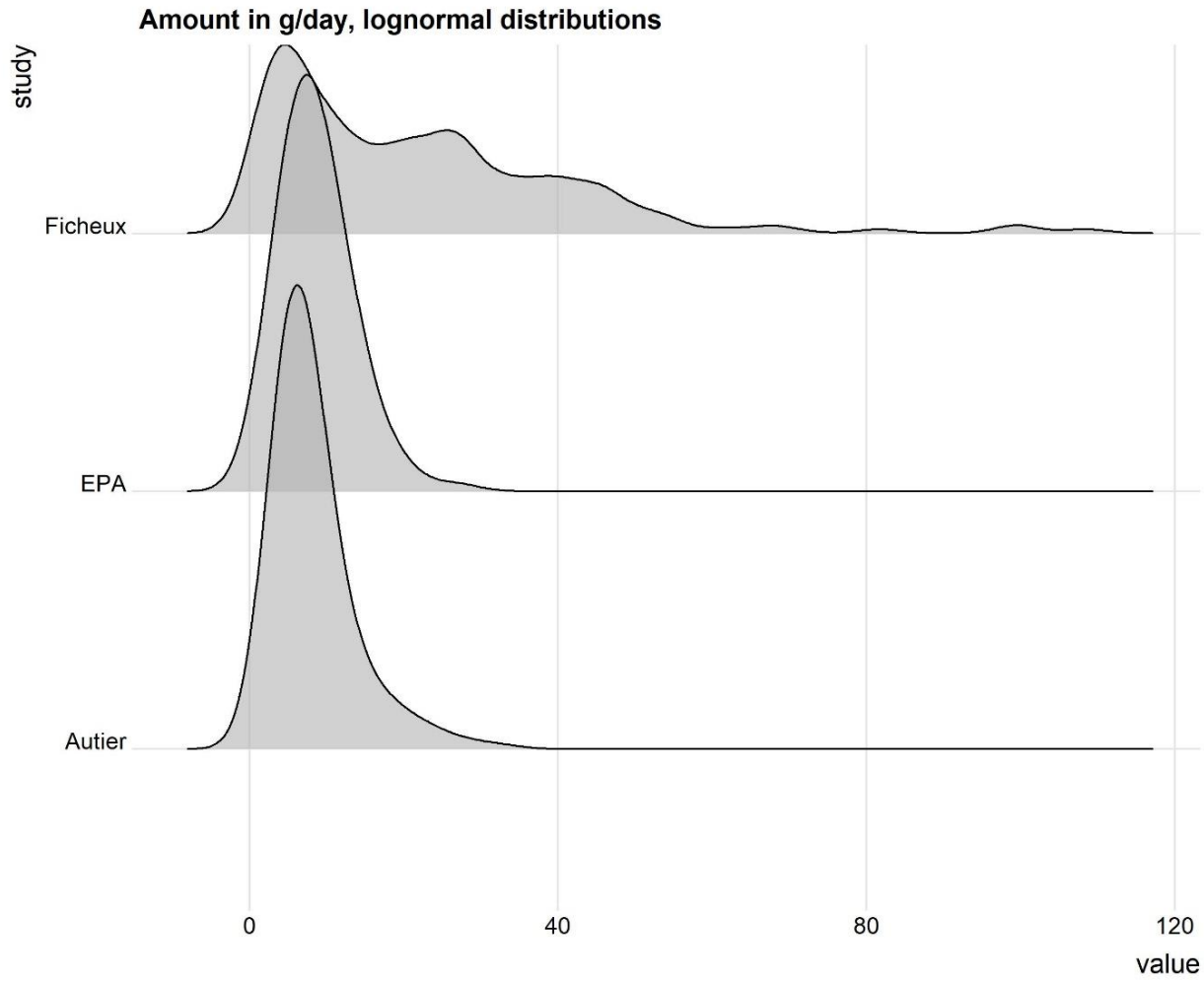


Figure 4.3.1-1. Distribution of the individual sunscreen amount data from EPA (2016) and the simulated individual data from Autier et al. (2001) and Ficheux et al. (2016) using a lognormal distribution.

The distribution of the individual amount data from EPA (2016) and simulated amount data from Autier et al. (2001) and Ficheux et al. (2016) (Figure 4.3.1-1) shows overlapping. Thus, these amount data can be combined in the exposure assessment of the UV filters.

4.4 Method used for the exposure estimation

The exposure was estimated for chronic, daily use of sunscreen (see discussion, Chapter 12). We aimed to obtain more realistic exposure estimates for the selected UV filters, by including all data of sufficient quality in the exposure estimate, instead of applying the more conservative approach using central estimates and default values. Therefore, a probabilistic approach using all data for each parameter, concentration, percentage dermal absorption and amount applied, were used in the exposure estimate. This gives the exposure estimates as distributions of probable exposures to each UV filter, and the variability in the parameters are included in the estimated exposure.

The internal exposure to the UV filters was estimated using a probabilistic approach based on the following equation (Equation 3):

$$Internal\ exposure\ \left[\frac{mg}{day}\right] = C \times amt_{Sunscreen} \times Rf \times \frac{Abs_{UV\,filter}}{100} \qquad \textbf{Equation 3}$$

where *C* is the concentration of UV filters (mg/g), $amt_{Sunscreen}$ is the amount of sunscreen used per day (g/day), $\%\ Abs_{UV\ filter}$ is the dermal absorption value of the UV filters and Rf is the retention fraction of the product on the skin. The *Rf* value is 1 for sunscreen, which is a leave-on product, and thus, this value will not influence the exposure estimate. The external exposure is the exposure estimate before including the dermal absorption.

A probabilistic exposure estimate was performed using Monte-Carlo (MC) simulation; *i.e.* all data for each parameter (concentration, amount, percentage dermal absorption) were used in the calculations. The resulting exposure estimate was a distribution of probable exposures to each UV filter, which included the variability in the parameters used. Table 4.4-1 shows the parameters used for the Monte-Carlo simulation. The summary of the results from one MC simulation is shown in the results chapter (Chapter 4.5). It should be noted that a re-run of the exposure will result in slightly different results due to the use of probabilistic MC simulation. The variation will be largest in the tail of the distribution and will be reduced with increasing number of MC iterations. The exposure assessment was run with 1000 MC iterations.

Table 4.4-1. Monte-Carlo parameters used in the exposure assessment of the UV filters. r: random sampling from individual data; ln: lognormal distribution; C: UV filter concentration; $amt_{Sunscreen}$: amount of sunscreen applied; Abs %: percentage dermal absorption of UV filter; n.a.: not applicable.

UV filter	**Input for distribution**		
	C range (mg/g), (n)	**Mean $amt_{Sunscreen}$ (SD) (g/day)**	**Abs %**
	Estimation method		
	r	ln	r
BEMT	10-71 (5)	n.a.	0.01, 0.06
BMDBM	0-63.4 (68)		0.1, 0.8, 1.8, 4.5, 7.3
EHS	0-51.6 (30)		0.2, 1.0, 3.0
EHT	21-21 (1)		0.1, 4.1, 6.5, 10.4
OC	0-108 (58)		0.1, 0.33
NP-TiO_2	0-212.5 (39)		0
Amount	n.a.	12.2 (12.7)	n.a

The exposure assessment was performed in R. The data and R scripts are available in a separate publication here.

4.5 Results; exposure estimation

The estimated exposure to the UV filters is shown in Table 4.5-1 (external exposure, mg/day), 4.5-2 (external exposure, mg/kg bw/day), 4.5-3 (internal exposure, mg/day), and 4.5-4 (internal exposure, mg/kg bw/day).

Table 4.5-1. External exposure (mg/day) of selected UV filters.

UV filter	mean	SD	P5	P25	P50	P75	P95
BEMT	293.49	583.63	27.61	60.83	130.3	284.57	1122.07
BMDBM	204.12	299.77	0	24.11	98.62	250.78	742.58
EHS	418.49	537.93	0	97.18	254.58	528.23	1378.21
EHT	119.3	148.01	7.75	33.98	73.7	144.59	399.96
OC	367.3	669.75	3.4	24.47	98.57	378.23	1668.13
NP-TiO_2	379.62	689.21	0	0.62	84.62	473.07	1679.24

Table 4.5-2. External exposure for a 70 kg person (mg/kg bw/day) of selected UV filters.

UV filter	mean	SD	P5	P25	P50	P75	P95
BEMT	4.19	8.34	0.39	0.87	1.86	4.07	16.03
BMDBM	2.92	4.28	0	0.34	1.41	3.58	10.61
EHS	5.98	7.68	0	1.39	3.64	7.55	19.69
EHT	1.70	2.11	0.11	0.49	1.05	2.07	5.71
OC	5.25	9.57	0.05	0.35	1.41	5.40	23.83
NP-TiO_2	5.42	9.85	0	0.01	1.21	6.76	23.99

Table 4.5-3. Internal exposure (mg/day) of selected UV filters.

UV filter	mean	SD	P5	P25	P50	P75	P95
BEMT	0.11	0.30	0	0.01	0.03	0.09	0.45
BMDBM	6.07	11.97	0	0.13	1.44	6.06	27.88
EHS	6.08	10.89	0	0.52	1.90	7.06	25.99
EHT	6.44	11.42	0.03	0.28	2.89	7.24	26.13
OC	0.82	1.81	0	0.04	0.16	0.75	3.78

Table 4.5-4. Internal exposure for a 70 kg person (mg/kg bw/day) of selected UV filters.

UV filter	mean	SD	P5	P25	P50	P75	P95
BEMT	0.0015	0.0043	0.0001	0.0002	0.0005	0.0013	0.0064
BMDBM	0.0866	0.1710	0	0.0018	0.0206	0.0865	0.3982
EHS	0.0868	0.1556	0	0.0075	0.0272	0.1009	0.3713
EHT	0.092	0.1632	0.0004	0.004	0.0412	0.1035	0.3733
OC	0.0117	0.0259	0.0001	0.0006	0.0023	0.0108	0.0540

The highest internal exposure (P50 and P95) is observed for EHT, BMDBM and EHS, while the internal exposure for OC and BEMT is more than one order of magnitude lower. The exposure assessment for EHT is based on a single measured concentration. The average absorption for EHS, EHT and BMDBM is of the same order of magnitude, while the average absorption of OC and BEMT is approximately one and two orders of magnitude lower, respectively. Therefore, the internal exposure to OC and BEMT is low compared to its external exposure. No absorption is reported for NP-TiO_2 (see description in Chapter 3), and therefore no internal exposure is expected.

The distribution of the probabilistic internal exposure estimates for all UV filters, except BEMT, is skewed to the right, having a long tail towards high exposure (Figure 4.5-1). This is caused by the high variability in the input data. Due to the small number of data points both for the BEMT concentration in sunscreen and the dermal absorption of the filter, as well as less variability in these parameters, the distribution is more centered for BEMT than the other UV filters.

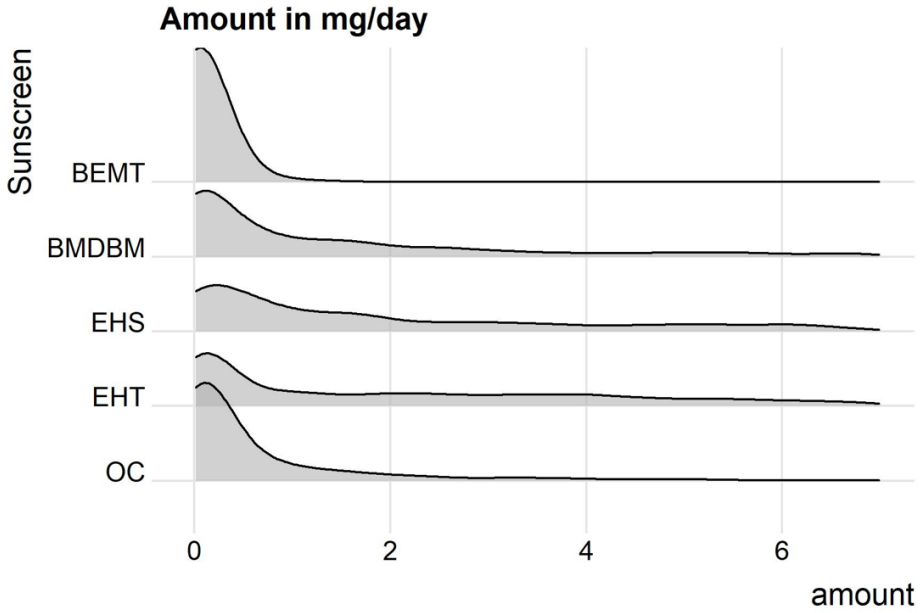


Figure 4.5-1. Distribution of the internal exposure (mg/day) for the UV filters. The graph shows values up to 7 mg/day.

4.5.1 **Sensitivity analysis**

To assess the importance of the different parameters for the internal exposure assessment, a sensitivity analysis was performed for the parameters amount, concentration and absorption, separately for all UV filters (Figure 4.5.1-1, and Table 4.5.1-1 to 4.5.1-5). One SD from the summary data was added to each individual value for each parameter, and the output using the value +1 SD in the exposure estimate is compared with the original exposure estimate. The sensitivity analysis will be affected by the variability in the individual data for each parameter.

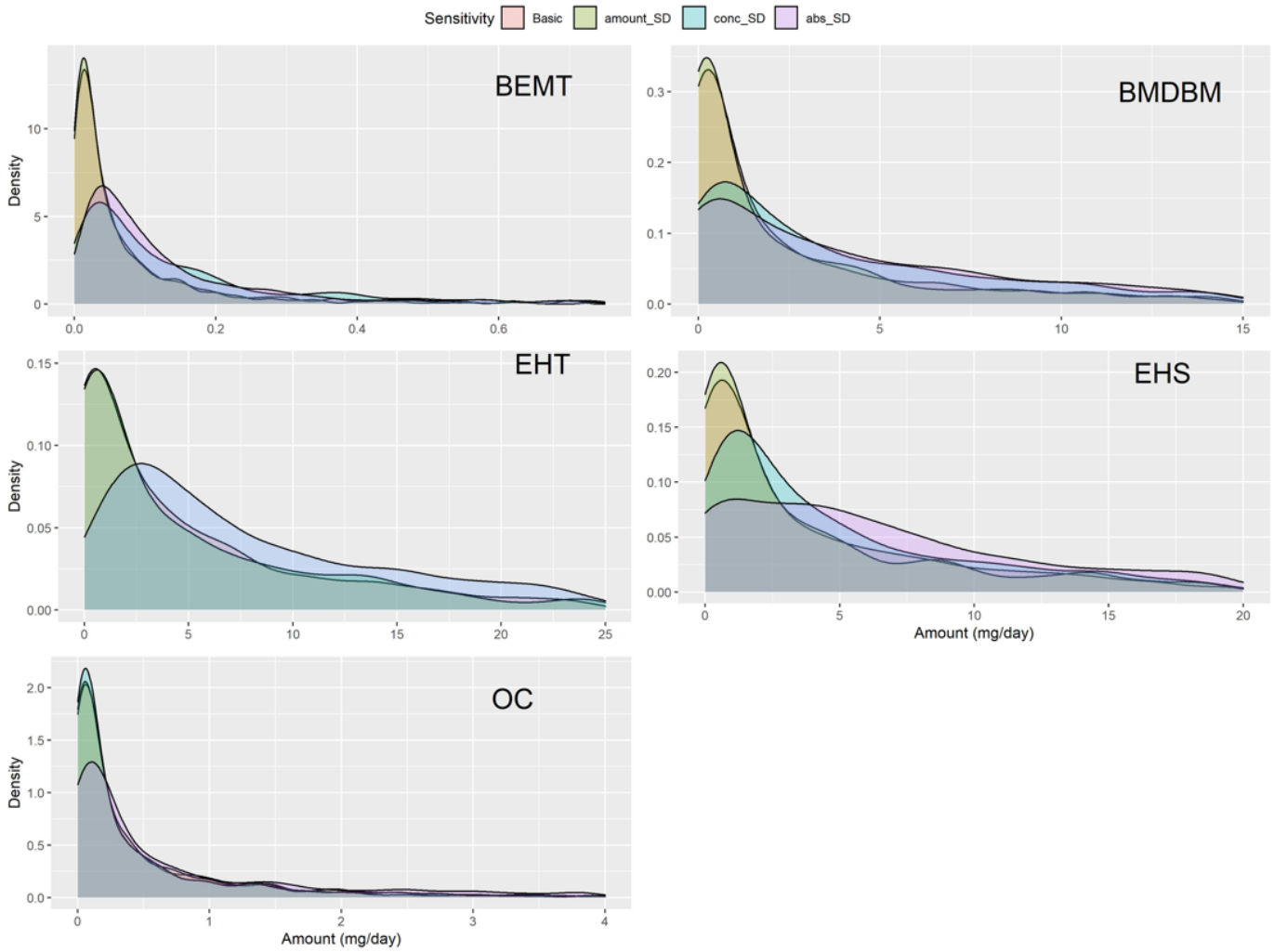


Figure 4.5.1-1. Sensitivity analysis for internal exposure estimates for the UV filters.

Table 4.5.1-1. Sensitivity analysis of BEMT. Abs: absorption; conc: concentration; SD: standard deviation.

Parameter changed (mg/day)	mean	SD	P5	P25	P50	P75	P95
BEMT	0.11	0.3	0	0.01	0.03	0.09	0.45
BEMT amount + SD	0.19	0.35	0.01	0.03	0.09	0.19	0.84
BEMT conc + SD	0.2	0.32	0.01	0.04	0.09	0.24	0.73
BEMT abs + SD	0.21	0.48	0.02	0.04	0.09	0.19	0.78

Table 4.5.1-2. Sensitivity analysis of BMDBM. Abs: absorption; conc: concentration; SD: standard deviation.

Parameter changed (mg/day)	mean	SD	P5	P25	P50	P75	P95
BMDBM	6.07	11.97	0	0.13	1.44	6.06	27.88

Parameter changed (mg/day)	mean	SD	P5	P25	P50	P75	P95
BMDBM amount + SD	12.13	20.77	0	0.38	3.77	13.52	53.69
BMDBM conc + SD	11.5	20.54	0.15	1.19	4.45	13.41	49.56
BMDBM abs + SD	11.68	18.95	0	1.23	5.11	14.44	44.99

Table 4.5.1-3. Sensitivity analysis of EHS. Abs: absorption; conc: concentration; SD: standard deviation.

Parameter changed (mg/day)	mean	SD	P5	P25	P50	P75	P95
EHS	6.08	10.89	0	0.52	1.9	7.06	25.99
EHS amount + SD	12.32	15.87	0	1.53	6.49	16.61	45.48
EHS conc + SD	8.11	13.79	0.24	1.06	3.09	9.16	31.54
EHS abs + SD	11.79	16.79	0	2.14	6.49	14.31	44.4

Table 4.5.1-4. Sensitivity analysis of EHT. Abs: absorption; conc: concentration; SD: standard deviation.

Parameter changed (mg/day)	mean	SD	P5	P25	P50	P75	P95
EHT	6.44	11.42	0.03	0.28	2.89	7.24	26.13
EHT amount + SD	14.55	18.13	0.09	0.55	8.66	21.38	50.49
EHT abs + SD	11.32	14.82	0.73	2.81	6.3	13.97	37.64

Table 4.5.1-5. Sensitivity analysis of OC. Abs: absorption; conc: concentration; SD: standard deviation.

Parameter changed (mg/day)	mean	SD	P5	P25	P50	P75	P95
OC	0.82	1.81	0	0.04	0.16	0.75	3.78
OC + SD	1.53	2.68	0.02	0.1	0.34	1.65	7.03
OC conc+SD	1.61	2.32	0.12	0.35	0.84	1.84	5.67
OC abs + SD	1.39	2.66	0.01	0.09	0.37	1.44	6.15

Due to the skewness of the exposure distribution for four of the selected UV filters, the mean is affected by the high values of the estimated exposure. In addition, the sensitivity analysis shows that P50 is more affected by changes in the input parameters than the mean, while the magnitude of the changes in P95 is more similar to the mean.

In general, the three parameters influenced the exposure assessment for P50 and P95 with the same order of magnitude for all UV filters, with minor variations. A 2-5 fold change in the P50 exposure estimate was observed for BMDBM, EHS, EHT and OC by changing one of the

parameters by one SD, while the changes were less for the P95 estimate. UV filter concentration in sunscreen was the most important parameter for the OC exposure resulting in a 5-fold change, while it was the least important parameter for the exposure to EHS. The difference in the influence of the parameters was smallest for BEMT, which was probably due to few data points for several of the parameters.

5 Identification of health protective and adverse health effects

Health protective and adverse health effects were identified for sunscreens and the UV filters BEMT, BMDBM, EHS, EHT, OC and NP-TiO_2. An overview of the identification of health protective and adverse health effects is given in Figure 5-1.

In this risk-benefit assessment, health protective effects are defined as prevention of harmful UVR-induced effects. Such UV-induced negative health effects constitute a number of outcomes which are as diverse as *e.g.* mild erythema and mortality. The outcomes represent different degrees of importance in evaluating the severity of health effects. Only outcomes above a certain level of importance were included in the assessment of the sunscreen protective ability against the UVR-induced adverse effects. The rating of harmful UVR-induced health effects is described in Chapter 5.1.

Chapter 5.2 gives a general overview of the literature searches, study selection, and evaluation of internal validity.

Chapters 5.3 to 5.6 describe identification of potential adverse or health protective effects related to sunscreen use and the six selected UV filters. Studies addressing potential health protective effects of sunscreen use were identified from literature searches (Chapter 5.4 to 5.5). Studies addressing potential adverse health effects were identified from literature searches (sunscreen and UV filters) (Chapter 5.3 to 5.6), and ECHA registration dossiers (UV filters) (Chapter 5.7).

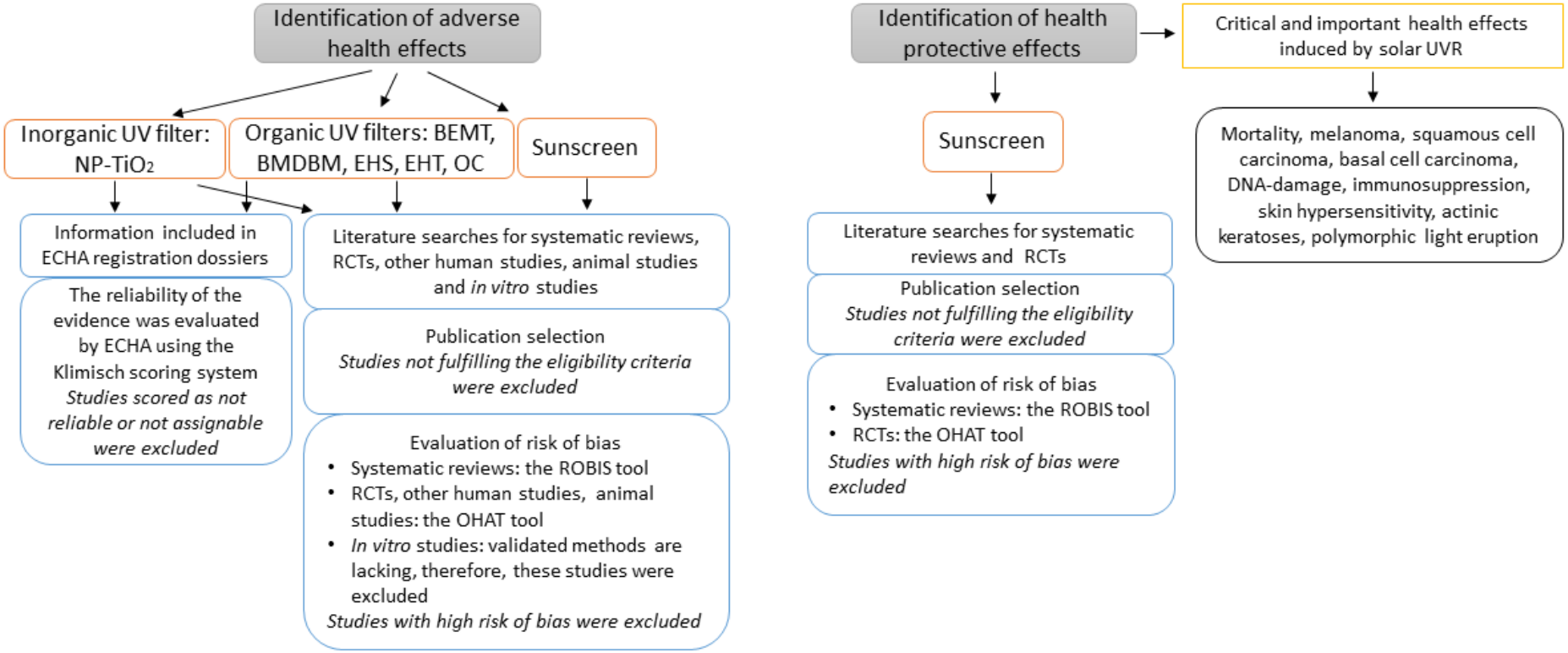


Figure 5-1. An overview of the identification of health protective effects. The terms "critical" and ""important" refer to categories defined in GRADE (Schünemann et al., 2013).

5.1 UVR-induced human adverse health effects: identification of critical and important outcomes

Adverse health outcomes and endpoints (collectively denoted "outcomes" below) associated with UVR were identified through literature searches and expert judgements. According to GRADE (Schünemann et al., 2013) the importance of an outcome for a patient (or individual) is related to decision making. In the current risk-benefit assessment, we rated the outcomes according to their relative importance based on the severity of health effects. VKM considered the most important factor determining importance to be the impact on the individual including quality of life. In addition, the impact on private and public economy as well as the impact on the general resources of the health-care system were taken into consideration. The identified outcomes were rated on a scale from 1 (least importance) to 9 (highest importance) (Schünemann et al., 2013), of which outcomes rated from 7 to 9 were termed "critical", from 4 to 6 were termed "important", and from 1 to 3 were termed" of limited importance" (Table 5.1-1). Outcomes evaluated to be "of limited importance" were not included in the evidence profile. This limitation does not imply that the outcomes rated "of limited importance" were considered insignificant or could not *e.g.* progress into more severe disease, but rather that they constituted a lesser burden to the individual and the health care system than did the outcomes with a higher rating.

Table 5.1-1. Rating of adverse UVR-induced health effects identified by expert judgement and from literature searches. Rating of clinical outcomes are based on a total evaluation such as their impact on the individual and the burden on the health care system. For a sunscreen to be protective the effects below must be reduced. *Excluding photobiological effects following UV absorption in UV filters (evaluated in Chapter 6: Hazard characterisation and evidence synthesis)(Moore, 2002).

Importance category	Adverse effects of UVR identified	Rating
Clinical outcomes		
Critical	• Mortality • Melanoma	9 7-9
Important, but not critical	• Squamous cell carcinoma (SCC) • Basal cell carcinoma (BCC) • Actinic (solar) keratoses (AC) • Polymorphic light eruption (PLE)	4-7 4-6 4-6 4
Of limited importance	• Sunburn • Photoirritation (phototoxicity) and photoallergy • Pigmentation disorders • Erythema • Number and modification of nevi • Photoaging	1-3 1-3 2 1-2 1 1

Mechanistic effects		
Critical	• Genotoxicity (DNA damage)	7-9
Important, but not critical	• Immunosuppression	4-6
Of limited importance	• Oxidative stress	3

5.2 Introduction to the literature searches

Literature searches were performed to retrieve studies relevant for answering the research questions in Table 2.4-1 and 2.4-2. A research librarian was involved in the planning and conducted the search. The eligibility criteria and the priority sequence of the publications according to study design were predefined in the protocol (VKM et al., 2020a) and were as follows (in order from highest to lowest priority): Systematic reviews, human randomised controlled trials (RCTs), human observational studies, in vivo animal studies and *in vitro* studies. Animal and *in vitro* studies were included only when additional data was needed. An additional search, not included in the protocol, was also performed to identify other human studies addressing skin irritation and skin sensitisation.

The publication selection was performed by pairs of reviewers. To ensure between-reviewer calibration, all reviewers screened a sample of the retrieved titles and abstracts and checked consistent application of the inclusion criteria. Publications that passed the screening were evaluated in full text. A similar calibration process was performed before pairs of reviewers independently evaluated the publications based on the eligibility criteria. To ensure that the eligible publications retrieved from the literature searches were of sufficient quality, risk of bias (RoB) was evaluated. The ROBIS tool (Whiting et al., 2016) was used to evaluate RoB in systematic reviews (Chapter 5.3.3). The OHAT tool (OHAT, 2015; OHAT, 2019) was used in the evaluation of RoB in RCTs (Chapter 5.4.3), other human studies and animal experimental studies (Chapter 5.5.3). Only publications classified as having low or moderate RoB (termed "unclear" in the case of systematic reviews) were included in the evidence synthesis for adverse and protective effects (Chapter 6 and 7, respectively). Study characteristics of these publications were extracted using data extraction forms developed by the project group (VKM et al., 2020). One reviewer extracted data and another independently checked the data extraction forms for accuracy and completeness. The literature searches, the publication selection and the evaluation of RoB are described in Chapter 5.3 for the systematic reviews, Chapter 5.4 for the RCTs, and 5.5 for the other human studies, animal studies and *in vitro* studies. An overall summary of the literature searches is given in Chapter 5.6.

5.3 Systematic reviews of human studies

5.3.1 Literature search

Literature searches in the electronic databases from MEDLINE (Ovid), Embase (Ovid), and Web of Science were performed 03.03.2020 (see Chapter 17.1 for search terms and search strategy).

5.3.2 Publication selection

The study selection was based on the eligibility criteria in Table 5.3.2-1.

Table 5.3.2-1. Eligibility criteria for systematic reviews of human studies addressing potential adverse and protective health effects associated with the use of sunscreen products and UV filters.

Study design	Systematic reviews
Population	All age groups, males and females
Exposure	Dermal application The tested substances are sunscreen products and UV filter ingredients tested alone
Outcome of interest	Protective health effects of sunscreen use when exposed to UVR Adverse health effects of sunscreen products and UV filters
Language of the full text	Danish, English, German, Norwegian, and Swedish
Publication type	Scientific publications, reports and risk assessments

A publication was considered to be a systematic review if 1) a specific research question and clear criteria for relevant studies to include were described, 2) a systematic literature search was performed, and 3) quality assessment of the included studies was performed (Higgins and Green, 2011).

Titles and abstracts of 365 records were screened prior to assessment of 70 full-text articles. Eight publications fulfilled the eligibility criteria (Figure 5.3.5-1.)

5.3.3 Evaluation of internal validity of systematic reviews of human studies

ROBIS, a tool for assessing RoB in systematic reviews, was used (Whiting et al., 2016). The tool includes three phases: First, the relevance is assessed, next, concerns with the review process are identified, and last, the risk of bias is appraised. The relevance is rated as yes (relevant), partial relevant, or not relevant. Four domains through which bias may be introduced into a systematic review are covered in the evaluation of concerns with the review process: study eligibility, identification and selection of studies, data collection and study appraisal, and synthesis and findings. The last phase considers whether the systematic

review as a whole is at risk of bias. The bias in each domain in phase two, and the overall RoB in the last phase, is rated as low, unclear or high.

The reviewers evaluated RoB to be low in two systematic reviews, unclear in one and high in five (Table 5.3.3-1, detailed evaluations in Chapter 17.1.2.3).

Table 5.3.3-1. Assessment of risk of bias (RoB) of systematic reviews of human studies using the ROBIS tool.

Reference	Relevance	Concerns with the review process				RoB category
		Eligibility criteria	Identification and selection of studies	Data collection and study appraisal	Synthesis and findings	
(Dennis et al., 2003)	Yes	Low	Unclear	Low	Unclear	Unclear
(Green and McBride, 2014)	Partial	Unclear	High	High	High	High
(Horsham et al., 2014)	Partial	Low	Low	High	High	High
(Neale et al., 2019)	Yes	Low	Low	High	High	High
(Rueegg et al., 2019)	Yes	Low	Low	Low	Low	Low
(Sanchez et al., 2016)	Yes	Unclear	Low	Low	Low	Low
(Silva et al., 2018)	Yes	High	Unclear	Low	Low	High
(Thoonen et al., 2020)	Partial	Low	High	Low	High	High

5.3.4 Data extraction

The data extraction forms are included in the Appendix (Chapter 17) and a brief overview is given in Chapter 6.1.1 and 7.1.1.

5.3.5 Summary of the literature search for systematic reviews of human studies

For systematic reviews, Figure 5.3.5-1 gives an overview of the study selection and the evaluation of the RoB process. An overview of the outcomes addressed in the systematic reviews that are included in the evidence synthesis is given in Table 5.3.5-1.

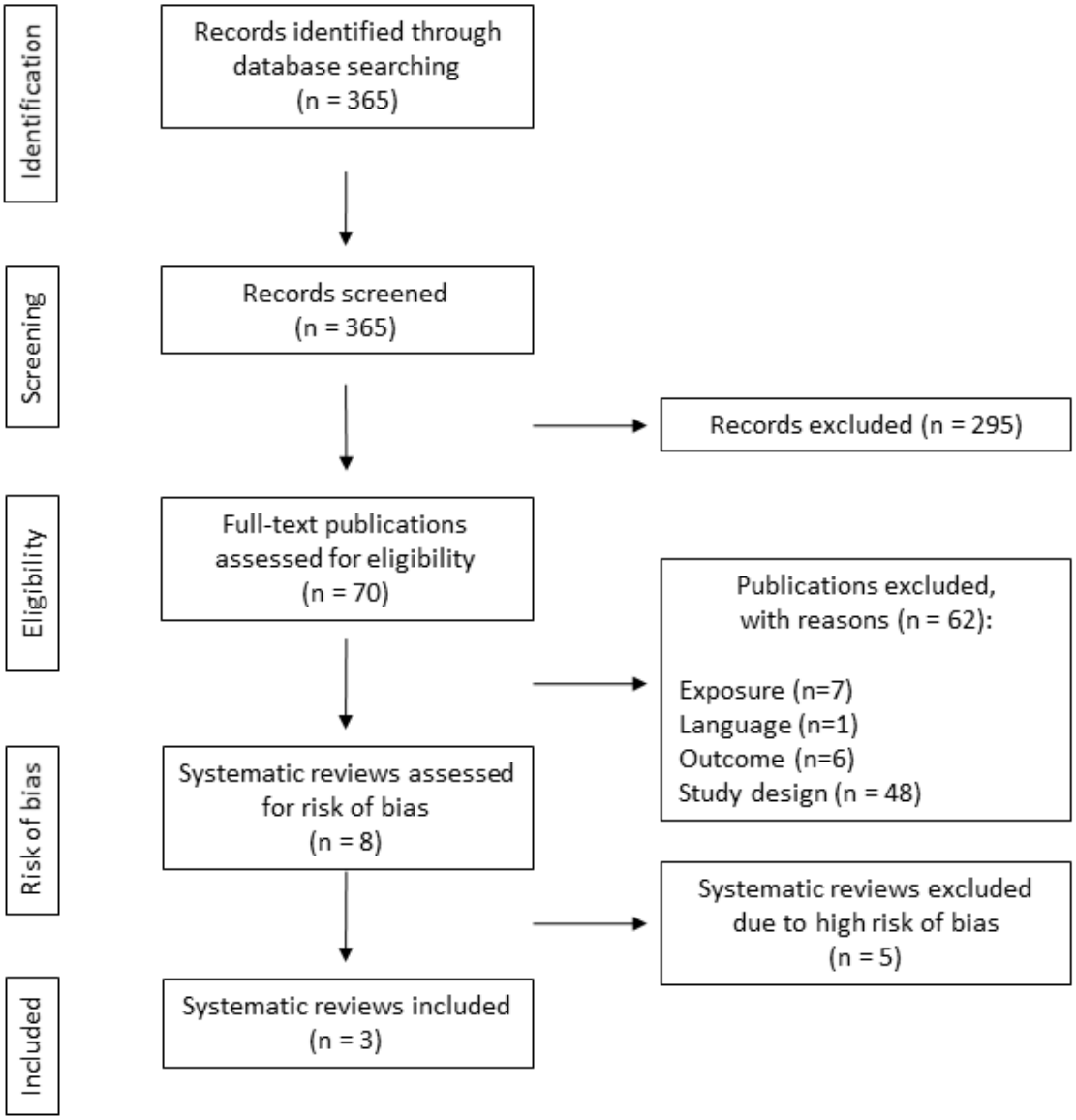


Figure 5.3.5-1. Flowchart for the selection of systematic reviews of human studies with low or unclear risk of bias and addressing human health effects of sunscreen products and UV filters (modified from Moher et al. (2009).

Table 5.3.5-1. UVR-induced health outcomes addressed in the systematic reviews that are included in the evidence synthesis. Outcomes were rated according to categories of importance.

Outcomes according to category	Reference	Sunscreen effect evaluated (protective or adverse)
CRITICAL		
Melanoma	Dennis et al. (2003); Rueegg et al. (2019)	Protective and adverse
IMPORTANT, BUT NOT CRITICAL		
Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)	Sanchez et al. (2016)	Protective

5.4 Randomised controlled trials

5.4.1 Literature search

Literature searches in the electronic databases from MEDLINE (Ovid), Embase (Ovid), and Web of Science were performed on 03 March, 2020 (see Chapter 17.1 terms and search strategy).

5.4.2 Publication selection

The study selection was based on the eligibility criteria in Table 5.4.2-1.

Table 5.4.2-1. Eligibility criteria for RCTs addressing potential adverse and protective health effects associated with the use of sunscreen products and UV filters.

Study design	RCTs
Population	All age groups, males and females
Exposure	Dermal application The tested substances are sunscreen products and UV filters tested separately
Outcome of interest	Protective health effects of sunscreen use when exposed to UVR Adverse health effects of sunscreen products and UV filters
Language of the full text	Danish, English, German, Norwegian, and Swedish
Publication type	Scientific publications

Titles and abstracts of 4193 records were screened prior to assessment of 105 full-text articles. Thirty-seven RCTs fulfilled the eligibility criteria and 19 were not included as they addressed protection against UVR-induced adverse effects rated as "of limited importance" (Table 5.1-1).

5.4.3 Evaluation of internal validity of RCTs

RoB was evaluated using the OHAT (Office of Health Assessment and Translation) tool (OHAT, 2015; OHAT, 2019). This evaluation tool offers a method to evaluate RoB in human and animal studies. Eight questions addressing selection bias, performance bias, detection bias, selective reporting bias, attrition/exclusion bias and other sources of bias were used to evaluate RoB in human controlled trials. The questions addressing the elements selection bias (randomisation and allocation to study groups), performance bias (identical experimental conditions across study groups and blinding of personnel and participants), detection bias (confidence in the exposure characterisation and the outcome assessment), and selective reporting bias were defined as key questions. The questions addressing the elements attrition/exclusion bias and other sources of bias were defined as non-key questions. The rating of key and non-key questions was integrated to classify the RCTs into tiers to characterise the overall RoB for each outcome in a study (modified from EFSA et al.

(2017)) as shown in Table 5.4.3-1. Tiers 1, 2 and 3 represent low, moderate and high RoB, respectively.

Table 5.4.3-1. Classification of studies into tiers according to overall RoB for each outcome/study. Definitely low risk of bias (++); probably low risk of bias (+); probably high risk of bias (-); definitely high risk of bias (--).

Tier	1 (low RoB)	2 (moderate RoB)	3 (high RoB)
Criteria for classification	All key questions are scored +/++ AND No more than one non-key question is scored – AND No non-key question is scored - -	All combinations not falling under tier 1 or 3	Any key or non-key question is scored - - OR More than one key question is scored -

RoB was evaluated in RCTs addressing associations between sunscreen and the following UVR-induced effects: actinic keratosis (Table 5.4.3-2), basal cell carcinoma (BCC) (Table 5.4.3-3), immunosuppression (Table 5.4.3-4), polymorphic light eruption (PLE) (Table 5.4.3-5), other reversible skin reactions (Table 5.4.3-6), squamous cell carcinoma (SCC) (Table 5.4.3-7), and vitamin D synthesis (Table 5.4.3-8).

Table 5.4.3-2. RoB rating and classification into tiers for the outcome actinic keratoses.
*Key question. **The sunscreen investigated contained more than one UV filter. Definitely low risk of bias (++); probably low risk of bias (+); probably high risk of bias (-); definitely high risk of bias (--).

Reference	1.* Was administered dose or exposure level adequately randomized?	2.* Was allocation to study groups adequately concealed?	3.* Were the research personnel and human subjects blinded to the study group during the study?	4. Were outcome data complete without attrition or exclusion from analysis?	5.* Can we be confident in the exposure characterisation?	6.* Can we be confident in the outcome assessment?	7.* Were all measured outcomes reported?	8. Were there no other potential threats to internal validity?	Tier	UV filter of relevance
Darlington et al. (2003)	++	++	+	+	-	+	++	+	1	BMDBM**
Naylor et al. (1995)	+	-	+	+	-	+	++	-	3	EHS**
Thompson et al. (1993)	+	-	+	++	++	+	++	+	2	BMDBM**

Table 5.4.3-3. RoB rating and classification into tiers for the outcome BCC.
*Key question. **The sunscreen investigated contained more than one UV filter. Definitely low risk of bias (++); probably low risk of bias (+); probably high risk of bias (-); definitely high risk of bias (--).

Reference	1.* Was administered dose or exposure level adequately randomized?	2.* Was allocation to study groups adequately concealed?	3.* Were the research personnel and human subjects blinded to the study group during the study?	4. Were outcome data complete without attrition or exclusion from analysis?	5.* Can we be confident in the exposure characterisation?	6.* Can we be confident in the outcome assessment?	7.* Were all measured outcomes reported?	8. Were there no other potential threats to internal validity?	Tier	UV filter of relevance
Green et al. (1999)	++	++	+	-	-	+	++	+	2	BMDBM**
Pandeya et al. (2005)	++	++	+	++	-	+	++	+	2	BMDBM**
van der Pols et al. (2006)	++	++	+	++	-	+	++	+	2	BMDBM**

Table 5.4.3-4. RoB rating and classification into tiers for the outcome immunosuppression.
*Key question. **The sunscreen investigated contained more than one UV filter. Definitely low risk of bias (++); probably low risk of bias (+); probably high risk of bias (-); definitely high risk of bias (--).

Reference	1.* Was administered dose or exposure level adequately randomized?	2.* Was allocation to study groups adequately concealed?	3.* Were the research personnel and human subjects blinded to the study group during the study?	4. Were outcome data complete without attrition or exclusion from analysis?	5.* Can we be confident in the exposure characterisation?	6.* Can we be confident in the outcome assessment?	7.* Were all measured outcomes reported?	8. Were there no other potential threats to internal validity?	Tier	UV filter of relevance
Moyal and Fourtanier (2001)	+	-	-	++	+	-	++	+	3	BMDBM, OC, TiO_2**
Moyal and Fourtanier (2003)	-	-	-	-	+	-	-	-	3	BMDBM, OC**
Neale et al. (1997)	++	++	+	++	-	+	++	+	2	BMDBM
Serre et al. (1997)	+	-	-	++	+	-	+	++	3	BMDBM, OC**

Table 5.4.3-5. RoB rating and classification into tiers for the outcome polymorphic light eruption (PLE).
*Key question. **The sunscreen tested contained more than one UV filter. Definitely low risk of bias (++); probably low risk of bias (+); probably high risk of bias (-); definitely high risk of bias (--).

Reference	1.* Was administered dose or exposure level adequately randomized?	2.* Was allocation to study groups adequately concealed?	3.* Were the research personnel and human subjects blinded to the study group during the study?	4. Were outcome data complete without attrition or exclusion from analysis?	5.* Can we be confident in the exposure characterisation?	6.* Can we be confident in the outcome assessment?	7.* Were all measured outcomes reported?	8. Were there no other potential threats to internal validity?	Tier	UV filter of relevance
DeLeo et al. (2009b)	+	+	+	++	+	+	++	+	1	BMDBM, OC, TiO_2**
Moyal et al. (1999)	+	+	+	++	++	-	++	-	2	BMDBM, TiO_2**
Schleyer et al. (2008)	-	+	-	++	+	+	++	++	3	BEMT, EHT, BMDBM**

Table 5.4.3-6. An overview of the RoB rating and the classification into tiers for the outcome other reversible skin reactions.
*Key question. **The sunscreen tested contained more than one UV filter. Definitely low risk of bias (++); probably low risk of bias (+); probably high risk of bias (-); definitely high risk of bias (--).

Reference	1.* Was administered dose or exposure level adequately randomized?	2.* Was allocation to study groups adequately concealed?	3.* Were the research personnel and human subjects blinded to the study group during the study?	4. Were outcome data complete without attrition or exclusion from analysis?	5.* Can we be confident in the exposure characterisation?	6.* Can we be confident in the outcome assessment?	7.* Were all measured outcomes reported?	8. Were there no other potential threats to internal validity?	Tier	UV filter of relevance
Naylor et al. (1995)	+	-	+	+	-	-	+	-	3	EHS**

Table 5.4.3-7. RoB rating and classification into tiers for the outcome SCC.
*Key question. **The sunscreen investigated contained more than one UV filter. Definitely low risk of bias (++); probably low risk of bias (+); probably high risk of bias (-); definitely high risk of bias (--).

Reference	1.* Was administered dose or exposure level adequately randomized?	2.* Was allocation to study groups adequately concealed?	3.* Were the research personnel and human subjects blinded to the study group during the study?	4. Were outcome data complete without attrition or exclusion from analysis?	5.* Can we be confident in the exposure characterisation?	6.* Can we be confident in the outcome assessment?	7.* Were all measured outcomes reported?	8. Were there no other potential threats to internal validity?	Tier	UV filter of relevance
Green et al. (1999)	++	++	+	-	-	+	++	+	2	BMDBM**
van der Pols et al. (2006)	++	++	+	++	-	+	++	+	2	BMDBM**

Table 5.4.3-8. An overview of the RoB rating and the classification into tiers for the outcome vitamin D synthesis.
*Key question. **The sunscreen tested contained more than one UV filter. Definitely low risk of bias (++); probably low risk of bias (+); probably high risk of bias (-); definitely high risk of bias (--).

Reference	1.* Was administered dose or exposure level adequately randomized?	2.* Was allocation to study groups adequately concealed?	3.* Were the research personnel and human subjects blinded to the study group during the study?	4. Were outcome data complete without attrition or exclusion from analysis?	5.* Can we be confident in the exposure characterisation?	6.* Can we be confident in the outcome assessment?	7.* Were all measured outcomes reported?	8. Were there no other potential threats to internal validity?	Tier	UV filter of relevance
Faurschou et al. (2012)	++	++	+	++	-	++	++	++	2	TiO_2
Libon et al. (2017a)	+	-	+	++	-	++	++	+	3	BEMT, BMDBM, EHS, OC**
Marks et al. (1995)	+	-	+	+	+	++	++	+	2	BMDBM**
Matsuoka et al. (1990)	+	-	+	++	--	+	++	-	3	Filters not specified

5.4.4 Data extraction

5.4.4 Data extraction

The data extraction forms are included in the Appendix (Chapter 17.1.2.4). A brief overview of study characteristics is given in Chapters 6.1.2 and 7.1.2.

5.4.5 Summary of the literature search for randomised controlled trials

Figure 5.4.5-1 gives an overview of the RCT study selection and the evaluation of risk of bias. An overview of the outcomes addressed in the studies that are included in the evidence synthesis is given in Table 5.4.5-1.

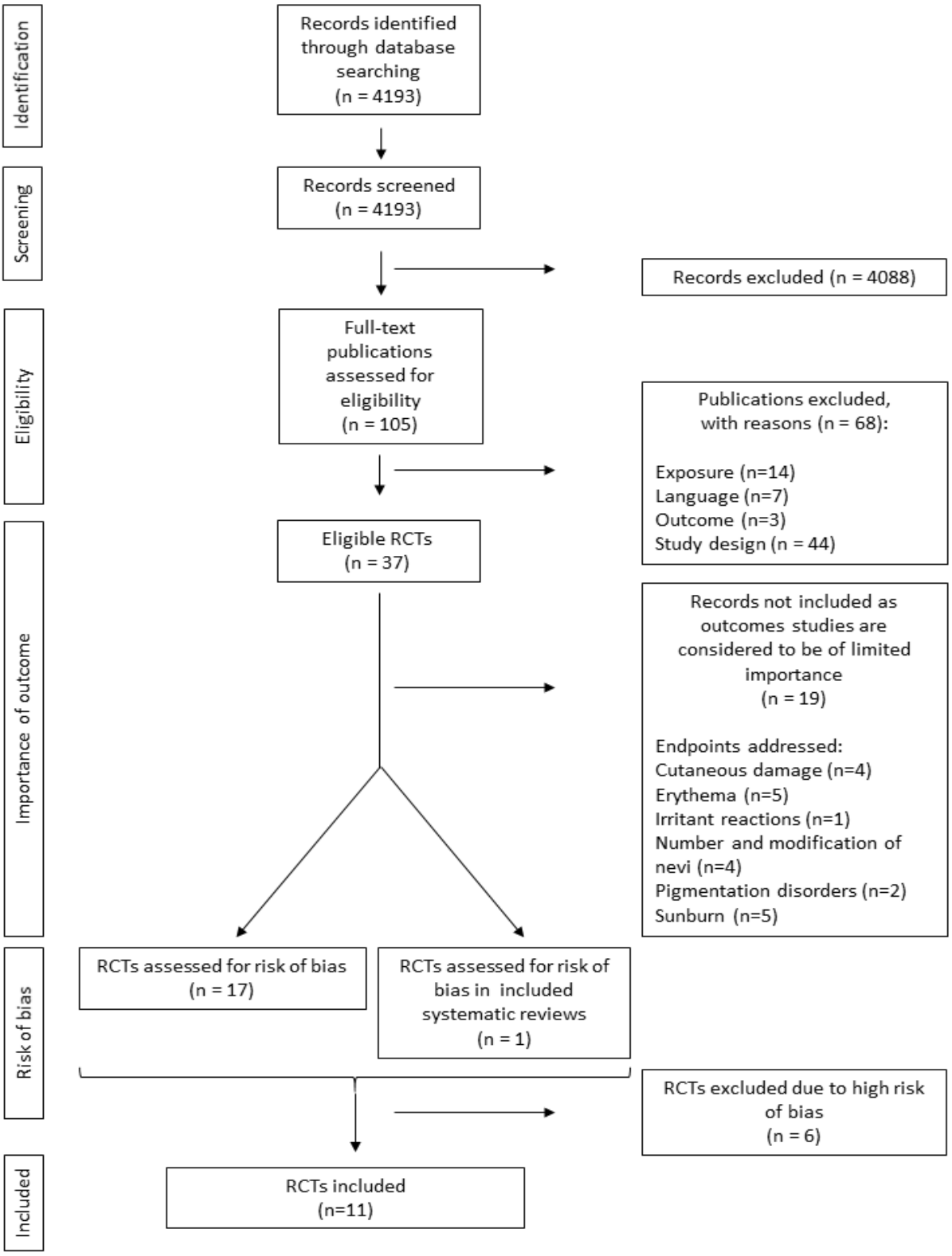


Figure 5.4.5-1. Flowchart for the selection of RCTs addressing human health effects of sunscreens containing the selected UV filters. The included RCTs had low or moderate RoB (modified from Moher et al. (2009)). "Of limited importance", see Table 5.1-1.

Table 5.4.5-1. Health outcomes addressed in the included RCTs reporting on potential protective or adverse effects of sunscreens. n.a.: not applicable

Outcomes addressed in RCT	References	Effect of sunscreen addressed	Rating of UVR-induced health outcomes (Table 5.1-1)
Melanoma	Green et al. (2011)*	Protective	Critical
Actinic keratosis	Darlington et al., 2003; Thompson et al., 1993	Protective	Important, but not critical
Basal cell carcinoma (BCC)	Green et al. (1999); van der Pols et al. (2006); Pandeya et al. (2005)	Protective	
Immunosuppression	Neale et al. (1997)	Protective	
Polymorphic light eruption (PLE)	DeLeo et al. (2009b)(not included in the evidence synthesis); Moyal et al. (1999) (not included in the evidence synthesis)	Protective	
Squamous cell carcinoma (SCC)	Green et al. (1999); van der Pols et al. (2006)	Protective	
Vitamin D synthesis	Faurschou et al. (2012); Marks et al. (1995)	Adverse	n.a.

*Risk of bias was not evaluated by VKM as this study was evaluated in an included systematic review (Rueegg et al., 2019).

Two of the studies on reduction of PLE, DeLeo et al. (2009b) and Moyal et al. (1999), were not included in the evidence synthesis since in these studies, treatments with different UV filters were compared. This type of comparison was not considered to be relevant for the current risk-benefit assessment. This issue could have been solved by introducing a check for relevance prior to internal validity assessment or by explicitly including a demand for appropriate control in the RoB criteria related to exposure.

5.5 Other human studies, animal studies and *in vitro* studies

5.5.1 Literature search

Literature searches in the electronic databases from MEDLINE (Ovid), Embase (Ovid), and Web of Science were performed to identify studies addressing adverse effects of the UV filters BEMT, BMDBM, EHS and EHT (see Chapter 17.2 for search terms and search strategy). We did not include OC and NP-TiO_2 in the search as the available data for these UV filters were considered to be sufficient to evaluate adverse effects.

5.5.2 Publication selection

The study selection was based on the predefined eligibility criteria (Table 5.5.2-1).

Table 5.5.2-1. Eligibility criteria for other human studies, animal studies and *in vitro* studies addressing potential adverse health effects associated with UV filters.

Population	Humans Animals: rat, mice, rabbit, guinea pig *In vitro* studies
Exposure to a single UV filter	Dermal application UV filters (tested separately, with or without UV exposure): BEMT, BMDBM, EHS, EHT
Outcome of interest	Adverse health effects related to BEMT, BMDBM, EHS, EHT
Language of the full text	Danish, English, German, Norwegian, and Swedish
Publication type	Scientific publications

Two independent reviewers performed the publication selection. Titles and abstracts of 1000 records were screened prior to assessment of 68 full-text articles. Thirteen human studies, all reporting results from patch tests, two animal studies, and 13 *in vitro* studies fulfilled the eligibility criteria.

As validated methods for evaluation of relevance, internal validity, and confidence in evidence for the *in vitro studies* were not available, such studies were not included in this assessment.

5.5.3 Evaluation of internal validity of other human studies and animal studies

RoB evaluation questions considered appropriate for the evaluation of the patch studies were identified (OHAT, 2019). Five questions were included to evaluate bias related to confounding, detection, selective reporting, and other sources. The two questions addressing detection bias were considered to be key questions.

For animal studies, nine questions considering selection bias, performance bias, attrition/exclusion bias, detection bias, selective reporting bias, and other sources of bias were included in the RoB evaluation (OHAT, 2019). The questions considered to be key questions included one question on selection bias, one question on performance bias, and the two questions on detection bias.

The method used to evaluate RoB and the classification into tiers are described in 5.3.3. The RoB evaluation results for the human patch test and animal studies are shown in Table 5.5.3-1 and 5.5.3-2, respectively.

Table 5.5.3-1. RoB rating and classification into tiers of human photopatch test studies.
*Key question. Definitely low risk of bias (++); probably low risk of bias (+); probably high risk of bias (-); definitely high risk of bias (--).

Reference	1.* Did the study design or analysis account for important confounding and modifying variables?	2.* Can we be confident in the exposure characterisation?	3.* Can we be confident in the outcome assessment?	4. Were all measured outcomes reported?	5. Were there no other potential threats to internal validity?	Tier	UV filter of relevance
Bryden et al. (2006)	++	++	+	++	Not found	1	BMDBM
Cook and Freeman (2001)	--	+	+	++	Not found	3	BMDBM
Darvay et al. (2001)	--	++	+	++	Not found	3	BMDBM
English et al. (1987)	--	-	-	-	Not found	3	BMDBM
Greenspoon et al. (2013)	--	-	+	++	Not found	3	BMDBM, EHS
Haylett et al. (2014)	++	++	+	++	Not found	1	BMDBM
Katsarou-Katsari et al. (2008)	++	+	+	+	Not found	1	BMDBM
Kerr et al. (2012)	++	+	+	++	Not found	1	BMDBM, BEMT, EHS, EHT
Schauder and Ippen (1986)	--	++	-	++	Not found	3	BMDBM
Schauder and Ippen (1988)	--	++	-	++	Not found	3	BMDBM

Reference	1.* Did the study design or analysis account for important confounding and modifying variables?	2.* Can we be confident in the exposure characterisation?	3.* Can we be confident in the outcome assessment?	4. Were all measured outcomes reported?	5. Were there no other potential threats to internal validity?	Tier	UV filter of relevance
Shaw et al. (2010)	--	-	--	++	Not found	3	BEMT, BMDBM, EHS
Subiabre-Ferrer et al. (2019)	+	++	+	++	Not found	1	BMDBM
Valbuena Mesa and Hoyos Jimenez (2016)	++	++	+	++	Not found	1	BEMT, BMDBM, EHS, EHT

Table 5.5.3-2. RoB rating and classification into tiers of animal studies.
*Key question. Definitely low risk of bias (++); probably low risk of bias (+); probably high risk of bias (-); definitely high risk of bias (--).

Reference	1.* Was administered dose or exposure level adequately randomized?	Was allocation to study groups adequately concealed?	2.* Were experimental conditions identical across study groups?	3. Were the research personnel blinded to the study group during the study?	4. Were outcome data complete without attrition or exclusion from analysis?	5.* Can we be confident in the exposure characterisation?	6.* Can we be confident in the outcome assessment?	7. Were all measured outcomes reported?	8. Were there no other potential threats to internal validity?	Tier	UV filter of relevance
Ashby et al. (2001)	-	+	+	-	++	+	-	++	+	3	BEMT
Schlumpf et al. (2001) (dermal)	-	+	++	-	--	-	++	++	-	3	BMDBM

5.5.4 Data extraction

An overview of study characteristics is given in Chapter 6.2 to 6.6.

5.5.5 Summary of the literature search for human photopatch test studies, animal studies and *in vitro* studies

Literature searches were performed to identify studies addressing potential adverse effects of the UV filters BEMT, BMDBM, EHS and EHT. An overview of the study selection and the evaluation of risk of bias is given in Figure 5.5.5-1. An overview of the outcomes addressed in the studies that will be included in the evidence synthesis is given in Table 5.5.5-1.

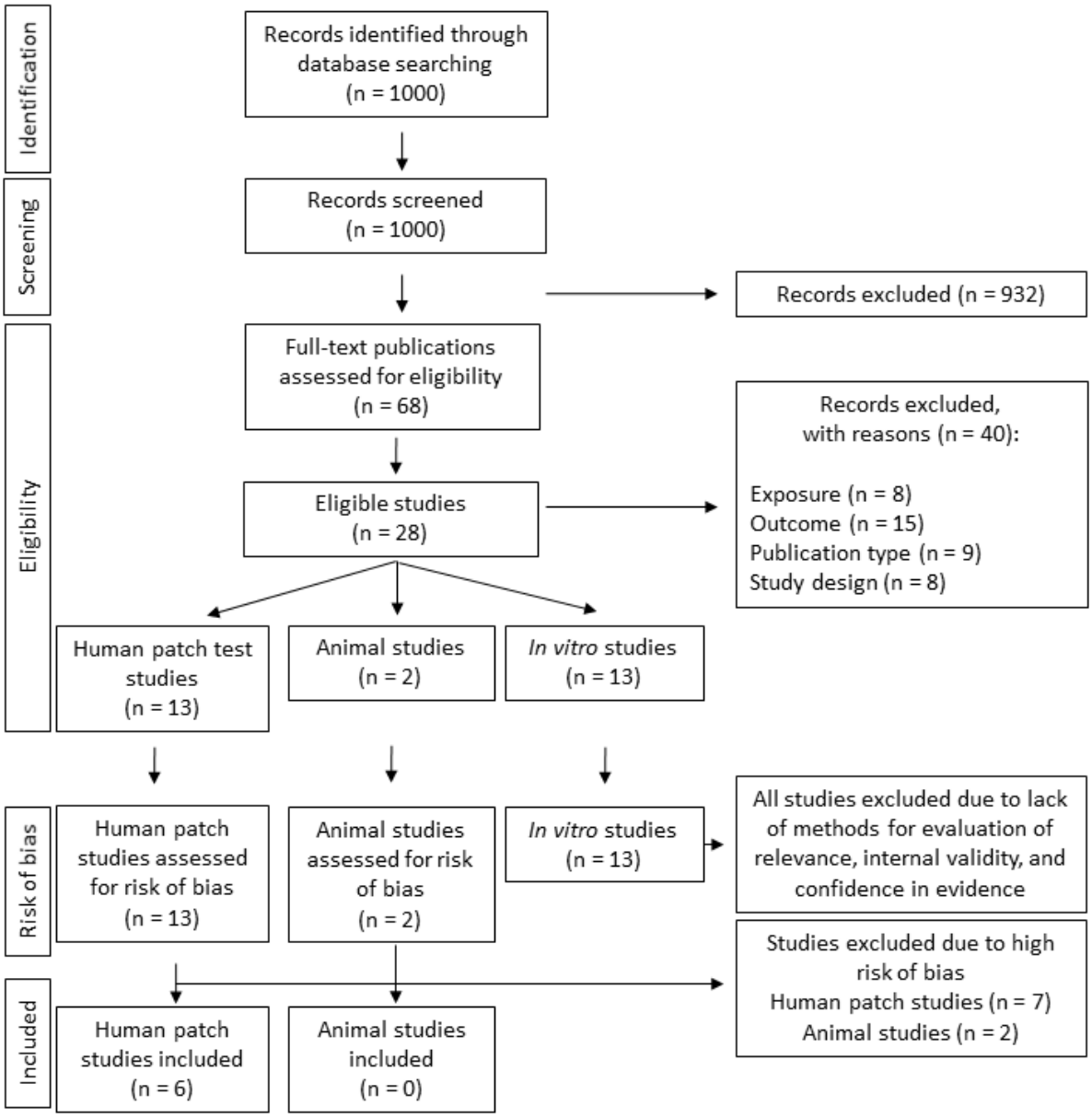


Figure 5.5.5-1. Flowchart for the selection of human (photo-)patch test studies, animal studies and *in vitro* studies addressing potential adverse health effects of UV filters. The included studies had low or moderate RoB (modified from Moher et al. (2009).

Table 5.5.5-1. Outcomes addressed in the included human (photo-)patch test studies investigating adverse effects of UV filters.

Outcome	Reference
Photoallergic and allergic contact dermatitis	Bryden et al. (2006); Haylett et al. (2014); Katsarou-Katsari et al. (2008); Kerr et al. (2012); Subiabre-Ferrer et al. (2019); Valbuena Mesa and Hoyos Jimenez (2016)
Irritant contact dermatitis	Bryden et al. (2006); Haylett et al. (2014); Kerr et al. (2012); Valbuena Mesa and Hoyos Jimenez (2016)

5.6 Summary literature searches

Literature searches were performed to identify studies investigating:

- Health protective effects, *i.e.* reduction of solar UVR-induced adverse health effects, related to sunscreen use
- Any adverse health effects related to the use of sunscreen and to exposure to six selected UV filters

As specified in the protocol (VKM et al., 2020), the priority sequence of the publications was determined by study design in the following order from highest to lowest priority: Systematic reviews of human studies, RCTs, human observational studies, animal and *in vitro* studies. The two latter study types were included only when additional evidence was needed.

The ROBIS tool (Whiting et al., 2016) was used for the RoB evaluation of the systematic reviews. The OHAT tool for RoB evaluation (OHAT, 2015; OHAT, 2019) was used for RCTs, non-randomised controlled human studies, and animal studies.

Included studies fulfilled the eligibility criteria, the overall RoB was categorised as low or moderate (unclear in the case of systematic reviews), and the protective effects addressed were reduction of the UV-induced adverse outcomes categorised as "critical" or "important, but not critical" (Table 5.1-1).

5.6.1 Protective effects of sunscreens

Three systematic reviews and six RCTs addressing health protective effects, identified in the literature searches, were included in the evidence synthesis (Chapter 7). An overview is given in Table 5.6.1-1. No further literature searches for other study designs were considered necessary as data from systematic reviews and RCTs in which RoB was low or moderate were available.

Table 5.6.1-1. Included studies addressing potential protective effects of sunscreen use. The UV-induced outcomes are categorised according to level of importance (Table 5.1-1).

Potential protective effect (direction) in health outcomes according to category	Reference	Study type
Critical		
Melanoma (reduction)	Dennis et al. (2003); Rueegg et al. (2019)	Systematic review
Melanoma (reduction)	Green et al. (2011)	RCT
Important, but not critical		
Actinic keratosis (reduction)	Darlington et al., 2003; Thompson et al., 1993	RCT
Basal cell carcinoma (BCC) (reduction)	Sanchez et al. (2016)	Systematic review
Basal cell carcinoma (BCC) (reduction)	Green et al. (1999); van der Pols et al. (2006); Pandeya et al. (2005)	RCT
Immunosuppression (reduction)	Neale et al. (1997)	RCT
Squamous cell carcinoma (SCC) (reduction)	Green et al. (1999); van der Pols et al. (2006)	RCT

5.6.2 Adverse effects of sunscreen use and UV filter exposure

Systematic reviews, RCTs and non-randomised controlled human studies (patch test studies) identified in the literature searches are included in the evidence synthesis (Chapter 6). An overview is given in Table 5.6.2-1.

Table 5.6.2-1. Included studies addressing potential adverse effects related to sunscreen use and exposure to the UV filters BEMT, BMDBM, EHS, and EHT .

Potential adverse effect (direction)	Reference	Study type (treatment)
Melanoma (increase)	Dennis, 2003; Rueegg, 2019	Systematic reviews (any sunscreen)
Vitamin D synthesis (reduction)	Faurschou et al. (2012); Marks et al. (1995)	RCTs (sunscreen containing selected filter)
Skin irritation (increase)	Bryden et al. (2006); Haylett et al. (2014); Kerr et al. (2012); Valbuena Mesa and Hoyos Jimenez (2016)	Other controlled human studies (≥1 of selected filter(s))
Skin sensitisation (increase)	Bryden et al. (2006); Haylett et al. (2014); Katsarou-Katsari et al. (2008); Kerr et al. (2012); Subiabre-Ferrer et al. (2019); Valbuena Mesa and Hoyos Jimenez (2016)	

5.7 Toxicology data from ECHA

Relevant hazard data from ECHA registration dossiers are included (study characteristics are available in Chapter 6.3 to 6.8). Information in the ECHA registration dossiers includes substance identity, results of studies on intrinsic properties and hazard profiles, and the levels where no adverse effects are expected. The companies that manufacture or import (>1 tonne/year) the substances are responsible for providing the dossier information.

6 Hazard characterisation and evidence synthesis

The hazard characterisation is based on evidence identified from the literature searches for systematic reviews, RCTs, non-randomised, controlled human studies ((photo-)patch studies), and ECHA registration dossiers (Chapter 5). All identified adverse health effects associated with sunscreens and the selected UV filters were included in the hazard characterisation. An overview of the hazard characterisation is given in Figure 6-1.

The methods used for the evaluation of certainty in the evidence are described in Chapter 6.1.

The adverse effects addressed in the studies on sunscreen include development of melanoma (*i.e.* a positive correlation between sunscreen use and melanoma) and reduced vitamin D synthesis (Chapter 6.2).

The adverse effects addressed in the studies on the six selected UV filters are divided in systemic toxicity and local effects. Systemic toxicity includes acute, subacute, subchronic and chronic toxicity, genetic toxicity and carcinogenicity, and reproductive and developmental toxicity. Local effects include skin irritation and skin sensitisation. The evidence for different systemic and local effects is presented in Chapter 6.3 to 6.8. For each line of evidence, a conclusion on the health effect and the certainty in the evidence is given, and the no observed adverse effect level (NOAEL) is identified as a PoD when possible.

An overview of the lines of evidence and the hazard conclusions are is shown in Chapter 6.9. The hazard conclusion is expressed as the derived no effect level (DNEL) for the animal studies. The DNEL is the level of chemical exposure above which humans should not be exposed, and is derived by dividing the NOAEL by the overall uncertainty factor (UF). Identification of uncertainty in the NOAEL values and derivation of the overall UF is presented in Chapter 6.10, and the derivation of DNELs is presented in Chapter 6.11. The DNEL-value for each UV filter is the answer to question 3 in Table 2.4-1, and is used in the risk characterisation as shown Figure 8-1. When no adverse effects are observed, the highest DNEL is used in the risk characterisation. When adverse effects are observed, the lowest DNEL derived from studies where an effect is observed is used in the risk characterisation.

The overall hazard conclusions are given in Chapter 6.12.

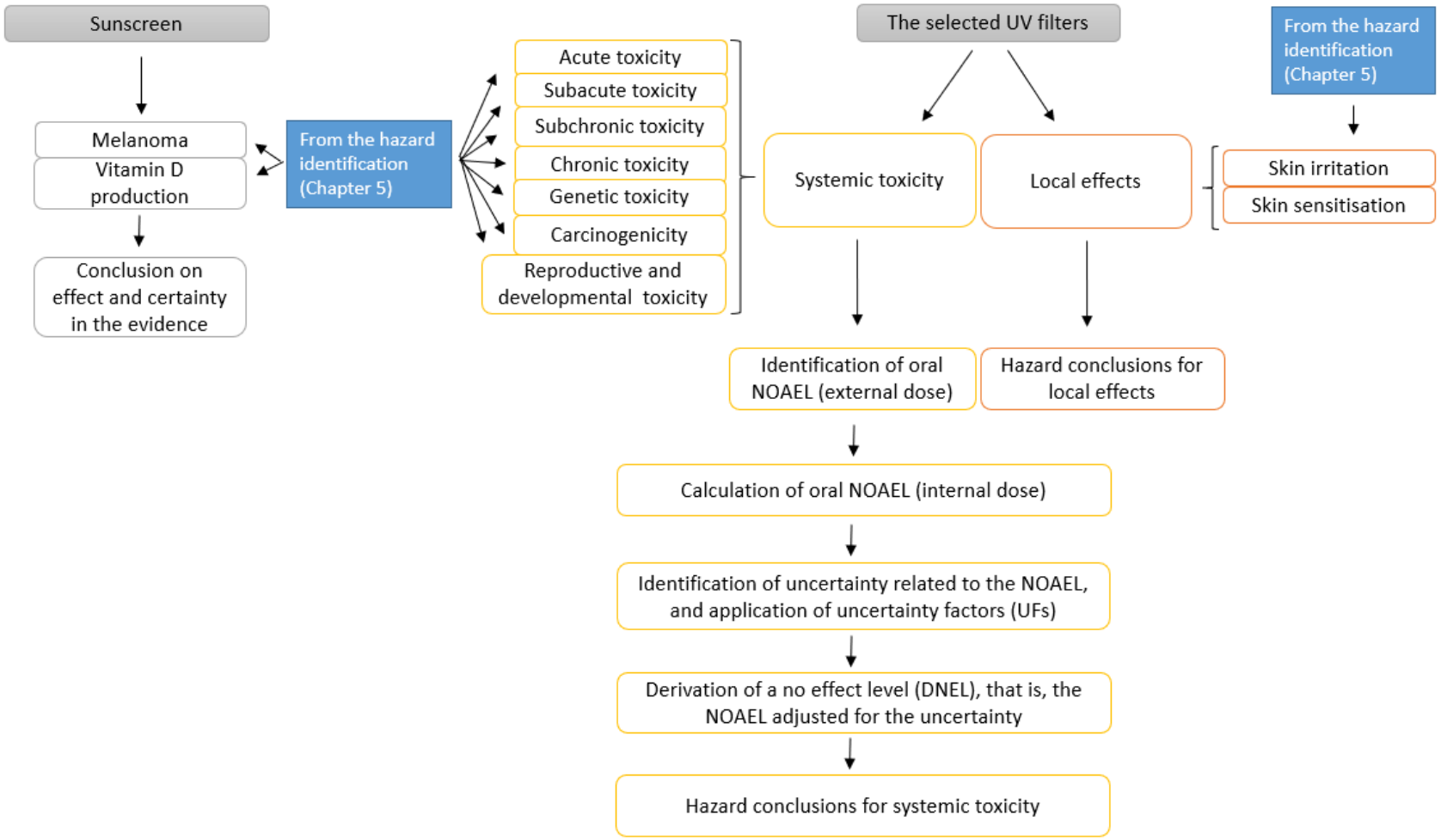


Figure 6-1. An overview of the hazard characterisation and the outcomes evaluated.

6.1 Methods used in the evaluation of the included evidence

6.1.1 Systematic reviews; evaluation of certainty in the evidence

The certainty in the evidence as evaluated by the study authors of the systematic reviews was included in the present risk-benefit assessment.

6.1.2 RCTs and non-randomised human studies; evaluation of certainty in the evidence

VKM evaluated the certainty in the body of evidence for outcomes across studies for each line of evidence according to OHAT (2019).

- An initial certainty rating was made to determine the ability of the study design to ensure that exposure preceded, and was associated with, the outcome. The parameters evaluated were whether i) the exposure was experimentally controlled, ii) the exposure occurred prior to the development of the outcome, iii) the outcome was assessed on the individual level (*i.e.*, not through population aggregate data) and iv) an appropriate comparison group was included in the study. Fulfilment of all features will receive an initial rating of high certainty (++++). The lower ratings, moderate (+++), low (++) or very-low (+), correspond to the number of features fulfilled.
- Factors that may downgrade the initial certainty rating are i) risk of bias (downgraded when 50% or more of the studies were classified as tier 2), ii) unexplained inconsistency (not evaluated when only one study was available), iii) indirectness, and iv) imprecision.
- The evaluation of factors that may upgrade the certainty in the evidence follows the evaluation of factors that may downgrade the certainty in the evidence. However, limitations in the certainty due to downgrading will normally not favour upgrading. Observational studies or studies receiving less than high initial rating, may be upgraded if no further downgrading from the initial rating has occured. Factors that may upgrade the initial certainty rating are i) large magnitude of effect (*e.g.* incidence, degrees of severity), ii) the presence of a dose-response relationship, and iii) consistency across study design type/dissimilar populations for the relevant studies combined. In the present risk-benefit assessment, in which the studies were RCTs or other controlled studies which normally receive an initial evidence rating of high, upgrading was not evaluated when downgrading had been performed due to serious limitations.

6.1.3 Studies in the ECHA database; evaluation of reliability

The reliability of the evidence included in the ECHA database has been evaluated by ECHA using the Klimisch scoring system (Klimisch et al., 1997). Similar to the evaluation of the

systematic reviews, the evaluation of reliability performed by ECHA is used in the evaluation of the certainty in the evidence in the present risk-benefit assessment.

The Klimisch scoring system considers both reporting and methodological quality and adherence to standardized test guidelines (TG). However, it is important to note that a study can be biased despite adherence to TG. The risk of bias evaluation includes evaluation of factors not addressed in the Klimisch scoring system, such as randomisation and blinding.

Only studies with score 1 or 2 are included in the present assessment. The Klimisch score assigns studies to one of four categories as follows:

- 1 – Reliable without restriction. *"This includes studies or data from the literature or reports which were carried out or generated according to generally valid and/or internationally accepted testing guidelines (preferably performed according to GLP) or in which the test parameters documented are based on a specific (national) testing guideline (preferably performed according to GLP) or in which all parameters described are closely related/comparable to a guideline method."*
- 2 – Reliable with restriction. *"This includes studies or data from the literature, reports (mostly not performed according to GLP), in which the test parameters documented do not totally comply with the specific testing guideline, but are sufficient to accept the data or in which investigations are described which cannot be subsumed under a testing guideline, but which are nevertheless well documented and scientifically acceptable."*
- 3 – Not reliable. *"This includes studies or data from the literature/reports in which there are interferences between the measuring system and the test substance or in which organisms/test systems were used which are not relevant in relation to the exposure (e.g., unphysiologic pathways of application) or which were carried out or generated according to a method which is not acceptable, the documentation of which is not sufficient for an assessment and which is not convincing for an expert judgment."*
- 4 – Not assignable. *"This includes studies or data from the literature, which do not give sufficient experimental details and which are only listed in short abstracts or secondary literature (books, reviews, etc.)."*

6.1.4 Translation into evidence for health effects

6.1.4.1 Human studies

The certainty in the body of evidence, given as high, moderate, low or very low (Chapter 6.1.2) for health effect or no health effect, is translated into level of evidence for health effects according to OHAT (2019). An overview is given in Table 6.1.4.1-1.

Table 6.1.4.1-1. Translation of the certainty in the body of evidence to level of evidence for health effect (OHAT, 2019).

Confidence in the body of evidence	Level of evidence for health effect/no health effect	Definition
Health effect		
High	High	There is high confidence in the body of evidence for an association between exposure to the substance and the health outcome(s).
Moderate	Moderate	There is moderate confidence in the body of evidence for an association between exposure to the substance and the health outcome(s).
Low	Low	There is low confidence in the body of evidence for an association between exposure to the substance and health outcome(s), or no data are available.
Very low or no evidence identified	Inadequate	There is insufficient evidence available to assess if the exposure to the substance is associated with the health outcome(s).
No health effect		
High	Evidence of no health effect	There is high confidence in the body of evidence that exposure to the substance is not associated with the health outcome(s).
Moderate	Inadequate	There is insufficient evidence available to assess if the exposure to the substance is associated with the health outcome(s).
Low	Inadequate	There is insufficient evidence available to assess if the exposure to the substance is associated with the health outcome(s).
Very low or no evidence identified	Inadequate	There is insufficient evidence available to assess if the exposure to the substance is associated with the health outcome(s).

As described in OHAT (2019), the overall certainty in the body of evidence for a given outcome was reported as:

- "*High certainty (++++) in the association between exposure to the substance and the outcome. The true effect is highly likely to be reflected in the apparent relationship.*
- *Moderate certainty (+++) in the association between exposure to the substance and the outcome. The true effect may be reflected in the apparent relationship.*
- *Low certainty (++) in the association between exposure to the substance and the outcome. The true effect may be different from the apparent relationship.*
- *Very-low certainty (+) in the association between exposure to the substance and the outcome. The true effect is highly likely to be different from the apparent relationship*."

6.1.4.2 Animal studies

For each line of evidence from animal studies in Chapter 6.3 to 6.8, the evidence for health effects is given in the conclusions, with the identification of a NOAEL when possible.

6.1.5 Integration of evidence and hazard conclusions

Hazard conclusions are reached on individual outcomes (adverse health effects).

First, the integration of evidence and the derivation of hazard conclusions were performed separately for each evidence line for human and animal studies. Next, evidence lines for a given outcome from human studies and animal studies were considered together, and an overall hazard conclusion was reached. Hazard conclusions were reached by integrating the highest level-of-evidence conclusion, where applicable, for an outcome from the human and animal evidence lines (adapted from OHAT (2019)).

The hazard conclusion categories for human studies alone or in combination with animal data were adopted from OHAT (2019). In sequence from high to low evidence when a health effect is observed: Known to be a hazard to humans; presumed to be a hazard to humans; suspected to be a hazard to humans; not classifiable as a hazard to humans. When a health effect is not observed or is of minor importance: Not identified as a hazard to humans.

Note that OHAT (2019) uses the term "hazard identification conclusion", whereas VKM uses "hazard conclusion".

The hazard conclusions of the animal studies were the derived level of chemical exposure above which humans should not be exposed, *i.e.* the derived no-effect level (DNEL). The DNEL is derived by dividing the PoD by the overall uncertainty factor (UF).

6.2 Sunscreens: Study characteristics, evaluation of certainty in the evidence for adverse effects, and translation into evidence for health effects

6.2.1 Evidence from literature searches

6.2.1.1 Systematic reviews

Two systematic reviews addressed the relationship between sunscreen use and melanoma (Table 6.2.1.1-1). Another systematic review addressed the relationship between sunscreen use and the skin cancers squamous cell and basal cell carcinomas (Sanchez et al., 2016). However, since this systematic review included only the RCT by Green et al. (1999) which is already included in the current risk assessment, the systematic review by Sanchez (2016) is not included in the hazard characterisation.

Table 6.2.1.1-1. Study characteristics and certainty in the evidence for the hazard association between sunscreen use and melanoma.

Reference	Aim	Trials on this outcome (n)	Literature search period	Countries where the studies were conducted	UV exposure by type and number of studies	RoB (authors' assessment)	Key finding
Dennis et al. (2003)	Examine the strength and consistency of associations between melanoma and sunscreen use in the published literature.	Case–control studies (9 population-based case–control studies, 7 non–population-based studies and 2 case–control studies)	From 1966 through April 2003	Australia, Austria, Belgium, Brazil, Denmark, France, Germany, Italy, Spain, Sweden, USA	Cumulative sun exposure: 13; residential sun exposure: 6; recreational sun exposure: 10; occupational sun exposure:13; sunny vacations: 11; sunbathing: 9; sunlamps/beds: 11; "solar": 1	Unclear	The meta-analysis did not provide clear evidence for an increased risk for melanoma with sunscreen use. The authors noted that the included studies did not describe newer sunscreens with a sun protection factor greater than 15, protection against UVA, or water resistance.
Rueegg et al. (2019)	Answer whether sunscreen use affects melanoma risk.	23 case–control studies (11 hospital-based, 12 population-based), 1 ecological study, 3 cohort studies and 1	Articles published by 28.02.2018	Australia, Austria, Belgium, Brazil, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy,	Sun exposure (including time of day): 6; sunny holidays (time): 5; sunbathing: 5; time spent outdoors: 2; solarium: 3; outdoors employment, summer: 1	Low	Ever- vs. never-use of sunscreen was not associated with melanoma in the population-based case–control studies. Ever- vs. never-use of sunscreen was

Reference	Aim	Trials on this outcome (n)	Literature search period	Countries where the studies were conducted	UV exposure by type and number of studies	RoB (authors' assessment)	Key finding
		randomised controlled trial		Norway, Spain, Sweden, USA			positively associated with melanoma in the cohort studies.

Summary: Dennis et al. (2003) found no positive association between melanoma and sunscreen use in the meta-analysis of 18 case-control studies. The relevant studies included in Dennis (2003) were also included in Rueegg et al. (2019). Rueegg et al. (2019) included more study designs, and the literature search included studies published up to end of February 2018. According to Rueegg et al. (2019), the data used to assess an association between sunscreen use and melanoma were heterogenous across study designs and the level of the evidence varied as follows:

- In the hospital-based case–control studies and the ecological study, an association between sunscreen use and reduced development of melanoma was shown. The overall level of the evidence for an association between sunscreen use and melanoma in these studies was very low.
- In the population-based case–control studies no association between sunscreen use and development of melanoma was shown. The overall level of the evidence for an association between sunscreen use and melanoma in these studies was very low.
- In thecohort studies an association between sunscreen use and increased development of melanoma was shown. The overall level of the evidence for an association between sunscreen use and melanoma in these studies was very low.
- In the RCT, a protective effect of sunscreen was reported. The overall level of the evidence for an association between sunscreen use and melanoma in this study was moderate.

VKM conclusion on the evidence (based on the systematic review by Rueegg et al. (2019)): The overall confidence in the evidence for an association between sunscreen use and increase in development of melanoma is very low, resulting in an inadequate level of evidence for health effect. There is insufficient evidence to assess whether the exposure to sunscreen is associated with melanoma.

6.2.1.2 RCTs

Two RCTs addressed the relationship between sunscreen use and reduction in vitamin D synthesis (25-hydroxyvitamin D_3) (Table 6.2.1.2-1).

Table 6.2.1.2-1. Study characteristics and certainty in the evidence for the hazard association between sunscreen and reduction in vitamin D synthesis (25-hydroxyvitamin D_3). SED: standard erythema dose

Reference, study type	Participants/ intervention/duration	RoB	Results
Faurschou et al. (2012)	37 healthy volunteers participated and completed. Study location: Denmark Gender: 20 women and 17 men Age: 18–49 years Fitzpatrick skin types I–III Controls: n=10; intervention: n=27 Sunscreen: SPF 8, titanium dioxide (concentration not reported). The exact amount of sunscreen was weighed and applied in layer thickness (mg/cm^2) of 0.0, 0.5, 1.0, 1.5, or 2.0. Each participant was treated with sunscreen on the back and front of the upper body, approximately 25% of the body area. Placebo cream not used for zero level. The procedure was repeated four times with a 2 to 3-day interval, total study duration: 8 - 12 days. UV dose: 300 J/cm^2 (3 SED; erythemally weighted) from artificial UVB source (290-360 nm).	2	The sunscreen thickness applied, in mg/cm^2, was 0.0; 0.5; 1.0; 1.5; 2.0. The vitamin D serum level increased in an exponential manner with decreasing thickness of sunscreen layer in response to UVB exposure. For all thicknesses of sunscreen, the level of 25-hydroxyvitamin D_3 increased significantly after irradiation, except for the group treated with 2 mg/cm^2, in which the increase in 25-hydroxyvitamin D_3 was not statistically significant. Mean increase in 25-hydroxyvitamin D_3 (in nmoL^{-1}) measured 2-3 days after the final irradiation were 25.8, 12.5, 11.5, 10.2, and 6.4, for the sunscreen layer thickness 0, 0.5, 1.0, 1.5 and 2.0, respectively. The vitamin D increase was adjusted for baseline and the SD in the various sunscreen groups.

Reference, study type	Participants/ intervention/duration	RoB	Results
Marks et al. (1995)	n=113 Gender: 46 men and 67 women Age: 59 were aged 40-70 years and 54 were aged 70 years and above. Study location: Australia Skin type: self-reported as burn only and never tan (n=31), burn first and then tan (n=56), or tan only and never burn (n=26) Control: n=55; intervention: n=58 Sunscreen: SPF 17, containing 8% (wt/wt) 2-ethylhexyl p-methoxycinnamate and 2% (wt/wt) BMDBM. Application amount: approximately 1.5 ml to the head and neck and the same amount to each forearm and hand once every morning. Reapplication if necessary, during the day. UV dose: Mean daily solar UV exposure (285-315 nm) measured by personal dosimetry for 7 consecutive days: Sunscreen group: 137.9 J/cm^2 (95% CI, 62.6 -304.0 J/cm^2); placebo group: 138.7 J/cm^2 (95% CI, 60.8 -316.6 J/cm^2) (P= 0.99). "The subjects received on average between 5% and 8% of the ambient irradiation at ground level during the week of the study period". Study duration: seven summer months	2	Mean levels of 25-hydroxyvitamin D_3 increased significantly by the same amount in intervention and placebo groups over the period of the study (placebo, +12.8 nmol/L (95% CI, 8.4-17.1); sunscreen, + 11.8 nmol/L (95% CI, 7.6-15.9)).

Overall evaluation of certainty in the evidence on reduction in vitamin D (25-hydroxyvitamin D_3) synthesis			
Initial rating	Elements triggering downgrading	Elements triggering upgrading	Overall rating

Overall evaluation of certainty in the evidence on reduction in vitamin D (25-hydroxyvitamin D_3) synthesis								
	Risk of bias	Unexplained inconsistency	Indirectness	Imprecision	Large effect	Dose–response relationship	Consistency	
++++	Two studies classified as tier 2 (Table 5.3.3-8) Downgrade once Serious	Not serious	Not serious	The calculated SD was higher than the mean value in Marks et al. (1995). Downgrade once Serious	Not evaluated*	Not evaluated*	Not evaluated*	++ Low
Summary: The effect of sunscreen on 25-hydroxyvitamin D_3 synthesis was studied in two RCTs. In one RCT, the UVR source was from an artificial source and different thickness layers of sunscreen were applied; the UVR induced increase in the 25-hydroxyvitamin D_3 synthesis was reduced by increasing amount of sunscreen applied. In the other RCT, solar UVR was the irradiation source, the amount of sunscreen applied was similar for the participants, and a significant increase by the same amount in the 25-hydroxyvitamin D_3 synthesis was reported for the control and the sunscreen group. VKM conclusion on the evidence: There is low confidence in the body of evidence for an association between sunscreen use and reduction in vitamin D synthesis. The true effect may be different from the apparent relationship. The level of evidence for health effect is inadequate.								

* Elements triggering upgrading were not evaluated since downgrading was performed due to serious study limitations and imprecision.

6.3 UV filter BEMT: Study characteristics, evaluation of certainty in the evidence for adverse effects, and translation into evidence for health effects

6.3.1 Evidence from literature searches

Two patch studies addressed skin sensitisation, one included contact allergic reactions (Table 6.3.1-1) whereas both included photoallergic contact reactions (Table 6.3.1-2). Both also reported on skin irritation (Table 6.3.1-3).

Table 6.3.1-1. Study characteristics and certainty in the evidence for contact allergic reactions of BEMT. F: female; PPT: photopatch; COADEX: see definitions and Bruynzeel et al. (2004); ICDRG: International Contact Dermatitis Research Group

Reference	Type of test/ participants/ inclusion and exclusion criteria/ scoring system	Dose and duration	RoB	Number of reactions (in % of n)
Kerr et al. (2012)	Humans, n=1031, 18-92 (median=46 years)/ 715 F. A prospective, multicentre PPT study including 30 centres/ 12 European countries. Recruitment period: August 2008 to February 2011 Inclusion criteria: The inclusion criteria specified that subjects must be aged 18 years or older and have sufficient understanding to give written informed consent. Those included had at least one of the following four indications for performing photopatch testing: an exposed-site dermatitis during summer months; any exposed-site dermatitis; history of a sunscreen reaction; or history of a topical non-steroidal anti-inflammatory drug (NSAID) skin reaction. Exclusion criteria: Potent topical steroid applied to the PPT site on the back in the 5 days prior to photopatch testing; skin disease activity on the back which was too	The test agents were applied, removed at 24 or 48 h, one set was then irradiated with maximum 5 J/cm^2 UVA (minimum: 0.5 J/cm^2) while the other set was covered with a UV-impermeable material. Readings of the test site: pre-irradiation, post-irradiation: immediately, 24 h,	1	Allergic contact dermatitis: 1(0.1%). Severity: Grades 3, 4 and 5 (of 5): 1 (0.1%); 0 (0%); 0 (0%), respectively. Assessment of relevance was not included.

Reference	Type of test/ participants/ inclusion and exclusion criteria/ scoring system	Dose and duration	RoB	Number of reactions (in % of n)
	active to allow PPT; and subjects prescribed systemic immuno-suppressant medication. Testing according to the European consensus methodology; reaction scoring: ICDRG visual system; relevance evaluation: COADEX.	48, and 72 h or later. Readings from 48 h are presented. Concentration of BEMT: 10%		

Overall evaluation of certainty in the evidence on sensitisation (contact allergic reactions) of BEMT								
Initial rating	Elements triggering downgrading				Elements triggering upgrading			Overall rating
	Risk of bias	Unexplained inconsistency	Indirectness	Imprecision	Large effect	Dose–response relationship	Consistency	
++++	Not serious	Not evaluated (one study)	Not serious	Not serious	Not evaluated	Not evaluated	Not evaluated	++++ High
Summary: One study addressed contact allergic reactions of BEMT. One reaction with severity graded as 3 on a scale from 1-5, was reported for the 1031 subjects tested. VKM conclusion on the evidence: There is high confidence in the body of evidence for a low frequency of contact allergic reactions in susceptible individuals exposed to BEMT. The level of evidence is high.								

Table 6.3.1-2. Study characteristics and certainty in the evidence for photocontact allergic reactions of BEMT. PPT: photopatch; F: female; COADEX: see definitions and Bruynzeel et al. (2004); ICDRG: International Contact Dermatitis Research Group

Reference	Model/administration route/ guideline/ GLP	Dose and duration	RoB	Number of reactions (in % of n)
Kerr et al. (2012)	Photopatch test, humans, n=1031, 18-92 (median=46 years)/ 715 F. A prospective, multicentre PPT study including 30 centres/ 12 European countries. Recruitment period: August 2008 to February 2011 Inclusion criteria: The inclusion criteria specified that subjects must be aged 18 years or older and have sufficient understanding to give written informed consent. Those included had at least one of the following four indications for performing photopatch testing: an exposed-site dermatitis during summer months; any exposed-site dermatitis; history of a sunscreen reaction; or history of a topical NSAID skin reaction. Exclusion criteria: Potent topical steroid applied to the PPT site on the back in the 5 days prior to photopatch testing; skin disease activity on the back which was too active to allow PPT; and subjects prescribed systemic immuno-suppressant medication. Testing according to the European consensus methodology; reaction scoring: ICDRG visual system; relevance evaluation: COADEX	The test agents were applied, removed at 24 or 48 h, one set was then irradiated with maximum 5 J/cm^2 UVA (minimum: 0.5 J/cm^2) while the other set was covered with a UV-impermeable material. Readings of the test site: pre-irradiation, post-irradiation: immediately, 24 h, 48, and 72 h or later. Readings from 48 h are presented. Concentration of BEMT: 10%	1	Photoallergic contact dermatitis: 3 (0.2%). Severity: Grades 3, 4 and 5 (of 5): 1 (0.1%); 1 (0.1%); 1 (0.1%), respectively. Certain relevance: 1 (0.1%) Uncertain relevance: 2 (0.2%)
Valbuena Mesa and Hoyos	Photopatch test, humans, 100 participants, 13-88 years (mean = 49 years)/ 63 F	Application in duplicate, irradiation with 5 J/cm^2 after 48 h. The readings were performed on days 2, 4 and 6, in accordance	1	No photoallergic or allergic contact dermatitis observed

Reference	Model/administration route/ guideline/ GLP	Dose and duration	RoB	Number of reactions (in % of n)
Jimenez (2016)	Prospective descriptive cross-sectional study, 1 centre/ Colombia. Time period: 2001-2003 Inclusion criteria: Patients with suspected photo allergic contact dermatitis (a dermatitis affecting mainly light-exposed skin, those with a history of a sunscreen skin reaction or a topical NSAID skin reaction). Exclusion criteria: Patients with a clinical diagnosis of porphyria, solar urticaria or systemic lupus erythematosus were excluded from the testing procedure, as were pregnant woman and patients who received systemic steroid treatments or immunosuppressive drugs in the month before the test or who applied topical steroids on their backs in the 8 days prior to the test. Reaction scoring: ICDRG visual system	with the guidelines of the International Contact Dermatitis Research Group. Concentration of BEMT: 10%		

Overall evaluation of certainty in the evidence on sensitisation (photocontact allergic reactions) of BEMT

Initial rating	Elements triggering downgrading				Elements triggering upgrading			Overall rating
	Risk of bias	Unexplained inconsistency	Indirectness	Imprecision	Large effect	Dose–response relationship	Consistency	
++++	Not serious	Not serious	Not serious	Not serious	Not evaluated	Not evaluated	Not evaluated	++++ High

Summary: Two studies addressed photocontact allergic reactions and contact allergic reactions of BEMT. In one study, three photocontact allergy dermatitis reactions with severity graded as 3, 4 and 5 on a scale from 1-5 were reported for the 1031 subjects tested. One reaction was of certain

Overall evaluation of certainty in the evidence on sensitisation (photocontact allergic reactions) of BEMT
relevance whereas the two others were of uncertain relevance. The corresponding number for allergic contact dermatitis was one reaction with severity graded as 3. In the other study, no photocontact allergic reactions or contact allergic reactions reactions were reported for the 100 participants. VKM conclusion on the evidence: There is high confidence in the body of evidence for a low frequency for occurrence of (photo-)contact allergic reactions in susceptible individuals exposed to BEMT. The level of evidence is high.

Table 6.3.1-3. Study characteristics and certainty in the evidence for skin irritation reactions of BEMT. F: female; M: male; ICDRG: International Contact Dermatitis Research Group; COADEX: see definitions and Bruynzeel et al. (2004).

Reference	Type of test/ participants/ inclusion and exclusion criteria/ scoring system	Dose and duration	RoB	Number of reactions (in % of n)
Kerr et al. (2012)	Photopatch test, humans, n=1031, 18-92 (median=46 years)/ 715 F. A prospective, multicentre PPT study including 30 centres/ 12 European countries. Recruitment period: August 2008 to February 2011 Irritant reactions were scored, but not for individual UV filters Inclusion criteria: The inclusion criteria specified that subjects must be aged 18 years or older and have sufficient understanding to give written informed consent. Those included had at least one of the following four indications for performing photopatch testing: an exposed-site dermatitis during summer months; any exposed-site dermatitis; history of a	The test agents were applied, removed at 24 or 48 h, one set was then irradiated with maximum 5 J/cm^2 UVA (minimum: 0.5 J/cm^2) while the other set was covered with a UV-impermeable material. Readings of the test site: pre-irradiation, post-irradiation: immediately, 24 h, 48, and 72 h or later. Readings from 48 h are presented. Concentration of BEMT: 10%	1	Irritant reactions were rare: 7 reactions in 6 (0.6%) subjects. The specific test substances in the panel causing irritant reactions were not reported.

Reference	Type of test/ participants/ inclusion and exclusion criteria/ scoring system	Dose and duration	RoB	Number of reactions (in % of n)
	sunscreen reaction; or history of a topical NSAID skin reaction. Exclusion criteria: Potent topical steroid applied to the PPT site on the back in the 5 days prior to photopatch testing; skin disease activity on the back which was too active to allow PPT; and subjects prescribed systemic immuno-suppressant medication. Testing according to the European consensus methodology; reaction scoring: ICDRG visual system; relevance evaluation: COADEX			
Valbuena Mesa and Hoyos Jimenez (2016)	Patch test, humans, 100 participants, 13-88 years (mean = 49 years)/ 63 F Prospective descriptive cross-sectional study, 1 centre/ Colombia. Time period: 2001-2003 Inclusion criteria: Patients with suspected photo allergic contact dermatitis (a dermatitis affecting mainly light-exposed skin, those with a history of a sunscreen skin reaction or a topical NSAID skin reaction). Exclusion criteria: Patients with a clinical diagnosis of porphyria, solar urticaria or systemic lupus erythematosus were excluded from the testing procedure, as were pregnant woman and patients	Application in duplicate, irradiation with 5 J/cm^2 after 48 h. The readings were performed on days 2, 4 and 6 Concentration of BEMT: 10%	1	No irritant reactions observed.

Reference	Type of test/ participants/ inclusion and exclusion criteria/ scoring system	Dose and duration	RoB	Number of reactions (in % of n)
	who received systemic steroid treatments or immunosuppressive drugs in the month before the test or who applied topical steroids on their backs in the 8 days prior to the test. Testing according to ICDRG; relevance evaluated according to COADEX			

Overall evaluation of certainty in the evidence on skin irritation

Initial rating	Elements triggering downgrading				Elements triggering upgrading			Overall rating
	Risk of bias	Unexplained inconsistency	Indirectness	Imprecision	Large effect	Dose–response relationship	Consistency	
++++	Not serious	Not serious	Not serious	Not serious	Not evaluated	Not evaluated	Not evaluated	++++ High

Summary: Two studies addressed skin irritation due to BEMT. Kerr et al. (2012) reported that irritant reactions were rare; 7 reactions in 6 (0.6%) subjects. Note that test substance(s) causing reactions was not reported for the 1031 subjects tested. Valbuena Mesa and Hoyos Jimenez (2016) reported 0 irritant reactions caused by BEMT in the 100 subjects tested.

VKM conclusion on the evidence: There is high confidence in the body of evidence that exposure to BEMT is not associated with irritant reactions in susceptible individuals. There is evidence of no health effect.

6.3.2 Evidence from dossiers in the ECHA database

Note that a "study report" is an unpublished document in the dossier submitted by from the manufacturer. Information on dose and duration is reproduced with the abbreviations as used in the original document. VKM has not explained these abbreviations.

6.3.2.1 Systemic toxicity

The evidence addressed acute toxicity, subchronic and chronic toxicity, carcinogenicity and genetic toxicity, and reproductive and developmental toxicity (Table 6.3.2.1-1 to 6.3.2.1-4).

Table 6.3.2.1-1 Study characteristics and certainty in the evidence for acute toxicity of BEMT.

Reference	Model and administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
ECHA (2021c)	Rat, oral (gavage) OECD Guideline 401 GLP compliance: yes Study report, 1997	2000 mg/kg bw A single dose, observation period 14 days	Key study 1 - reliable without restrictions	No mortality, clinical signs, no changes in body weight or gross pathology were observed. Conclusion as given by ECHA: LD50 is >2000 mg/kg bw.
ECHA (2021c)	Rat, dermal OECD Guideline 402 GLP compliance: yes Study report, 1997	2000 mg/kg bw 24 h exposure, 14-day observation period	Key study 1 - reliable without restriction	No mortality, clinical signs, no changes in body weight or gross pathology were observed. Conclusion as given by ECHA: LD50 is >2000 mg/kg bw.
VKM conclusion on the evidence: BEMT has low acute toxicity in rats both by dermal and oral administration. For both routes, LD50 was above 2000 mg/kg bw.				

Table 6.3.2.1-2. Study characteristics and certainty in the evidence for subchronic and chronic toxicity of BEMT.

Reference	Model/administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
ECHA (2021c)	Rat, oral (gavage) OECD Guideline 408 (repeated dose 90-day oral toxicity study in rodents) GLP compliance: yes Study report, 1998	0, 100, 500, 1000 mg/kg bw	Key study 1 - reliable without restrictions	Clinical signs and mortality were not observed. No effects on the following were observed: body weight and body weight changes, food consumption, ophthalmological changes, haematological, clinical biochemistry, and urinalysis parameters, behaviour, organ weight, histopathological findings. ECHA concluded that the NOAEL for oral systemic toxicity is ≥1000 mg/kg bw/day.
ECHA (2021c)	Rat, dermal OECD Guideline 411 (subchronic dermal toxicity) GLP compliance: yes Study report, 2004	0, 250, 500, 1000 mg/kg bw for 90 days	Supporting study 1 – reliable without restriction	Clinical signs and mortality were not observed. No effects on the following were observed: body weight and body weight changes, food consumption, ophthalmology, haematological, clinical biochemistry, and urinalysis parameters, behaviour, organ weight, histopathological findings. ECHA concluded that the NOAEL for dermal systemic toxicity is ≥1000 mg/kg bw/day.
ECHA (2021c)	Rat, dermal OECD Guideline 451 (carcinogenicity study) GLP compliance: yes Study report, 2006	0, 100, 500, 1000 mg/kg bw Daily dermal application for 104 weeks	Key study 1- reliable without restriction	Local effects were observed. No systemic treatment-related adverse effects were observed (clinical signs, mortality, body weight changes, food consumption, ophthalmological, haematological, or clinical biochemistry findings, behaviour, organ weight (absolute and relative weights), gross pathological findings, histopathological findings). 2-year dermal NOAEL: ≥1000 mg/kg bw/day.
Summary: In one 90-day repeated toxicity study in rats, oral administration of BEMT at doses up to 1000 mg/kg bw did not cause adverse effects as assessed by ECHA. In both a sub-chronic and chronic repeated dose toxicity study in rats, dermal administration of BEMT at doses up to 1000 mg/kg bw did not cause systemic toxicity. VKM notes that the studies were performed according to GLP and OECD TG without deviations and have been judged to be reliable without restrictions. VKM considers that the available data are sufficient to identify a PoD for oral and dermal sub-chronic toxicity.				

Reference	Model/administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
VKM conclusion on the evidence: VKM identifies a NOAEL of ≥1000 mg/kg bw for sub-chronic toxicity following oral administration and a NOAEL of ≥1000 mg/kg bw for sub-chronic and chronic toxicity following dermal administration.				

Table 6.3.2.1-3. Study characteristics and certainty in the evidence for carcinogenicity and genetic toxicity of BEMT.

Reference	Enpoint/ Species, tissue, cell line, metabolic activation/ test guideline/GLP compliance (yes/no)/ publication type and year	Dose	Reliability	Results
ECHA (2021c)	*In vitro*, gene mutation *S. typhimurium* TA 1535, TA 1537, TA 98 and TA 100 With and without metabolic activation (S9) OECD Guideline 471 (bacterial reverse mutation assay) GLP compliance: yes Study report, 1997	33.3, 100, 333.3, 1000, 2500, and 5000 µg/plate	Key study 1- reliable without restriction	Negative
ECHA (2021c)	*In vitro*, gene mutation *S. typhimurium E. coli* WP2 uvr A, with and without metabolic activation (S9) OECD Guideline 471 (bacterial reverse mutation assay) GLP compliance: yes Study report, 1998	33.3, 100, 333.3, 1000, 2500, and 5000 µg/plate	Key study 1- reliable without restriction	Negative
ECHA (2021c)	*In vitro*, chromosome aberration Chinese hamster lung fibroblasts (V79) With and without metabolic activation (S9)	6.5, 13.1, 26.3, 52.5, 105.0, 210.0 µg/ml	Key study 1- reliable without restriction	Negative

Reference	Enpoint/ Species, tissue, cell line, metabolic activation/ test guideline/GLP compliance (yes/no)/ publication type and year	Dose	Reliability	Results
	OECD Guideline 473 (*in vitro* mammalian chromosome aberration test) GLP compliance: yes Study report, 1998			
ECHA (2021c)	*In vitro*, chromosome aberration Chinese hamster lung fibroblasts (V79) With and without metabolic activation (UV irradiation) OECD Guideline 473 (*in vitro* mammalian chromosome aberration test) GLP compliance: yes Study report, 1998	6.25, 12.5, 25.0, 50.0, 75.0, and 100.0 µg/ml	Key study 1- reliable without restriction	Negative
Reference	**Model/administration route/ guideline/ GLP compliance (yes/no)/ publication type and year**	**Dose and duration**	**Quality assessment by ECHA**	**Results**
ECHA (2021c)	Rat, oral (gavage), OECD Guideline 486 (unscheduled dna synthesis (uds) test with mammalian liver cells *in vivo*) GLP compliance: yes Study report, 2004	1000 and 2000 mg/kg bw	Key study 1- reliable without restriction	Negative
ECHA (2021c)	Rat, dermal OECD Guideline 451 (carcinogenicity studies) GLP compliance: yes Study report, 2006	0, 100, 500, 1000 mg/kg bw Daily dermal application for 104 weeks	Key study 1- reliable without restriction	Not carcinogenic following daily dermal exposures up to 1000 mg/kg bw/day for 104 weeks in male and female rats.

Reference	Enpoint/ Species, tissue, cell line, metabolic activation/ test guideline/GLP compliance (yes/no)/ publication type and year	Dose	Reliability	Results
				2-year dermal NOAEL: ≥1000 mg/kg bw/day.
Summary: BEMT was not genotoxic in one GLP UDS test with mammalian liver cells. The use of UDS test in the assessment on whether a substance is genotoxic is disputed and VKM will therefore only use this information as supporting evidence. BEMT did not induce mutations or chromosome aberrations *in vitro*. In one 2-year study, BEMT was not carcinogenic in rats exposed dermally to BEMT at doses up to 1000 mg/kg bw for 104 weeks. The substance induced dose-dependent non-neoplastic lesions, indicating that the substance caused irritation. VKM notes that the study was performed according to GLP and OECD TG without deviations and was judged to be reliable without restrictions. VKM considers that the available data is sufficient to identify a PoD for dermal carcinogenicity. VKM conclusion on the evidence: NOAEL for dermal carcinogenicity is ≥1000 mg/kg. The absence of carcinogenic effect following chronic exposure is considered sufficient evidence to conclude that BEMT is not genotoxic by the dermal route.				

Table 6.3.2.1-4. Study characteristics and certainty in the evidence for reproductive and developmental toxicity of BEMT.

Reference	Model/administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
ECHA (2021c)	Rat, oral (gavage) Japanese MHW (No. 316) guidelines for reproductive/developmental toxicity studies of drugs GLP compliance: yes Study report, 2002	0, 100, 300, 1000 mg/kg bw Daily administration for 2 weeks	Key study 1 - reliable without restrictions	No maternal toxicity or teratogenic effects were observed. ECHA identified a NOAEL of ≥1000 mg/kg bw/day for maternal and fetal toxicity.

Reference	Model/administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
ECHA (2021c)	Rabbit, oral (gavage) U.S. Food and Drug Administration (FDA), guideline on detection of toxicity to reproduction for medicinal products. Federal Register, Sept. 22, 1994, Vol. 59, No. 183 GLP compliance: yes Study report, 2005	0, 100, 300, 1000 mg/kg bw Daily exposure at gestation days 6 through 19	Key study 1 - reliable without restriction	No maternal toxicity or teratogenic effects were observed. ECHA identified a NOAEL of ≥1000 mg/kg bw/day for maternal and fetal toxicity.
ECHA (2021c)	Rat, oral (gavage) OECD Guideline 414 (prenatal developmental toxicity study) GLP compliance: yes Study report, 1998	0, 100, 300, 1000 mg/kg bw Daily exposure on day 6 through day 17 post coitum	Key study 1 - reliable without restriction	No maternal toxicity or teratogenic effects were observed. ECHA identified a NOAEL of ≥1000 mg/kg bw/day for maternal and developmental toxicity.
Summary: In three reproductive and developmental studies in rats and rabbits, no maternal, reproductive or developmental toxicity following oral exposure to BEMT at doses up to 1000 mg/kg bw was observed. All three studies were assessed by ECHA as reliable without restrictions. VKM notes that the studies were performed according to GLP and TG without deviations and have been judged to be reliable without restriction. VKM considers that the available data are sufficient to identify a PoD for maternal and developmental toxicity. VKM conclusion on the evidence: VKM identifies a NOAEL of ≥1000 mg/kg bw for maternal and developmental effects.				

6.3.2.2 Local effects

The evidence addressed skin irritation and skin sensitisation (Table 6.3.2.2-1 and 6.3.2.2-2).

Table 6.3.2.2-1. Study characteristics and certainty in the evidence for skin irritation of BEMT.

Reference	Model/administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
ECHA (2021c)	Rabbit, dermal OECD Guideline 404 (acute dermal irritation / corrosion) GLP compliance: yes Study report, 1997	Amount(s) applied: 0.5 g per animal. 4 h exposure, 72 h observation period	Key study 1- reliable without restriction	Neither edema nor erythema was observed.
ECHA (2021c)	Rat, dermal OECD Guideline 411 (subchronic dermal toxicity: 90-day study) GLP compliance: yes Study report, 2004	0, 250, 500, 1000 mg/kg bw	Supporting study 1 – reliable without restriction	On the untreated and treated areas of skin, the main microscopic changes were minimal to slight hyperkeratosis sometimes with parakeratosis, acanthosis, spongiosis and empty hair follicles. As the incidence and severity of these findings were not dose-related, often lower in the animals of the high-dose group II (wearing a protective plastic collar) than in the animals of the high dose group I (without protective collar), and without prominent differences between the untreated and treated areas, these skin microscopic changes were considered to be unrelated to any irritant potency of the test item and most likely due to mechanical injuries incurred during dose-site preparation (clipping, cleaning etc.).
ECHA (2021c)	Rat, dermal OECD Guideline 451 (carcinogenicity studies) GLP compliance: yes Study report, 2006	0, 100, 500, 1000 mg/kg bw per day Daily dermal application for 104 weeks	Key study 1- reliable without restriction	At the treated skin, a dose-related pattern of epidermal injury, accompanied by inflammatory and progressive changes, was observed that was considered to be indicative of a chronic and moderate local skin irritation, caused by long-term exposure to the test item dosage form. Scab formation at test site at 100 mg/kg bw.

Reference	Model/administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
				ECHA identified a LOAEL of ~0.075 cm^3 for local irritation based on scab formation at test site at 100 mg/kg-bw dose level and based on an estimated skin surface area of 380 cm^2 for a 285 g rat.
Summary: In rabbits, neither erythema nor edema was observed following dermal acute exposure to the substance. In rats, dermal application of BEMT for 90 days did not induce substance-related skin irritation. Following dermal application in rats for 104 weeks, dose-dependent and treatment-related dermal irritation was observed at all doses. VKM notes that the studies were performed according to GLP and OECD TG without deviations and have been judged to be reliable without restrictions. VKM considers that the available data are sufficient to conclude on whether BEMT is a skin irritant. VKM conclusion on the evidence: BEMT has low potency for skin irritation.				

Table 6.3.2.2-2. Study characteristics and certainty in the evidence for sensitisation of BEMT. PEG: polyethylene glycol

Reference	Model/administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
ECHA (2021c)	Guinea pig, dermal OECD Guideline 406 (skin sensitisation) GLP compliance: yes Study report, 1997	3% in PEG 400 and 3% in Freund's Complete Adjuvant and physiological saline. Induction exposure: intradermal and epidermal, dorsal skin in the scapular region, intradermal injection once on day 1 and epidermal application once on day 8 for 48 hours. 3% in intradermal injection and 30% in epicutaneous application. Challenge exposure: one epidermal exposure day 22, challenge two weeks after the epidermal induction application.	Key study 1 - reliable without restriction	No skin reactions.

Reference	Model/administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
		Test groups: 30% and PEG 400, control group: 30% and PEG 400: application at the left and right flank of each guinea pig. Evaluation performed 24 hours and 48 hours after removal of the dressing.		
Summary: In one study, BEMT did not cause skin reactions in guniea pigs following dermal application. VKM notes that the study is performed according to GLP and OECD TG without deviations and have been judged to be reliable without restrictions. VKM considers that the available data are sufficient to make a conclusion on the sensitisation potential of BEMT. VKM conclusion on the evidence: BEMT does not exhibit sensitising potential.				

6.4 UV filter BMDBM: Study characteristics, evaluation of certainty in the evidence for adverse effects, and translation into evidence for health effects

6.4.1 Evidence from literature searches

(Photo-)patch studies addressed skin sensitisation, including contact allergic reactions (Table 6.4.1-1) and photoallergic contact reactions (Table 6.4.1-2), and skin irritation (Table 6.4.1-3).

Table 6.4.1-1. Study characteristics and certainty in the evidence for contact allergic reactions of BMDBM. F: female; M: male; ICDRG: International Contact Dermatitis Research Group; COADEX: see definitions and Bruynzeel et al. (2004); PPT: photopatch test.

Reference	Type of test/ participants/ inclusion and exclusion criteria/ scoring system	Dose and duration	RoB	Number of reactions (in % of n)
Bryden et al. (2006)	Patch test, humans, dermal, n=1155. Mean age 46 years [3–99]; 797 F and 358 M 17 centres in UK, Ireland and the Netherlands. Time period: 1 year Inclusion criteria: Known photosensitivity disease; history of sunscreen reaction; exposed-site dermatitis during the summer months; an exposed-site skin problem. Exclusion criteria: Patients who had applied potent topical steroids to the back within 5 days and those with active skin disease. Reaction scoring system: ICDRG; relevance system: COADEX.	Duplicate allergen series applied, left for 24 or 48 h. One set was covered and the other irradiated with maximum 5 J/cm^2 UVA (1-5 J/cm^2). The critical reading was performed 48 h post irradiation and, if possible, at 24 and 72 h. Concentration of BMDBM: 10%.	1	Contact allergic reactions including photoinhibition: Certain relevance: 10 (0.9%) Uncertain relevance: 1 (0.09%)
Haylett et al. (2014)	Photopatch test, humans, n=157, 3-17 years/ 88 F, 69 M Retrospective analysis in 1 centre/ UK. Time period: 2000-2011 Inclusion criteria: Children below 18 years undergoing investigation for suspected photosensitivity. Testing according to European consensus methodology and recommendations of the British Photodermatology Group.	Duplicate series of UV filters and the children's own sunscreen products were applied to the back, with readings taken at sample removal, and at 24 and 48 h after 5 J/cm^2 UVA exposure of one series. Concentration of BMDBM: 10%	1	Allergic contact dermatitis reactions: 0
Kerr et al. (2012)	Patch test, humans, n=1031, 18-92 (median=46 years)/ 715 F	The test agents were applied, removed at 24 or 48 h, one set was then irradiated with maximum 5 J/cm^2 UVA (minimum: 0.5 J/cm^2) while the	1	Allergic contact dermatitis: 3 (0.2%) Severity: grades 3, 4 and 5 (of 5):

Reference	Type of test/ participants/ inclusion and exclusion criteria/ scoring system	Dose and duration	RoB	Number of reactions (in % of n)
	A prospective, multicentre PPT study including 30 centres/ 12 European countries. Recruitment period: August 2008 to February 2011 Inclusion criteria: The inclusion criteria specified that subjects must be aged 18 years or older and have sufficient understanding to give written informed consent. Those included had at least one of the following four indications for performing photopatch testing: an exposed-site dermatitis during summer months; any exposed-site dermatitis; history of a sunscreen reaction; or history of a topical NSAID skin reaction. Exclusion criteria: Potent topical steroid applied to the PPT site on the back in the 5 days prior to photopatch testing; skin disease activity on the back which was too active to allow PPT; and subjects prescribed systemic immuno-suppressant medication. Testing according to the European consensus methodology; reaction scoring: ICDRG visual system; relevance evaluation: COADEX.	other set was covered with a UV-impermeable material. Readings of the test site: preirradiation, postirradiation: immediately, 24 h, 48, and 72 h or later. Readings from 48 h are presented. Concentration of BMDBM: 10%		2 (0.2%); 1 (0.1%); 0, respectively
Subiabre-Ferrer et al. (2019)	Patch test, humans, n=116, 18-93 years (mean = 55.9)/ 80 F Retrospective analysis – 1 centre/ Spain. Time period: 2014-2016 Testing and inclusion/exclusion criteria according to European consensus methodology; reaction scoring: European Society of Contact Dermatitis guideline for diagnostic patch testing/ ICDRG.	Application in duplicate, irradiation after 24 h (UVA: 5 J/cm^2). The readings were performed immediately after removal of the patches and UV irradiation, and on day 2 and 4. Readings at 48 h were reported.	1	Positive patch-test: 1 (0.9%)

Reference	Type of test/ participants/ inclusion and exclusion criteria/ scoring system	Dose and duration	RoB	Number of reactions (in % of n)
		Concentration of BMDBM: 10%		
Valbuena Mesa and Hoyos Jimenez (2016)	Patch test, humans, 100 participants, 13-88 years (mean = 49 years)/ 63 F Prospective descriptive cross-sectional study, 1 centre/ Colombia. Time period: 2001-2003 Inclusion criteria: Patients with suspected photo allergic contact dermatitis (a dermatitis affecting mainly light-exposed skin, those with a history of a sunscreen skin reaction or a topical NSAID skin reaction). Exclusion criteria: Patients with a clinical diagnosis of porphyria, solar urticaria or systemic lupus erythematosus were excluded from the testing procedure, as were pregnant woman and patients who received systemic steroid treatments or immunosuppressive drugs in the month before the test or who applied topical steroids on their backs in the 8 days prior to the test. Testing according to ICDRG; relevance evaluated according to COADEX.	Application in duplicate, irradiation with 5 J/cm^2 after 48 h. The readings were performed on days 2, 4 and 6. Concentration of BMDBM: 10%	1	Contact allergic reactions: Certain: 1 (1%) Uncertain: 0

Overall evaluation of certainty in the evidence on sensitisation (contact allergic reactions)

Initial rating	Elements triggering downgrading				Elements triggering upgrading			Overall rating
	Risk of bias	Unexplained inconsistency	Indirectness	Imprecision	Large effect	Dose–response relationship	Consistency	
++++	Not serious	Not serious	Not serious	Not serious	Not evaluated	Not evaluated	Not evaluated	++++

Overall evaluation of certainty in the evidence on sensitisation (contact allergic reactions)								
								High
Summary: Five studies addressed contact allergic reactions of BMDBM. In the study by Bryden et al. (2006), 1155 presons were tested, and 10 (0.9%) contact allergic reactions of certain relevance and 1 (0.09%) of uncertain relevance were reported. Haylett et al (2014) reported 0 reactions in 157 subjects. Kerr et al. (2012) reported 3 (0.2%) allergic contact dermatitis reactions, two with severity graded as 3 and one with severity graded as 4 on a scale from 1-5 for the 1031 subjects tested. Subiabre-Ferrer et al. (2019) reported one positive patch test in 116 subjects. Valbuena Mesa and Hoyos Jimenez (2016) reported one contact allergic reaction in 100 subjects. VKM conclusion on the evidence: There is high confidence in the body of evidence for a low frequency of contact allergic reactions in susceptible individuals exposed to BMDBM. The level of evidence is high.								

Table 6.4.1-2. Study characteristics and certainty in the evidence for photoallergic contact reactions of BMDBM. F: female; M: male; ICDRG: International Contact Dermatitis Research Group; COADEX: see definitions and Bruynzeel et al. (2004); PPT: photopatch test

Reference	Type of test/ participants/ inclusion and exclusion criteria/ scoring system	Dose and duration	RoB	Number of reactions (in % of n)
Bryden et al. (2006)	Photopatch test, humans, dermal, n=1155. Mean age 46 years [3–99]; 797 F and 358 M 17 centres in UK, Ireland and the Netherlands. Time period: 1 year Inclusion criteria: Known photosensitivity disease; history of sunscreen reaction; exposed-site dermatitis during the summer months; an exposed-site skin problem.	Duplicate allergen series applied, left for 24 or 48 h. One set was covered and the other irradiated with maximum 5 J/cm^2 UVA (1-5 J/cm^2). The critical reading was performed 48 h post irradiation and, if possible, at 24 and 72 h. Concentration of BMDBM: 10%.	1	Photoallergic contact reactions including photoaugmentation: Certain relevance: 19 (1.6%) Uncertain relevance: 5 (0.4%)

Reference	Type of test/ participants/ inclusion and exclusion criteria/ scoring system	Dose and duration	RoB	Number of reactions (in % of n)
	Exclusion criteria: Patients who had applied potent topical steroids to the back within 5 days and those with active skin disease. Reaction scoring system: ICDRG; relevance system: COADEX.			
Haylett et al. (2014)	Photopatch test, humans, n=157, 3-17 years/ 88 F, 69 M Retrospective analysis in 1 centre/ UK. Time period: 2000-2011 Inclusion criteria: Children below 18 years undergoing investigation for suspected photosensitivity. Testing according to European consensus methodology and recommendations of the British Photodermatology Group.	Duplicate series of UV filters and the children's own sunscreen products were applied to the back, with readings taken at sample removal, and at 24 and 48 h after 5 J/cm^2 UVA exposure of one series. Concentration of BMDBM: 10%	1	Photoallergic contact reactions: 1 (0.6%) Severity: 2 (*i.e.* level 3 on a scale from 0 to 5: erythema, infiltration/papular response)
Katsarou-Katsari et al. (2008)	Photopatch test, humans, n=207, 14-74 (mean 49)/ 125 F, 82 M Retrospective evaluation, 1 centre/ Greece. Time period: 1992-2006 Inclusion criteria: Patients presenting with a presumed photosensitivity disorder.	Photoallergens were applied to the patient's back in duplicate. After 48-hour application, the allergens were removed and one set was covered with a light-impermeable occlusive dressing and the other irradiated with 5 J/cm^2 of fluorescent UVA. Reactions were evaluated immediately and 48 hrs after the UVA irradiation.	1	Photocontact reaction: 1 (0.5%)

Reference	Type of test/ participants/ inclusion and exclusion criteria/ scoring system	Dose and duration	RoB	Number of reactions (in % of n)
	Reaction scoring system: ICDRG.	Concentration of BMDBM: 10%		
Kerr et al. (2012)	Photopatch test, humans, n=1031, 18-92 (median=46 years)/ 715 F A prospective, multicentre PPT study including 30 centres/ 12 European countries. Recruitment period: August 2008 to February 2011 Irritant reactions were scored, but not for individual UV filters. Inclusion criteria: The inclusion criteria specified that subjects must be aged 18 years or older and have sufficient understanding to give written informed consent. Those included had at least one of the following four indications for performing photopatch testing: an exposed-site dermatitis during summer months; any exposed-site dermatitis; history of a sunscreen reaction; or history of a topical NSAID skin reaction. Exclusion criteria: Potent topical steroid applied to the PPT site on the back in the 5 days prior to photopatch testing; skin disease activity on the back which was too active to allow PPT; and subjects prescribed systemic immuno-suppressant medication.	The test agents were applied, removed at 24 or 48 h, one set was then irradiated with maximum 5 J/cm^2 UVA (minimum: 0.5 J/cm^2) while the other set was covered with a UV-impermeable material. Readings of the test site: preirradiation, postirradiation: immediately, 24 h, 48, and 72 h or later. Readings from 48 h are presented. Concentration of BMDBM: 10%	1	Photoallergic contact dermatitis: Certain: 14 (1.4%) Uncertain: 4 (0.4%) Severity: grades 3, 4 and 5 (of 5): 10 (1%); 6 (0.6%); 2 (0.2%), respectively

Reference	Type of test/ participants/ inclusion and exclusion criteria/ scoring system	Dose and duration	RoB	Number of reactions (in % of n)
	Testing according to the European consensus methodology; reaction scoring: ICDRG visual system; relevance evaluation: COADEX.			
Subiabre-Ferrer et al. (2019)	Photopatch test, humans, n=116, 18-93 years (mean = 55.9)/ 80 F Retrospective analysis – 1 centre/ Spain. Time period: 2014-2016 Testing and inclusion/exclusion criteria according to European consensus methodology; reaction scoring:European Society of Contact Dermatitis guideline for diagnostic patch testing/ ICDRG.	Application in duplicate, irradiation after 24 h (UVA: 5 J/cm^2). The readings were performed immediately after removal of the patches and UV irradiation, and on day 2 and 4. Readings at 48 h were reported. Concentration of BMDBM: 10%	1	Positive photopatch test: 0
Valbuena Mesa and Hoyos Jimenez (2016)	Photopatch test, humans, 100 participants, 13-88 years (mean = 49 years)/ 63 F Prospective descriptive cross-sectional study, 1 centre/ Colombia. Time period: 2001-2003 Inclusion criteria: Patients with suspected photo allergic contact dermatitis (a dermatitis affecting mainly light-exposed skin, those with a history of a sunscreen skin reaction or a topical NSAID skin reaction). Exclusion criteria: Patients with a clinical diagnosis of porphyria, solar urticaria or systemic lupus	Application in duplicate, irradiation with 5 J/cm^2 after 48 h. The readings were performed on days 2, 4 and 6 Concentration of BMDBM: 10%	1	Photoallergic contact reactions: Certain: 1 (1%) Uncertain: 0

Reference	Type of test/ participants/ inclusion and exclusion criteria/ scoring system	Dose and duration	RoB	Number of reactions (in % of n)
	erythematosus were excluded from the testing procedure, as were pregnant woman and patients who received systemic steroid treatments or immunosuppressive drugs in the month before the test or who applied topical steroids on their backs in the 8 days prior to the test. Testing according to ICDRG; relevance evaluated according to COADEX.			

Overall evaluation of certainty in the evidence on sensitisation (photoallergic contact reactions)

Initial rating	Elements triggering downgrading				Elements triggering upgrading			Overall rating
	Risk of bias	Unexplained inconsistency	Indirectness	Imprecision	Large effect	Dose–response relationship	Consistency	
++++	Not serious	Not serious	Not serious	Not serious	Not evaluated	Not evaluated	Not evaluated	++++ High

Summary: Six studies addressed photocontact allergic reactions of BMDBM. In the study by Bryden et al. (2006), 1155 persons were tested, and 19 (1.6%) photoallergic contact reactions of certain relevance and 5 (0.4%) of uncertain relevance were reported. Haylett et al. (2014) reported 1 (0.6%) photoallergic contact reactions of severity level 3 on a scale from 0 to 5 in a total of 157 tested persons. Katsarou-Katsari et al. (2008) reported 1 (0.5%) photocontact reactions in 207 tested persons. Kerr et al. (2012) reported 14 (1.4%) certain and 4 (0.4%) uncertain photoallergic contact dermatitis reactions, ten with severity graded as 3, 6 with severity graded as 4 and 2 with severity graded as 5 on a scale from 1 to 5 in the 1031 subjects tested. Subiabre-Ferrer et al. (2019) reported no positive photopatch reactions in the 116 subjects tested. Valbuena Mesa and Hoyos Jimenez (2016) reported 1 (1%) certain photoallergic contact reaction in the 100 subjects tested.

VKM conclusion on the evidence: There is high confidence in the body of evidence for a low frequency for occurrence of photocontact allergic reactions in susceptible individuals exposed to BMDBM. The level of evidence is high.

Table 6.4.1-3. Study characteristics and certainty in the evidence for skin irritant reactions of BMDBM. F: female; M: male; ICDRG: International Contact Dermatitis Research Group; COADEX: see definitions and Bruynzeel et al. (2004).

Reference	Type of test/ participants/ inclusion and exclusion criteria/ scoring system	Dose and duration	RoB	Number of reactions (in % of n)
Bryden et al. (2006)	Photopatch test, humans, dermal, n=1155. Mean age 46 years [3–99]; 797 F and 358 M 17 centres in UK, Ireland and the Netherlands. Time period: 1 year Inclusion criteria: Known photosensitivity disease; history of sunscreen reaction; exposed-site dermatitis during the summer months; an exposed-site skin problem. Exclusion criteria: Patients who had applied potent topical steroids to the back within 5 days and those with active skin disease. Reaction scoring system: ICDRG; relevance system: COADEX.	Duplicate allergen series applied, left for 24 or 48 h. One set was covered and the other irradiated with maximum 5 J/cm^2 UVA (1-5 J/cm^2). The critical reading was performed 48 h post irradiation and, if possible, at 24 and 72 h. Concentration of BMDBM: 10%.	1	Irritant reactions: 3 (0.3%)
Haylett et al. (2014)	Photopatch test, humans, n=157, 3-17 years/ 88 F, 69 M Retrospective analysis in 1 centre/ UK. Time period: 2000-2011	Duplicate series of UV filters and the children's own sunscreen products were applied to the back, with readings taken at sample removal, and at 24 and 48 h after 5 J/cm^2 UVA exposure of one series. Concentration of BMDBM: 10%	1	Irritant reactions: 0

Reference	Type of test/ participants/ inclusion and exclusion criteria/ scoring system	Dose and duration	RoB	Number of reactions (in % of n)
	Inclusion criteria: Children below 18 years undergoing investigation for suspected photosensitivity. Testing according to European consensus methodology and recommendations of the British Photodermatology Group.			
Kerr et al. (2012)	Photopatch test, humans, n=1031, 18-92 (median=46 years)/ 715 F A prospective, multicentre PPT study including 30 centres/ 12 European countries. Recruitment period: August 2008 to February 2011 Irritant reactions were scored, but not for individual UV filters. Inclusion criteria: The inclusion criteria specified that subjects must be aged 18 years or older and have sufficient understanding to give written informed consent. Those included had at least one of the following four indications for performing photopatch testing: an exposed-site dermatitis during summer months; any exposed-site dermatitis; history of a sunscreen reaction; or history of a topical NSAID skin reaction. Exclusion criteria: Potent topical steroid applied to the PPT site on the back in the 5 days prior to photopatch	The test agents were applied, removed at 24 or 48 h, one set was then irradiated with maximum 5 J/cm^2 UVA (minimum: 0.5 J/cm^2) while the other set was covered with a UV-impermeable material. Readings of the test site: pre-irradiation, post-irradiation: immediately, 24 h, 48, and 72 h or later. Readings from 48 h are presented. Concentration of BMDBM: 10%	1	Irritant reactions to the substances in the test panel were rare: 7 reactions in 6 (0.6%) subjects. Irritant reactions to BMDBM was not specifically reported.

Reference	Type of test/ participants/ inclusion and exclusion criteria/ scoring system	Dose and duration	RoB	Number of reactions (in % of n)
	testing; skin disease activity on the back which was too active to allow PPT; and subjects prescribed systemic immuno-suppressant medication. Testing according to the European consensus methodology; reaction scoring: ICDRG visual system; relevance evaluation: COADEX			
Valbuena Mesa and Hoyos Jimenez (2016)	Patch test, humans, 100 participants, 13-88 years (mean = 49 years)/ 63 F Prospective descriptive cross-sectional study, 1 centre/ Colombia. Time period: 2001-2003 Inclusion criteria: Patients with suspected photo allergic contact dermatitis (a dermatitis affecting mainly light-exposed skin, those with a history of a sunscreen skin reaction or a topical NSAID skin reaction). Exclusion criteria: Patients with a clinical diagnosis of porphyria, solar urticaria or systemic lupus erythematosus were excluded from the testing procedure, as were pregnant woman and patients who received systemic steroid treatments or immunosuppressive drugs in the month before the test or who applied topical steroids on their backs in the 8 days prior to the test.	Application in duplicate, irradiation with 5 J/cm^2 after 48 h. The readings were performed on days 2, 4 and 6 Concentration of BMDBM: 10%	1	No reactions to BMDBM.

Reference	Type of test/ participants/ inclusion and exclusion criteria/ scoring system	Dose and duration	RoB	Number of reactions (in % of n)
	Testing according to ICDRG; relevance evaluated according to COADEX.			

Overall evaluation of certainty in the evidence on skin irritation

Initial rating	Elements triggering downgrading				Elements triggering upgrading			Overall rating
	Risk of bias	Unexplained inconsistency	Indirectness	Imprecision	Large effect	Dose–response relationship	Consistency	
++++	Not serious	Not serious	Not serious	Not serious	Not evaluated	Not evaluated	Not evaluated	++++ High

Summary: Four studies addressed skin irritation of BMDBM. In the study by Bryden et al. (2006), 1155 presons were tested, and 3 (0.3%) irritant reactions were reported. Haylett et al. (2014) reported no irritant reactions in 157 tested subjects. Kerr et al. (2012) reported that irritant reactions were generally rare; 7 reactions in 6 (0.6%) subjects (test substance not reported) for the 1031 subjects tested. Valbuena Mesa and Hoyos Jimenez (2016) reported 0 irritant reactions for BMDBM in the 100 subjects tested.

VKM conclusion on the evidence: There is high confidence in the body of evidence for a low frequency for occurrence of irritant reactions in susceptible individuals exposed to BMDBM. The level of evidence is high.

6.4.2 Evidence from ECHA

Note that a "study report" is an unpublished document in the dossier submitted by the manufacturer. Information on dose and duration is reproduced with the abbreviations as used in the original document. VKM has not explained these abbreviations.

6.4.2.1 Systemic effects

The evidence addresses acute toxicity, subacute and subchronic toxicity, genetic toxicity, and developmental toxicity (Table 6.4.2.1-1 to 6.4.2.1-4).

Table 6.4.2.1-1. Study characteristics and certainty in the evidence for acute toxicity for BMDBM.

Reference	Model/administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
ECHA (2021a)	Rat, oral (gavage) OECD Guideline 401 (acute oral toxicity) GLP compliance: no Study report, 1980	16000 mg/kg bw Single administration, 14-day observation period	Key study 2 - reliable with restrictions	No mortality, changes in body weight or gross pathology were observed. No treatment-related clinical signs were observed. Loss of sperm and accumulation of cellular debris in epidymal tubules of 5 males (dose group not specified) might be treatment-related, however, no control animals were included. Testes appeared normal. Conclusion as given by ECHA: LD50 is >16 000 mg/kg bw.
ECHA (2021a)	Rat, dermal OECD Guideline 402 (acute dermal toxicity) GLP compliance: no Study report, 1979	0, 500, 1000 mg/kg bw 24 h exposure, 14-day observation period	Key study 2 - reliable with restrictions	No mortality was observed. No substance-related changes in body weight, clinical signs or gross pathology were observed. Conclusion as given by ECHA: LD50 is >1000 mg/kg bw.
Summary: BMDBM has low acute toxicity in rats both by dermal and oral administrations. Both studies were found to be reliable with restrictions. VKM conclusion on the evidence: LD50 is >16 000 mg/kg bw following oral exposure and >1000 mg/kg bw following dermal application.				

Table 6.4.2.1-2. Study characteristics and certainty in the evidence for subacute and subchronic toxicity for BMDBM.

Reference	Model/administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
ECHA (2021a)	Rat oral (feed) OECD Guideline 408 (repeated dose 90-day oral toxicity study in rodents) GLP compliance: yes Study report, 1983	0, 200, 450, 1000 mg/kg bw Duration: 91-94 days, daily administration	Key study 2 - reliable with restrictions	No effects were observed for ophthalmological findings and urinalysis. No treatment-related effects on clinical signs, mortality, body weight and weight changes, food intake, gross pathological findings. Treatment related effects were observed for haematological and clinical biochemistry parameters, organ weight and histopathology. A decrease in RBC was observed for female rats treated with 1000 mg/kg bw. Several of the parameters of clinical chemistry were outside of the physiological range for rats. These findings were considered to be treatment-related, but not of toxicological importance. Reversible statistically significant increase in absolute and relative liver weight was observed in female rats treated with 450 and 1000 mg/kg bw/day and in male rats treated with 1000 mg/kg bw/day. An increase in the size of hepatic parenchyma cells. ECHA concluded that the NOAEL for oral systemic toxicity is 450 mg/kg bw/day.
ECHA (2021a)	Rabbit, dermal OECD Guideline 410 (repeated dose dermal toxicity: 21/28-day study) GLP compliance: no Study report, 1980	2 mL/kg bw/day Concentration: 30, 100, and 360 mg/kg bw per day. Six hours exposure per day for 21 days.	Key study 2 - reliable with restrictions	No effects on haematological and clinical biochemistry parameters, organ weight or gross pathological findings were observed. No treatment-related clinical signs, mortality, effects on body weight or histopathological findings were observed.

				ECHA concluded that the NOAEL for dermal systemic toxicity is 360 mg/kg bw/day.
Summary: In one 90-day repeated toxicity study in rats, oral administration of BMDBM at 1000 mg/kg bw caused adverse effects and ECHA identified a NOAEL of 450 mg/kg bw for both male and female rats. In a 21-day repeated toxicity study in rabbits, dermal application at doses up to 360 mg/kg bw/day, did not cause systemic toxicity. There are insufficient details for VKM to judge internal validity and certainty in the evidence. However, VKM notes that the studies are performed according to GLP and OECD TG (with a few deviations) and have been judged to be reliable with restrictions. VKM considers the short-term dermal study in rabbits not to be suitable as a basis for establishing a PoD, due to the short exposure time. VKM considers the 90-day oral study suitable for establishing a PoD. VKM conclusion on the evidence: VKM identifies an oral NOAEL of 450 mg/kg bw for subchronic toxicity.				

Table 6.4.2.1-3. Study characteristics and certainty in the evidence for genetic toxicity of BMDBM.

Reference	Enpoint/ Species, tissue, cell line, metabolic activation/ test guideline/a GLP compliance/ publication type and year	Dose	Reliability	Results
ECHA (2021a)	Hgprt mutation Chinese hamster lung fibroblasts (V79), with and without metabolic activation (S9) OECD Guideline 476 (*in vitro* mammalian cell gene mutation test), GLP compliance: yes Study report, 1984	5, 10, 15, 20 µg/mL	Key study 2 - reliable with restrictions	Negative
ECHA (2021a)	Reverse mutation Salmonella typhimurium, TA1535, TA 1537, TA 1538, TA 98, TA100 and TA102, with and without metabolic activation (S9) OECD Guideline 471 (bacterial reverse mutation assay) GLP compliance: yes Study report: 2000	50, 150, 500, 1500, 5000 µg/plate with metabolic activation (S9) 5, 15, 50, 150, 500, 1500, 5000 µg/plate without metabolic activation	Key study 1-reliable without restrictions	Negative

Reference	Enpoint/ Species, tissue, cell line, metabolic activation/ test guideline/a GLP compliance/ publication type and year	Dose	Reliability	Results
Reference	**Model/administration route/ guideline/ GLP compliance/ publication type and year**	**Dose and duration**	**Quality assessment by ECHA**	**Results**
ECHA (2021a)	Mouse, oral (unspecified) OECD Guideline 474 (mammalian erythrocyte micronucleus test) GLP compliance: yes Study report: 1983	1000, 2500 and 5000 mg/kg bw. The substance was administered twice, 30 and 6 h prior to sacrifice	Key study 2-reliable with restrictions	Negative
Summary: BMDBM did not induce reverse mutation in six strains of Salmonella typhimurium in the presence or absence of exogenous metabolic activation. VKM notes that the selection of strains is in line with the OECD TG. No mutagenic effect was reported in the hypoxanthine-guanine phosphoribosyl transferase (Hgprt) assay in V79 cells exposed to BMDBM. No *in vitro* studies for cytogenicity were available from the ECHA database. Both *in vitro* mutagenicity studies were performed according to GLP and OECD TG and have been judged to be reliable with/without restrictions. In mice, no increase in the frequency of micronucleus formation was observed. VKM notes that there was no evidence of target tissue exposure. VKM conclusion on the evidence: There is sufficient evidence to conclude that BMDBM is not mutagenic. There is insufficient data to conclude on cytogenic potential of BMDBM.				

Table 6.4.2.1-4. Study characteristics and certainty in the evidence for developmental toxicity of BMDBM.

Reference	Model/administration route/ guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
ECHA (2021a)	Rat, oral (gavage) OECD Guideline 414 (prenatal developmental toxicity study) GLP compliance: yes Study report, 1984	0, 250, 500, 1000 mg/kg bw Daily exposure on day 6 through day 17 post coitum	Key study 2 - reliable with restriction	No maternal toxicity or teratogenic effects were observed. ECHA identified a NOAEL for maternal and

Reference	Model/administration route/ guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
				developmental toxicity of 1000 mg/kg bw/day.
Summary: In one developmental study in rats, no maternal or developmental toxicity following oral exposure to BMDBM at doses up to 1000 mg/kg bw were observed. VKM notes that the study is performed according to GLP and OECD TG (with a few deviations) and has been judged to be reliable with restrictions. VKM considers the study to be suitable for establishing a PoD. VKM conclusion on the evidence: VKM identifies a NOAEL of ≥1000 mg/kg bw for maternal and developmental effects.				

6.4.2.2 Local effects

The evidence addresses skin irritation and skin sensitisation (Table 6.4.2.2-1 and 6.4.2.2-2).

Table 6.4.2.2-1. Study characteristics and certainty in the evidence for irritation for BMDBM.

Reference	Model/administration route/ guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
ECHA (2021a)	Rabbit, dermal OECD Guideline 404 (acute dermal irritation / corrosion) GLP compliance: no Study report, 1982	Amount applied: 0.5 mL. Concentration: 10 % in ethanol / 2-phenylethanol (50/50)	Key study 2 - reliable with restrictions	From no to well-defined erythema and from not to very slight edema were observed. ECHA concluded that the substance has a slight irritating potential which is mainly caused by the solvent used.
ECHA (2021a)	Rabbit, dermal OECD Guideline 410 (repeated dose dermal toxicity: 21/28-day study)	2 mL/kg bw/day	Key study	The severity of erythema/edema was generally greater for BMDBM-treated animals compared to controls.

Reference	Model/administration route/ guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
	GLP compliance: no Study report, 1980	Concentration: 30, 100, and 360 mg/kg bw per day. Six hours exposure per day for 21 days.	2 - reliable with restrictions	ECHA concluded that the LOAEL for dermal irritation is 100 mg/kg bw/day.
ECHA (2021a)	Rat, dermal OECD Guideline 402 (acute dermal toxicity) GLP compliance: no Study report, 1979	0, 500, 1000 mg/kg bw 24 h exposure, 14-day observation period	Key study 2 - reliable with restrictions	No substance-related local effects were observed.
Summary: Acute dermal exposure applied to rabbit skin did not cause irritation other than that caused by the solvent used. Actue dermal exposure to rat skin did not cause substance related irritation. Repeated dermal exposure to BMDBM for 21 days caused dose-dependent irritation. VKM notes that the studies were not performed according to GLP; however, they were judged to be reliable with restrictions. VKM considers the data sufficient to identify a PoD. VKM conclusion on the evidence: LOAEL for subacute dermal irritation is identified at 100 mg/kg bw/day. BMDBM does not cause irritiation following acute exposure.				

Table 6.4.2.2-2. Study characteristics and certainty in the evidence for skin sensitisation of BMDBM.

Reference	Model and administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
ECHA (2021a)	Guinea pig, dermal OECD Guideline 406 (skin sensitisation) GLP compliance: no Study report, 1982	Induction day 0: 5% in FCA, day 8: 20% in 2-phenylethanol. Challenge day 21: 20% and 6% in 2-phenylethanol	Key study 2 - reliable with restrictions	None of the animals developed skin reactions.

Reference	Model and administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
Summary: A dermal acute challenge did not cause allergic reactions in guinea pigs. The study was non-GLP, but was deemed as reliable with restrictions. VKM conclusion on the evidence: BMDBM is not a skin sensitiser under the test conditions used.				

6.5 UV filter EHS: Study characteristics, evaluation of certainty in the evidence for adverse effects, and translation into evidence for health effects

6.5.1 Evidence from literature searches

Two patch studies addressed skin sensitisation, one included contact allergic reactions (Table 6.5.1-1) whereas both included photoallergic contact reactions (Table 6.5.1-2) and skin irritation (Table 6.5.1-3).

Table 6.5.1-1. Study characteristics of and certainty in the evidence for contact allergic reactions to EHS. F: female; PPT: photopatch test; ICDRG: International Contact Dermatitis Research Group; COADEX: see definitions and Bruynzeel et al. (2004).

Reference	Type of test/ participants/ inclusion and exclusion criteria/ scoring system	Dose and duration	RoB	Number of reactions (in % of n)
Kerr et al. (2012)	Humans, n=1031, 18-92 (median=46 years)/ 715 F A prospective, multicentre PPT study including 30 centres/ 12 European countries. Recruitment period: August 2008 to February 2011	The test agents were applied, removed at 24 or 48 h, one set was then irradiated with maximum 5 J/cm^2 UVA (minimum: 0.5 J/cm^2) while the other set was covered with a UV-impermeable material. Readings of the test site: preirradiation,	1	Allergic contact dermatitis: 1 (0.1%) Severity: grades 3, 4 and 5 (of 5): 1 (0.1%); 0; 0, respectively

Reference	Type of test/ participants/ inclusion and exclusion criteria/ scoring system	Dose and duration	RoB	Number of reactions (in % of n)
	Inclusion criteria: The inclusion criteria specified that subjects must be aged 18 years or older and have sufficient understanding to give written informed consent. Those included had at least one of the following four indications for performing photopatch testing: an exposed-site dermatitis during summer months; any exposed-site dermatitis; history of a sunscreen reaction; or history of a topical non-steroidal anti-inflammatory drug (NSAID) skin reaction. Exclusion criteria: Potent topical steroid applied to the PPT site on the back in the 5 days prior to photopatch testing; skin disease activity on the back which was too active to allow PPT; and subjects prescribed systemic immuno-suppressant medication. Testing according to the European consensus methodology; reaction scoring: ICDRG visual system; relevance evaluation: COADEX.	postirradiation: immediately, 24 h, 48, and 72 h or later. Readings from 48 h are presented. Concentration of EHS: 10%		
Valbuena Mesa and Hoyos Jimenez (2016)	Patch test, humans, 100 participants, 13-88 years (mean = 49 years)/ 63 F Prospective descriptive cross-sectional study, 1 centre/ Colombia. Time period: 2001-2003 Inclusion criteria: Patients with suspected photo allergic contact dermatitis (a dermatitis affecting mainly light-	Application in duplicate, irradiation with 5 J/cm^2 after 48 h. The readings were performed on days 2, 4 and 6 Concentration of EHS: 5%	1	Allergic contact dermatitis: Certain: 1 (1%) Uncertain: 1 (1%)

Reference	Type of test/ participants/ inclusion and exclusion criteria/ scoring system	Dose and duration	RoB	Number of reactions (in % of n)
	exposed skin, those with a history of a sunscreen skin reaction or a topical NSAID skin reaction). Exclusion criteria: Patients with a clinical diagnosis of porphyria, solar urticaria or systemic lupus erythematosus were excluded from the testing procedure, as were pregnant woman and patients who received systemic steroid treatments or immunosuppressive drugs in the month before the test or who applied topical steroids on their backs in the 8 days prior to the test. Testing according to ICDRG; relevance evaluated according to COADEX.			

Overall evaluation of certainty in the evidence on senstitisation (contact allergic reactions) of EHS

Initial rating	Elements triggering downgrading				Elements triggering upgrading			Overall rating
	Risk of bias	Unexplained inconsistency	Indirectness	Imprecision	Large effect	Dose–response relationship	Consistency	
++++	Not serious	Not serious	Not serious	Not serious	Not evaluated	Not evaluated	Not evaluated	++++ High

Summary: Two studies addressed contact allergic reactions of EHS. Kerr et al. (2012) reported 1 (0.1%) allergic contact dermatitis reaction, severity graded as 3 on a scale from 1-5, in the 1031 subjects tested. Valbuena Mesa and Hoyos Jimenez (2016) reported 1 (1%) certain and 1 (1%) uncertain contact allergic dermatitis reaction in the 100 subjects tested.

Overall evaluation of certainty in the evidence on senstitisation (contact allergic reactions) of EHS
VKM conclusion on the evidence: There is high confidence in the body of evidence for a low frequency of contact allergic reactions in susceptible individuals exposed to EHS. The level of evidence is high.

Table 6.5.1-2. Study characteristics and certainty in the evidence for photoallergic contact reactions of EHS. F: female; PPT: photopatch test; ICDRG: International Contact Dermatitis Research Group; COADEX: see definitions and Bruynzeel et al. (2004).

Reference	Type of test/ participants/ inclusion and exclusion criteria/ scoring system	Dose and duration	RoB	Number of reactions (in % of n)
Kerr et al. (2012)	Photopatch test, humans, n=1031, 18-92 (median=46 years)/ 715 F. A prospective, multicentre PPT study including 30 centres/ 12 European countries. Recruitment period: August 2008 to February 2011 Inclusion criteria: The inclusion criteria specified that subjects must be aged 18 years or older and have sufficient understanding to give written informed consent. Those included had at least one of the following four indications for performing PPT: an exposed-site dermatitis during summer months; any exposed-site dermatitis; history of a sunscreen reaction; or history of a topical NSAID skin reaction. Exclusion criteria: Potent topical steroid applied to the PPT site on the back in the 5 days prior to PPT; skin disease activity on the back which was too active to	Photopatch testing was conducted according to the European consensus methodology. The test agents were applied, removed at 24 or 48 h, one set was then irradiated with 5 J/cm^2 UVA while the other set was covered with a UV-impermeable material. Readings of the test site: pre-irradiation, pos-tirradiation: immediately, 24 h, 48, and 72 h or later. Reactions were scored using the International Contact Dermatitis Research Group visual system. Concentration of EHS: 10%	1	Photoallergic contact dermatitis: Certain: 2 (0.2%) Uncertain: 0 Severity: grades 3, 4 and 5 (of 5): 2 (0.2%); 0; 0, respectively

Reference	Type of test/ participants/ inclusion and exclusion criteria/ scoring system	Dose and duration	RoB	Number of reactions (in % of n)
	allow PPT; and subjects prescribed systemic immuno-suppressant medication.			
Valbuena Mesa and Hoyos Jimenez (2016)	Photopatch test, humans, 100 participants, 13-88 years (mean = 49 years)/ 63 F Prospective descriptive cross-sectional study, 1 centre/ Colombia. Time period: 2001-2003 Inclusion criteria: Patients with suspected photo allergic contact dermatitis (a dermatitis affecting mainly light-exposed skin, those with a history of a sunscreen skin reaction or a topical NSAID skin reaction). Exclusion criteria: Patients with a clinical diagnosis of porphyria, solar urticaria or systemic lupus erythematosus were excluded from the testing procedure, as were pregnant woman and patients who received systemic steroid treatments or immunosuppressive drugs in the month before the test or who applied topical steroids on their backs in the 8 days prior to the test.	Application in duplicate, irradiation with 5 J/cm^2 after 48 h. The readings were performed on days 2, 4 and 6, in accordance with the guidelines of the International Contact Dermatitis Research Group. Concentration of EHS: 5%	1	Photoallergic contact reactions: Certain: 0 Uncertain 1 (1%)

Overall evaluation of certainty in the evidence on sensitisation (photoallergic contact reactions) of EHS								
Initial rating	Elements triggering downgrading				Elements triggering upgrading			Overall rating
	Risk of bias	Unexplained inconsistency	Indirectness	Imprecision	Large effect	Dose–response relationship	Consistency	

Overall evaluation of certainty in the evidence on sensitisation (photoallergic contact reactions) of EHS								
++++	Not serious	Not serious	Not serious	Not serious	Not evaluated	Not evaluated	Not evaluated	++++ High
Summary: Two studies addressed photocontact allergic reactions of EHS. Kerr et al. (2012) reported 2 (0.2%) certain photoallergic contact dermatitis reactions with severity grade 3 on a scale from 1-5 in the 1031 subjects tested. Valbuena Mesa and Hoyos Jimenez (2016) reported 1 uncertain photoallergic contact reaction in the 100 subjects tested. VKM conclusion on the evidence: There is high confidence in the body of evidence for a low frequency for occurrence of photocontact allergic reactions in susceptible individuals exposed to EHS. The level of evidence is high.								

Table 6.5.1-3. Study characteristics and certainty in the evidence for skin irritant reactions of EHS. F: female; M: male; ICDRG: International Contact Dermatitis Research Group; COADEX: see definitions and Bruynzeel et al. (2004).

Reference	Type of test/ participants/ inclusion and exclusion criteria/ scoring system	Dose and duration	RoB	Number of reactions (in % of n)
Kerr et al. (2012)	Photopatch test, humans, n=1031, 18-92 (median=46 years)/ 715 F A prospective, multicentre PPT study including 30 centres/ 12 European countries. Recruitment period: August 2008 to February 2011 Irritant reactions were scored, but not for individual UV filters Inclusion criteria: The inclusion criteria specified that subjects must be aged 18 years or older and have sufficient understanding to give written informed	The test agents were applied, removed at 24 or 48 h, one set was then irradiated with maximum 5 J/cm^2 UVA (minimum: 0.5 J/cm^2) while the other set was covered with a UV-impermeable material. Readings of the test site: pre-irradiation, post-irradiation: immediately, 24 h, 48, and 72 h or later. Readings from 48 h are presented. Concentration of EHS: 10%	1	Irritant reactions were rare: 7 reactions in 6 (0.6%) subjects. The specific test substances in the panel causing irritant reactions were not reported.

Reference	Type of test/ participants/ inclusion and exclusion criteria/ scoring system	Dose and duration	RoB	Number of reactions (in % of n)
	consent. Those included had at least one of the following four indications for performing photopatch testing: an exposed-site dermatitis during summer months; any exposed-site dermatitis; history of a sunscreen reaction; or history of a topical NSAID skin reaction. Exclusion criteria: Potent topical steroid applied to the PPT site on the back in the 5 days prior to photopatch testing; skin disease activity on the back which was too active to allow PPT; and subjects prescribed systemic immuno-suppressant medication. Testing according to the European consensus methodology; reaction scoring: ICDRG visual system; relevance evaluation: COADEX.			
Valbuena Mesa and Hoyos Jimenez (2016)	Patch test, humans, 100 participants, 13-88 years (mean = 49 years)/ 63 F Prospective descriptive cross-sectional study, 1 centre/ Colombia. Time period: 2001-2003 Inclusion criteria: Patients with suspected photo allergic contact dermatitis (a dermatitis affecting mainly light-exposed skin, those with a history of a sunscreen skin reaction or a topical NSAID skin reaction).	Application in duplicate, irradiation with 5 J/cm^2 after 48 h. The readings were performed on days 2, 4 and 6 Concentration of EHS: 5%	1	Five irritant reactions were found in four (4%) patients to four test substances, among which was EHS, *i.e.*, frequency between 1 and 2%

Reference	Type of test/ participants/ inclusion and exclusion criteria/ scoring system	Dose and duration	RoB	Number of reactions (in % of n)
	Exclusion criteria: Patients with a clinical diagnosis of porphyria, solar urticaria or systemic lupus erythematosus were excluded from the testing procedure, as were pregnant woman and patients who received systemic steroid treatments or immunosuppressive drugs in the month before the test or who applied topical steroids on their backs in the 8 days prior to the test. Testing according to ICDRG; relevance evaluated according to COADEX.			

Overall evaluation of certainty in the evidence on skin irritation

Initial rating	Elements triggering downgrading				Elements triggering upgrading			Overall rating
	Risk of bias	Unexplained inconsistency	Indirectness	Imprecision	Large effect	Dose–response relationship	Consistency	
++++	Not serious	Not serious	Not serious	Not serious	Not evaluated	Not evaluated	Not evaluated	++++ High

Summary: Two studies addressed skin irritation of EHS. Kerr et al. (2012) reported that irritant reactions were rare; 7 reactions in 6 (0.6%) subjects (EHS was not specifically reported) in the 1031 subjects tested. Valbuena Mesa and Hoyos Jimenez (2016) reported a frequency of minimum 1% and maximum 2% of irritant reactions to EHS in the 100 subjects tested.

VKM conclusion on the evidence: There is high confidence in the body of evidence for a low frequency for occurrence of irritant reactions in susceptible individuals exposed to EHS. The level of evidence is high.

6.5.2 Evidence from ECHA

Note that a "study report" is an unpublished document in the dossier submitted by the manufacturer. Information on dose and duration is reproduced with the abbreviations as used in the original document. VKM has not explained these abbreviations.

6.5.2.1 Systemic toxicity

The evidence addresses acute toxicity, chronic toxicity, genetic toxicity, and reproductive and developmental toxicity (Table 6.5.2.1-1 to 6.5.2.1-4).

Table 6.5.2.1-1. Study characteristics and certainty in the evidence for acute toxicity of EHS.

Reference	Model and administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
ECHA (2021b)	Rat, oral (gavage) OECD Guideline 401 (acute oral toxicity) GLP compliance: yes Study report, 1990	5000 mg/kg x1, 14 days observation	Key study 1 - reliable without restriction	No mortality or evidence of substance-related toxicity were observed. Conclusion as given by ECHA: LD50 is >5000 mg/kg bw.
ECHA (2021b)	Rat, dermal OECD Guideline 402 (acute dermal toxicity) GLP compliance: yes Study report, 1990	5000 mg/kg, exposure for 24 hours, 14 days observation	Key study 1 - reliable without restriction	No mortality or evidence of substance-related toxicity were observed. Conclusion as given by ECHA: LD50 is >5000 mg/kg bw.
Summary: EHS has low acute toxicity in rats both by dermal and oral administrations. Both studies were found to be reliable without restrictions. VKM conclusion on the evidence: LD50 is >5000 mg/kg bw following acute oral and dermal exposure.				

Table 6.5.2.1-2. Study characteristics and certainty in the evidence for subacute, subchronic and chronic toxicity of EHS (*read-across).

Reference	Model and administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
ECHA (2021b)	Rat, oral (feed) TG not specified (oral sub-chronic toxicity study) GLP compliance: no Publication, Webb and Hansen (1963)	Methyl salicylate* 0, 50, 500 mg/kg daily for 17 weeks	Supporting study 2 - reliable with restrictions	Reduction in body weight gain was reported in females and males at 500 mg/kg bw/. Effect level as given by ECHA: NOAEL for methyl salicylate is 50 mg/kg bw/day. Applying read-across, NOAEL for EHS is 83 mg/kg bw/day.
ECHA (2021b)	Dog, oral (capsule) TG not specified (oral sub-chronic toxicity study) GLP compliance: no Publication, Webb and Hansen (1963)	Methyl salicylate* 0, 50, 500 mg/kg bw/day for 17 weeks	Supporting publication	No clinical signs and mortality were observed at 50, 150 and 250 mg/kg/day. At 500, 800 and 1200 mg/kg/day, all dogs died within the first month of the study. The livers of both dogs on the 1200 and one on the 800 mg/kg/day levels had moderate to marked degrees of fatty metamorphosis. Ophtalmological findings, haematological and clinical biochemistry parameters, urinalysis were not examined. The results are based on one animal per sex per dose. Effect level as given by ECHA: NOAEL for methyl salicylate is 250 mg/kg bw/day. Applying read-across, NOAEL for EHS is 386 mg/kg bw/day.
ECHA (2021b)	Rat, oral (feed) OECD Guideline 408 (repeated dose 90-day oral toxicity study in rodents) Study report, 1994	0, 50, 100 and 250 mg/kg/day, for 13 weeks	Weight of evidence 1 – reliable without restriction	No adverse effects reported. Effect level as given by ECHA: NOAEL is 250 mg/kg bw per day.

Reference	Model and administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
ECHA (2021b)	Rat, oral (feed) TG not specified (oral chronic toxicity study) GLP compliance: no Publication, Webb and Hansen (1963)	Methyl salicylate* 0, 50, 250, 500, and 1000 mg/kg bw daily for 2 years	Experimental study 2 – reliable with restrictions	In the 1000 g/kg bw/day group, half of the animals died by week 8 and all of the animals died by week 49 of the study. At 500 and 1000 mg/kg bw/day, significant growth inhibition and development of rough hair coats. Average organ weights were similar for all animals, however, relative organ to body weight ratios for the testes of male animals and for the heart and kidneys of the female animals of the 500 mg/kg bw/day groups were significantly increased. Gross lesions of the pituitary gland were observed in 10 animals in the 250 mg/kg bw/day group as compared to four animals in the control group. In the 1000 mg/kg bw/day group, 29 of the 50 animals had pneumonia, which appeared to be more acute than regularly observed. There was a pronounced change in the bones of the rats in the 1000 mg/kg bw/day group. Cancellous bone in the metaphysis was increased as compared to same-age controls; this was observed to a moderate degree in five and a marked degree in four of the nine bones examined from animals of the 1000 mg/kg bw/day group. Bone lesions were slight in 2 of 11 and 1 of 11 bones examined from animals of the 500 and 250 mg/kg bw/day groups, respectively. The affected bones had fewer osteoclasts, and the number was inversely proportional to the degree of change.

Reference	Model and administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
				Malignant pituitary tumors occurred in 1 male and 2 female rats in the 250 mg/kg bw/day group. Mammary tumors occurred in females rats on all diets. Effect level as given by ECHA: NOAEL for methyl salicylate is 50 mg/kg bw/day. Applying read-across, NOAEL for EHS is 83 mg/kg bw/day.
ECHA (2021b)	Dog, oral (capsule) TG not specified (oral chronic toxicity study) GLP compliance: no Publication, Webb and Hansen (1963)	Methyl salicylate* 0, 50, 150 and 350 mg/kg bw/day, 2 years, daily for 6 days/week.	Weight of evidence 2 - reliable with restrictions	Retarded growth was observed for the dogs administered 350 and 150 mg/kg/day. Enlarged livers were seen at necropsy of the dogs on the 150 and 350 mg/kg/day levels. At necropsy, the dogs treated at 150 and 350 mg/kg body weight/day had enlarged livers. Microscopically, these livers had larger hepatic cells than those seen in the control dogs. Fatty metamorphosis was not greater in the livers of the treated dogs than the very small amounts seen in the livers of the control dogs. Effect level as given by ECHA: NOAEL for methyl salicylate is 50 mg/kg bw/day. Applying read-across, NOAEL for EHS is 83 mg/kg bw/day.
ECHA (2021b)	Rat oral (gavage) OECD Guideline 421 (reproduction / developmental toxicity screening test) GLP compliance: yes Study report, 2012	0, 25, 80, 250 mg/kg/day Duration of treatment / exposure: Males: 28 days; Females: approximately 7 weeks	Supporting study 1 – reliable without restriction	One female rat in the 250 mg/kg bw/day group was found dead on day 23 of the gestation period, which was considered to be substance-related. At the highest dose, there was statistically significant reduction in body weight gain. No effects on absolute and relative organ weight, gross pathology and histopathology were observed.

Reference	Model and administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
				ECHA identified a NOAEL of 250 mg/kg bw/day for systemic toxicity.
Summary: In one 90-day repeated toxicity study in rats, oral administration of EHS of doses up to 250 mg/kg bw/day did not cause adverse effects. In one reproduction and developmental toxicity study, subacute exposure of 250 mg/kg bw/day caused substance-related mortality (one dam). *Methyl salicylate: a metabolite of EHS. VKM considers applying methyl salicylate as a read-across substance for EHS as appropriate. Four toxicity studies of methyl salicylate were available. Chronic exposure to methyl salicylate to both dogs and rats caused several adverse effects, including organ effects and mortality. The NOAEL was identified at 83 mg/kg bw/day for EHS, calculated from the methyl salicylate dose of 50 mg/kg bw/day, for both studies. All studies were not GLP compliant, but were judged as reliable with/without restrictions. VKM conclusion on the evidence: VKM identifies an oral NOAEL of 83 mg/kg bw/day for sub-chronic and chronic toxicity.				

Table 6.5.2.1-3. Study characteristics and certainty in the evidence for genetic toxicity of EHS.

Reference	Enpoint/ Species, tissue, cell line, metabolic activation/ test guideline/a GLP compliance/ publication type and year	Dose	Reliability	Results
ECHA (2021b)	*In vitro*, reverse mutation *S. typhimurium* TA 1535, TA 1537, TA 98, TA 100 and TA 102, with and without metabolic activation (Arochlor 1254 induced rat liver) OECD Guideline 471 (bacterial reverse	Doses without activation: 156.3, 312.5, 625, 1250, 2500 and 5000 µg/plate in the first experiment and 312.5, 625, 1250, 2500 and 5000 µg/plate in the second experiment. Doses with activation (S9): 156.3, 312.5, 625, 1250, 2500 and 5000 µg/plate, for the TA 1537 and	Key study 1- reliable without restrictions	Negative

Reference	Enpoint/ Species, tissue, cell line, metabolic activation/ test guideline/a GLP compliance/ publication type and year	Dose	Reliability	Results
	mutation assay) GLP compliance: yes Study report, 2006	the TA 98 strains in the first experiment; 15.6, 31.3, 62.5, 125, 250 and 500 µg/plate for the TA 1535, TA 100 and TA 102 strains in the first experiment; 312.5, 625, 1250, 2500 and 5000 µg/plate, for the TA 1537 and TA 98 strains in the second experiment; 39.06, 78.13, 156.3, 312.5, 625, 1250 µg/plate, for the TA 1535 strain in the second experiment; and 19.53, 39.06, 78.13, 156.3, 312.5, 625 µg/plate, for the TA 100 and the TA 102 strains in the second experiment. Revertants were scored after 48 to 72 hours.		
ECHA (2021b)	*In vitro*, chromosomal aberrations Chinese hamster Ovary (CHO), with and without metabolic activation (Arochlor 1254 induced rat liver S9) OECD Guideline 473 (*in vitro* mammalian chromosome aberration test) GLP compliance: yes Study report, 1992	2.5, 5, 10, 20 and 40 µg/ml	Key study 1- reliable without restriction	Negative No cytotoxicity
ECHA (2021b)	*In vitro*, Hprt mutation, Chinese hamster lung fibroblasts (V79), with and without metabolic activation (Phenobarbital/beta-naphthoflavone induced rat liver S9)	Experiment 1. 4 hours without metabolic activation: 0.08, 0.15, 0.3, 0.6, 1.2 µg/ml. 4 hours with metabolic activation (S9): 20.0, 40.0, 80.0, 160.0, 640.0 µg/ml.	Key study 1- reliable without restriction	Experiment 1: negative. Cytotoxicity at 1.2 µg/mL and above. Experiment 2: negative. Cytotoxicity at 20 µg/mL and above.

Reference	Enpoint/ Species, tissue, cell line, metabolic activation/ test guideline/a GLP compliance/ publication type and year	Dose	Reliability	Results
	OECD guideline study (test number not reported) GLP compliance: yes Study report, 2013	Experiment II: 24 hours without metabolic activation: 1.3, 2.5, 5.0, 10.0, 20.0 µg/ml. 4 hours with metabolic activation (S9): 20.0, 40.0, 320.0, 640.0 µg/ml.		
Reference	**Model/administration route/ guideline/ GLP compliance/ publication type and year**	**Dose and duration**	**Quality assessment by ECHA**	**Results**
ECHA (2021b)	Mouse, oral (gavage) OECD Guideline 474 (mammalian erythrocyte micronucleus test) GLP compliance: yes Oral (gavage) Study report, 1989	2000 mg/kg x 1, sampling at 24, 48 and 72 hours after dosing.	Key study 2- reliable with restrictions	Following administration of the test substance, all animals showed reduced mobility. No other effects were observed. Negative
Summary: EHS did not induce reverse mutation in five strains of Salmonella typhimurium in the presence or absence of exogenous metabolic activation. VKM notes that the selection of strains is in line with the OECD TG. No mutagenic effect was reported in the hypoxanthine-guanine phosphoribosyl transferase (Hgprt) assay in V79 cells exposed to EHS both in the absence and presence of exogenous metabolic activation. EHS did not induce chromosomal aberrations in CHO cells with and without metabolic activation. EHS did not increase micronucleus formation in vivo; however, no evidence of target tissue exposure was provided. Furthermore, available repeated dose toxicity studies and ADME studies do not provide sufficient information. Therefore, VKM considers that the in vivo micronucleus study is invalid. VKM conclusion on the evidence: There is sufficient evidence to conclude that EHS is not mutagenic. There is insufficient data to conclude on cytogenic potential of EHS.				

Table 6.5.2.1-4. Study characteristics and certainty in the evidence for reproductive and developmental effects of EHS.

Reference	Model and administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
ECHA (2021b)	Rat oral (gavage) OECD Guideline 421 (reproduction / developmental toxicity screening test) GLP compliance: yes Study report, 2012	0, 25, 80, 250 mg/kg/day Duration of treatment / exposure: Males: 28 days Females: Approximately 7 weeks	Key study 1 - reliable without restriction	Maternal toxicity: One female rat in the 250 mg/kg bw/day group was found dead on day 23 of the gestation period, which was considered to be substance-related. At the dose levels of 250 and 80 mg/kg bw/day, reduced food consumption was noted during lactation. At the dose level of 250 mg/kg bw/day, statistically significant reduction in body weight gain was noted on day 4 of the lactation period Developmental toxicity: Treatment with the test item at the dose levels of 250 and 80 mg/kg bw/day caused a reduction in gestation index (number of females with living pups as a percentage of females pregnant) as well as an increase in incidence of post-implantation loss resulting in a lower litter size. Further, at the dose levels of 250 and 80 mg/kg bw/day, prolonged gestation period was noted. These findings were dose-dependent and considered to be test item-related adverse effects. At the 250 mg/kg bw/day dose group, a reduction of pup absolute body weight was observed.
Summary: In one reproductive and developmental study in rats, developemental toxicity (dose-dependent) and teratogenicity were observed. The study has been assessed by ECHA as reliable without restrictions. VKM notes that the study is performed according to GLP and TG and has been judged to be reliable without restrictions. VKM considers that the available data are sufficient to identify a PoD for maternal and developmental toxicity. VKM conclusion on the evidence: VKM identifies a LOAEL of 80 mg/kg bw/day for maternal toxicity, a NOAEL of 25 mg/kg bw/day for developmental toxicity.				

6.5.2.2 Local effects

The evidence addresses skin irritation and skin sensitisation (Table 6.5.2.2-1 and 6.5.2.2-2).

Table 6.5.2.2-1. Study characteristics and certainty in the evidence for irritation of EHS.

Reference	Model and administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
ECHA (2021b)	Rabbit, dermal OECD Guideline 404 (acute dermal irritation/corrosion) and EU Method B.4 (Acute Toxicity: Dermal Irritation / Corrosion) GLP compliance: yes Study report: 2006	0.5 mL of the undiluted test item were placed on a dry gauze, which was then applied to an area of approximately 6 cm^2. The skin was examined approximately 1 hour, 24, 48 and 72 hours after removal of the dressing	Key study 1 - reliable without restriction	A well-defined erythema was noted 1 h after removal of patches but reversed fully within 24 hours in two animals and within 48 hours in one animal. No edema was recorded in any of the animals at any time.
ECHA (2021b)	Rat, dermal OECD Guideline 402 (acute dermal toxicity) GLP compliance: yes Study report, 1990	5000 mg/kg, exposure for 24 hours, 14 days observation	Key study 1 - reliable without restriction	No skin irritation was observed.
Summary: In rabbits, acute dermal application of EHS caused slight, reversible irritation. In rats, acute dermal application did not cause skin irritation. The studies have been judged as reliable without restrictions. VKM notes that the studies are performed according to GLP and test guideline. VKM conclusion on the evidence: EHS is considered not to be a skin irritant under the test conditions.				

Table 6.5.2.2-2. Study characteristics and certainty in the evidence for sensitisation of EHS.

Reference	Model and administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
ECHA (2021b)	Guinea pig, dermal (maximisation test) OECD Guideline 406 (skin sensitisation) GLP compliance: yes Study report, 1990	25% (w/w) test article, observation 24, 48 and 72 hours after challenge	Key study 1 - Reliable without restrictions	No skin reactions.
Summary: In one in vivo study, EHS did not cause skin reactions in guniea pigs following dermal application. VKM notes that the study is performed according to GLP and OECD TG without deviations and has been judged to be reliable without restrictions. VKM considers that the available data are sufficient to make a conclusion on the sensitisation potential of EHS. VKM conclusion on the evidence: EHS does not exhibit sensitising potential.				

6.6 UV filter EHT: Study characteristics, evaluation of certainty in the evidence for adverse effects, and translation into evidence for health effects

6.6.1 Evidence from literature searches

Two patch studies addressed skin sensitisation, contact allergic reactions (Table 6.6.1-1), photoallergic contact reactions (Table 6.6.1-2), and skin irritation (Table 6.6.1-3).

Table 6.6.1-1. Study characteristics and certainty in the evidence for contact allergic reactions for EHT. F: female; PPT: photopatch test; ICDRG: International Contact Dermatitis Research Group;

Reference	Type of test/ participants/ inclusion and exclusion criteria/ scoring system	Dose and duration	RoB	Number of reactions (in % of n)
Kerr et al. (2012)	Photopatch test, humans, n=1031, 18-92 (median=46 years)/ 715 F A prospective, multicentre PPT study including 30 centres/ 12 European countries. Recruitment period: August 2008 to February 2011 Inclusion criteria: The inclusion criteria specified that subjects must be aged 18 years or older and have sufficient understanding to give written informed consent. Those included had at least one of the following four indications for performing PPT: an exposed-site dermatitis during summer months; any exposed-site dermatitis; history of a sunscreen reaction; or history of a topical NSAID skin reaction. Exclusion criteria: Potent topical steroid applied to the PPT site on the back in the 5 days prior to PPT; skin disease activity on the back which was too active to allow PPT; and subjects prescribed systemic immuno-suppressant medication.	Photopatch testing was conducted according to the European consensus methodology. The test agents were applied, removed at 24 or 48 h, one set was then irradiated with 5 J/cm^2 UVA while the other set was covered with a UV-impermeable material. Readings of the test site: pre-irradiation, post-irradiation: immediately, 24 h, 48, and 72 h or later. Reactions were scored using the International Contact Dermatitis Research Group visual system. EHT: 10%	1	Allergic contact dermatitis: 0
Valbuena Mesa and Hoyos Jimenez (2016)	Patch test, humans, 100 participants, 13-88 years (mean = 49 years)/ 63 F Prospective descriptive cross-sectional study, 1 centre/ Colombia. Time period: 2001-2003	Application in duplicate, irradiation with 5 J/cm^2 after 48 h. The readings were performed on days 2, 4 and 6 Concentration of EHT: 10%	1	No allergic contact dermatitis observed

Reference	Type of test/ participants/ inclusion and exclusion criteria/ scoring system	Dose and duration	RoB	Number of reactions (in % of n)
	Inclusion criteria: Patients with suspected photo allergic contact dermatitis (a dermatitis affecting mainly light-exposed skin, those with a history of a sunscreen skin reaction or a topical NSAID skin reaction). Exclusion criteria: Patients with a clinical diagnosis of porphyria, solar urticaria or systemic lupus erythematosus were excluded from the testing procedure, as were pregnant woman and patients who received systemic steroid treatments or immunosuppressive drugs in the month before the test or who applied topical steroids on their backs in the 8 days prior to the test. Testing according to ICDRG; relevance evaluated according to COADEX.			

Overall evaluation of certainty in the evidence on sensitisation (contact allergic reactions)

Initial rating	Elements triggering downgrading				Elements triggering upgrading			Overall rating
	Risk of bias	Unexplained inconsistency	Indirectness	Imprecision	Large effect	Dose–response relationship	Consistency	
++++	Not serious	Not serious	Not serious	Not serious	Not evaluated	Not evaluated	Not evaluated	++++ High

Summary: Two studies addressed contact allergic reactions of EHT. Kerr et al. (2012) reported 0 (0%) reactions in the 1031 subjects tested. Valbuena Mesa and Hoyos Jimenez (2016) reported no allergic contact reactions in the 100 subjects tested.

Overall evaluation of certainty in the evidence on sensitisation (contact allergic reactions)
VKM conclusion on the evidence: There is high confidence in the body of evidence that exposure to EHT is not associated with contact allergic reactions in susceptible individuals. There is evidence of no health effect.

Table 6.6.1-2. Study characteristics and certainty in the evidence for photoallergic contact reactions for EHT. F: female; PPT: photopatch test; ICDRG: International Contact Dermatitis Research Group; COADEX: see definitions and Bruynzeel et al. (2004).

Reference	Type of test/ participants/ inclusion and exclusion criteria/ scoring system	Dose and duration	RoB	Number of reactions (in % of n)
Kerr et al. (2012)	Photopatch test, humans, n=1031, 18-92 (median=46 years)/ 715 F A prospective, multicentre PPT study including 30 centres/ 12 European countries. Recruitment period: August 2008 to February 2011 Inclusion criteria: The inclusion criteria specified that subjects must be aged 18 years or older and have sufficient understanding to give written informed consent. Those included had at least one of the following four indications for performing PPT: an exposed-site dermatitis during summer months; any exposed-site dermatitis; history of a sunscreen reaction; or history of a topical NSAID skin reaction. Exclusion criteria: Potent topical steroid applied to the PPT site on the back in the 5 days prior to PPT; skin disease activity on the back which was too active to	Photopatch testing was conducted according to the European consensus methodology. The test agents were applied, removed at 24 or 48 h, one set was then irradiated with 5 J/cm^2 UVA while the other set was covered with a UV-impermeable material. Readings of the test site: pre-irradiation, post-irradiation: immediately, 24 h, 48, and 72 h or later. Reactions were scored using the International Contact Dermatitis Research Group visual system. EHT: 10%	1	Photoallergic contact dermatitis: Certain: 1 (0.1%) Uncertain: 2 (0.2%) Severity: grades 3, 4 and 5 (of 5): 3 (0.2%); 0; 0

Reference	Type of test/ participants/ inclusion and exclusion criteria/ scoring system	Dose and duration	RoB	Number of reactions (in % of n)
	allow PPT; and subjects prescribed systemic immuno-suppressant medication.			
Valbuena Mesa and Hoyos Jimenez (2016)	Patch test, humans, 100 participants, 13-88 years (mean = 49 years)/ 63 F Prospective descriptive cross-sectional study, 1 centre/ Colombia. Time period: 2001-2003 Inclusion criteria: Patients with suspected photo allergic contact dermatitis (a dermatitis affecting mainly light-exposed skin, those with a history of a sunscreen skin reaction or a topical NSAID skin reaction). Exclusion criteria: Patients with a clinical diagnosis of porphyria, solar urticaria or systemic lupus erythematosus were excluded from the testing procedure, as were pregnant woman and patients who received systemic steroid treatments or immunosuppressive drugs in the month before the test or who applied topical steroids on their backs in the 8 days prior to the test. Testing according to ICDRG; relevance evaluated according to COADEX.	Application in duplicate, irradiation with 5 J/cm^2 after 48 h. The readings were performed on days 2, 4 and 6 Concentration of EHT: 10%	1	No photoallergic contact dermatitis observed

Overall evaluation of certainty in the evidence on sensitisation (photoallergic contact reactions)								
Initial rating	Elements triggering downgrading				Elements triggering upgrading			Overall rating
	Risk of bias	Unexplained inconsistency	Indirectness	Imprecision	Large effect	Dose–response relationship	Consistency	
++++	Not serious	Not serious	Not serious	Not serious	Not evaluated	Not evaluated	Not evaluated	++++ High
Summary: Two studies addressed photocontact allergic reactions of EHT. Kerr et al. (2012) reported 1 (0.1%) certain and 2 (0.2%) uncertain photoallergic contact dermatitis reactions with severity grade 3 on a scale from 1-5 in the 1031 subjects tested. Valbuena Mesa and Hoyos Jimenez (2016) reported no photoallergic contact reaction in the 100 subjects tested. VKM conclusion on the evidence: There is high confidence in the body of evidence for a low frequency of photocontact allergic reactions in susceptible individuals exposed to EHT. The level of evidence for health effect is high.								

Table 6.6.1-3. Study characteristics and certainty in the evidence for skin irritant reactions of EHT. F: female; M: male; ICDRG: International Contact Dermatitis Research Group; COADEX: see definitions and Bruynzeel et al. (2004).

Reference	Type of test/ participants/ inclusion and exclusion criteria/ scoring system	Dose and duration	RoB	Number of reactions (in % of n)
Kerr et al. (2012)	Photopatch test, humans, n=1031, 18-92 (median=46 years)/ 715 F A prospective, multicentre PPT study including 30 centres/ 12 European countries. Recruitment period: August 2008 to February 2011	The test agents were applied, removed at 24 or 48 h, one set was then irradiated with maximum 5 J/cm^2 UVA (minimum: 0.5 J/cm^2) while the other set was covered with a UV-impermeable material. Readings of the test site: pre-irradiation, post-irradiation: immediately, 24 h, 48, and 72 h or later. Readings from 48 h are presented.	1	Irritant reactions were rare: 7 reactions in 6 (0.6%) subjects. The specific test substances in the panel causing irritant reactions were not reported.

Reference	Type of test/ participants/ inclusion and exclusion criteria/ scoring system	Dose and duration	RoB	Number of reactions (in % of n)
	Irritant reactions were scored, but not for individual UV filters Inclusion criteria: The inclusion criteria specified that subjects must be aged 18 years or older and have sufficient understanding to give written informed consent. Those included had at least one of the following four indications for performing photopatch testing: an exposed-site dermatitis during summer months; any exposed-site dermatitis; history of a sunscreen reaction; or history of a topical NSAID skin reaction. Exclusion criteria: Potent topical steroid applied to the PPT site on the back in the 5 days prior to photopatch testing; skin disease activity on the back which was too active to allow PPT; and subjects prescribed systemic immuno-suppressant medication. Testing according to the European consensus methodology; reaction scoring: ICDRG visual system; relevance evaluation: COADEX	Concentration of EHT: 10%		
Valbuena Mesa and Hoyos Jimenez (2016)	Patch test, humans, 100 participants, 13-88 years (mean = 49 years)/ 63 F Prospective descriptive cross-sectional study, 1 centre/ Colombia. Time period: 2001-2003	Application in duplicate, irradiation with 5 J/cm^2 after 48 h. The readings were performed on days 2, 4 and 6 Concentration of EHT: 10%	1	No irritant reactions observed.

Reference	Type of test/ participants/ inclusion and exclusion criteria/ scoring system	Dose and duration	RoB	Number of reactions (in % of n)
	Inclusion criteria: Patients with suspected photo allergic contact dermatitis (a dermatitis affecting mainly light-exposed skin, those with a history of a sunscreen skin reaction or a topical NSAID skin reaction). Exclusion criteria: Patients with a clinical diagnosis of porphyria, solar urticaria or systemic lupus erythematosus were excluded from the testing procedure, as were pregnant woman and patients who received systemic steroid treatments or immunosuppressive drugs in the month before the test or who applied topical steroids on their backs in the 8 days prior to the test. Testing according to ICDRG; relevance evaluated according to COADEX.			

Overall evaluation of certainty in the evidence on skin irritation								
Initial rating	Elements triggering downgrading				Elements triggering upgrading			Overall rating
	Risk of bias	Unexplained inconsistency	Indirectness	Imprecision	Large effect	Dose–response relationship	Consistency	
++++	Not serious	Not serious	Not serious	Not serious	Not evaluated	Not evaluated	Not evaluated	++++ High

Overall evaluation of certainty in the evidence on skin irritation
Summary: Two studies addressed skin irritation of EHT. Kerr et al. (2012) reported that irritant reactions were rare; 7 reactions in 6 (0.6%) subjects (reaction to EHT was not specified) in the 1031 subjects tested. Valbuena Mesa and Hoyos Jimenez (2016) reported 0 irritant reactions from EHT in the 100 subjects tested. VKM conclusion on the evidence: There is high confidence in the body of evidence that exposure to EHT is not associated with irritant reactions in susceptible individuals. There is evidence of no health effect.

6.6.2 Evidence from ECHA

Note that a "study report" is an unpublished document in the dossier submitted by manufacturer. Information on dose and duration is reproduced with the abbreviations as used in the original document. VKM has not explained these abbreviations.

6.6.2.1 Systemic toxicity

The evidence addresses acute toxicity and subchronic toxicity (Table 6.6.2.1-1, 6.6.2.1-2).

Table 6.6.2.1-1. Study characteristics and certainty in the evidence for acute toxicity of EHT.

Reference	Model and administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
ECHA (2021f)	Rat, oral OECD 401 (acute oral toxicity) GLP compliance: yes ECHA summary, 2010	5 000 mg/kg bw	Key study 2 - reliable with restrictions	No mortality, clinical signs or gross pathology were observed. ECHA concluded that LD50 was >5000 mg/kg bw.
ECHA (2021f)	Rat, dermal OECD Guideline 402 (acute dermal toxicity) GLP compliance: yes	2000 mg/kg bw	Key study 2 - reliable with restrictions	No mortality, clinical signs or gross pathology were observed. ECHA concluded that LD50 was >2000 mg/kg bw.

Reference	Model and administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
	ECHA summary, 1987			
Summary: EHT has low acute toxicity in rats both by dermal and oral administrations. Both studies were judged to be reliable with restrictions. VKM conclusion on the evidence: LD50 is >5000 mg/kg bw following oral exposure and >2000 mg/kg bw following dermal application.				

Table 6.6.2.1-2. Study characteristics and certainty in the evidence for subchronic toxicity of EHT.

Reference	Model and administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
ECHA (2021f)	Rat, oral (unspecified) OECD 408 (repeated dose 90-day oral toxicity study in rodents) GLP compliance: yes ECHA summary, 2010	1000 mg/kg bw per day 90 days, dosing 7 days/week	Key study 2-reliable with restrictions	No adverse effects were observed. ECHA concluded that the NOEL for oral systemic toxicity is 1000 mg/kg bw/day.
Summary: In one 90-day repeated toxicity study in rats, oral administration of EHT at 1000 mg/kg bw did not cause adverse effects. VKM notes that the studies are performed according to GLP and OECD TG and have been judged to be reliable with restrictions. VKM considers the 90-day oral study suitable for establishing a PoD. VKM conclusion on the evidence: VKM identifies a NOAEL of ≥1000 mg/kg bw for systemic toxicity following oral exposure.				

Table 6.6.2.1-3. Study characteristics and certainty in the evidence for genetic toxicity of EHT.

Reference	Enpoint/ Species, tissue, cell line, metabolic activation/ test guideline/a GLP compliance/ publication type and year	Dose	Reliability	Results
ECHA (2021f)	*In vitro*, reverse mutation E. coli WP2, without metabolic activation. *In vitro* gene mutation study in bacteria according to guideline (guideline not reported) GLP compliance: yes ECHA summary, 2010	1.6-1000 µg/plate	Key study 2-reliable with restrictions	Negative No cytotoxicity
ECHA (2021f)	*In vitro*, reverse mutation Salmonella typhimurium, TA1535, TA 1537, TA 98, and TA100, with and without metabolic activation (S9) OECD Guideline 471 (bacterial reverse mutation assay) GLP compliance: yes ECHA summary, 2010	20-5000 µg/plate	Key study 2-reliable with restrictions	Negative No cytotoxicity
ECHA (2021f)	*In vitro*, chromosomal aberrations Chinese hamster V79 cells, with and without metabolic activation (S9) OECD Guideline 473 (*in vitro* mammalian chromosome aberration test) GLP compliance: yes ECHA summary, 2010	10-100 µg/mL Exposure period (with metabolic activation): 4 hours Exposure period (without metabolic activation): 18 hours Expression time: 18 and 28 hours	Key study 2-reliable with restrictions	Negative No cytotoxicity

Reference	Enpoint/ Species, tissue, cell line, metabolic activation/ test guideline/a GLP compliance/ publication type and year	Dose	Reliability	Results
ECHA (2021f)	*In vitro*, chromosomal aberrations Chinese hamster ovary cells, without metabolic activation. *In vitro* mammalian cytogenicity according to guideline (guideline not reported) GLP compliance: yes ECHA summary, 2010	32.77-80 µg/mL for 2 h	Key study 2-reliable with restrictions	Negative No cytotoxicity
ECHA (2021f)	*In vitro*, hprt mutation Chinese hamster ovary (CHO) cells, with and without metabolic activation (S9) OECD Guideline 476 (*in vitro* mammalian cell gene mutation test) GLP compliance: yes Study report, 2007	1st Experiment (4 h-exposure) - without S9 mix: 0; 6.3; 12.5; 25.0; 50.0; 100.0 µg/mL - with S9 mix: 0; 12.5; 25.0; 50.0; 2500.0; 3750.0; 5000.0 µg/mL 2nd experiment: - without S9 mix (24-h exposure period): 0; 3.1; 6.3; 12.5;25.0; 50.0; 75.0; 100.0 µg/mL - with S9 mix (4-h exposure period): 0; 6.3; 12.5; 25.0; 50.0; 100.0 µg/mL	Key study 1-reliable without restrictions	Negative. Cytotoxicity was observered after treatment with the highest dose for 4 h in the presence of S9. Cytotoxicity was observed after treatment with the two top doses for 24 h in the absence of S9.
Summary: EHT did not induce reverse mutation in four strains of Salmonella typhimurium in the presence or absence of exogenous metabolic activation and without metabolic activation in E. coli WP2. VKM notes that the selection of strains is in line with the OECD TG, however the substance was only tested without metabolic activation in E. coli WP2. No mutagenic effect was reported in the hypoxanthine-guanine phosphoribosyl transferase (Hgprt) assay. EHT did not induce chromosomal aberrations. The *in vitro* studies were performed according to GLP and OECD TG and have been judged to be reliable with/without restrictions. No in vivo genotoxicity studies were available and none of the available studies assessed anugenicity. No *in vitro* studies for cytogenicity were available from the ECHA database.				

Reference	Enpoint/ Species, tissue, cell line, metabolic activation/ test guideline/a GLP compliance/ publication type and year	Dose	Reliability	Results
VKM conclusion on the evidence: There is sufficient evidence to conclude that EHT is not mutagenic or clastogenic. There is insufficient data to conclude on the anugenic potential of EHT.				

Table 6.6.2.1-4. Study characteristics and certainty in the evidence for developmental toxicity of EHT.

Reference	Model and administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
ECHA (2021f)	Rat, oral (unspecified) OECD Guideline 414 (prenatal developmental toxicity study) GLP compliance: yes ECHA summary, 2001	0, 100, 400 and 1000 mg/kg	Key study 2-reliable with restrictions	No substance-related maternal or fetal toxicity. A NOAEL of 1000 mg/kg bw/day was identified for maternal toxicity and embryotoxicity.
Summary: In one developmental toxicity study in rats, no adverse effects were observed in the dams or embryos. Fetal abnormalities were not reported. VKM notes that the study is performed according to GLP and TG and has been judged to be reliable with restrictions. VKM considers that the available data are sufficient to identify a PoD for maternal toxicity and embryotoxicity. VKM conclusion on the evidence: VKM identifies a NOAEL of ≥1000 mg/kg bw/day for maternal toxicity and teratogenicity.				

6.6.2.2 Local effects

The evidence addresses skin irritation (Table (6.6.2.2-1) and sensitisation (Table 6.6.2.2-2).

Table 6.6.2.2-1. Study characteristics and certainty in the evidence for irritation (EHT).

Reference	Model and administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
ECHA (2021f)	Rabbit, dermal OECD Guideline 404 (acute dermal irritation/ corrosion) GLP compliance: yes ECHA summary, 2010	500 mg for 4 h	Key study 2-reliable with restrictions	No erythema or edema was observed.
Summary: In rabbits, neither erythema nor edema was observed following dermal acute exposure to EHT. The study was judged to be reliable with restrictions. VKM conclusion on the evidence: EHT is considered not to be a skin irritant under the test conditions.				

Table 6.6.2.2-2. Study characteristics and certainty in the evidence for sensitisation of EHT.

Reference	Model and administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
ECHA (2021f)	Guinea pig dermal (maximization test) OECD 406 (skin sensitisation) GLP compliance: yes ECHA summary, 2010	Concentration of test material and vehicle used at induction: i.c.: 5 % in olive oil DAB 8. p.c.: 60 % in olive oil DAB 8. Concentration of test material and vehicle used for each challenge: p.c.: 40 % in olive oil DAB 8. 24 and 48 hours after challenge	Key study 2-reliable with restrictions	No skin reactions.

Reference	Model and administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
Summary: In one in vivo study, EHT did not cause skin reactions in guniea pigs following dermal application. VKM notes that the study is performed according to GLP and OECD TG and has been judged to be reliable with restrictions. VKM considers that the available data are sufficient to make a conclusion on the sensitisation potential of EHT. VKM conclusion on the evidence: EHT does not exhibit sensitising potential.				

6.7 UV filter OC: Study characteristics, reliability in the evidence for adverse effects, and translation into evidence for health effects

6.7.1 Evidence from ECHA

Note that a "study report" is an unpublished document in the dossier submitted by the manufacturer. Information on dose and duration is reproduced with the abbreviations as used in the original document. VKM has not explained these abbreviations.

6.7.1.1 Systemic toxicity

The evidence addresses acute toxicity, subacute and subchronic toxicity, genetic toxicity, and reproductive and developmental toxicity (Table 6.7.1.1-1 to 6.7.1.1-4).

Table 6.7.1.1-1. Study characteristics and certainty in the evidence for acute toxicity of OC.

Reference	Model and administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
ECHA (2021d)	Rat, dermal OECD TG 402 (acute dermal toxicity) GLP compliance: yes Study report, 1992	2000 mg/kg bw x 1 for 24 h, 10% of body surface area. 14-day observation period	Key study 1 - reliable without restriction	No mortality, treatment related clinical signs or systemic toxicity, necropsy findings or changes in body weight were observed. ECHA concluded that LD50 was >2000 mg/kg bw.
ECHA (2021d)	Rat, oral (gavage) OECD Guideline 401 (acute dermal toxicity) GLP compliance: yes Study report, 1993	5000 mg/kg bw x1, 14-day observation peridod	Key study 1 - reliable without restriction	No mortality was observed. ECHA concluded that LD50 was >5000 mg/kg bw.
Summary: OC has low acute toxicity in rats both by dermal and oral administrations. Both studies were found to be reliable without restrictions. VKM conclusion on the evidence: LD50 is >5000 mg/kg bw following oral exposure and >2000 mg/kg bw following dermal application.				

Table 6.7.1.1-2. Study characteristics and certainty in the evidence for subacute and subchronic toxicity of OC.

Reference	Model and administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
ECHA (2021d)	Rat, oral (feed) Short-term repeated dose toxicity GLP compliance: Not specified Study report, 2000	0, 4500 or 15000 ppm in the feed. 0, 456 and 1369 mg/kg bw/day (males); 0, 449 and 1393 mg/kg bw /day (females)	Other information 2 - reliable with restrictions	Minor effects on body weight and body weight change in males and females exposed to 15000 ppm in the feed. At the end of the study, a slight reduction in body weight of the animals of the 15000 ppm group compared with the control rats was observed.

Reference	Model and administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
		14 days		Food consumption was slightly impaired in males and females in the 15000 ppm dose group during the first week.
ECHA (2021d)	Rat, oral (feed) OECD Guideline 407 (repeated dose 28-day oral toxicity study in rodents) GLP compliance: yes Study report, 2019	0 ppm, 1000 ppm (males: 63-65 mg/kg bw/ day and females: 69-72 mg/kg bw day) 3000 ppm (males: 188-193 mg/kg bw/ day and females: 207-215 mg/kg bw/ day) 10000 ppm (males: 188-193 mg/kg bw/ day and females: 207-215 mg/kg bw/ day) 28 days	Supporting study 1 - reliable without restrictions	No mortality was observed. No substance-related effects on clinical signs, food consumption, or gross pathology were observed. Treatment-related effects were observed for body weights, haematology, clinical biochemistry, organ weights, histopathology (non-neoplastic effects), and on bioanalytical examinations for animals dosed 3000 and 10 000 ppm.
ECHA (2021d)	Rabbit, dermal TG not specified (percutaneous dermal 91-day sub-chronic toxicity study) GLP compliance: not specified Publication, Odio et al. (1994a)	Doses / Concentrations: 0, 130, 264, 534 mg/kg for 5 days per week (total of 65 applications) over a period of 91 days	Supporting study 2 - reliable with restrictions	No mortality or clinical signs (other than skin irritation was observed. In both sexes, mid- and high-dose treatments significantly depressed body weight gain relative to the corresponding controls. At the low dose, no significant body weight effect was noted in females, whereas in male animals, a statistically significant depression of body weight gain was still observed.

Reference	Model and administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
				In male rabbits, morphological examination of epididymis and testicles showed no signs of octocrylene-associated abnormalities. A NOEL of 130 mg/kg bw was identified for females. However, for males a NOEL could not be established due to effects on body weight gain for all dose groups.
ECHA (2021d)	Rats, oral (feed) OECD Guideline 408 (repeated dose 90-day oral toxicity in rodents) GLP compliance: yes Study report, 1993	0, 750, 2250, 4500, 15000 ppm in the diet for 90 days (equals ~ 58, 175, 340, 1085 mg/kg bw/day)	Key study 1 - reliable without restriction	No substance-related clinical signs or mortality were observed. No substance-related effects on gross pathology were observed. The high dose increased body weight in both males and females. Food consumption was reduced in male and female rats exposed to the high dose. Increased number of hypertrophic cells in the pars distalis of the pituitary gland of males exposed to 15 000 ppm of OC. Slight or moderate hypertrophy of the thyroid foilicular epithelium (all animals) and associated pale staining colloid in both sexes exposed at 15 000 ppm. 4500 ppm group: Minimal or slight hypertrophy of the thyroid follicular epithelium and associated pale staining colloid in both sexes exposed to 4500 ppm.

Reference	Model and administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
				A NOAEL of 2250 ppm (~175 mg/kg bw/day) was identified.
Summary: In one 90-day repeated toxicity study in rats, oral administration in feed of OC caused adverse effects in animals in the two top doses, and ECHA identified a NOAEL of 175 mg/kg bw for both male and female rats. In a 91-day repeated toxicity study in rabbits, percuteneous application of OC caused substance-related decrease in body weight gain which was observed for both males (all dose groups) and females (two highest dose groups). A NOEL of 130 mg/kg bw could be established only for female rabbits. VKM notes that the studies are performed according to OECD TG and have been judged to be reliable with or without restrictions. The oral study is also performed according to GLP; however, GLP compliance is not specified for the dermal study. VKM considers that the two oral subacute studies are not suitable for establishing a PoD for systemic toxicity, due to the short exposure time. VKM considers the 90-day oral study suitable for establishing a PoD. VKM conclusion on the evidence: VKM identifies a NOAEL of 175 mg/kg bw for subchronic following oral exposure.				

Table 6.7.1.1-3. Study characteristics and certainty in the evidence for genetic toxicity of OC.

Reference	Endpoint/ Species, tissue, cell line, metabolic activation/ test guideline/a GLP compliance/ publication type and year	Dose	Reliability	Results
ECHA (2021d)	*In vitro*, reverse mutation Salmonella typhimurium, TA1535, TA1537, TA98, TA100 and Escherichia coli WP2 uvr A, with and without metabolic activation (S9) OECD TG 471 (bacterial reverse mutation assay) GLP compliance: yes Study report, 2001	20 - 5000 µg/plate (SPT); 4 - 2500 µg/plate (PIT)	Key study 1 - reliable without restriction	Negative Cytotoxicity and precipitation at ≥2500 µg/plate

Reference	Endpoint/ Species, tissue, cell line, metabolic activation/ test guideline/a GLP compliance/ publication type and year	Dose	Reliability	Results
ECHA (2021d)	*In vitro*, Hprt mutation Mouse lymphoma L5178Y cells, with and without metabolic activation (Aroclor 1254 induced rat liver S9). OECD TG 476 (*in vitro* mammalian cell gene mutation test) GLP compliance: not specified Study report, 1993	12.5 - 200 µg/ml	Key study 1 - reliable without restriction	Negative
ECHA (2021d)	*In vitro*, chromomsomal aberrations Chinese hamster lung fibroblasts (V79), without metabolic activation (Aroclor 1254 induced rat liver S9). OECD TG 473 (*in vitro* mammalian chromosome aberration test) GLP compliance: yes Study report, 2001	3.75 - 90 µg/ml	Key study 1 - reliable without restriction	Negative
Reference	**Model/administration route/ guideline/ GLP compliance/ publication type and year**	**Dose and duration**	**Quality assessment by ECHA**	**Results**
ECHA (2021d)	Mouse, oral (gavage) OECD Guideline 474 (mammalian erythrocyte micronucleus test) GLP compliance: yes Study report: 1993	500, 1000 and 2000 mg/kg bw x1. Animals were sacrificed at 16, 24 and 48 hours after dosing	Key study 1 - reliable without restriction	After test substance application transient piloerection was observed at all dose levels. Negative
Summary: OC did not induce reverse mutation in four strains of Salmonella typhimurium or in E. coli WP2 in the presence or absence of exogenous metabolic activation. VKM notes that the selection of strains is in line with the OECD TG. No mutagenic effect was reported in the hypoxanthine-guanine phosphoribosyl transferase (Hgprt) assay in V79 cells exposed to OC both in the absence and presence of exogenous metabolic activation. OC did not induce chromosomal aberrations in V79 cells with and without metabolic activation.				

Reference	Endpoint/ Species, tissue, cell line, metabolic activation/ test guideline/a GLP compliance/ publication type and year	Dose	Reliability	Results
OC did not increase micronucleus formation in vivo; however, no evidence of target tissue exposure was provided. Furthermore, available repeated dose toxicity studies and ADME studies do not provide sufficient information. Therefore, VKM considers that the in vivo micronucleus study is invalid. VKM conclusion on the evidence: OC is not mutagenic or clastogenic. There is insufficient data to conclude on the anugenic potential of OC.				

Table 6.7.1.1-4. Study characteristics and certainty in the evidence for reproductive and developmental toxicity of OC.

Reference	Model and administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
ECHA (2021d)	Rats, oral (feed) OECD Guideline 443 (extended one-generation reproductive toxicity study) GLP compliance: yes Study report, 2019	0, 750, 2100 and 7000 ppm. Anticipated doses: 55, 153, 534 mg/kg bw/day for males and 58, 163, 550 mg/kg bw/day for females. Males: 10-week premating period, during mating up to the day of sacrifice (approx. 13 weeks). Females: P: 10-week premating period, during mating, gestation and	Key study 1-reliable without restrictions	Parental and second parental generation: High dose: decreased body weight, reduced food consumption, lower mean number of implantation sites, and lower number of pups delivered. Parenteral generation: High dose: increased GGT activity, increased incidence of activated appearance of the thyroid gland characterised by loss of colloid from the follicles and hypertrophy and hyperplasia of follicular epithelial cells (females). High and mid dose: increased incidence of activated appearance of the thyroid gland; characterised by loss of colloid from the

Reference	Model and administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
		lactation up to the day of sacrifice after lactation day 21. F1: from weaning up to sacrifice (approx. 10 weeks in Cohort 1A, approx. 13 weeks (males) and approx. 18 weeks (females) in Cohort 1B; approx. 8 weeks in cohort 2A). F2: indirectly exposed until weaning		follicles and hypertrophy and hyperplasia of follicular epithelial cells (males). F1 generation: Treatment related effects body weight, food consumption, sexual maturation, organ weight, histopathological findings.
ECHA (2021d)	Rat, oral (gavage) TG not specified (uterotrophic assay) GLP compliance: not specified Study report, 2001	0, 250, 1000 mg/kg bw/day 3 days	Supporting study 1 - reliable without restrictions	No substance-related changes in uterine weights or histopathological changes of the uterus were observed.
ECHA (2021d)	Rat, oral (feed) OECD Guideline 408 (repeated dose 90-day oral toxicity study in rodents)	0, 750, 2250 and 4500 and 15000 ppm. Equals ~58, 175, 340, 1085 mg/kg bw/day 90 days	Supporting study 1 - reliable without restrictions	No changes in absolute and relative testes weights in males and adrenal weigths in males/females were observed.

Reference	Model and administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
	GLP compliance: yes Study report, 1993			No treatment related incidences of microscopic findings were observed in adrenal glands, epididymides, prostate, testes of males. No treatment related incidences of microscopic findings were observed in adrenal glands, mammary gland, ovaries, uterus, vagina of females.
ECHA (2021d)	Rabbit, dermal TG not specified (percutaneous 91 day subchronic toxicity study) GLP: not specified Publication, Odio et al. (1994a)	0, 130, 264, 534 mg/kg/day 5 days per week, totally 65 applications 91 days	Supporting study 2 - reliable with restrictions	No substance-related effects on epididymis, testicles and sperm count were observed in male rabbits.
ECHA (2021d)	Rabbit, dermal Guideline: not specified GLP compliance: not specified Publication, Odio et al. (1994a)	0, 65, 267 mg/kg bw/day, days 6 through 18 of gestation, until day 29 of gestation	Weight of evidence 2-reliable with restrictions	No substance-related effects were observed for the dams or fetuses. A NOAEL of >267 mg/kg bw/day for maternal toxicity and fetal toxicity was identified.

Reference	Model and administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
ECHA (2021d)	Mouse, oral (gavage) Guideline: not specified GLP compliance: not specified Publication, Odio et al. (1994a)	0, 100, 300, 1000 mg/kg bw/day, days 8 through 12 of gestation until day 3 post partum	Weight of evidence 2-reliable with restrictions	No substance-related effects were observed for the dams or fetuses. A NOAEL of >1000 mg/kg bw/day for maternal toxicity and fetal toxicity was identified.
ECHA (2021d)	Rat, oral (gavage) OECD protocol and guidance for the conduct of the rodent hershberger assay ; Phase 2 of the Validation of the Rodent Hershberger Assay Study report, 2003	0, 300, 1000 mg/kg bw/day 10 days	Supporting study 1-reliable without restriction	Males that received testosterone: Decreased absolute and relative prostate ventral fixed weight. Males that did not receive testosterone: Decreased prostate ventral fixed and fresh and glans penis weight. No substance-related histopathological findings were observed.
ECHA (2021d)	Rat, oral (feed) No guideline followed GLP compliance: yes Study report, 2018	0, ~325, ~975 mg/kg bw/day) Male animals received the test item via the diet during a 4-week premating period, and during mating and up to the day of sacrifice. The female animals	Supporting study 1-reliable without restriction	Parental toxicity: No mortality was observed. Substance-related piloerection was obserbed both during gestation and lactation. Decreases in body weight and food consumption were observed both for male and female rats at both doses and the top dose, respectively. In the high-dosed males and

Reference	Model and administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
		were fed these diets during a 4-week premating period, and during mating, gestation and lactation until the day of sacrifice on day 21 of lactation or shortly thereafter. Throughout the lactation period the concentration in feed was halved.		females, substance-related decrease in number of eosinophils (54 and 73%, respectively) was observed. A decrease in Hb of 9% was detected for females in the high-dose group. Substance-related effects were also observed for clinical biochemistry parameters and organ weight. Non-neoplastic morphological changes in the thyroid gland were observed at both dose rates. Reproductive toxicity: In the high-dose group, one female was not mated, however, the mating index was comparable among the groups. Pre-coital time was comparable among the groups. The mean number of implantations in the high-dose group was lower than the historical control values (range 11.0-13.4) and corresponds with the lower number of pups born in the high-dose group. No effects were observed on post-implantation loss. Developmental toxicity and teratogenicity: The absolute number and the mean number of pups per litter that were delivered were statistically significantly

Reference	Model and administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
				lower in the high-dose group as compared to the control group.The mean number of pups delivered in the high-dose group was lower than the historical control values. From day 7 onwards, the number of runts and the number of litters with runts were higher in the high dose group as compared to the control- and low-dose group.
	Rat, oral (gavage) OECD TG 414 (prenatal developmental toxicity study) GLP compliance: yes Study report, 1993	0, 100, 400, 1000 mg/kg bw/day from day 6 through day 15 of gestation. Duration until day 20 of gestation	Key study 1 – reliable without restriction	Maternal toxicity: Substance-induced transient salivation occurred shortly after the daily treatment. Some dams of the high dose group showed a transient reddish-brown discoloration of the fur in the anogenital region or urine-smeared fur on some of the days. This discoloration, probably by the test substance itself or one of its metabolites, was considered to be consistent with systemic availability of the substance. Absolute and relative liver weights were slightly, but statistically significantly higher in the 1000 mg/kg group (approx. 9%) than in the control group For maternal toxicity a NOAEL of 1000 mg/kg bw/day was identified.

Reference	Model and administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
				No embryotoxic or teratogenic effects were observed. For developmental toxicity a NOAEL of 1000 mg/kg bw/day was identified.
Summary: Several studies assessing the reproductive and developmental effects of OC were available. Two studies were deemed as key studies, one prenatal developmental toxicity study on Extended One-Generation Reproductive Toxicity Study (EOGRTS). Both studies have been judged as reliable without restrictions. VKM conclusion on the evidence: VKM identifies a NOAEL of 153 and 163 mg/kg bw for males and females, respectively for parental and developmental toxicity.				

6.7.1.2 Local effects

The evidence address skin irritation and skin sensitisation (Table 6.7.1.2-1 and 6.7.1.2-2).

Table 6.7.1.2-1. Study characteristics and certainty in the evidence for skin irritation of OC.

Reference	Model and administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
ECHA (2021d)	Rabbit, dermal OECD Guideline 404 (acute dermal irritation / corrosion) GLP compliance: yes Study report, 1992	Amount(s) applied (volume or weight with unit): 0.5 mL, concentration: 1, 10, 25, 50, 100% (w/w) Dermally exposed for 4 h, 72 h observation period	Key study 1-reliable without restrictions	No erythema or edema.
ECHA (2021d)	Rat, dermal OECD TG 402 (acute dermal toxicity) GLP compliance: yes Study report, 1992	2000 mg/kg bw x 1 for 24 h, 10% of body surface area. 14-day observation period	Key study 1 - reliable without restriction	No skin irritation was observed.
Summary: In rabbits and rats, neither erythema nor edema was observed following dermal acute exposure to OC. Both studies have been judged as reliable without restrictions. VKM conclusion on the evidence: OC is considered not to be a skin irritant under the test conditions.				

Table 6.7.1.2-2. Study characteristics and certainty in the evidence for skin sensitisation of OC.

Reference	Model and administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
ECHA (2021d)	Guinea pig dermal (maximization test) OECD 406 (skin sensitisation)	5% Octocrilene in paraffin oil with/without Freund's Adjuvans for intradermal induction and undiluted Octocrilene for occlusive epicutaneous induction on day 7, followed by an occlusive	Key study	No substance-related skin reactions.

Reference	Model and administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
	GLP compliance: yes Study report, 2001	epicutaneous challenge with the undiluted Octocrilene 14 days after the epicutaneous induction.	1- reliable without restriction	
ECHA (2021d)	Guinea pig, dermal (maximization test) EU Method B.6 (skin sensitisation) GLP compliance: yes Study report, 1991	Induction 1: intradermal, 50%, duration not reported. Induction 2: epicutaneous, semiocclusive, test substance as such for 48 h. Challenge: epicutaneous, semiocclusive, test substance as such for 24 h.	Supporting study 2- reliable with restriction	No substance-related skin reactions.
Summary: In two in vivo studies, OC did not cause skin reactions in guniea pigs following dermal application. Both studies have been judged as reliable, with and without restrictions. VKM conclusion on the evidence: OC does not exhibit sensitising potential.				

6.8 UV filter NP-TiO_2: Study characteristics, reliability in the evidence for adverse effects, and translation into evidence for health effects

6.8.1 Evidence from ECHA

Note that a "study report" is an unpublished document in the dossier submitted by the manufacturer. Information on dose and duration is reproduced with the abbreviations as used in the original document. VKM has not explained these abbreviations.

6.8.1.1 Local effects

The evidence addresses skin irritation and skin sensitisation (Table 6.8.1.1-1 and 6.8.1.1-2).

Table 6.8.1.1-1. Study characteristics and certainty in the evidence for irritation of NP-TiO_2.

Reference	Model and administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
ECHA (2021e)	Rabbit, dermal OECD Guideline 404 (acute dermal irritation / corrosion) GLP compliance: yes Study report, 1994	TiO_2, nanoform 500 mg x1, in contact with the skin for 3 minutes and 1 hour in 1 animal and for 4 hours in 3 animals. Observation at 1, 24, 48 and 72 h and at day 9	Supporting study 2- reliable with restrictions	Two of three animals showed slight to moderate erythema at 1, 24, 48 and 72 h. One of three animals showed at 1 h slight edema. On day 9 all skin reactions were reversible.
ECHA (2021e)	Rabbit, dermal OECD Guideline 404 (acute dermal irritation / corrosion) GLP compliance: no Study report, 2006	TiO_2, nanoform 0.5 g for 4 h, observation period: 1, 24, 48 and 72 hours after removal	Key study 1- reliable without restrictions	No erythema or edema was observed.
ECHA (2021e)	Rabbit, semiocclusive OECD Guideline 404 (acute dermal irritation / corrosion) GLP compliance: no Study report, 1994	TiO_2, nanoform 0.5 g for 4 h, observation period: 1, 24, 48 and 72 hours after removal	Key study 1- reliable without restriction	No edema was observed. Slight to mild erythema was observed some animals at 1 and 24h. Only one of six displayed slight erythema at 48 and 72 h.

Reference	Model and administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
ECHA (2021e)	*In vitro*, human skin model OECD Guideline 439 (*in vitro* skin irritation: reconstructed human epidermis test method) GLP compliance: not specified Publication, Miyani and Hughes (2017)	TiO_2, nanoparticles 30 µl applied, concentration: 1 mg/mL, for 1 h. Duration of post-treatment incubation: 42 h	Supporting study 2- reliable with restrictions	No toxicity observed.
TiO_2 in nanoform caused reversible slight to moderate erythema following dermal application in two studies. In one study, no erythema or edema was observed. In an *in vitro* Epiderm assay, no toxicity was observed following exposure to TiO_2 nanoparticles. VKM conclusion on the evidence: NP-TiO_2 is not classifiable as a skin irritant under the test conditions used.				

Table 6.8.1.1-2. Study characteristics and certainty in the evidence for sensitisation of NP-TiO_2.

Reference	Model and administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
ECHA (2021e)	Mouse, dermal OECD Guideline 429 (skin sensitisation: local lymph node assay) GLP compliance: not specified Study report, 2006; publication, Warheit et al. (2007)	TiO_2, ultrafine 0% (vehicle control), 5%, 25%, 50%, or 100% H-27416 on both ears for three consecutive days. Sacrifice at day 5.	Key study 1- reliable without restrictions	Stimulation index < 3 for the 25%, 50% and 100% groups. The substance is not a dermal sensitiser.
ECHA (2021e)	Guinea pig, dermal (Buehler test) OECD Guideline 406 (skin sensitisation)	TiO_2, nanoform 100% Induction: 3x6h, Challenge: At day 14, 1x 6 h	Key study 1- reliable without restrictions	No skin reactions.

Reference	Model and administration route/ test guideline/ GLP compliance/ publication type and year	Dose and duration	Reliability	Results
	GLP compliance: yes Study report, 1994			
Summary: In two in vivo studies, TiO_2 in nanoform did not cause skin reactions in guniea pigs or mice following dermal application. Both studies have been judged as reliable without restrictions. VKM conclusion on the evidence: NP-TiO_2 does not exhibit sensitising potential.				

6.9 Overview of lines of evidence and hazard conclusions

In the previous chapters (6.2-6.8), the evidence for each outcome was assembled into one or more lines of evidence. An evidence line consists of studies of similar type, in this case, study design and distinction between animal and human studies.

In this chapter, the different lines of evidence for each outcome of hazardous effects of sunscreen (section 6.9.1) and UV filters (section 6.9.2) are assembled.

6.9.1 Sunscreen

Two systematic reviews addressed the relationship between sunscreen use and melanoma, and two RCTs addressed the relationship between sunscreen use and the synthesis of vitamin D (Table 6.9.1-1). Only one line of evidence was identified for both outcomes.

Table 6.9.1-1. Sunscreen: Summary of findings for the different lines of evidence for each outcome. Risk of bias (RoB) was evaluated in systematic reviews and RCTs using ROBIS and OHAT, respectively. GRADE was used to assess certainty in the evidence in Rueegg et al., 2019 by the review authors.

Evidence source	Study type	Countries where the studies were conducted	RoB (level or tier)	Adverse effect reported	VKM conclusions on effect and certainty in the evidence	Hazard conclusion
Melanoma						
Literature search	Systematic review	Australia, Austria, Belgium, Brazil, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, Norway, Spain, Sweden, USA	Low	Observational studies showed an inverse association in hospital-based case–control studies and the ecological study, no association in population-based case–control studies and a positive association in the three cohort studies. A protective effect of sunscreen was found in the RCT. The GRADE assessment performed by Rueegg et al. (2019) resulted in an overall very low quality of the evidence for sunscreen use and melanoma risk in the case-control studies, the ecological study and the cohort studies, and moderate quality of the RCT	KVM conclusion on the evidence (based on the systematic review by Rueegg et al. (2019)): The overall confidence in the evidence for an association between sunscreen use and increase in development of melanoma is very low, resulting in an inadequate level of evidence for health effect. There is insufficient evidence to assess whether the exposure to sunscreen is associated with melanoma.	Not classifiable as a hazard to humans
Vitamin D						
Literature search	RCT	Denmark	2	Sunscreen reduced the synthesis of 25-hydroxyvitamin D_3 in response to UVR in a dose-dependent manner	There is low confidence in the body of evidence for an association between sunscreen use and reduction in vitamin D synthesis. The true effect may be different from the apparent relationship. There is	Not classifiable as a hazard to humans
	RCT	Australia	2	Mean levels of 25-hydroxyvitamin D_3 increased significantly by the same		

				amount in intervention and placebo groups over the period of the study	insufficient evidence available to assess whether the sunscreen use is associated with reduction in vitamin D synthesis..	

See Chapter 6.12.1 for an expanded hazard conclusion.

6.9.2 UV filters

The hazard conclusion for the animal studies is expressed by the DNEL, which is the level of chemical exposure above which humans should not be exposed. The DNEL is derived by dividing the NOAEL on the overall uncertainty factor (UF) (described in Chapters 6.10 and 6.11).

6.9.2.1 BEMT

An overview of the lines of evidence for systemic toxicity and local effects is given in Table 6.9.2.1-1 and 6.9.2.1-2.

Several lines of evidence were available for systemic toxicity, and NOAEL values for subchronic toxicity (oral), carcinogenicity (dermal), and reproductive and developmental toxicity (oral), were identified.

For local effects, two lines of evidence were available, human (photo-)patch tests and in vivo animal experiments, for both skin irritation and sensitisation. The lines of evidence for skin sensitisation were human photopatch test and in vivo skin sensitisation study in guinea pig.

For skin irritation, evidence from human photopatch test and three animal in vivo dermal studies are available.

Table 6.9.2.1-1. BEMT: Summary of findings for the different lines of evidence for each outcome. Min.: minimum; max: maximum.

Evidence source	Test and model	Dose	Duration	Adverse effect reported	VKM conclusions on the evidence for each outcome and the derived PoD	Hazard conclusion
Carcinogenicity and genetic toxicity						
ECHA (2021c)	Mutation, *S. typhimurium* TA 1535, TA 1537, TA 98 and TA 100, with and without metabolic activation (S9)	33.3, 100, 333.3, 1000, 2500, and 5000 µg/plate		Negative	NOAEL for dermal carcinogenicity is ≥1000 mg/kg	No concern for carcinogenicity and genetic toxicity
	Mutation, *S. typhimurium E. coli* WP2 uvr A, with and without metabolic activation (S9)	33.3, 100, 333.3, 1000, 2500, and 5000 µg/plate		Negative		
	Chromosome Aberration, Chinese hamster lung fibroblasts, with and without metabolic activation (S9)	6.5, 13.1, 26.3, 52.5, 105.0, 210.0 µg/ml		Negative		
	Chromosome Aberration, Chinese hamster lung fibroblasts, with and without metabolic activation (UV irradiation)	6.25, 12.5, 25.0, 50.0, 75.0, and 100.0 µg/ml		Negative		
	Unscheduled DNA synthesis, rat, oral	1000 and 2000 mg/kg bw		Negative		
	Carcinogenicity, rat, dermal	0, 100, 500, 1000 mg/kg bw	104 weeks, daily	Not carcinogenic		

Acute toxicity						
ECHA (2021c)	Acute oral toxicity, rat	2000 mg/kg bw	14 days observation, single dose	No	Acute toxicity in rats, both by dermal and oral administration, is low. For both routes, LD50 was above 2000 mg/kg bw	Hazard conclusion not applicable
	Acute dermal toxicity, rat	2000 mg/kg bw	14 days observation, single application	No		
Subchronic and chronic toxicity						
ECHA (2021c)	Repeated dose toxicity, rat, oral	0, 100, 500, 1000 mg/kg bw	90 days, daily	No	The NOAEL is ≥1000 mg/kg bw for sub-chronic toxicity following oral administration. The NOAEL is 1000 mg/kg bw for sub-chronic and chronic toxicity following dermal administration	DNEL = 2.5 mg/kg bw/day (see Chapter 6.11 for derivation of the DNEL)
	Subchronic toxicity, rat, dermal	0, 250, 500, 1000 mg/kg bw	90 days, daily	No		
	Carcinogenicity study, rat, dermal	0, 100, 500, 1000 mg/kg bw	104 weeks, daily	Local effects		
Reproductive and developmental toxicity						

ECHA (2021c)	Reproductive/developmental toxicity, rat, oral	0, 100, 300, 1000 mg/kg bw	Daily, 2 weeks	No (reproductive functions of parent animals) No (early embryonic development)	The NOAEL is ≥1000 mg/kg bw for maternal and developmental effects	DNEL = 2.5 mg/kg bw/day (see Chapter 6.11 for derivation of the DNEL)
	Toxicity to reproduction, rat, oral	0, 100, 300, 1000 mg/kg bw	Daily, gestation days 6 through 19	No (embryo-fetal development)		
	Prenatal developmental toxicity, rat, oral	0, 100, 300, 1000 mg/kg bw	Daily, day 6 through day 17 post coitum	No (development of dams, embryos or foetuses)		
Skin irritation						
ECHA (2021c)	Acute dermal irritation/corrosion, rabbit	0.5 g per animal	4 hours exposure, 72 hours observation period	No	BEMT is not likely to be an irritant under conditions of use	No irritant potential identified (see Chapter 6.11)
	Subchronic dermal toxicity, rat	0, 250, 500, 1000 mg/kg bw	80 days	No effects considered related to BEMT		
	Carcinogenicity, rat, dermal	0, 100, 500, 1000 mg/kg bw	104 weeks, daily	Epidermal injury		

				indicative of a chronic and moderate local skin irritation		
Literature search	Skin irritation, human patch test	10%	Applied for 48 hours, readings at days 2, 4 and 6	No irritant reactions reported for the 100 subjects tested	There is high confidence in the body of evidence for a low frequency irritant reactions in susceptible individuals exposed to BEMT. The level of evidence is high	Irritant reactions shown in susceptible individuals in low frequency (0.6%)
	Skin irritation, human patch test	10%	Applied for 24 or 48 h, reading at 24 h, 48, and 72 h or later. Analysis from readings at 48 h	Frequency was not reported specifically for BEMT: 7 reactions occurred in 6 of 1031 (0.6%) subjects tested		
Skin sensitisation						
ECHA (2021c)	Skin sensitisation, guinea pig, dermal	3%, 30%	Induction exposure: a single intradermal injection day 1 and a single	No	BEMT does not exhibit sensitising potential	No sensitising potential identified (see Chapter 6.11)

			epidermal application day 8 for 48 hours. 3% in intradermal injection and 30% in epicutaneous application Challenge exposure: a single epidermal exposure day 22, challenge two weeks after the epidermal induction application			
Literature search	Contact allergic reactions, human, patch test	10%	Applied for 24 or 48 h, reading at 24 h, 48, and 72 h or later	1031 subjects tested, one reaction with severity graded as 3 (scale from 1-5)	There is high confidence in the body of evidence for a low frequency of contact allergic reactions in	Sensitising reactions shown in susceptible individuals in low frequency (≤0.2%)

	Contact allergic reactions, human, patch test	10%	Applied for 48 hours, readings at days 2, 4 and 6	100 persons, no reactions	susceptible individuals exposed to BEMT. The level of evidence is high	
	Photocontact allergic, human, patch test	10%	Applied for 48 hours, readings at days 2, 4 and 6	100 persons, no reactions	There is high confidence in the body of evidence that exposure to BEMT is not associated with photocontact allergic reactions in susceptible individuals. There is evidence of no health effect	
	Photocontact allergic, human, patch test	10%	Applied for 24 or 48 h, reading at 24 h, 48, and 72 h or later	1031 subjects tested, one reaction with severity graded as 3		

				(scale from 1-5)		

Table 6.9.2.1-2. Summary of integration of confidence across lines of evidence for each outcome.

		Acute toxicity		**Subchronic toxicity**		**Carcinogenicity and genetic toxicity**		**Reproductive and developmental toxicity**	**Skin irritation**	**Skin sensitisation**
		Dermal	Oral	Dermal	Oral	*In vitro*	Dermal	Oral	Dermal	Dermal
Human studies	Effects reported (yes/no)								No	Low frequency (≤0.2%)
	Confidence (high, moderate, low, very low)								High	High
Animal studies	Effects reported (yes/no)	No	No	No	No	Negative	No	No	Yes	No
	LD50/ NOAEL/ LOAEL (external dose)	LD50 >2000 mg/kg bw	LD50 > 2000 mg/kg bw	NOAEL ≥1000 mg/kg bw	NOAEL ≥1000 mg/kg bw	-	NOAEL (carcinogenicity) ≥1000 mg/kg	NOAEL (maternal and developmental effects) ≥1000 mg/kg bw	LOAEL = 100 mg/kg bw/day	
	NOAEL (internal dose, oral absorption assumed to be 50%)				NOAEL ≥500 mg/kg bw			NOAEL (maternal and developmental effects) ≥500 mg/kg bw		

		Acute toxicity		Subchronic toxicity		Carcinogenicity and genetic toxicity		Reproductive and developmental toxicity	Skin irritation	Skin sensitisation
		Dermal	Oral	Dermal	Oral	*In vitro*	Dermal	Oral	Dermal	Dermal
	Reliability (1: reliable without restrictions; 2: reliable with restriction)	1	1	1	1	1	1	1	1	1

6.9.2.2 BMDBM

An overview of the lines of evidence for systemic toxicity and local effects are given in Table 6.9.2.2-1 and 6.9.2.2-2.

Several lines of evidence were available for systemic toxicity, and NOAEL values for subchronic toxicity (oral) and developmental toxicity (oral), were identifed. As the NOAELs ware identified from toxicity studies with oral administration of BMDBM, they are converted to internal NOAELs/internal doses assuming 50% absorption. See chapter 6.11 for the derivation of an overall derived no-effect level (DNEL) for systemic toxicity.

For local effects, two lines of evidence were available, human (photo-)patch tests and in vivo animal experiments, for both skin irritation and sensitisation.

The lines of evidence for skin sensitisation were human photopatch test and in vivo skin sensitisation study in guniea pig. There are consistent findings across the two lines of evidence.

For skin irritation, evidence from human photopatch tests and three animal in vivo dermal studies (two acute and one subacute) was available. From the human patch studies, there is high certainty in the evidence that BMDBM has low potency for induction of skin irritation. No substance-related skin irritation was observed in the two acute animal studies, however, in the subacute study slight to moderate skin irritation was observed.

Table 6.9.2.2-1. BMDBM: Summary of findings for the different lines of evidence for each outcome.

Evidence source	Test and model	Dose	Duration	Adverse effect	VKM conclusions on the evidence for each outcome and the derived PoD	Hazard conclusion
Genetic toxicity						
ECHA (2021a)	Gene mutation, Chinese hamster lung fibroblasts, with and without metabolic activation (S9)	5, 10, 15, 20 µg/mL		Negative	BMDBM is not mutagenic. There is insufficient data to conclude on cytogenic potential of BMDBM	No concern for carcinogenicity and genetic toxicity
	Reverse mutation, *Salmonella typhimurium* TA1535, TA 1537, TA 1538, TA 98, TA100 and TA102, with and without metabolic activation (S9)	50, 150, 500, 1500, 5000 µg/plate with metabolic activation (S9) 5, 15, 50, 150, 500, 1500, 5000 µg/plate without metabolic activation		Negative		
	Erythrocyte micronucleus, mouse, oral	1000, 2500 and 5000 mg/kg bw.	The substance was administered twice, 30 and 6 hours prior to sacrifice	Negative		
Acute toxicity						

ECHA (2021a)	Acute oral toxicity, rat	16000 mg/kg bw	14 days observation, single dose	No	LD50 is >16 000 mg/kg bw following oral exposure and >1000 mg/kg bw following dermal application.	Hazard conclusion not applicable
	Acute dermal toxicity, rat	0, 500, 1000 mg/kg bw	14-day observation period, 24 hours exposure	No		
Subacute and subchronic toxicity						
ECHA (2021a)	Repeated dose toxicity, rat, oral	0, 200, 450, 1000 mg/kg bw	91-94 days, daily administration	Yes (significant increase in absolute and relative liver weight in female rats at 450 and 1000 mg/kg bw/day and in male rats at 1000 mg/kg bw/day; a decrease in red blood cells and hemoglobin was observed in female animals at 1000 mg/kg bw/day)	The oral NOAEL is 450 mg/kg bw for systemic toxicity	DNEL = 1.13 mg/kg bw/day (see Chapter 6.11 for derivation of the DNEL)
	Repeated dose toxicity, rabbit, dermal	2 mL/kg bw/day 30, 100, and 360 mg/kg bw	21 days, 6 hours exposure per day	No		
Developmental toxicity						
ECHA (2021a)	Prenatal developmental toxicity study, rat, oral	0, 250, 500, 1000 mg/kg bw	Daily exposure on day 6 through day 17 post coitum.	No	The NOAEL is ≥1000 mg/kg bw for maternal and developmental effects.	DNEL = 1.13 mg/kg bw/day (see Chapter 6.11 for derivation of the DNEL)

Skin irritation						
ECHA (2021a)	Acute dermal irritation/corrosion, rabbit	Amount(s) applied: 0.5 mL. Concentration: 10 %		No to slight (erythema and edema)	LOAEL for subacute dermal local effects is 100 mg/kg bw/day	No irritant potential identified (see Chapter 6.11)
	Repeated dose dermal toxicity, rabbit	2 mL/kg bw/day 30, 100, and 360 mg/kg bw per day.	Six hours exposure per day for 21 days.	Dosage-related increase in the severity of dermal reactions, including slight to moderate erythema and edema		
	Acute Dermal Toxicity, rat	0, 500, 1000 mg/kg bw	24 h exposure, 14-day observation period.	No substance-related local effects were observed		
Literature search	Skin irritation, human, patch test	10%	Application for 24 or 48 hours, readings 48 hours post irradiation	Irritant reactions were reported in three (0.3%) of 1155 subjects tested.	There is high confidence in the body of evidence for a low frequency of irritant reactions in susceptible individuals exposed to BMDBM. The level of evidence is high	Irritant reactions shown in susceptible individuals in low frequency (≤1.6%)
	Skin irritation, human, patch test	10%	Readings up to 48 h	No irritant reactions reported in 157 subjects tested		
	Skin irritation, human patch test	10%	Applied for 24 or 48 h, reading at 24 h, 48, and 72 h or later	Frequency was not reported specifically for BMDBM: 7 reactions occurred in 6 of 1031 (0.6%) subjects		

	Skin irritation, human patch test	10%	Applied for 48 hours, readings at days 2, 4 and 6	No irritant reactions reported in the 100 subjects tested		
Skin sensitisation						
ECHA (2021a)	Skin sensitisation, guinea pig, dermal	5%, 20%	Induction day 0: 5%, day 8: 20%. Challenge day 21: 20% and 6%	No	BMDBM is not a skin sensitiser under the test conditions used	No sensitising potential identified (see Chapter 6.11)
Literature search	Contact allergic reactions, humans, human, patch test	10%	Application for 24 or 48 hours, readings 48 hours post irradiation	Ten (0.9%) reactions of certain relevance and 1 (0.09%) of uncertain relevance in 1155 subjects tested	There is high confidence in the body of evidence for a low frequency for contact allergic reactions in susceptible individuals exposed to BMDBM. The level of evidence is high	Sensitising reactions shown in susceptible individuals in low frequency (≤0.3%)
	Contact allergic reactions, humans, human, patch test	10%	Readings 24 and 48 hours post irradiation	No positive reactions in the 157 subjects tested		
	Contact allergic reactions, humans, human, patch test	10%	Application for 24 or 48 hours, readings immediately, 24, 48 and 72 hours post irradiation	Three (0.2%) reactions (grades 3, 4 and 5 of 5) in 1031 subjects tested		
	Contact allergic reactions, humans, human, patch test	10%	Application for 24 hours, readings 48 hours post irradiation	One (0.9%) positive reaction in 116 subjects tested		

	Contact allergic reactions, humans, human, patch test	10%	Application for 48 hours, readings on days 2, 4 and 6 post irradiation	One reaction (0.1%) in 100 subjects tested		
	Photoallergic contact reactions, humans, human, patch test	10%	Application for 24 or 48 hours, readings 48 hours post irradiation	Nineteen (1.6%) reactions of certain relevance and 5 (0.4%) of uncertain relevance in 1155 subjects tested	There is high confidence in the body of evidence for a low frequency of photocontact allergic reactions in susceptible individuals exposed to BMDBM. The level of evidence is high	
	Photoallergic contact reactions, humans, human, patch test	10%	Readings 24 and 48 hours post irradiation	One (0.6%) reaction in 157 subjects <18 years tested. Severity 2 (scale from 0 to 5)		
	Photoallergic contact reactions, humans, human, patch test	10%	Application for 48 hours, readings 48 hours post irradiation	Two (0.5%) reactions in 207 subjects tested		
	Photoallergic contact reactions, humans, human, patch test	10%	Application for 24 or 48 hours, readings immediately, 24, 48 and 72 hours post irradiation	Fourteen (1.4%) certain and 4 (0.4%) uncertain reactions in 1031 subjects tested		
	Photoallergic contact reactions, humans, human, patch test	10%	Application for 24 hours, readings 48 hours post-irradiation	No positive reaction in 116 subjects tested		
	Photoallergic contact reactions, humans, human, patch test	10%	Application for 48 hours, readings	One (1%) certain reaction in 100 subjects tested		

			on days 2, 4 and 6 post-irradiation			

Table 6.9.2.2-2. Summary of integration of confidence across lines of evidence for each outcome.

		Acute toxicity		**Subacute and subchronic toxicity**	**Genetic toxicity**	**Developmental toxicity**	**Skin irritation**	**Skin sensitisation**
		Dermal	Oral	Oral	*In vitro*	Oral	Dermal	Dermal
Human studies	Effects reported (yes/no)						Low frequency (≤0.3%)	Low frequency (≤1.6%)
	Confidence (high, moderate, low, very low)						High	High
Animal studies	Effects reported (yes/no)	No	No	Yes	Negative (mutagenicity)	No	No-slight - moderate	No
	LD50/ NOAEL/ LOAEL (external dose)	LD50>1000 mg/kg bw	LD50 >16 000 mg/kg bw	NOAEL 450 mg/kg bw	Insufficient evidence	NOAEL ≥1000 mg/kg bw	LOAEL (subacute dermal local effects) 100 mg/kg bw/day	
	NOAEL (internal dose, oral absorption assumed to be 50%)			NOAEL 225 mg/kg bw		NOAEL ≥500 mg/kg bw		

		Acute toxicity		Subacute and subchronic toxicity	Genetic toxicity	Developmental toxicity	Skin irritation	Skin sensitisation
		Dermal	Oral	Oral	*In vitro*	Oral	Dermal	Dermal
	Reliability (1: reliable without restrictions; 2: reliable with restriction)	2	2	2	1 and 2	2	2	2

6.9.2.3 EHS

An overview of lines of evidence for systemic toxicity and local effects is given in Table 6.9.2.3-1 and 6.9.2.3-2.

Several lines of evidence were available for systemic toxicity, and NOAEL values for chronic toxicity (oral) and reproductive and developmental toxicity (oral), were identifed. As the NOAELs ware identified from toxicity studies with oral administration of BMDBM, they are converted to internal NOAELs/internal doses assuming 100% absorption. See chapter 6.11 for the derivation of an overall DNEL for systemic toxicity.

For local effects, two lines of evidence were available, human (photo-)patch tests and in vivo animal experiments, for both skin irritation and sensitisation. The lines of evidence for skin sensitisation were human photopatch test and in vivo skin sensitisation study in guinea pig.

For skin irritation, evidence from human photopatch tests and two dermal animal in vivo studies are available.

Table 6.9.2.3-1. EHS: Summary of findings for the different lines of evidence for each outcome.

Evidence source	Test and model	Dose	Duration	Adverse effect	VKM conclusions on the evidence for each outcome and the derived PoD	Hazard conclusion
Genetic toxicity						
ECHA (2021b)	Reverse mutation assay, *S. typhimurium* TA 1535, TA 1537, TA 98, TA 100 and TA 102, with and without metabolic activation	Doses without activation: 156.3, 312.5, 625, 1250, 2500 and 5000 µg/plate in the first experiment and 312.5, 625, 1250, 2500 and 5000 µg/plate in the second experiment. Doses with activation (S9): 156.3, 312.5, 625, 1250, 2500 and 5000 µg/plate, for the TA 1537 and the TA 98 strains in the first experiment; 15.6, 31.3, 62.5, 125, 250 and 500 µg/plate for the TA 1535, TA 100 and TA 102 strains in the first experiment; 312.5, 625, 1250, 2500 and 5000 µg/plate, for the TA 1537 and TA 98 strains in the second experiment; 39.06, 78.13, 156.3, 312.5, 625, 1250	Revertants were scored after 48 to 72 hours	Negative	There is sufficient evidence to conclude that BMDBM is not mutagenic. There is insufficient data to conclude on cytogenic potential of EHS	No concern for carcinogenicity and genetic toxicity

		µg/plate, for the TA 1535 strain in the second experiment; and 19.53, 39.06, 78.13, 156.3, 312.5, 625 µg/plate, for the TA 100 and the TA 102 strains in the second experiment				
	Chromosome aberration, Chinese hamster ovary (CHO), with and without metabolic activation (S9)	2.5, 5, 10, 20 and 40 µg/ml		Negative No cytotoxicity		
	Mutation, Chinese hamster lung fibroblasts, with and without metabolic activation (S9)	Experiment 1. 4 hours without metabolic activation: 0.08, 0.15, 0.3, 0.6, 1.2 µg/ml. 4 hours with metabolic activation (S9): 20.0, 40.0, 80.0, 160.0, 640.0 µg/ml Experiment II: 24 hours without metabolic activation: 1.3, 2.5, 5.0, 10.0, 20.0 µg/ml. 4 hours with metabolic activation (S9): 20.0, 40.0, 320.0, 640.0 µg/ml		Experiment 1: Negative, cytotoxicity at 1.2 µg/mL and above Experiment 2: Negative, cytotoxicity at 20 µg/mL and above		

	Erythrocyte micronucleus test, mammalian, oral	2000 mg/kg	24, 48 and 72 hours after dosing	Negative		
Acute toxicity						
ECHA (2021b)	Acute oral toxicity, rat	5000 mg/kg	14 days observation, single dose	No	LD50 is >5000 mg/kg bw following acute oral and dermal exposure	Hazard conclusion not applicable
	Acute dermal toxicity, rat	5000 mg/kg	14 days observation, 24 hours exposure	No		
Subacute, subchronic and chronic toxicity						
ECHA (2021b)	Subchronic toxicity, rat (oral)	Methyl salicylate (read-across) 0, 50, 500 mg/kg bw/day	17 weeks	Yes	NOAEL is 83 mg/kg bw/day	DNEL = 2.4 mg/kg bw/day (see Chapter 6.11 for derivation of the DNEL)
	Subchronic toxicity study, dog (oral)	Methyl salicylate (read-across) 0, 50, 500 mg/kg bw/day	17 weeks	Yes		
	Repeated Dose Toxicity, rat (oral)	0, 50, 100 and 250 mg/kg/day, for 13 weeks	90 days	No		
	Chronic toxicity, rat (oral)	Methyl salicylate (read-across) 0, 50, 250, 500 and 1000 mg/kg bw/day	2 years	Yes		
	Chronic toxicity, dog (oral)	Methyl salicylate (read-across) 0, 50, 150 and 350 mg(kg bw/day	2 years, daily for 6 days/week	Yes		
	Reproduction/developmental toxicity, rat (oral)	0, 25, 80, 250 mg/kg/day	Males: 28 days Females: Approximately 7 weeks	Yes		
Reproductive and developmental effects						

ECHA (2021b)	Reproduction/developmental toxicity screening test, rat, oral	0, 25, 80, 250 mg/kg/day	Males: 28 days Females: Approximately 7 weeks	Increased post-implantation loss, reduction in gestation index and lower litter size	The NOAEL is ≥80 mg/kg bw/day for maternal toxicity. The NOAEL is 25 mg/kg bw/day developmental toxicity	DNEL = 2.4 mg/kg bw/day (see Chapter 6.11 for derivation of the DNEL)
Skin irritation						
ECHA (2021b)	Acute dermal irritation/corrosion, rabbit	0.5 mL of the undiluted test item were placed on a dry gauze, which was then applied to an area of approximately 6 cm2	The skin was examined approximately 1 hour, 24, 48 and 72 hours after removal of the dressing		EHS is considered not to be a skin irritant under the test conditions	No irritant potential identified (see Chapter 6.11)
	Acute dermal toxicity, rat	5000 mg/kg	Exposure for 24 hours, 14 days observation	No skin irritation was observed		
Literature search	Skin irritation, human patch test	5%	Applied for 48 hours, readings at days 2, 4 and 6	Min. 1% and max. 2% irritant reactions for the 100 subjects tested	There is high confidence in the body of evidence for a low frequency of irritant reactions in susceptible individuals exposed to EHS. The level of evidence is high	Irritant reactions shown in susceptible individuals in low frequency (≤0.2%)
	Skin irritation, human patch test	10%	Applied for 24 or 48 h, reading at 24 h, 48, and 72 h or later. Readings at 48 h presented.	Frequency was not reported specifically for EHS: 7 reactions occurred in 6		

				of 1031 (0.6%) subjects tested		
Skin sensitisation						
Literature search	Contact allergic reactions, humans, patch test	10%	Applied for 24 or 48 h, reading at 24 h, 48, and 72 h or later. Readings at 48 h presented.	One reaction (0.1%) in 1031 subjects tested (grade 3 of 5)	There is high confidence in the body of evidence for a low frequency for occurrence of contact allergic reactions in susceptible individuals exposed to EHS. The level of evidence is high	Sensitising reactions shown in susceptible individuals in low frequency (≤max 2%)
	Contact allergic reactions, humans, patch test	5%	Application for 48 h, readings on days 2, 4 and 6 post irradiation	One (1%) certain and 1 (1%) uncertain reactions in 100 subjects tested		
	Photocontact allergic reactions, humans, patch test	10%	Application for 24 or 48 h, readings immediately, 24, 48 and 72 h post-irradiation. Readings at 48 h presented.	Two (0.2%) certain reactions in 1031 subjects tested (grade 3 of 5)	There is high confidence in the body of evidence for a low frequency for occurrence of photocontact allergic reactions in susceptible individuals exposed to EHS. The level of evidence is high	
	Photocontact allergic reactions, humans, patch test	5%	Application for 48 h, readings on days 2, 4 and 6 post-irradiation	One (1%) uncertain reactions in 100 subjects tested		
ECHA (2021b)	Skin sensitisation, guinea pig, intradermal and epicutaneous	25%(w/w)	Observation 24, 48 and 72 hours after challenge	No	EHS does not exhibit sensitising potential.	No sensitising potential

						identified (see Chapter 6.11)

Table 6.9.2.3-2. Summary of integration of confidence across lines of evidence for each outcome.

		Acute toxicity		**Chronic toxicity**	**Carcinogenicity and genetic toxicity**		**Reproductive and developmental toxicity**	**Skin irritation**	**Skin sensitisation**
		Dermal	Oral	Oral	*In vitro*	Oral	Oral	Dermal	Dermal
Human studies	Effects reported (yes/no)							Low frequency (≤max 2%)	Low frequency (≤0.2%)
	Confidence (high, moderate, low, very low)							High	High
Animal studies	Effects reported (yes/no)	No	No	Yes	Negative (mutation and chromosome aberration)	Negative (cytogenic potential, invalide)	Yes	No	No
	LD50/ NOAEL/ LOAEL (external dose)	LD50 >5000 mg/kg bw	LD50 >5000 mg/kg bw	NOAEL 83 mg/kg bw/day			NOAEL (25 mg/kg bw/daymg/kg bw/day		

		Acute toxicity		Chronic toxicity	Carcinogenicity and genetic toxicity		Reproductive and developmental toxicity	Skin irritation	Skin sensitisation
		Dermal	Oral	Oral	*In vitro*	Oral	Oral	Dermal	Dermal
	NOAEL (internal dose, oral absorption assumed to be 100%)			NOAEL 83 mg/kg bw/day			NOAEL 25 mg/kg bw/day		
	Reliability (1: reliable without restrictions; 2: reliable with restriction)	1	1	2	1	2	1	1	1

6.9.2.4 EHT

An overview of the lines of evidence for systemic toxicity and local effects are given in Table 6.9.2.4-1 and 6.9.2.4-2.

Several lines of evidence were available for systemic toxicity, and NOAEL values for subchronic toxicity (oral) and developmental toxicity (oral), were identified. As the NOAELs were identified from toxicity studies with oral administration of EHT, they are converted to internal NOAELs/internal doses assuming 10% absorption. See chapter 6.11 for the derivation of an overall derived no-effect level (DNEL) for systemic toxicity.

For local effects, two lines evidence were available, human (photo-)patch tests and in vivo animal experiments, for both skin irritation and sensitisation. The lines of evidence for skin sensitisation were human photopatch test and in vivo skin sensitisation study in guinea pig.

For skin irritation, evidence from human photopatch test and one study in rabbits are available. No substance-related skin irritation was observed following acute dermal exposure in rabbits.

Table 6.9.2.4-1. EHT: Summary of findings for the different lines of evidence for each outcome.

Evidence source	Test and model	Dose	Duration	Adverse effect	VKM conclusions on the evidence for each outcome and the derived NOAEL/LOAEL values	Hazard conclusion
Genetic toxicity						
ECHA (2021f)	Reverse mutation, E.coli WP2, without metabolic activation	1.6-1000 µg/plate		Negative	There is sufficient evidence to conclude that EHT is not mutagenic or clastogenic. There is insufficient data to conclude on the anugenic potential of EHT	No concern for carcinogenicity and genetic toxicity (insufficient data on anugenic potential)
	Reverse mutation, Salmonella typhimurium, TA1535, TA 1537, TA 98, and TA100, with and without metabolic activation (S9)	20-5000 µg/plate		Negative		
	Chromosome Aberration, Chinese hamster V79 cells, with and without metabolic activation (S9)	10-100 µg/mL	Exposure period (with metabolic activation): 4 hours Exposure period (without metabolic activation): 18 hours	Negative		

			Expression time: 18 and 28 hours			
	Chromosome Aberration, Chinese hamster ovary cells, without metabolic activation.	32.77-80 µg/mL	2 hours	Negative		
	Mutation, Chinese hamster ovary cells, with and without metabolic activation (S9)	1st Experiment: without S9 mix: 0; 6.3; 12.5; 25.0; 50.0; 100.0 µg/mL; with S9 mix: 0; 12.5; 25.0; 50.0; 2500.0; 3750.0; 5000.0 µg/mL 2nd experiment: without S9 mix 0; 3.1; 6.3; 12.5;25.0; 50.0; 75.0; 100.0 µg/mL; with S9 mix (4-h exposure period): 0; 6.3; 12.5; 25.0; 50.0; 100.0 µg/mL	1st Experiment: 4 h-exposure 2nd experiment - without S9 mix: 24-h exposure period); - with S9 mix: 4-h exposure period	Negative		
Acute toxicity						
ECHA (2021f)	Rat, oral	5 000 mg/kg bw		No	LD50 is >5000 mg/kg bw following oral exposure and >2000 mg/kg bw following dermal application	Hazard conclusion not applicable
	Rat, dermal	2000 mg/kg bw		No		
Subchronic toxicity						

ECHA (2021f)	Repeated dose toxicity, rat, oral	1000 mg/kg bw per day	90 days	No	VKM identifies a NOAEL of ≥1000 mg/kg bw for systemic toxicity following oral exposure	DNEL = 0.5 mg/kg bw/day (see Chapter 6.11 for derivation of the DNEL)
Developmental toxicity						
ECHA (2021f)	Prenatal Developmental Toxicity, rat (oral)	0, 100, 400 and 1000 mg/kg	7 days/week, duration length not specified	No	VKM identifies a NOAEL of ≥1000 mg/kg bw/day for maternal toxicity and teratogenicity.	DNEL = 0.5 mg/kg bw/day (see Chapter 6.11 for derivation of the DNEL)
Skin irritation						
ECHA (2021f)	Acute Dermal Irritation/ Corrosion, rabbit (dermal)	500 mg	4 hours	No	EHT is considered not to be a skin irritant under the test conditions	No irritant potential identified (see Chapter 6.11)
Literature search	Skin irritation, human patch test	10%	Applied for 48 hours, readings at days 2, 4 and 6	No reactions in the 100 subjects tested	There is high confidence in the body of evidence that exposure to EHT is not associated with irritant reactions in susceptible individuals. There is evidence of no health effect	No irritant reactions shown in susceptible individuals
	Skin irritation, human patch test	10%	Applied for 24 or 48 h, reading at 24 h, 48, and 72 h or later. Readings at 48 h reported.	Frequency was not reported specifically for EHT: 7 reactions occurred in 6 of 1031 (0.6%) subjects tested		
Skin sensitisation						

ECHA (2021f)	Guinea pig maximization test	Induction: i.c. 5 % in Olivenöl DAB 8, p.c. 60 % in Olivenöl DAB 8 Concentration of test material and vehicle used for each challenge: p.c.: 40 % in Olivenöl DAB 8	24 and 48 h after challenge	No	EHT does not exhibit sensitising potential	No sensitising potential identified (see Chapter 6.11)
Literature search	Contact allergic reactions, human, patch test	10%	Applied for 24 or 48 h, reading at 24 h, 48, and 72 h or later. Readings at 48 h reported.	No reactions reported in 1031 subjects tested.	There is high confidence in the body of evidence that exposure to EHT is not associated with contact allergic reactions in susceptible individuals. There is evidence of no health effect	Sensitising reactions shown in susceptible individuals in low frequency (≤0.1%)
	Contact allergic reactions, human, patch test	10%	Applied for 48 hours, readings at days 2, 4 and 6	No reactions reported in 100 subjects tested.		
	Photocontact allergic, human, patch test	10%	Applied for 24 or 48 h, reading at 24 h, 48, and 72 h or later. Readings at 48 h reported.	One certain (0.1%) reaction with severity graded as 3 (scale from 1-5) in 1031 subjects tested.	There is high confidence in the body of evidence for a low frequency for occurrence of photocontact allergic reactions in susceptible individuals exposed to EHT. The level of evidence for health effect is high	
	Photocontact allergic, human, patch test	10%	Applied for 48 hours, readings at days 2, 4 and 6	No reactions reported in 100 subjects tested.		

Table 6.9.2.4-2. EHT: Summary of integration of confidence across lines of evidence for each outcome.

		Acute toxicity		**Subchronic toxicity**	**Genetic toxicity**	**Developmental toxicity**	**Skin irritation**	**Skin sensitisation**
		Dermal	Oral	Oral	*In vitro*	Oral	Dermal	Dermal
Human studies	Effects reported (yes/no)						No	Low frequency (≤0.1%)
	Confidence (high, moderate, low, very low)						High	High
Animal studies	Effects reported (yes/no)	No	No	No	Negative (mutagenic or clastogenic)	No	No	No
	LD50/ NOAEL/ LOAEL (external dose)	LD50 >2000 mg/kg bw	LD50 >5000 mg/kg bw	NOAEL ≥1000 mg/kg bw per day		NOAEL (maternal toxicity and teratogenicity) ≥1000 mg/kg bw/day		
	NOAEL (internal dose, oral absorption assumed to be 10%)			NOAEL ≥100 mg/kg bw per day		NOAEL (maternal toxicity and teratogenicity) ≥100 mg/kg bw/day		
	Reliability (1: reliable without restrictions; 2: reliable with restriction)	2	2	2	1 and 2	2	2	2

6.9.2.5 OC

An overview of the lines of evidence for systemic toxicity and local effects are given in Table 6.9.2.5-1 and 6.9.2.5-2.

Several lines of evidence were available for systemic toxicity, and NOAEL values for subchronic toxicity (oral), and reproductive and developmental toxicity (oral), were identifed. As the NOAELs ware identified from toxicity studies with oral administration of OCM, they are converted to internal NOAELs/internal doses assuming 50% absorption. See chapter 6.11 for the derivation of the DNEL for systemic toxicity.

For local effects, two lines evidence were available, human (photo-)patch tests and in vivo animal experiments, for skin sensitisation. The lines of evidence for skin sensitisation were human patch tests and in vivo skin sensitisation study in guinea pig. There are consistent findings across the two lines of evidence and VKM conclude that OC is not a sensitisation agent, neither with nor without combined exposure to UV.

For skin irritation, only one line of evidence, one acute study in rabbits, is available. VKM concludes that OC is not a skin irritant under the test conditions.

Table 6.9.2.5-1. OC: Summary of findings for the different lines of evidence for each outcome.

Evidence source	Test and model	Dose	Duration	Adverse effect	VKM conclusions on the evidence for each outcome and the derived PoD	Hazard conclusion
Genetic toxicity						
ECHA (2021d)	Mutation, Salmonella typhimurium, TA1535, TA1537, TA98, TA100 and Escherichia coli strain WP2 uvr A	20 - 5000 µg/plate (SPT); 4 - 2500 µg/plate (PIT)		Negative	OC is not mutagenic or clastogenic. There is insufficient data to conclude on the anugenic potential of OC	No concern for carcinogenicity and genetic toxicity

	with and without metabolic activation (S9)					
	Mutation, Mouse lymphoma L5178Y cells, with and without metabolic activation (S9)	12.5 - 200 µg/ml		Negative		
	Chromomsomal aberrations, Chinese hamster lung fibroblasts (V79), without metabolic activation (S9)	3.75 - 90 µg/ml		Negative		
	Micronucleus, mouse, oral (gavage)	500, 1000 and 2000 mg/kg bw x1. Animals were sacrificed at 16, 24 and 48 hours after dosing		Negative		
Acute toxicity						
ECHA (2021d)	Rat, dermal	2000 mg/kg bw x1 for 24 h, 10% of body surface area	14-day observation period.	No	LD50 is >5000 mg/kg bw following oral exposure and >2000 mg/kg bw following dermal application	Hazard conclusion not applicable
	Rat, oral (gavage)	5000 mg/kg bw x1	14-day observation period	No		
Subacute and subchronic toxicity						
ECHA (2021d)	Rat, oral (feed)	0, 456 and 1369 mg/kg bw/day (males); 0, 449	14 days	Minor effects on body weight in the high dose	VKM identifies a NOAEL of 175	DNEL = 0.38 mg/kg bw/day

		and 1393 mg/kg bw /day (females)		group. Slightly impaired food consumption	mg/kg bw per day for systemic toxicity following oral exposure	(see Chapter 6.11 for derivation of the DNEL)
	Rat, oral (feed)	0 ppm, 1000 ppm (males: 63-65 mg/kg bw day and females: 69-72 mg/kg bw day), 3000 ppm (males: 188-193 mg/kg bw day and females: 207-215 mg/kg bw day), and 10000 ppm (males: 188-193 mg/kg bw day and females: 207-215 mg/kg bw day)	28 days	Treatment-related effects were observed for body weights, for haematology, for clinical biochemistry, organ weights, histopathology (non-neoplastic effects), and on bioanalytical examinations		
	Rabbit, dermal	Doses / Concentrations: 0, 130, 264, 534 mg/kg/day	5 days per week (65 applications) over a period of 91 days	Mid- and high-dose treatments significantly depressed body weight		
	Rats, oral (feed)	0, 750, 2250, 4500, 15000 ppm in the diet (equals ~ 58, ~175, ~340, ~1085 mg/kg bw/day)	90 days	Increased body weight in both males and females (high dose). Reduced food consumption (high dose). Increased number of hypertrophic cells in the pars distalis of the pituitary gland of males exposed to 15 000 ppm of OC. Slight or		

				moderate hypertrophy of the thyroid foilicular epithelium (all animals) and associated pale staining colloid in both sexes exposed ot 15 000 ppp. 4500 ppm group: Minimal or slight hypertrophy of the thyroid follicular epithelium and associated pale staining colloid in both sexes exposed to 4500 ppm		
Reproductive and developmental toxicity						
ECHA (2021d)	Rat, oral (gavage)	0, 250, 1000 mg/kg bw/day	3 days		VKM identifies a NOAEL of 153 and 163 mg/kg bw for males and females, respectively, for maternal and developmental toxic	DNEL = 0.38 mg/kg bw/day (see Chapter 6.11 for derivation of the DNEL)
	Rat, oral (feed)	About 0, 58, 175, 340, 1085 mg/kg bw/day	90 days	No		
	Rabbit, dermal	0, 130, 264, 534 mg/kg/day	5 days per week (65 applications) over a period of 91 days	No		
	Rabbit, dermal	0, 65, 267 mg/kg bw/day	Days 6 through 18 of gestation, until day 29 of gestation	No		
	Mouse, oral	0, 100, 300, 1000 mg/kg bw/day	Days 8 through 12 of gestation until day 3 post partum			

	Rats, oral (feed)	Anticipated doses: 55, 153, 534 mg/kg bw/day for males and 58, 163, 550 mg/kg bw/day for females, oral intake (feed).	Males: 10-week premating period, during mating up to the day of sacrifice (approx. 13 weeks) Females: P: 10-week premating period, during mating, gestation and lactation up to the day of sacrifice after lactation day 21 F1: from weaning up to sacrifice (approx. 10 weeks in Cohort 1A, approx. 13 weeks (males) and approx. 18 weeks (females) in Cohort 1B; approx. 8 weeks in cohort 2A) F2: indirectly exposed until weaning			
	Rat, oral (gavage)	0, 300, 1000 mg/kg bw/day	10 days	Reproductive effects were not specified		
	Rat, oral (feed)	0, 325, 975 mg/kg bw/day	Male animals received the test item via the diet	The mean number of implantations in the		

			during a 4-week premating period, and during mating and up to the day of sacrifice. The female animals were fed these diets during a 4-week premating period, and during mating, gestation and lactation until the day of sacrifice on day 21 of lactation or shortly thereafter	high-dose group was lower than the historical control values (range 11.0-13.4) and corresponds with the lower number of pups born in the high-dose group		
	Rat, oral (gavage)	0, 100, 400, 1000 mg/kg bw/day	From day 6 through day 15 of gestation. Duration until day 20 of gestation	Absolute and relative liver weights were slightly, but statistically significantly higher in the 1000 mg/kg group (approx. 9%) than in the control group No embryotoxic or teratiogenic effects were observed		
Skin irritation						
ECHA (2021d)	Rabbit	Amount(s) applied (volume or weight with unit): 0.5 mL, concentration: 1, 10, 25, 50, 100% (w/w)	Dermally exposed for 4 hours	No	OC is considered not to be a skin irritant under the test conditions	No irritant potential identified (see Chapter 6.11)

	Acute Dermal Toxicity, rat	2000 mg/kg bw x 1	24 h, 10% of body surface area. 14-day observation period	No skin irration was observed		
Skin sensitisation						
ECHA (2021d)	Guinea pigs	5% Octocrilene in paraffin oil with/without Freund's Adjuvans for intradermal induction and undiluted octocrilene for occlusive epicutaneous induction, followed by an occlusive epicutaneous challenge with the undiluted octocrilene	Induction: Day 7 Challenge: 14 days after the induction	No	OC does not exhibit sensitising potential	No sensitising potential identified (see Chapter 6.11)
	Guinea pigs	Induction 1: intradermal, 50% Induction 2: epicutaneous, semiocclusive Challenge: epicutaneous, semiocclusive	Induction 1: duration not reported Induction 2: 48 hours Challenge: 24 hours	No		

Table 6.9.2.5-2. EHT: Summary of integration of confidence across lines of evidence for each outcome.

		Acute toxicity		Subchronic toxicity	Genetic toxicity	Reproductive and developmental toxicity	Skin irritation	Skin sensitisation
		Dermal	Oral	Oral	*In vitro*	Oral	Dermal	Dermal
Animal studies	Effects reported (yes/no)	No	No	Yes	Negative (mutagenic or clastogenic)	Yes	No	No
	LD50/ NOAEL/ LOAEL (external dose)	>2000 mg/kg bw	>5000 mg/kg bw	175 mg/kg bw/day		NOAEL of 153 and 163 mg/kg bw for males and females, respectively		
	NOAEL (internal dose, oral absorption assumed to be 50%)			87.5 mg/kg bw/day		NOAEL of 76.5 and 81.5 mg/kg bw for males and females, respectively		
	Reliability (1: reliable without restrictions; 2: reliable with restriction)	1	1	1	1	1	1	1

6.9.2.6 NP-TiO_2

An overview of the lines of evidence of local effects are given in Table 6.9.2.6-1 and 6.9.2.6-2. Due to the lack of dermal absorption of NP-TiO_2, lines of evidence for systemic toxicity have not been assessed. For both skin sensitisation and irritation, only one line of evidence is available. VKM concludes that NP-TiO_2 is not a skin sensitiser or irritant.

Table 6.9.2.6-1. NP-TiO_2: Summary of findings for the different lines of evidence for each outcome.

Evidence source	Test and model	Dose	Duration	Adverse effect	VKM conclusions on the evidence for each outcome and the derived PoD	Hazard conclusion
Skin irritation						
ECHA (2021e)	Acute Dermal Irritation / Corrosion, rabbit (semiocclusive)	Ultrafine anatase TiO_2 A single dose of 500 mg	3 minutes and 1 hour in one animal and for 4 hours in three animals. The observation period was 72 hours	No (slight to moderate erythema and edema in some animals, all reversible)	NP-TiO_2 is not classifiable as a skin irritant under the test conditions used	No irritant potential identified (see Chapter 6.11)
	Acute Dermal Irritation / Corrosion, rabbit (semiocclusive)	TiO_2 ultrafine 0.5 g	4 h, observation period: 1, 24, 48 and 72 hours after removal	No		
	Acute Dermal Irritation / Corrosion, rabbit (semiocclusive)	TiO_2 ultrafine 0.5 g	4 h, observation period: 1, 24, 48 and 72 hours after removal	No (slight to moderate erythema and edema in some animals, all reversible)		
	Skin Irritation, reconstructed Human Epidermis Test Method	TiO_2 nanoparticles 30 µl applied, concentration: 1 mg/mL	1 hour, duration of post-treatment incubation: 42 h	No		
Skin sensitisation						

ECHA (2021e)	Mouse	Ultrafine TiO_2, 0% (vehicle control), 5%, 25%, 50%, or 100%	Administration for 3 consecutive days (test days 0-2), test days 3-4 were days of rest followed by intravenous injection of 20 µCi of ^{3}H-Thymidine per mouse on test day 5. Approximately 5 hours after the injection, animals were sacrificed by carbon dioxide asphyxiation, draining auricular lymph nodes were removed, and single cell suspensions were prepared. The single cell suspensions were incubated at 2-8°C overnight. On test day 6, the single cell suspensions were counted on a beta counter	No	NP-TiO_2 does not exhibit sensitising potential	No sensitising potential identified (see Chapter 6.11)
	Guinea pig	Ultrafine TiO_2, preliminary test: Concentrations: 50 and 100%; main test: Induction concentration: 100% w/w	Exposure: 6h, occlusive; Challenge concentration: 100% w/w; Exposure: 6h, occlusive	No		

Table 6.9.2.6-2. Summary of integration of confidence across lines of evidence for each outcome.

		Skin irritation	**Skin sensitisation**
		Dermal	Dermal
Animal studies	Effects reported (yes/no)	No	No
	LD50/ NOAEL/ LOAEL	-	-

		Skin irritation	Skin sensitisation
		Dermal	Dermal
	Reliability (1: reliable without restrictions; 2: reliable with restriction)	1 and 2	1

6.10 Animal studies: Derivation of uncertainty factors

For endpoints which may potentially be used to derive a DNEL, uncertainties related to the hazard data should be identified and quantified as uncertainty factors (UFs). UFs are based on default values from EFSA (2012) and ECHA (2012) where this is available, considered on a case-by-case basis, and justified (Table 6.10-1).

Table 6.10-1. Areas of uncertainty that are considered.

Area of uncertainty (in general)	Area of uncertainty (specific)	Uncertainty factor (UF)
Duration of exposure	Extrapolation from subchronic to chronic study duration in rodents. Adjusts for the possibility of identifying a lower PoD for chronic toxicity when extrapolation from a subchronic study.	2 (ECHA, 2012; EFSA, 2012)
Dose-response relationship	Uncertainty factor when the PoD is based on a LOAEL or if a higher BMD response than 5% is used. Dose spacing, the extent and severity of the effect seen at the LOAEL/>BMD5.	3-10 (ECHA)
Quality of the toxicological database	Adjusts for the certainty/reliability in the evidence.	High reliability:1 In case of moderate or lower reliability: 2-5 Expert judgement, on a case-by-case basis (ECHA, 2012; EFSA, 2012)

Area of uncertainty (in general)	Area of uncertainty (specific)	Uncertainty factor (UF)
Lack of data	The available data does not cover all relevant endpoints. Adjusts for the possibility of identifying av lower PoD if more data were available.	No lack of data: 1 In case of lack of data: 3-10 (expert judgement, on a case-by-case basis) (EFSA, 2012)
Lack of data on toxicokinetics	Inter-species extrapolation from rodent and rabbit to human. Adjusts for inter-species variability.	4 (EFSA, 2012)
	Inter-species extrapolation from dog to human. Adjusts for inter-species variability.	1.4 (ECHA, 2012)
	Intra-human extrapolation. Adjusts for intra-human variability.	3.16 (EFSA, 2012)
Lack of data on toxicodynamics	Inter-species extrapolation. Adjusts for inter-species variability.	2.5 (EFSA, 2012)
	Intra-human extrapolation. Adjusts for intra-human variability.	3.16 (EFSA, 2012)
Overall UF that adjusts for all uncertainty considered to be of relevance:		Multiply all factors

6.11 Animal studies: Identification of point of departure (PoD) and derivation of the no-effect level (DNEL)

The NOAEL values established from experimental data are used as PoDs, *i.e.* the points used to derive a safe level. Each NOAEL value is divided by an overall uncertainty factor (UF) (described in section 6.10) to obtain the DNEL, which is defined as the level of chemical exposure above which humans should not be exposed (Regulation (EC) No 1907/2006, 2006).

The NOAELs for subchronic, chronic/carcinogenicity toxicity studies and reproductive and developmental toxicity studies were used to establish DNELs. An overview of the outcomes addressed and the effects reported is given in Table 6.11-1.

When no adverse effects were observed, the highest DNEL was used in the risk characterisation. For those UV filters for which adverse effects were identified, DNELs were calculated for all studies where adverse effects were observed, and the lowest DNEL was used in the risk characterisation.

For NOAELs identified from toxicity studies with oral administration of the UV filter, the external dose was adjusted for the oral absorption values to obtain the internal dose estimate. The data on oral absorption is obtained from ECHA registration dossiers for the selected UV filter. In absence of experimentally determined oral absorption, default values from the SCCS were used (SCCS, 2021). According to SCCS (2021): "*It is considered that not more than 50% of an orally administered dose is systemically available*". "*If there is information to suggest poor oral bioavailability, a default value of 10% oral absorption could be considered*".

An overview of the assumed oral absorption used for the calculation of internal NOAELs from external NOAELs is given in Table 6.11-1.

Table 6.11-1. Values used to convert external oral NOAELs to internal NOAELs.

UV filter	Potential for oral absorption as reported by ECHA	Assumed absorption (%)
BEMT	BEMT has a very low potential for absorption via oral routes.	50
BMDBM	Results indirectly indicates the bioavailability of BMDBM or metabolites following oral intake at high dosage but gives no indication of the amount absorbed.	50
EHS	100% oral absorption is assumed for EHS.	100

UV filter	Potential for oral absorption as reported by ECHA	Assumed absorption (%)
EHT	The physiochemical parameters such as molecular weight, water solubility and log P strongly suggest that the majority of any dose would not be absorbed following either oral or dermal exposure.	10
OC	Octocrylene is likely to be absorbed in the GI tract by micellular solubilization.	50
NP-TiO_2	Negligible oral absorption assumed.	0

6.11.1 Systemic toxicity

An overview of the outcomes addressed and the presence of effects identified is given in Table 6.11.1-1.

Table 6.11.1-1. An overview of reported effects/no effects in studies addressing systemic toxicity outcomes.

UV filter	Acute toxicity studies	Subchronic/ chronic toxicity studies	Genetic toxicity studies	Carcinogenicity studies	Reproductive and developmental toxicity studies	DNEL value used for the risk characterisation (highest or lowest)
BEMT	No effect	No effect DNEL is established	Negative	No effect DNEL is established	No effect	Highest
BMDBM	No effect	Yes (haematological and clinical biochemistry parameters, organ weight and histopathology) DNEL is established	Negative (mutagenicity)	No studies included	No effect (developmental)	Lowest

UV filter	Acute toxicity studies	Subchronic/ chronic toxicity studies	Genetic toxicity studies	Carcinogenicity studies	Reproductive and developmental toxicity studies	DNEL value used for the risk characterisation (highest or lowest)
EHS	No effect	Yes (retarded growth, enlarged livers) DNEL is established	Negative (mutation and chromosome aberration)	No studies included	Yes (maternal mortality, reduced gestation index, increased post-implantation loss, prolonged gestation period) DNEL is established	Lowest
EHT	No effect	No effect DNEL is established	Negative (mutagenic or clastogenic)	No studies included	No effect (developmental toxicity)	Highest
OC	No effect	Yes (increased body weight, reduced food consumption, increased number of hypertrophic cells and slight hypertrophy) DNEL is established	Negative (mutagenic or clastogenic)	No studies included	Yes (reduced number of implantation sites and pups delivered) DNEL is established	Lowest
NP-TiO_2	No studies included	No studies included	No studies included	No studies included	No studies included	N.A.

6.11.1.1 BEMT

No adverse effects were reported in the toxicity studies. Therefore, the NOAELs for subchronic toxicity and carcinogenicity are used to establish DNELs. An overview of the identified uncertainties related to the studies on subchronic toxicity and carcinogenicity, the UFs applied to adjust for the uncertainty, and the established DNELs is given in Table 6.11.1.1-1. As no adverse effects were observed the highest DNEL is used in the risk characterisation. The DNEL of 2.5 mg/kg bw/day derived from the NOAEL for internal dose will be compared to the internal exposure in the risk characterisation.

Table 6.11.1.1-1. BEMT: Identification of uncertainty factors (UFs) and derivation of derived no-effect level (DNEL) for systemic toxicity.

Areas of uncertainty	**Subchronic toxicity**	**Chronic**
	NOAEL, rat, oral (internal dose): ≥500 mg/kg bw/day	NOAEL, rat, dermal (external dose): ≥1000 mg/kg bw/day
Duration of exposure	UF = 2 Subchronic toxicity study	UF = 1 Chronic toxicity study
Quality of the toxicological database	UF = 1 Reliable without restrictions	UF = 1 Reliable without restrictions
Lack of data on toxicity	UF = 1 Sufficient data on toxicity	UF = 1 Sufficient data on toxicity
Adjusts for intra-human variability	UF =10 Intraspecies extrapolation	UF =10 Intraspecies extrapolation
Adjusts for inter-species variability	UF =10 Intraspecies extrapolation	UF =10 Intraspecies extrapolation
Overall UF	200	100
DNEL (NOAEL/overall UF)	2.5 mg/kg bw/day	10 mg/kg bw/day

6.11.1.2 BMDBM

No adverse effects for outcomes other than subchronic toxicity were reported, and no carcinogenicity studies were available. Therefore, the NOAEL identified in a subchronic toxicity is used to establish a DNEL. An overview of the identified uncertainties related to the subchronic toxicity study, the UFs applied to adjust for the uncertainty, and the established DNEL is given in Table 6.11.1.2-1. The DNEL used in the risk characterisation is 1.13 mg/kg bw/day.

Table 6.11.1.2-1. BMDBM: Identification of adjustment factors for uncertainty (UFs) and derivation of derived no-effect level (DNEL) for systemic toxicity.

Areas of uncertainty	**Subchronic toxicity**
	NOAEL, oral: 225 mg/kg bw/day
Duration of exposure	UF = 2 Subchronic
Quality of the toxicological database	UF = 1 Reliable with restrictions
Lack of data on toxicity	UF = 1 Sufficient data on toxicity
Adjusts for intra-human variability	UF =10 Intraspecies extrapolation
Adjusts for inter-species variability	UF =10 Intraspecies extrapolation
Overall UF	200
DNEL (NOAEL/overall UF)	1.13 mg/kg bw/day

6.11.1.3 EHS

No adverse effects for outcomes other than subchronic toxicity and reproduction and developmental toxicity were reported, and no carcinogenicity studies were available. Therefore, the NOAELs for subchronic toxicity and reproduction and developmental toxicity are used to establish DNELs. An overview of the identified uncertainties, the UFs applied to adjust for the uncertainty, and the established DNELs is given in Table 6.11.1.3-1. The DNEL used in the risk characterisation is 2.4 mg/kg bw/day.

Table 6.11.1.3-1. EHS: Identification of adjustment factors for uncertainty (UFs) and derivation of derived no-effect level (DNEL) for systemic toxicity.

Areas of uncertainty	**Chronic toxicity**	**Teratogenicity**
	NOAEL, dog, oral: 83 mg/kg bw/day	NOAEL, rat oral: 25 mg/kg bw/day
Duration of exposure	UF = 1 Chronic toxicity	UF = 1 Reproductive and developmental toxicity study
Quality of the toxicological database	UF = 1 Reliable with restrictions	UF = 1 Reliable without restrictions
Lack of data on toxicity	UF = 1 Sufficient data on toxicity	UF = 1 Sufficient data on toxicity
Adjusts for intra-human variability	UF =10 Intraspecies extrapolation	UF =10 Intraspecies extrapolation
Adjusts for inter-species variability	UF =3.5 Intraspecies extrapolation	UF =1 Intraspecies extrapolation (no interspecies differences were applied since considerable species differences in sensitivity were described with the rat being more sensitive than humans according to the ECHA registration dossier)
Overall UF	35	100
DNEL (NOAEL/overall UF)	2.4 mg/kg bw/day	2.5 mg/kg bw/day

6.11.1.4 EHT

No adverse effects were reported in the toxicity studies. Therefore, the NOAEL for subchronic toxicity is used to establish DNEL. An overview of the identified uncertainties related to the study on subchronic toxicity, the UFs applied to adjust for the uncertainty, and the established DNEL is given in Table 6.11.1.4-1. The DNEL used in the risk characterisation is 0.5 mg/kg bw/day.

Table 6.11.1.4-1. EHT: Identification of adjustment factors for uncertainty (UFs) and derivation of derived no-effect level (DNEL) for systemic toxicity.

Areas of uncertainty	**Subchronic toxicity**
	NOAEL, oral: ≥100 mg/kg bw/day
Duration of exposure	UF = 2 Subchronic
Quality of the toxicological database	UF = 1 Reliable with restrictions
Lack of data on toxicity	UF = 1 Sufficient data on toxicity
Adjusts for intra-human variability	UF =10 Intraspecies extrapolation
Adjusts for inter-species variability	UF =10 Intraspecies extrapolation
Overall UF	200
DNEL (NOAEL/overall UF)	0.5 mg/kg bw/day

6.11.1.5 OC

No adverse effects for outcomes other than subchronic toxicity and reproduction and developmental toxicity were reported, and no carcinogenicity studies were available. Therefore, the NOAELs for subchronic toxicity and reproduction and developmental toxicity are used to establish DNELs. An overview of the identified uncertainties, the UFs applied to adjust for the uncertainty, and the established DNELs is given in Table 6.11.1.5-1. The DNEL used in the risk characterisation is 0.38 mg/kg bw/day.

Table 6.11.1.5-1. OC: Identification of adjustment factors for uncertainty (UFs) and derivation of derived no-effect level (DNEL) for systemic toxicity.

Areas of uncertainty	**Subchronic toxicity**	**Reproductive and developmental toxicity**
	NOAEL, rat, oral: 87.5 mg/kg bw/day	NOAEL, rat oral: 76.1 and 81.5 mg/kg bw/day for males and females, respectively
Duration of exposure	UF = 2 Subchronic toxicity study	UF =1 Prenatal Developmental Toxicity study
Quality of the toxicological database	UF = 1 Reliable without restrictions	UF = 1 Reliable without restrictions
Lack of data on toxicity	UF = 1 Sufficient data on toxicity	UF = 1 Sufficient data on toxicity
Adjusts for intra-human variability	UF =10 Intraspecies extrapolation	UF =10 Intraspecies extrapolation
Adjusts for inter-species variability	UF =10 Intraspecies extrapolation	UF =10 Intraspecies extrapolation
Overall UF	200	200
DNEL (NOAEL/overall UF)	0.44 mg/kg bw/day	0.38 and 0.41 mg/kg bw/day for males and females, respectively

6.11.1.6 NP-TiO_2

Dermal absorption of NP-TiO_2 is considered to be negligible. Derivation of DNEL for systemic toxicity is therefore not applicable.

6.11.2 Local toxicity

An overview of the outcomes addressed and effects reported is given in Table 6.11.2-1. Hazard conclusion for the animal studies addressing local toxicity: No irritant or sensitising potential was identified for any of the six UV filters investigated.

Table 6.11.1-1. An overview of adverse effects reported in animal toxicity studies."-": endpoints not investigated in studies on local toxicity.

UV filter	Acute toxicity studies	Subchronic/ chronic toxicity studies	Genetic toxicity studies	Carciongenicity studies	Reproductive and developmental toxicity studies	Skin irritation studies	Skin sensitisation studies
BEMT	-	No effect		Yes (considered to be indicative of a chronic and moderate local skin irritation)	-	No effect	No effect
BMDBM	-	Yes (erythema/edema)	-	-	-	No	No effect
EHS	-	-	-	-	-	No (reversible erythema)	No effect
EHT	-	-	-	-	-	No effect	No effect
OC	-	-	-	-	-	No effect	No effect
NP-TiO_2	-	-	-	-	-	No effect	No effect

6.12 Integration of evidence and overall hazard conclusions

6.12.1 Sunscreen

Due to low confidence in the body of evidence of a health effect of sunscreen of the outcomes melanoma and reduction in vitamin D synthesis, there is insufficient evidence to assess whether sunscreen use is associated with these outcomes. The hazard conclusion for these outcomes is "not classifiable as a hazard to humans", according to OHAT (2019) terminology. Therefore, the risk related to either melanoma or reduced vitamin D synthesis due to sunscreen use cannot be determined.

The hazard conclusion is based on human health data alone.

6.12.2 UV filtres

Two evidence lines were available for skin sensitisation and irritation. VKM concludes that considering the low frequency of effects for BEMT, BMDBM, EHS and EHT in a susceptible human population, and lack of identification of local effects in the ECHA animal toxicity studies for any of the UV filters assessed, the six selected UV filters are "not identified as a hazard to humans" in the general population.

The integration of the hazard conclusions for these evidence lines is shown in Table 6.12-1.

Table 6.12-1. Integration of hazard conclusions for local toxicity (skin irritation and sensitisation).

UV filter	Skin irritation: human studies	Skin irritation: Animal studies	Overall hazard conclusion for skin irritation
BEMT	Irritant reactions shown in susceptible individuals in low frequency (0.6%)	No irritant potential identified	Not identified as a hazard to humans
BMDBM	Irritant reactions shown in susceptible individuals in low frequency (≤1.6%)	No irritant potential identified	Not identified as a hazard to humans
EHS	Irritant reactions shown in susceptible individuals in low frequency (≤0.2%)	No irritant potential identified	Not identified as a hazard to humans
EHT	No irritant reactions shown in susceptible individuals	No irritant potential identified	Not identified as a hazard to humans
OC	No studies included	No irritant potential identified	Not identified as a hazard to humans
NP-TiO_2	No studies included	No irritant potential identified	Not identified as a hazard to humans
UV filter	**Skin sensitisation: human studies**	**Skin sensitisation: animal studies**	**Overall hazard conclusion for skin sensitisation**

UV filter	Skin irritation: human studies	Skin irritation: Animal studies	Overall hazard conclusion for skin irritation
BEMT	Sensitising reactions shown in susceptible individuals in low frequency (≤0.2%)	No sensitising potential identified	Not identified as a hazard to humans
BMDBM	Sensitising reactions shown in susceptible individuals in low frequency (≤0.3%)	No sensitising potential identified	Not identified as a hazard to humans
EHS	Sensitising reactions shown in susceptible individuals in low frequency (≤max 2%)	No sensitising potential identified	Not identified as a hazard to humans
EHT	Sensitising reactions shown in susceptible individuals in low frequency (≤0.1%)	No sensitising potential identified	Not identified as a hazard to humans
OC	No studies included	No sensitising potential identified	Not identified as a hazard to humans
NP-TiO_2	No studies included	No sensitising potential identified	Not identified as a hazard to humans

There wasone line of evidence for systemic toxicity. The hazard conclusion for systemic toxicity is given as the DNEL for the critical endpoint (see Chapter 6.11). An overview of the overall hazard conclusions for systemic and local toxicity is given in Table 6.12-2.

Table 6.12-2. The overall hazard conclusions.

UV filter	Overall hazard conclusion for systemic toxicity (the DNEL values)	Overall hazard conclusion for local toxicity
BEMT	2.5 mg/kg bw/day	Not identified as a hazard to humans
BMDBM	1.13 mg/kg bw/day	Not identified as a hazard to humans
EHS	2.4 mg/kg bw/day	Not identified as a hazard to humans
EHT	0.5 mg/kg bw/day	Not identified as a hazard to humans
OC	0.38 mg/kg bw/day	Not identified as a hazard to humans
NP-TiO_2	Derivation of DNEL for systemic toxicity is not applicable as NP-TiO_2 is not absorbed when applied dermally	Not identified as a hazard to humans

The DNELs for systemic toxicity are used in the risk characterisation step. A DNEL is not derived for local effects. As no skin irritation or sensitisation hazard was identified for any of the six UV filters investigated, no risk characterisation is performed for these outcomes.

7 Characterisation and evidence synthesis of health protective effects

The included evidence on protective effects is limited to studies of low or moderate RoB (denoted "unclear" in the case of systematic reviews) retrieved from the literature searches. In all studies, the intervention was use of sunscreen containing one or more UV filters with concurrent exposure to UVR. The health protective effects addressed in the included literature (Chapter 5) were prevention of the following outcomes: melanoma, actinic keratosis, BCC, SCC, and immunosuppression.

7.1 Sunscreen: Study characteristics, evaluation of certainty in the evidence for health protective effects, and translation into evidence for health effects

7.1.1 Systematic reviews

Two systematic reviews addressed the relationship between sunscreen use and melanoma, and one systematic review addressed the relationship between sunscreen use and SCC and BCC (Table 7.1.1-1 and 7.1.1-2). Note that evaluation of certainty in the evidence for adverse effects of sunscreen is described in Chapter 6.1.2.

Table 7.1.1-1. Study characteristics and certainty in the evidence for protective effects on melanoma. RoB: risk of bias; CI: confidence interval; OR: odds ratio; RR: rate ratio; RCT: randomised controlled trial; HR: hazard ratio

Reference	Aim	Trials on this outcome (n)	Literature search period	Countries where the studies were conducted	RoB	Key finding
Dennis et al. (2003)	Examine the strength and consistency of associations between melanoma and sunscreen use in the published literature.	Case–control studies (9 population-based case–control studies, 7 non–population-based studies and 2 case–control studies)	From 1966 through April 2003	Australia, Austria, Belgium, Brazil, Denmark, France, Germany, Italy, Spain, Sweden, USA	Unclear	No association was found between melanoma and sunscreen use.
Rueegg et al. (2019)	Answer whether sunscreen use affects melanoma risk.	23 case–control studies, 1 ecological study, 3 cohort studies and 1 randomised controlled trial	Articles published up to 28.02.2018	Australia, Austria, Belgium, Brazil, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, Norway, Spain, Sweden, USA	Low	Ever-vs. never-use of sunscreen was inversely associated with melanoma in hospital-based case–control studies (adjusted OR = 0.57, 95% CI 0.37–0.87, p heterogeneity <0.001), the ecological study (RR = 0.48, 95% CI 0.35–0.66), and the RCT (HR = 0.49, 95% CI 0.24–1.01).

Summary: Dennis et al. (2003) found no association between melanoma and sunscreen use in the meta-analysis of 18 case-control studies. The relevant studies included in Dennis (2003) were also included in Rueegg et al. (2019). Rueegg et al. (2019) included more study designs, and the literature search included studies published up to end of February 2018. According to Rueegg et al. (2019), the data used to assess an association between sunscreen use and melanoma were heterogenous across study designs and the level of the evidence varied as follows:

- In the hospital-based case–control studies and the ecological study, an association between sunscreen use and reduced development of melanoma was shown. The overall level of the evidence for an association between sunscreen use and melanoma risk in these studies was very low.
- In the population-based case–control studies no association between sunscreen use and development of melanoma was shown. The overall level of the evidence for an association between sunscreen use and melanoma risk in these studies was very low.
- In the cohort studies an association between sunscreen use and increased development of melanoma was shown. The overall level of the evidence for an association between sunscreen use and melanoma risk in these studies was very low.

Reference	Aim	Trials on this outcome (n)	Literature search period	Countries where the studies were conducted	RoB	Key finding
• In the RCT, a protective effect of sunscreen was reported. The overall level of the evidence for an association between sunscreen use and melanoma risk in this study was moderate. VKM conclusion on the evidence (based on the systematic review by Rueegg et al. (2019): The overall confidence in the evidence for an association between sunscreen use and reduced development of melanoma is low, resulting in a low confidence in the body of evidence for a health protective effect. The true effect may be different from the apparent relationship.						

Table 7.1.1-2. Study characteristics and certainty in the evidence for protective effects on basal cell carcinoma (BCC) and squamus cell carcinoma (SCC). RCT: randomised controlled trials

Reference, country	Aim	Trials on this outcome (n)	Literature search period	Countries where the studies were conducted	RoB (according to reference)	Key finding
Sanchez et al., 2016	Assess the effects of sun protection strategies for preventing BCC and SCC of the skin in the general population.	One RCT	Articles published up to May 2016	Australia	Low	Comparing daily application of sunscreen with discretionary use, no difference in terms of the number of participants developing BCC or SCC was found.
Summary: Only one RCT was included in Sanchez et al., 2016. This study, Green et al. (1999), is also included in the current risk-benefit assessment. See Table 7.1.2-2 and 7.1.2-5 for study characteristics and evaluation of certainty in the evidence.						

7.1.2 RCTs

Two RCTs addressed the relationship between sunscreen use and protective effects on actinic keratoses (Table 7.1.2-1). Three papers from the same RCT (with follow-ups) addressed the relationship between sunscreen use and protective effects on BCC (Table 7.1.2-2). One RCT addressed the relationship between sunscreen use and protective effects on immunosuppression (Table 7.1.2-3). Two references from the same RCT addressed the relationship between sunscreen use and protective effects on SCC (Table 7.1.2-4)

Table 7.1.2-1. Study characteristics and certainty in the evidence for protective effects on actinic keratosis.

Reference, study type	Participants/ intervention/ duration	RoB	Results
Darlington et al., 2003	Nambour study, same trial as in Green 1999. 1621 participants randomized to sunscreen/betacarotene/ sunscreen and betacarotene, or placebo. Daily sunscreen (not betacarotene): n = 404, mean age = 48.7 years (SD = 13.6). Discretionary sunscreen (not betacarotene): n = 393, mean age = 49.8 years (SD = 12.7). Skin colours reported (of 1433 participants): fair (62.6%), medium (42.7%), olive (7.6%) Sunscreen: 8% (by weight) 2-ethylhexyl-p-methoxycinnamate and 2% (by weight) BMDBM, SPF, 16 according to Australian Standard 2604.	2	Of 1116 participants, the percent participants with no solar keratoses was 54 in 1992, 50 in 1994, and 47 in 1996. The ratio of solar keratoses counts in 1994 relative to 1992 was lower in people randomised to daily sunscreen use (1.20; 95% confidence interval, 1.04-1.39) than in those randomized to discretionary sunscreen use (1.57; 95% confidence interval, 1.35-1.84). A not significant reduction in the rate of change of solar keratose prevalence was seen in the sunscreen intervention group relative to the discretionary sunscreen group between 1994 and 1996.

Reference, study type	Participants/ intervention/ duration	RoB	Results
	Self-application of a layer to all exposed sites on the head, neck, arms, and hands every morning. UV exposure was determined in the two groups (daily vs. discretionary use) through interviews. Exposure site: Nambour, Queensland, Australia: latitude 26°S. Duration: 4.5 years		
Thompson et al., 1993	403 participants, 180 men and 251 women, mean age [±SD]: 63 ±11 years, age range: 40 to 93 years. All invited participants had from 1 to 30 solar keratoses. "White" subjects with self-rated skin types described as: burn only and never tan, burn first and then tan, or tan only and never burn. There were 221 subjects (89 men and 132 women) in the base-cream group and 210 subjects (91 men and 119 women) in the sunscreen group. The sunscreen cream contained 8% (wt/wt) 2-ethylhexyl p-methoxycinnamate and 2% (wt/wt) 4-BMDBM. The participants were instructed to (but determined their own level) apply minimum 4.5 ml of the sunscreen per day distributed as follows: 1.5 ml to the head and neck and the same amount to each forearm and hand once every morning. Participants were encouraged to reapply if necessary, during the day. Ambient UVR conditions:	2	The mean (+/- SD) number of solar keratoses increased by 1.0 (+/- 0.3) per subject in the base-cream group and decreased by 0.6 (+/- 0.3) per subject in the sunscreen group (difference, 1.53; 95 % confidence interval (CI), 0.81 to 2.25). The relative change in the total number of solar keratoses in the sunscreen group, with the relative change in the base-cream group used as a reference, was 0.83 (95% CI, 0.78 to 0.89). There was a sex-based difference in the change in the number of lesions during the study (smaller change in women compared to men) (rate ratio, 0.87; 95% CI, 0.80 to 0.94). The sunscreen group had 1.6 new mean lesions per subject, whereas the base-cream group had 2.3. The difference in the mean number of new lesions per subject between the groups was 0.72 (95% CI, 0.15 to 1.28; P= 0.014). The sunscreen group had fewer new lesions (rate ratio, 0.62; 95% CI, 0.54 to 0.71) and more remissions (odds ratio, 1.53; 95 % CI, 1.29 to 1.80) than the base-cream group. Remission (mean) throughout the study was 28% in

Reference, study type	Participants/ intervention/ duration	RoB	Results
	Maryborough, Victoria (about 37°S), Australia, September 1991 to March 1992. Sun avoidance measures were encouraged. Study duration: Seven months (one summer: September 1991 to March 1992)		the sunscreen group vs. 20% in the base-cream group (difference of 8%; 95% CI, 2 to 13%). There was a dose-response relation: the amount of sunscreen cream used was related to both the development of new lesions and the remission of existing ones. Number of new lesions and the probability of remission were affected by the amount of cream used (X^2=6.3, P = 0.04 for new lesions; X^2=13.3, P = 0.001 for remissions).

Overall evaluation of certainty in the evidence on actinic keratosis

Initial rating	Elements triggering downgrading				Elements triggering upgrading			Overall rating
	Risk of bias	Unexplained inconsistency	Indirectness	Imprecision	Large effect	Dose–response relationship	Consistency	
++++	Tiers 2 (Table 5.3.3-2) Serious	Not serious	Not serious	Not serious	Not evaluated*	Not evaluated*	Not evaluated*	+++ Moderate

Summary: The relationship between sunscreen use and reduction in the development of actinic keratosis was studied in two RCTs. In both studies with Australian populations, sunscreen prevented actinic keratosis formation in trials of different study durations, similar age range and skin types. In Thompson et al. (1993), participants were followed for seven months. The sunscreen group had fewer new actinic keratosis lesions and more remissions than the control group. Notably, only persons with 1 to 30 solar keratoses were invited to participate, so the study participants might not be representative for the general population. A dose-response relationship was found between the amount of sunscreen cream used and the development of new and remission of existing actinic keratosis. In Darlington et al. (2003), participants were followed for 4.5 years. In the first 2 years of the study, the solar keratosis counts were lower in people randomised to daily sunscreen use than in those randomised to discretionary sunscreen use. However, in the following 2 years, the reduction in the rate of change of solar keratosis prevalence in the sunscreen group relative to the discretionary sunscreen group, was not statistically significant.

VKM conclusion on the evidence: There is moderate confidence in the body of evidence for a protective association between sunscreen use and development of actinic keratosis. The true effect may be reflected in the apparent relationship.

*Elements triggering upgrading were not evaluated as downgrading was performed due to serious study limitations.

Table 7.1.2-2. Study characteristics and certainty in the evidence for protective effects on basal cell carcinoma (BCC).

Reference, study type	Participants/ intervention/ duration	RoB	Results
Green et al. (1999), RCT	Follow-up of the Nambour skin cancer trial, as described in Green et al., 1994 after 4.5 years. Initially, 1621 participants were randomised to the intervention groups: sunscreen and betacarotene tablets; sunscreen and placebo tablets, betacarotene only, or placebo only. Participants not assigned to the sunscreen application group were asked to continue use of sunscreen at their own discretionary rate. Sunscreen group: Self-application of a layer to all exposed sites on the head, neck, arms, and hands every morning. Daily sunscreen use (no betacarotene): n = 404, mean age = 48.7 years (SD = 13.8). Discretionary sunscreen (no betacarotene): n = 393, mean age = 49.8 years (SD = 12.7).	2	Basal-cell carcinoma seems not to be amenable to prevention through the routine use of sunscreen by adults for 4.5 years. 1383 participants underwent full skin examination by a dermatologist in the follow-up period. 250 of them developed 758 new skin cancers during the follow-up period. There were no significant differences in the incidence of first new skin cancers between groups randomly assigned daily sunscreen and no daily sunscreen (basal-cell carcinoma 2588 vs 2509 per 100 000; rate ratio 1.03 [95% CI 0.73–1.46]. In terms of the number of tumours, there was no effect on incidence of basal-cell carcinoma by sunscreen use.

Reference, study type	Participants/ intervention/ duration	RoB	Results
	Skin colours reported (of 1433 participants): fair (62.6%), medium (42.7%), olive (7.6%) . Sunscreen : 8% (by weight) 2-ethylhexyl-p-methoxycinnamate and 2% (by weight) BMDBM, SPF 16 according to Australian Standard 2604. UV exposure was determined in the two groups (daily vs. discretionary use) through interviews. Exposure site: Nambour, Queensland, Australia: latitude 26°S.		
Pandeya et al. (2005), RCT	Data from 4.5 years of follow-up of the Nambour skin cancer trial, as described in Green et al., 1994 (see Green et al, 1999 above). N= 1362 (assumes random loss to follow-up).	2	Sunscreen treatment was not associated with time to first occurrence of a BCC (hazard ratio =1.04, 95% confidence interval (CI): 0.79, 1.45). Time to subsequent BCC tumors using the Andersen-Gill model resulted in a lower estimated hazard among the daily sunscreen application group, although statistical significance was not reached (hazard ratio =0.82, 95% confidence interval: 0.59, 1.15). Similarly, both the Wei-Lin-Weissfeld marginal-hazards and the Prentice-Williams-Peterson gap-time models revealed trends toward a lower risk of subsequent BCC tumors among the sunscreen intervention group. Hazard ratios (crude); 95% CI; p-value for the combined effect of sunscreen intervention on repeated occurrences of BCC: Time to first episode: 1.03; 0.77, 1.38; 0.83. Andersen-Gill model: 0.90; 066, 1.23; 0.49. Wei-Lin Weissfeld model: 0.89; 0.65, 1.24; 0.50. Prentice-Williams-Peterson: 0.91; 0.72, 1.15; 0.42.

Reference, study type	Participants/ intervention/ duration	RoB	Results
van der Pols et al. (2006), RCT	Eight-years follow-up after cessation of the Nambour skin cancer trial, as described in Green et al., 1994 (see Green et al, 1999 above). N= 875 of the initial 1621 participants.	2	Regular application of sunscreen had no clear benefit in reducing BCC. BCC tumor rates tended to decrease but not significantly in people formerly randomised to daily sunscreen use compared with those not applying sunscreen daily. For the entire follow-up period the rate ratio for BCC was 0.89; 95% CI, 0.64-1.25.

Overall evaluation of certainty in the evidence for protective effects on BCC								
Initial rating	Elements triggering downgrading				Elements triggering upgrading			Overall rating
	Risk of bias	Unexplained inconsistency	Indirectness	Imprecision	Large effect	Dose–response relationship	Consistency	
++++	Tier 2 (Table 5.3.3-3) Serious	The same study and population	Not serious	Not serious	Not evaluated*	Not evaluated*	Not evaluated*	+++ Moderate
Summary: The relationship between regular sunscreen use and reduction in the development of BCC in participants in the RCT, the Nambour skin cancer trial, was reported in three publications. Participants from the same initial study population were included, of whom 84% and 54% were left after follow-up at 4.5 years (Green et al, 1999; Pandeya et al, 2005) and 8 years (van der Pols et al., 2006), respectively. None of the three publications reported a statistically significant decrease in BCC rates in the daily sunscreen application group compared to the discretionary sunscreen control group. However, the trends were pointing in direction of reduction with regards to subsequent BCC and tumour rates after 8 years. VKM conclusion on the evidence: There is moderate confidence in the body of evidence for a protective effect of sunscreen use to reduce development of basal cell carcinoma. The effect was little no none. The true effect may be reflected in the apparent relationship. There is insufficient evidence available to assess whether sunscreen use protects against basal cell carcinoma.							

*Elements triggering upgrading were not evaluated as downgrading was performed due to serious study limitations.

Table 7.1.2-3. Study characteristics and certainty in the evidence for protective effects on immunosuppression.

Reference, study type	Participants/ intervention/ duration	RoB	Results
Neale et al. (1997)	The Nambour skin cancer trial, as described in Green et al., 1994. Determination of the number of Langerhans cells in UV-exposed an unexeposed skin following daily sunscreen use for 3 years. Initially, 1621 participants were randomised to the intervention groups: sunscreen and betacarotene tablets; sunscreen and placebo tablets, betacarotene only, or placebo only. Participants not assigned to the sunscreen application group were asked to continue use of sunscreen at their own discretionary rate. Of the 1621 participants, 110 were included in this 2-week substudy on Langerhans cells. At the end of the 2-week period with documented sun exposure, skin samples were collected from 104 participants. Sunscreen group: Self-application of a layer to all exposed sites on the head, neck, arms, and hands every morning. Daily sunscreen use (no betacarotene): n = 404, mean age = 48.7 years (SD = 13.8). Discretionary sunscreen (no betacarotene): n = 393, mean age = 49.8 years (SD = 12.7). Skin colours reported (of 1433 participants): fair (62.6%), medium (42.7%), olive (7.6%) Sunscreen: 8% (by weight) 2-ethylhexyl-p-methoxycinnamate and 2% (by weight) BMDBM, SPF 16 according to Australian Standard 2604.	2	Significantly fewer Langerhans cells on the UV-exposed (463 cells/mm^2) than on the unexposed forearm (528 cells/mm^2) ($p = 0.0001$). High sun exposure in the previous 2 weeks and a history of predominantly outdoor occupations were both associated with a reduced number of Langerhans cells. Sunscreen use was protective against the effects of current but not chronic sun exposure, with a suggestion of a greater effect at higher levels of exposure.

Reference, study type	Participants/ intervention/ duration	RoB	Results
	UV exposure was determined in the two groups (daily vs. discretionary use) through interviews. Exposure site: Nambour, Queensland, Australia: latitude 26°S.		

Overall evaluation of certainty in the evidence for protective effects on immunosuppression

Initial rating	Elements triggering downgrading				Elements triggering upgrading			Overall rating
	Risk of bias	Unexplained inconsistency	Indirectness	Imprecision	Large effect	Dose–response relationship	Consistency	
++++	Tier 2 (Table 5.3.3-4) Serious	Not evaluated (one study)	The outcome addressed is considered to be insufficient as a certain marker for immunosuppression Serious	Not serious	Not evaluated*	Not evaluated*	Not evaluated*	++ Low

Summary: One RCT evaluated protective effects of sunscreen use on UV-exposed and unexposed skin on immunosuppression. The outcome addressed was the number of Langerhans cells in skin biopsies. High sun exposure was associated with a reduction in the number of Langerhans cells. Since UV-induced immunosuppression depends on several mediators and immune cells, the assessment of Langerhans cells only was considered not to be a sufficient marker on its own for immunosuppression. Sunscreen use was protective against effects of current, but not chronic, sun exposure. The overall rating of the certainty in evidence is low.

VKM conclusion on the evidence: There is low certainty in the body of evidence for a protective effect of sunscreen use on immunosuppression (assessed as depletion of Langerhans cells). The true effect may be different from the apparent relationship. The level of evidence for a health protective effect is low.

*Elements triggering upgrading were not evaluated as downgrading was performed due to serious study limitations and indirectness.

Table 7.1.2-4. Study charcteristics and certainty in the evidence for protective effects on SCC.

Reference, study type	Participants/ intervention/ duration	RoB	Results
Green et al. (1999), RCT	Follow-up of the Nambour skin cancer trial, as described in Green et al., 1994 after 4.5 years. Initially, 1621 participants were randomised to the intervention groups: sunscreen and betacarotene tablets; sunscreen and placebo tablets, betacarotene only, or placebo only. Participants not assigned to the sunscreen application group were asked to continue use of sunscreen at their own discretionary rate. Sunscreen group: Self-application of a layer to all exposed sites on the head, neck, arms, and hands every morning. Daily sunscreen use (no betacarotene): n = 404, mean age = 48.7 years (SD = 13.8). Discretionary sunscreen (no betacarotene): n = 393, mean age = 49.8 years (SD = 12.7). Skin colours reported (of 1433 participants): fair (62.6%), medium (42.7%), olive (7.6%) Sunscreen: 8% (by weight) 2-ethylhexyl-p-methoxycinnamate and 2% (by weight) BMDBM, SPF 16 according to Australian Standard 2604.	2	1383 participants underwent full skin examination by a dermatologist in the follow-up period. 250 of them developed 758 new skin cancers during the follow-up period. There were no significant differences in the incidence of first new skin cancers between groups randomly assigned daily sunscreen and no daily sunscreen (squamous-cell carcinoma 876 vs 996 per 100 000; rate ratio 0.88[0.50–1.56]). The incidence of squamous-cell carcinoma was significantly lower in the sunscreen group than in the no daily sunscreen group (1115 vs 1832 per 100 000; 0.61 [0.46–0.81]).

Reference, study type	Participants/ intervention/ duration	RoB	Results
	UV exposure was determined in the two groups (daily vs. discretionary use) through interviews. Exposure site: Nambour, Queensland, Australia: latitude 26°S.		
van der Pols et al. (2006), RCT	Eight-years follow-up after cessation of the Nambour skin cancer trial, as described in Green et al., 1994 (see Green et al, 1999 above). N= 875 of the initial 1621 participants.	2	Regular application of sunscreen had prolonged preventive effects on SCC. SCC tumor rates were significantly decreased by almost 40% during the entire follow-up period (rate ratio, 0.62; 95% confidence interval, 0.38-0.99).

Overall evaluation of certainty in the evidence for protective effects on SCC

Initial rating	Elements triggering downgrading				Elements triggering upgrading			Overall rating
	Risk of bias	Unexplained inconsistency	Indirectness	Imprecision	Large effect	Dose–response relationship	Consistency	
++++	Tier 2 (Table 5.3.3-7) Serious	The same study and population Not evaluated	Not serious	Not serious	Not evaluated*	Not evaluated*	Not evaluated*	+++ Moderate

Summary: The relationship between regular sunscreen use and reduction in the development of SCC in participants in the RCT, the Nambour skin cancer trial, was reported in two publications. Participants from the same initial study population were included, of whom 84% and 54% were left after follow-up at 4.5 years (Green et al, 1999) and 8 years (van der Pols et al., 2006), respectively. SCC tumor rates were significantly decreased by almost 40% during the entire follow-up period.

VKM conclusion on the evidence: There is moderate certainty in the body of evidence for a protective association between sunscreen use and reduction in squamous cell carcinoma. The true effect may be reflected in the apparent relationship. The level of evidence for a health protective effect is moderate.

*Elements triggering upgrading were not evaluated as downgrading was performed due to serious study limitations

7.2 Integration of evidence and conclusions on health protection

Two systematic reviews reported on the association between sunscreen use and melanoma. The following numbers of RCTs addressed the relationship between sunscreen use and protection against the outcomes: Two RCTs on actinic keratosis; three papers from the same RCT on BCC; one RCT on immunosuppression; two papers of the same RCT on SCC.

One line of evidence was identified for each outcome.

Table 7.2-1. Sunscreen: Summary of findings for the different lines of evidence for each outcome. Risk of bias (RoB) was evaluated in systematic reviews and RCTs using ROBIS and OHAT, respectively. GRADE was used to assess certainty in the evidence in Rueegg et al., 2019 by the authors.

Evidence source	Study type	RoB (level or tier)	Evaluation of health protective effect	VKM conclusions on effect and certainty in the evidence	Hazard conclusion on health protection of sunscreen of each outcome
Melanoma					
Literature search	Systematic review	Low	Yes	The overall confidence in the evidence for an association between sunscreen use and reduced development of melanoma is low, resulting in a low confidence in the body of evidence for a health protective effect. The true effect may be different from the apparent relationship.	Not classifiable as health protective in humans
Actinic keratosis					
Literature search	RCT	2	Yes	There is moderate confidence in the body of evidence for a protective association between sunscreen use and development of actinic keratosis. The true effect may be reflected in the apparent relationship. The body of evidence consists of a few well-designed and conducted studies with large study populations or group sizes with a small effect. There is low expectation that new studies would impact the hazard conclusion.	Presumed to be health protective in humans
	RCT	2	Yes		
Basal cell carcinoma					

Literature search	RCT	2	No	There is moderate confidence in the body of evidence for a protective effect of sunscreen use to reduce development of basal cell carcinoma. The effect was little no none. The true effect may be reflected in the apparent relationship. There is insufficient evidence available to assess whether sunscreen use protects against basal cell carcinoma.	Not classifiable as health protective in humans
	RCT	2			
	RCT	2			
Immunosuppression					
Literature search	RCT	2	Yes	There is low confidence in the body of evidence for a protective effect of sunscreen use on immunosuppression (assessed as depletion of Langerhans cells). The true effect may be different from the apparent relationship. The level of evidence for a health protective effect is low.	Not classifiable as health protective in humans
Squamous cell carcinoma					
Literature search	RCT	2	Yes	There is moderate confidence in the body of evidence for a protective association between sunscreen use and development of squamous cell carcinoma. The true effect may be reflected in the apparent relationship. The level of evidence for a health protective effect is moderate. The body of evidence consists of a single well-designed and conducted study with 8 years follow-up with large magnitude of effect. There is low expectation that new studies would impact the hazard conclusion.	Presumed to be health protective in humans
	RCT	2			

The outcomes related to skin (pre-) cancers were grouped.

Table 7.2-2. Sunscreen: Overall hazard conclusion for the health outcome skin (pre-) cancers.

Skin (pre-) cancer	Evaluation of health protective effect	Evidence of health effect	Conclusion on single oucome	Overall hazard conclusion on combined outcome
Melanoma	Yes	Low confidence	Not classifiable as a hazard	Presumed to be health protective
Actinic keratosis	Yes	Moderate evidence	Presumed to be health protective	
Basal cell carcinoma	No	Insufficient evidence	Not classifiable as a hazard	

Skin (pre-) cancer	Evaluation of health protective effect	Evidence of health effect	Conclusion on single oucome	Overall hazard conclusion on combined outcome
Squamous cell carcinoma	Yes	Moderate confidence	Presumed to be health protective	

7.3 Conclusion on health protection of sunscreen

Immunosuppression (Table 7.2-1)

There is low confidence in the body of evidence for a protective effect of sunscreen use on immunosuppression (assessed as depletion of Langerhans cells). Since UV-induced immunosuppression depends on several mediators and immune cells, a change in Langerhans cells as the only marker was considered to be insufficient evidience.

Skin (pre-)cancers (Table 7.2-1)

There is insufficient evidence available to assess whether sunscreen use protects against basal cell carcinoma. The effect was little to none.

There is low confidence in the body of evidence for a protective association between sunscreen use and melanoma.

There is moderate confidence in the body of evidence for a protective effect of sunscreen against actinic keratosis and squamous cell carcinoma.

Overall conclusion on skin (pre-)cancers (Table 7.2-2)

Due to the few well-designed and conducted studies with relatively large populations and a consistent pattern of effect for all skin (pre-) cancers with the exception of basal cell carcinoma which showed no protection from sunscreen, the hazard conclusion was denoted as

"presumed". Therefore, VKM concludes that, sunscreen use is presumed to protect against certain skin (pre-)cancers. The protection is larger for squamous cell carcinoma and actinic keratosis than for melanoma.

8 Risk characterisation

The risk characterisation is based on the estimated exposure (Chapter 4) and the DNEL-values (Chapter 6). The median (P50) is considered to be a more representative exposure estimate than the mean, as the distribution of the exposure estimates is skewed to the right (Chapter 4). The P95 is considered to be a representative exposure estimate for the high consumers. Therefore, the P50 and the P95 are used in the risk characterisation.

In the risk characterisation for systemic toxicity related to the UV filters, the ratio of the exposure (P50 and P95) to the DNEL is calculated. When this risk characterisation ratio is <1, the exposure is considered not to represent a risk for adverse health effects. If the ratio is ≥1, the exposure to the UV filter might represent a risk for adverse health effects. DNELs are not set for local effects. As the six UV filters were not identified as a hazard to humans, no risk characterisation is performed for these outcomes.

The evidence was insufficient for associations between sunscreen use and increased melanoma as well as reduction in vitamin D synthesis. Therefore, the potential risk related to these outcomes was not determined.

An overview of the risk characterisation process is given in Figure 8-1.

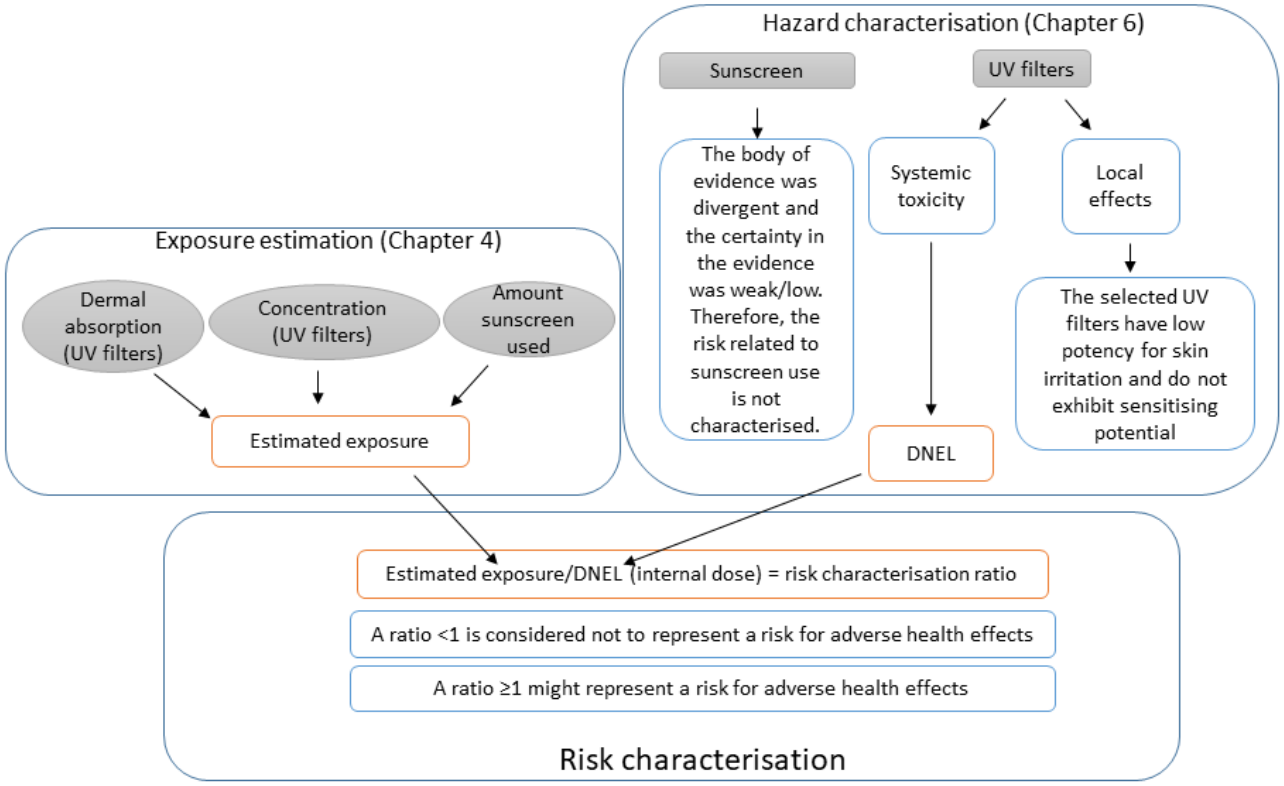


Figure 8-1. An overview of the risk characterisation process.

Table 8-1. The risk characterisation ratio for the evaluated UV filters: internal exposure/DNEL. P50: 50th percentile; median); P95: 95th percentile

UV filter	Estimated exposure (internal)		Derived no effect level	Risk characterisation ratio	
	P50 (mg/kg bw/day)	P95 (mg/kg bw/day)	DNEL (mg/kg bw/day)	P50/ DNEL	P95/ DNEL
BEMT	0.00	0.01	2.50	0.00	0.00
BMDBM	0.0206	0.3982	1.13	0.02	0.35
EHS	0.03	0.37	2.40	0.01	0.15
EHT	0.04	0.37	0.50	0.08	0.74
OC	0.00	0.05	0.38	0.00	0.13

The risk characterisation ratios for BEMT, BMDBM, EHS, EHT and OC were <1. As the dermal absorption of NP-TiO_2 was considered to be negligible, NP-TiO_2 was regarded not to represent a risk for adverse health effects. VKM therefore concludes that the risk for adverse health effects of the evaluated UV filters is little to none.

9 Benefit characterisation

To summarise the basis for health protective effects, the following key information is described in Chapter 5: The importance of UV-induced outcomes was evaluated and ranked according to the GRADE evaluation system (Schünemann et al., 2013) (Table 5.1-1.) Evaluation of the protective ability of sunscreen use was limited to outcomes that were considered to be "critical" and "important, but not critical". VKM considered protection of these outcomes to be relevant for health benefit.

No systematic reviews or RCTs were retrieved from the literature search or were eligible for inclusion that reported on a protective association between sunscreen use and mortality or genotoxicity (DNA-damage). Immunosuppression, assessed as depletion of Langerhans cells, was considered to be an insufficient marker on its own and was, therefore, not evaluated for health benefits.

Sunscreen and UV exposure data associated with protective effects of sunscreen were fraught with uncertainty (see discussion, Chapter 12) and were not quantified in this risk-benefit assessment. However, amounts of sunscreen used as reported in data from Denmark and other European countries were included in the exposure estimations for UV filters (Chapter 4.3 was assessed) in the absence of data for the Norwegian population. The data on amounts were assumed to be representative for the Norwegian conditions.

Sunscreen use is presumed to be beneficial as protection against certain skin (pre-)cancers. The benefit is larger for squamous cell carcinoma and actinic keratosis than for melanoma. There is probably no benefit of sunscreen in protection against basal cell carcinoma.

10 Risk-benefit comparison and conclusion

VKM considered that there is little to no risk for adverse health effects to the general population associated with the use of UV filters (BEMT, BMDBM, EHT, EHS, OC and NP-TiO_2). The risk of sunscreen use was not determined due to insufficient evidence.

Sunscreen use is presumed to be beneficial as protection against certain skin (pre-)cancers. The benefit is larger for squamous cell carcinoma and actinic keratosis than for melanoma. There is probably no benefit of sunscreen in protection against basal cell carcinoma.

Conclusion

VKM concludes that the risks related to use of the six evaluated UV filters are negligible since the real-life use of these UV filters is several-fold lower than the amounts that may cause any adverse health effect. The evidence for harmful health effects of sunscreens is insufficient to determine risk. Sunscreen use protects against certain skin cancers and is beneficial for the general Norwegian population.

11 Uncertainties

Limitations of the included ingredients

The six UV filters included in this assessment were selected from 21 identified UV filters present in 47 sunscreens in 2017. New UV filters may have been introduced on the market since then, so the most frequently occurring filters may be different in 2022. However, all filters are among those described on the positive list of the All filters were found on the list of ingredients in sunscreens offered on internet stores of pharmacies based in Norway when checked February 14, 2022 (data not shown).

With regard to the included ingredients, the conclusions are representative only for the six selected UV filters. To draw conclusions for other sunscreen ingredients, similar risk-benefit assessments are needed. Therefore, it cannot be excluded that a different selection of ingredients would have given another final risk-benefit result.

There is a possibility that adverse effects may occur due to combinations of UV filters and/or of other ingredients in sunscreen products. However, the inclusion of studies on sunscreen products and health protective and adverse health effects, was likely to have revealed reports on combination effects.

The exposure estimation

Not including exposure from the use of sunscreen spray application devices and sunscreen lip products, may cause underestimation of the estimated exposures to the UV filters.

The sensitivity analysis shows that variation in all three parameters in the estimation of internal exposure (concentration of the UV filter, amount sunscreen applied, and the dermal absorption of the UV filter), has a significant effect on the exposure estimate. Thus, unreliable data may cause under- or overestimation of the estimated exposure.

The amount of UV filter measured in the dermis, epidermis (without stratum corneum) and the receptor fluid are considered as dermally absorbed and is taken into account for further calculations. In the case of substances with very low dermal absorption and limited permeation (*e.g.* UV filters with high molecular weight and low solubility), the epidermis may be excluded from the calculations when it is demonstrated that no movement of the chemicals from the skin reservoir to the receptor fluid occurs (SCCS, 2021). However, in some of the studies where these criteria were fulfilled, the absorption value in epidermis was not given separately but as a total value for dermis and epidermis. Thus, using dermal absorption values from these studies may cause overestimation of the estimated exposures to the UV filter.

The number of samples for concentration analysis of two of the UV filters in sunscreen was very limited, with only one measurement of EHT and five of BEMT. This adds to the

uncertainty of the exposure estimate for these two UV filters and may cause under- or overestimation of the exposure estimate.

The identification of health protective and adverse health effects

Studies on adverse health effects related to sunscreen use demonstrated a pervasive shortcoming of inadequate reporting, notably purity, stability and concentrations of the UV filters. This may result in the classification of a study as having "high" risk of bias due to inadequate reporting on these parameters.

The hazard characterisation

A higher number of well-designed studies addressing potential adverse health effects related to sunscreen use, might reduce the uncertainty in the relationship between sunscreen use and adverse health effects.

With regard to the included ingredients, the conclusions are representative only for the six selected UV filters. To draw conclusions for other sunscreen ingredients, similar risk-benefit assessments are needed. Therefore, it cannot be excluded that a different selection of ingredients would have given another final risk-benefit result.

The NOAELs, and thus the DNELs, for BEMT and EHT were derived from the highest tested dose, as no adverse health effects were reported in the studies of these UV filters. Thus, it is possible that the true NOAEL values were higher.

12 Discussion

Selection of UV filters and exposure assessment

Including all ingredients in the list of allowed UV-filters in cosmetic products on the European market would not be feasible. Hence, VKM selected six UV filters; five organic UV-filters that are among the most frequently used in sunscreens on the Norwegian market, as well as the inorganic UV-filter TiO_2 in nanoform as this filter often is used in sunscreens marketed for children.

Dermally applied NP-TiO_2 was not suspected to give rise to adverse effects due to a negligible dermal absorption. However, it should be noted that due to the carcinogenic properties of NP-TiO_2 when ingested or inhaled (classified as CMR substance of category 2), it is not allowed to be used in sprayable sunscreen products on the European market.

The reasons for not including other ingredients of sunscreens, *e.g.* preservatives, emulsifiers, emollients, thickeners, film formers and fragrances, was that such ingredients are present also in a variety of other cosmetics and personal care products. Taking into account the sesonal and variable daily use of sunscreen, it is anticipated that the contribution to the exposure from other ingredients in sunscreen is considerably lower than from other personal care products.

Several cosmetic and personal care products contain UV filters, evident from their SPF labels. Examples of such products are face and hand moisturisers and makeup. However, to delimit the current assessment to the those that are defined as sunscreens according to the EU Commission Recommendation (2006), product types for which the intended use is not primarily UV protection, were not included.

It was not among the aims of the current assessment to investigate whether concentration values of the selected UV filters were within the maximum allowed concentrations set in the EU (Regulation (EC) No 1223/2009). However, provided that the concentration limits are expressed in weight-%, none of the concentration values reported for any of the six UV filters in the retrieved literature (Chapter 4) were higher than about one percentage point compared with the maximum allowed concentrations.

Exposure was estimated for chronic, daily use of sunscreen, a situation which is not realistic for the Norwegian population. However, according to the US EPA definition of chronic exposure: "repeated exposure by the oral, dermal, or inhalation route for more than approximately 10% of the life span in humans" (EPA, 2022), as well as that of EFSA (glossary): "chronic exposure is a long-term constant or intermittent exposure to a substance which may have an impact on health over time", VKM regards the exposure to sunscreen in the Norwegian population as chronic.

The exposure assessment was performed using probabilistic methods. Contrary to deterministic methods, where single numeric, representative values are used in the exposure calculations, probabilistic methods use distributions or a range of values. The benefit of using probabilistic methods is that they take into account the variability in the input data and allow uncertainty and sensitivity to be estimated. The uncertainty in the probabilistic estimates increases when the number of input data is limited. For some of the UV filters, data on concentration and absorption in sunscreen were limited, and the latter was also variable data on absorption in skin were limited and variable. These shortcomings increased uncertainty in the exposure estimate. However, the same uncertainty would apply to an exposure calculation using a deterministic approach using the same data set, but the variability in the possible exposure would not be quantified. A probabilistic approach was therefore used despite the fact that there was considerable limitations in the input data for some UV filters.

Protective effects and benefit characterisation

Subjects exposed to UV in the time period when commercially available sunscreens primarily contained UVB protection, may have been relatively more protected against lesions originating from layers more easily reached by UVB in the uppermost layer of the skin, namely actinic keratosis and squamous cell carcinoma. Conversely, cells in the deeper layer mainly reached by UVA, may have been less protected. Contributing factors to the heterogenous data reported regarding an association between sunscreen use and melanoma (see *e.g.* Rueegg et al., 2019) and sunscreen use and basal cell carcinoma, may be several-fold: i) there is no sharp, but rather a gradual, biological distinction between UVA and UVB despite different skin penetration depths, ii) the skin depth at which the susceptible cells reside in different subjects varies, and iii) lack of or less UVA protection was offered by sunscreens prior to about 2006.

In theory, more recent studies may to a larger extent be able to demonstrate a protective effect against skin cancers than studies conducted at the time when the subjects used UVB protection only and with lower SPF than is more common today. Sunscreens with a high SPF will have a correspondingly high UVA protection since a minimal factor of 1/3 of the protection must be against UVA. Some studies have reported an increased protective effect of sunscreens against melanoma for SPFs ≥15 relative to SPF <15 (see *e.g.* Ghiasvand et al. (2016). However, the systematic review by Rueegg et al. (2019) which also includes Ghiasvand et al. (2016), states that "*no clear pattern resulted when comparing the few studies that reported three-level estimates of sunscreen use regarding frequency of use, SPF of sunscreen used or duration of use. The association between sunscreen use and melanoma differed by latitude, region, adjustment for nevi/freckling, and proportion of never sunscreen users*".

A contributing factor to the apparent variable protective effect against melanoma, may be low user-adherence to sunscreen product declaration, *i.e.* frequency of application and amount applied. In addition, sunscreen use may affect the consumers' behaviour in that they may prolong the stay in the sun and, thus, increase the total UV exposure. Indeed, according

to Ghiasvand et al. (2016), sunscreen users reported more sunburns, sunbathing vacations and use of solaria than non-sunscreen users.

Study duration is a factor that may influence outcomes with long latency times, such as cancers. Comparing the different skin cancers, median ages for the onset of non-melanoma skin cancers are higher than those of melanoma (Norwegian Cancer Registry, 2021). The scorings on cancer types include exposure to solaria in addition to solar UV. While keeping in mind that solaria has a larger UVA to UVB ratio than that of sun emission (Aalerud et al., 2011), a systematic review of the association between skin cancers and use of solaria found increased risk for both melanoma and non-melanoma skin cancers (An et al., 2021). Thus, the influence of study time with respect to latency time alone for the different skin cancer types seems unclear. The UV exposure pattern, whether it is frequent or intermittent (Leiter et al., 2020) is also suggested to play a role for development of squamous cell carcinoma and melanoma, respectively. Although melanoma (and basal cell carcinoma) can develop after chronic exposure, melanoma seems to be less directly related to cumulative UV exposure than *e.g.* squamous cell carcinoma. This feature may make it more difficult to detect in clinical sunscreen studies.

Several of the studies included in the present opinion were based on the Nambour skin cancer trial (Green et al, 1999), (Chapter 7) where the reporting on suncreen use was not ideally controlled. For instance, the discretionary (optional) use of sunscreen in the control group included any use, no use and everyday use. However, VKM supports the authors' statement that for etichal reasons, subjects in the control groups in studies lasting for years cannot be denied the use of sun protection.

Data on exposure conditions reported in several of the included studies were fraught with uncertainties. Among the uncertainties were the UV exposure to study participants, ambient UV exposure and the relative exposure fraction of UVA to UVB over the time of day and year. Reduced uncertainty would require data on *e.g.* sunscreen use (amount, thickness of layer, identification of UV filters and their concentration present in sunscreen) in the studies under evaluation. However, VKM considered that the evidence found for a protective effect of sunscreen against skin cancer was relevant for the Norwegian population. Data on the amount of sunscreen used by the Norwegian population was absent; however, data from Denmark and other European countries were assumed to be representative for the Norwegian conditions. VKM assumed that the sunscreens protected against similar UV exposure in the Norwegian population as that of the Danish and other Northern European countries. This assumption may be flawed considering the difference in latitudes in Norway. However, sunbathing vacations may represent about half the annual UV dose to a Norwegian individual (Nilsen et al., 2015), which is likely to be the same for the Danish and other Northern European populations.

Photoaging was among the UV-induced effects graded as "of limited importance" (Table 5.1-1). This endpoint was included in the literature selection process, and studies reporting on

this endpoint were among the publications "excluded with reasons" in the selection process (Fig. 5.4.5-1). However, photoaging should not have been evaluated as a UV-induced adverse effects as VKM considers this endpoint to be a benign effect.

Adverse effects

The ability of sunscreens to substantially attenuate UVB is likely to result in reduced absorption of 7-dehydrocholesterol in the epidermis leading to reduced synthesis of vitamin D. However, sunscreens do not attenuate 100% of the incoming UVB. Considering the two studies reporting on the association between sunscreen use and vitamin D levels in the current assessment, the SPF was lower and the UV dose (radiant exposure) three times higher (Faurschou et al., 2011) compared with the study by Marks et al. (1995). The latter lasted for seven Australian summer months while the former was a short-term study performed in the clinic. Gradual sunscreen layers between 0 and 2 mg/cm^2 were tested in Faurschou et al. (2011). The Australian study mimicked realistic sunscreen use, and showed no significant difference in vitamin D (25(OH)) between sunsceren users and non-users. The significant decrease in vitamin D reported by Faurschou et al. (2011) was found for the highest sunscreen thickness, which is higher than thicknesses estimated from reports of user amounts (Heerfordt et al., 2017). Notwhitstanding the limitations of the two studies (see Chapter 6.2.1.2), they collectively demonstrate that it is likely that vitamin D is synthesised despite sunscreen use. However, in Norway the population cannot relay on UVB exposure alone throughout the year and should receive vitamin D from the diet and from supplements when necessary (Brustad and Meyer, 2011).

OC was not included in the literature searches from patch studies in the hazard assessment, since VKM considered the included literature to be sufficient. It is not likely that inclusion of such studies would have resulted in any discrepancies in the hazard and risk characterisation since the local effects due to photopatch tests occurred infrequently, typically below a few percent.

13 Data gaps

Data on concentration of UV filters in sunscreens on the Norwegian market would reduce the uncertainty in the exposure estimate.

Data on amounts of sunscreen applied in the Norwegian population would reduce the uncertainty in the exposure estimate.

Well-designed studies on dermal absorption would reduce the uncertainty in the estimated internal exposure.

Well-designed studies addressing health protective and adverse health effects related to sunscreen use would reduce the uncertainty in the risk and benefit characterisation.

If validated methods for the evaluation of *in vitro* studies in systematic reviews had been available, the identified *in vitro* studies could have been included in the hazard identification and characterisation steps to support a health effect conclusion.

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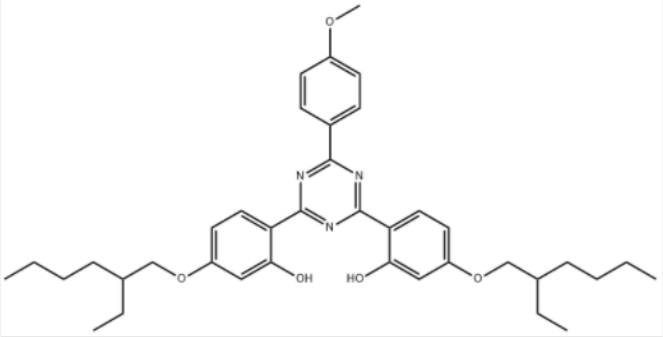
15 Appendix I. UV filters: Identity, physical and chemical properties

15.1 Bis-Ethyl-hexyloxyphenol methoxyphenyl triazine (BEMT)

Bis-ethyl-hexyloxyphenol methoxyphenyl triazine (BEMT) was found in 17 of the 47 products identified in physical and online stores in Scandinavia.

Name, other identifiers, and physical and chemical properties are presented in Table 15.1-1.

Table 15.1-1. Name, other identifiers, physical and chemical properties.

INCI[1] name	Bis-Ethylhexyloxyphenol methoxyphenyl triazine
UV absorption range	UVB/UVA
Highest concentration in ready-to-use product	10%
Chemical name	2,2'-[6-(4-Methoxyphenyl)-1,3,5-triazine-2,4-diyl]bis[5-[(2-ethylhexyl)oxy]-phenol]/ Bemotrizinol
IUPAC[2] name	(6Z)-3-(2-ethylhexoxy)-6-[(4Z)-4-[4-(2-ethylhexoxy)-6-oxocyclohexa-2,4-dien-1-ylidene]-6-(4-methoxyphenyl)-1H-1,3,5-triazin-2-ylidene]cyclohexa-2,4-dien-1-one
Trade names	Bemotrizinol, Escalol S, Tinosorb S, Tinsorb S(T-S) BEMT-S, CGF-C-1607
CAS[3] number	187393-00-6
EC[4] number	425-950-7
InChI Key[5]	LCULPNBYCKULDR-VGWJSVSZSA-N
Molecular formula	$C_{38}H_{49}N_3O_5$
Molecular weight (g/mol)	627.81
Structural formula	
Water solubility	<0.014 mg/L at 20 °C
Topological polar surface area	107 Å²
Partition coefficient (LogP/ Log Kow)	5.7 at 20 °C

1 International Nomenclature Cosmetic Ingredient
2 International Union of Pure and Applied Chemistry
3 Chemical Abstracts Service

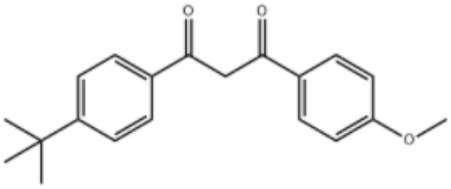
4 European Community number
5 International Chemical Identifier hash, based on IUPAC structure

15.2 Butyl methoxydibenzoylmethane (BMDBM)

Butyl methoxydibenzoylmethane (BMDBM) was found in 21 of the 47 products identified.

Name, other identifiers, and physical and chemical properties are presented in Table 15.2-1.

Table 15.2-1. Butyl methoxydibenzoyl methane; name, other identifiers, physical and chemical properties.

INCI[1] name	**Butyl methoxydibenzoylmethane (BMDBM)**
UV absorption range	UVA
Highest concentration in ready-to-use product	5%
Chemical name	1-[4-(1,1-Dimethylethyl)phenyl]-3-(4-methoxyphenyl)propane-1,3-dione / Avobenzone
IUPAC[2] name	1-(4-tert-butylphenyl)-3-(4-methoxyphenyl)propane-1,3-dione
Trade names	Avobenzone, Avis, Parsol 1789, Escalol 517, Eusolex 9020, NeoHeliopan 357
CAS[3] number	70356-09-1
EC[4] number	274-581-6
InChI Key[5]	XNEFYCZVKIDDMS-UHFFFAOYSA-N
Molecular formula	$C_{20}H_{22}O_3$
Molecular weight (g/mol)	310.39
Structural formula	
Water solubility	0.027 mg/L at 20 °C
Topological polar surface area	43.4 Å²
Vapour pressure	0 Pa at 25 °C
Partition coefficient (LogP/ Log Kow)	6.1 at 20 °C

1 International Nomenclature Cosmetic Ingredient
2 International Union of Pure and Applied Chemistry
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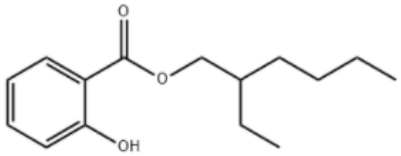
15.3 2-Ethylhexyl salicylate

2-Ethylhexyl salicylate was found in 16 of the 47 products identified.

Name, other identifiers, and physical and chemical properties are presented in Table 15.3-1.

Table 15.3-1. 2-Ethylhexyl salicylate; name, other identifiers, physical and chemical properties.

INCI[1] name	**Ethylhexyl salicylate**
UV absorption range	UVB (to about 330 nm)
Highest concentration in ready-to-use product	5%
Chemical name	2-Ethylhexyl salicylate / octyl salicylate
IUPAC[2] name	2-ethylhexyl 2-hydroxybenzoate
Trade names	Octisalate, Neo Heliopan OS, Uvinul 0-18, Eusolex OS, Sunarome O
CAS[3] number	118-60-5
EC[4] number	204-263-4
InChI Key[5]	FMRHJJZUHUTGKE-UHFFFAOYSA-N
Molecular formula	$C_{15}H_{22}O_3$
Molecular weight (g/mol)	250.33
Structural formula	
Water solubility	0.074 mg/L at 20 °C
Topological polar surface area	46.5 Å²
Vapour pressure	0.018 Pa at 20 °C
Partition coefficient (LogP/ Log Kow)	5.94 at 25 °C

1 International Nomenclature Cosmetic Ingredient
2 International Union of Pure and Applied Chemistry
3 Chemical Abstracts Service
4 European Community number
5 International Chemical Identifier hash, based on IUPAC structure

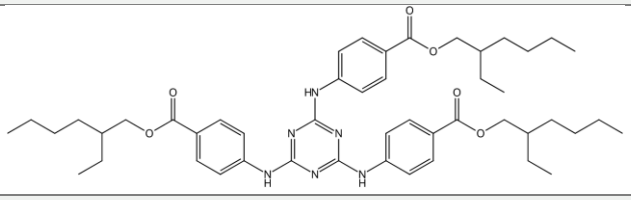
15.4 Ethylhexyl triazone (EHT)

Ethylhexyl triazone was found in 12 of the 47 products identified.

Name, other identifiers, and physical and chemical properties are presented in Table 15.4-1.

Table 15.4-1. 2-Ethylhexyl triazone; name, other identifiers, physical and chemical properties.

INCI[1] name	**Ethylhexyl triazone**
UV absorption range	UVB (to about 330 nm)

INCI[1] name	Ethylhexyl triazone
Highest concentration in ready-to-use product	5%
Chemical name	Tris(2-ethylhexyl)-4,4',4"-(1,3,5-triazine-2,4,6-triyltriimino)tribenzoate
IUPAC[2] name	2-Ethylhexyl 4-[[4,6-bis[4-(2-ethylhexoxycarbonyl)anilino]-1,3,5-triazin-2-yl]amino]benzoate
Trade names	Octyl triazone, Uvasorb ET, Uvinol T-150, Sunsafe EHT
CAS[3] number	88122-99-0
EC[4] number	402-070-1
InChI Key[5]	JGUMTYWKIBJSTN-UHFFFAOYSA-N
Molecular formula	$C_{48}H_{66}N_6O_6$
Molecular weight (g/mol)	823.1
Structural formula	
Water solubility	0.005 mg/L at 25 °C
Topological polar surface area	154 Å²
Vapour pressure	0 Pa at 20 °C
Partition coefficient (LogP/ Log Kow)	7 at 25 °C

1 International Nomenclature Cosmetic Ingredient
2 International Union of Pure and Applied Chemistry
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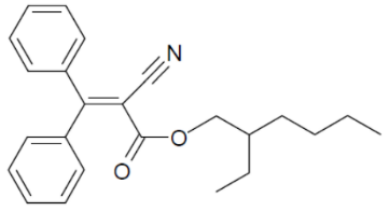
15.5 Octocrylene (OC)

Octocrylene (OC) was found in 16 of the 47 products identified.

Name, other identifiers, and physical and chemical properties are presented in Table 15.5-1.

Table 15.5-1. Octocrylene; name, other identifiers, physical and chemical properties.

INCI[1] name	Octocrylene
UV absorption range	UVB/UVA (to about 350 nm)
Highest concentration in ready-to-use product	10% (as acid)
Chemical name	2-Propenoic acid,2-cyano-3,3-diphenyl-,2-ethylhexyl ester / Octocrilene
IUPAC[2] name	2-ethylhexyl 2-cyano-3,3-diphenylprop-2-enoate

INCI[1] name	Octocrylene
Trade names	Octocrylene USP, Neo Helopan 303, Parsol 340, Sunkem OTC, Uvinul N 539 T, Uvinul 3039
CAS[3] number	6197-30-4
EC[4] number	228-250-8
InChI Key[5]	FMJSMJQBSVNSBF-UHFFFAOYSA-N
Molecular formula	$C_{24}H_{27}NO_2$
Molecular weight (g/mol)	361.5
Structural formula	
Water solubility	0.04 mg/L at 20 °C
Topological polar surface area	50.1 Å²
Vapour pressure	0 Pa at 20 °C
Partition coefficient (LogP/ Log Kow)	6.1 at 23 °C

1 International Nomenclature Cosmetic Ingredient
2 International Union of Pure and Applied Chemistry
3 Chemical Abstracts Service
4 European Community number
5 International Chemical Identifier hash, based on IUPAC structure

15.6 Titanium dioxide (TiO_2)

Titanium dioxide was found in six of the 47 products identified.

Name, other identifiers, and physical and chemical properties are presented in Table 15.6-1.

Table 15.6-1. Titanium dioxide; name, other identifiers, physical and chemical properties.

INCI[1] name	Titanium dioxide
UV absorption range	UVA/UVB
Highest concentration in ready-to-use product	25%
Chemical name	Titanium dioxide
IUPAC[2] name	Dioxotitanium
Trade names	CI 77891, Titane White, Rutile, Anatase, Pigment White 6 (PW6), Optisol,
CAS[3] number	13463-67-7/ 1317-70-0/ 1317-80-2
EC[4] number	236-675-5/ 205-280-1/ 215-282-2
InChI Key[5] number	GWEVSGVZZGPLCZ-UHFFFAOYSA-N
Molecular formula	TiO_2
Molecular weight (g/mol)	79.9

INCI[1] name	Titanium dioxide
Structural formula	
Water solubility	<0.001 mg/L at 20 °C
Topological polar surface area	34.1 Å²
Vapour pressure	
Partition coefficient (LogP/ Log Kow)	Not applicable for an inorganic substance

1 International Nomenclature Cosmetic Ingredient
2 International Union of Pure and Applied Chemistry
3 Chemical Abstracts Service
4 European Community number
5 International Chemical Identifier hash, based on IUPAC structure

16 Appendix II. Literature searches for studies addressing dermal absorption of UV-filters

16.1 Bis-ethyl-hexyloxyphenol methoxyphenyl triazine (BEMT)

Search strategy:

#1 Bis-ethyl-hexyloxyphenol methoxyphenyl triazine
#2 penetrat* OR absorb* OR permeat*
#1 AND #2

Result: 8

An overview of the result of the study selection	
Reference	Relevance
(Durand et al., 2009)	Exclude, not relevant
(Kopke et al., 2019)	Exclude, not relevant
(Munem et al., 2021)	Exclude, not relevant
(Nyeborg et al., 2010)	Exclude, not relevant
(Puglia et al., 2014)	Exclude, not relevant
(Souza et al., 2017)	Include
(Sauce et al., 2021)	Exclude, not relevant
(Teixeira Gomes et al., 2019)	Exclude, not relevant

16.2 Butyl methoxydibenzoyl methane (BMDBM)

Search strategy:

#1 Butyl methoxydibenzoyl methane
#2 penetrat* OR absorb* OR permeat*
#1 AND #2

Result: 5

An overview of the result of the study selection	
Reference	Relevance
(Chatelain et al., 2003)	Include
(Kaidbey and Barnes, 1991)	Exclude, not relevant
(Khalikova et al., 2018b)	Exclude, not relevant
(Montenegro and Puglisi, 2013a)	Include

(Schauder and Ippen, 1997)	Exclude, not relevant

16.3 2-Ethylhexyl salicylate (EHS)

Search strategy:

#1 (2-ethylhexyl salicylate OR ethyl hexyl salicylate OR octisalate or octylsalicylate OR salicylic acid 2-ethylhexyl ester OR trans-2-hexenyl salicylate*)
#2 penetrat* OR absorb* OR permeat*
#1 AND #2

Result: 23

An overview of the result of the study selection	
Reference	Relevance
(Chatelain et al., 2003)	Include
(Fukuchi et al., 2019)	Exclude, not relevant
(Gee et al., 2014)	Exclude, not relevant
(Herzog et al., 2018)	Exclude, not relevant
(Ikarashi et al., 2007a)	Exclude, not relevant
(Ioele et al., 2014)	Exclude, not relevant
(Krishnan and Nordlund, 2008)	Exclude, not relevant
(Matta et al., 2020a)	Exclude, not relevant
(Morgan et al., 1998)	Exclude, not relevant
(McVean and Liebler, 1999)	Exclude, not relevant
(McVean and Liebler, 1997)	Exclude, not relevant
(Nicolazzo et al., 2005a)	Exclude, not relevant
(Nicolazzo et al., 2005b)	Exclude, not relevant
(Nicolazzo et al., 2004)	Exclude, not relevant
(O'Keefe et al., 2016)	Exclude, not relevant
(Paz-Alvarez et al., 2018)	Exclude, not relevant
(Rehfeld et al., 2018b)	Exclude, not relevant
(Santos et al., 2012)	Exclude, not relevant
(Sarveiya et al., 2004)	Exclude, not relevant
(Sierra et al., 2013)	Exclude, not relevant
(Sugiyama et al., 2015)	Exclude, not relevant
(Vilela et al., 2012)	Exclude, not relevant
(Villa et al., 2005)	Exclude, not relevant
(Walters et al., 1997)	Include

16.4 Ethylhexyl triazone (EHT)

Search strategy:

#1 Ethylhexyl triazone
#2 penetrat* OR absorb* OR permeat*
#1 AND #2

Result: 8

An overview of the result of the study selection	
Reference	Relevance
(Baker et al., 2017)	Exclude, not relevant
(Hojerova et al., 2017)	Include
(Potard et al., 2000)	Relevant, however, excluded as data are not available
(Potard et al., 1999)	Include
(Puglia et al., 2014)	Exclude, not relevant
(Sauce et al., 2021)	Exclude, not relevant
(Scalia et al., 2018)	Exclude, not relevant
(Souza et al., 2017)	Include

17 Appendix III. Literature searches for studies addressing health effects related to sunscreens/UV filters

17.1 Literature search systematic reviews and RCTs

Database: Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions® <1946 to March 02, 2020>

Date: 03.03.2020
Result: 11939 (116 reviews, 1396 RCTs, 10427 others)

1	**Sunscreening Agents/**	**5487**
2	(sunblock? or "sun tan lotion?" or "suntan lotion?" or "sun screen?" or "sunscreen?" or "sunburn cream?" or "sun cream?" or "block out?" or ((ultraviolet or UV or UVA or UVB or UVC) adj2 filter?)).tw,kf.	6638
3	((Butyl adj2 (methoxydibenzoylmethane or "methoxydibenzoyl methane")) or avobenzone or butylmethoxydibenzoylmethane or "butylmethoxydibenzoyl methane" or parsol or "Ethylhexyl salicylate" or "salicylic acid 2 ethylhexyl ester" or "Octyl Salicylate" or octisalate or "Bis ethylhexyloxyphenol methoxyphenyl triazine" or "Bisethylhexyloxyphenol methoxyphenyl triazine" or Bemotrizinol or "escalol s" or "tinosorb s" or Octocrylene or octocrilene or "uvinul n 539" or (cyano adj3 (diphenylacrylic or diphenylacrylate) adj3 ethylhexyl) or "Ethylhexyl triazone" or "Titanium dioxide" or anatase or "bayertitan rc k 20" or rutile or titania or "titanic dioxide" or "titanium oxide" or titanox).tw,kf.	16990
4	1 or 2 or 3	24870
5	risk/ or risk assessment/ or risk factors/	1098556
6	(risk* or safety or adverse or "side effect?" or sideeffect? or hazard* or harm* or negative or toxicity or toxic or association? or associate? or relationship or connection? or pertaining or induction?).tw,kf.	8302153
7	«Prevention & Control».fs.	1263651
8	exp Skin Neoplasms/ or exp Melanoma/ or exp Carcinoma/ or Carcinogenesis/ or Cell Transformation, Neoplastic/ or Cocarcinogenesis/ or exp Neoplasms, Squamous Cell/	843249
9	(cancer? or Neoplasm? or Neoplasia? or tumor* or tumour* or carcinoma* or Melanoma? or "Melanotic Freckle?" or Acanthoma? or carcinogenes#s or	3200816

1	**Sunscreening Agents/**	**5487**
	Cocarcinogenes#s or cocancerogenes#s or cocarcinogen#city or metastas#s or (maligna* adj1 lentigo?) or "Neoplastic Cell Transformation?" or epithelioma? or Adenocarcinoma? or "Bowen* Disease" or "Rodent Ulcer?" or basalioma? or basaloma? or "nodular BCC" or "superficial BCC" or paget? or hidradenocarcinoma? or porocarcinoma? or "malignant eccrine poroma" or Acanthoma? or Papilloma*).tw,kf.	
10	Mutagenicity Tests/ or Carcinogenicity Tests/ or Endocrine Disruptors/ or exp Endocrine System/ or Reproductive Health/ or Reproduction/ or skin diseases/ or exp dermatitis/ or exp erythema/ or exanthema/ or exp photosensitivity disorders/ or exp pruritus/ or rosacea/ or Skin Manifestations/ or Ichthyosis/ or exp Skin Diseases, Vascular/ or Prurigo/ or exp Lupus Erythematosus, Systemic/ or exp Porphyrias/	829454
11	(mutagen#city or mutagen testing or genotoxicity or carcinogen#city or carcinogen testing or cancerogen#city or oncogen#city or endocrine or reproductive or reproduction or (skin adj (sensiti#ation? or disease? or disorder? or manifestation? or discomfort? or irritation? or swelling? or rash or rashes or dryness or inflammation? or reaction?)) or "skin blood vessel disorder?" or "dry skin" or drug eruption? or Drug Reaction? or dermatit#s or Dermatit#des or Neurodermatit#s or Neurodermatit#des or erythema? or erythroderma? or erythrodermia? or exanthema or photosensitivity disorder? or photodermatosis or Photodermatiti* or Photosensiti#ation or Photoallerg* or Phototoxic* or photocontact hypersensitivity or photocontact allerg* or ((Polymorphic or polymorphous) adj ("light* eruption?" or "light sensitive eruption?")) or photodermopathy or pruritus or Pruritis or rosacea or Ichthyosis or xeroderma? or Urticaria? or Angioedema? or "angioneurotic edema?" or "quincke* edema?" or Acrodermatit#s or Acrodermatit#des or Eczema or Seborrhea or Exanthem? or Hydroa Vacciniform* or (dermal adj (disease? or disorder? or inflammation?)) or dermatosis or dermatoses or epidermit#s or drug rash* or erythematous eruption? or erythematous rash* or erythemia? or cutaneous reaction? or dermatoxicity or prurigo or lupus or "erythematodes visceralis" or "libman sacks disease" or "libmansacks disease" or lupovisceritis or "sle rash*" or Porphyria? or ((porphyrin or porphyric) adj (disorder* or disease*)) or (deficienc* adj2 "uroporphyrinogen iii synthase") or "uros deficienc*" or "porphobilinogen deaminase deficiency syndrom*" or "ferrochelatase deficiency syndrom*" or ((gunther* or Guenther*) adj (syndrom* or disease*)) or "mckusick 26370" or	716960

1	**Sunscreening Agents/**	**5487**
	"mckusick 17700" or "mckusick 12130" or protoporphyria? or protoporphyrinuria? or coproporphyria? or pseudoporphyria?).tw,kf.	
12	exp Simplexvirus/	30217
13	(((herpesvirus or "herpes virus") adj1 (homini? or human or "2" or "type 2" or "1" or "type 1" or "B" or simiae or Simian or platyrrhinae or platyrrhine or "T" or tamarinus or "saimiri 1" or "saimiri type 1" or marmoset or Platyrhinae or "Papio 2")) or Simplexvirus* or "simplex virus*" or "herpes homini?" or hsv or hsv1 or hsv2 or alphaherpesvirus or "HHV 1" or HHV1 or "HHV 2" or HHV2 or "Allerton virus*" or "bovine mammillitis virus*" or "Bovine ulcerative mammillitis virus*" or "BHM Virus*" or "Bovine Herpes Mammillitis Virus" or "herpes B virus*" or "herpes simiae virus*" or "Cercopithecine Herpesvirus 16" or "Cercopithecine Herpes virus 16" or "herpes T virus*" or "herpesT virus*" or "Herpes Labialis Virus*" or "Marmoset Virus*").tw,kf.	50144
14	or/5-13	11828270
15	4 and 14	10405
16	Sunscreening Agents/ae, to [Adverse Effects, Toxicity]	809
17	(1 or 2) and (effectiveness or effective or effect? or efficacy or benefi* or (evidence adj9 prevent*)).tw,kf.	3789
18	3 and (effectiveness or effective or effect? or efficacy or benefi* or (evidence adj9 prevent*)).tw,kf. and (uv or ultraviolet or UVA or UVB or UVC).tw,kf.	1615
19	15 or 16 or 17 or 18	12221
20	limit 19 to (danish or english or german or multilingual or norwegian or swedish)	11939
21	limit 20 to "reviews (maximizes specificity)"	86
22	20 and (Meta-Analysis/ or ((systematic* adj2 review*) or metaanal* or "meta anal*" or (review and ((structured or database* or systematic*) adj2 search*)) or "integrative review*" or (evidence adj2 review*)).tw,kf,bt.)	103
23	21 or 22	116
24	limit 20 to "therapy (maximizes specificity)"	332
25	20 and (("randomized controlled trial" or "controlled clinical trial").pt. or (randomized or randomised or randomly or rct or placebo or trial or groups).tw,kf,bt.)	1424
26	24 or 25	1424
27	26 not 23	1396
28	20 not (23 or 27)	10427

Database: Embase 1974 to 2020 March 02
Date: 03.03.2020
Result: 15719 (183 reviews, 1842 RCTs, 13694 others)

1	**sunscreen/**	**10413**
2	(sunblock? or "sun tan lotion?" or "suntan lotion?" or "sun screen?" or "sunscreen?" or "sunburn cream?" or "sun cream?" or "block out?" or ((ultraviolet or UV or UVA or UVB or UVC) adj2 filter?)).tw,kw.	9063
3	avobenzone/ or octisalate/ or Bemotrizinol/ or Octocrylene/ or Titanium dioxide/	25311
4	((Butyl adj2 (methoxydibenzoylmethane or "methoxydibenzoyl methane")) or avobenzone or butylmethoxydibenzoylmethane or "butylmethoxydibenzoyl methane" or parsol or "Ethylhexyl salicylate" or "salicylic acid 2 ethylhexyl ester" or "Octyl Salicylate" or octisalate or "Bis ethylhexyloxyphenol methoxyphenyl triazine" or "Bisethylhexyloxyphenol methoxyphenyl triazine" or Bemotrizinol or "escalol s" or "tinosorb s" or Octocrylene or octocrilene or "uvinul n 539" or (cyano adj3 (diphenylacrylic or diphenylacrylate) adj3 ethylhexyl) or "Ethylhexyl triazone" or "Titanium dioxide" or anatase or "bayertitan rc k 20" or rutile or titania or "titanic dioxide" or "titanium oxide" or titanox).tw,kw.	16817
5	(70356-09-1 or 118-60-5 or 187393-00-6 or 6197-30-4 or 88122-99-0 or 13463-67-7 or 1317-70-0 or 1317-80-2).rn.	21389
6	or/1-5	41035
7	risk/ or risk assessment/ or risk factor/ or exp side effect/ or exp adverse drug reaction/ or adverse event/ or toxicity/ or acute toxicity/ or exp health hazard/ or hazard assessment/	2973686
8	(risk* or safety or adverse or "side effect?" or sideeffect? or hazard* or harm* or negative or toxicity or toxic or association? or associate? or relationship or connection? or pertaining or induction?).tw,kw.	11148782
9	exp skin cancer/ or skin tumor/ or exp melanoma/ or carcinoma/ or exp skin carcinoma/ or cocarcinogenesis/ or carcinogenesis/ or papilloma/ or skin papilloma/ or squamous cell carcinoma/ or carcinoma/ or squamous cell skin carcinoma/ or verrucous carcinoma/ or benign skin tumor/ or acanthoma/	560443

1	**sunscreen/**	**10413**
10	(cancer? or Neoplasm? or Neoplasia? or tumor* or tumour* or carcinoma* or Melanoma? or "Melanotic Freckle?" or Acanthoma? or carcinogenes#s or Cocarcinogenes#s or cocancerogenes#s or cocarcinogen#city or metastas#s or (maligna* adj1 lentigo?) or "Neoplastic Cell Transformation?" or epithelioma? or Adenocarcinoma? or "Bowen* Disease" or "Rodent Ulcer?" or basalioma? or basaloma? or "nodular BCC" or "superficial BCC" or paget? or hidradenocarcinoma? or porocarcinoma? or "malignant eccrine poroma" or Acanthoma? or Papilloma*).tw,kw.	4156510
11	mutagenicity/ or mutagen testing/ or genotoxicity/ or carcinogenicity/ or carcinogen testing/ or exp endocrine function/ or reproductive toxicity/ or reproductive health/ or reproduction/ or skin sensitization/ or skin disease/ or dry skin/ or skin discomfort/ or skin irritation/ or exp dermatitis/ or drug eruption/ or exp erythema/ or exp erythroderma/ or exp papular skin disease/ or exp photodermatosis/ or exp pruritus/ or skin manifestation/ or skin swelling/ or skin toxicity/ or xeroderma/ or exp urticaria/ or skin blood vessel disorder/ or exp lupus erythematosus/ or exp porphyria/	1216697

1	**sunscreen/**	**10413**
12	(mutagen#city or mutagen testing or genotoxicity or carcinogen#city or carcinogen testing or cancerogen#city or oncogen#city or endocrine or reproductive or reproduction or (skin adj (sensiti#ation? or disease? or disorder? or manifestation? or discomfort? or irritation? or swelling? or rash or rashes or dryness or inflammation? or reaction?)) or "skin blood vessel disorder?" or "dry skin" or drug eruption? or Drug Reaction? or dermatit#s or Dermatit#des or Neurodermatit#s or Neurodermatit#des or erythema? or erythroderma? or erythrodermia? or exanthema or photosensitivity disorder? or photodermatosis or Photodermatiti* or Photosensiti#ation or Photoallerg* or Phototoxic* or photocontact hypersensitivity or photocontact allerg* or ((Polymorphic or polymorphous) adj ("light* eruption?" or "light sensitive eruption?")) or photodermopathy or pruritus or Pruritis or rosacea or Ichthyosis or xeroderma? or Urticaria? or Angioedema? or "angioneurotic edema?" or "quincke* edema?" or Acrodermatit#s or Acrodermatit#des or Eczema or Seborrhea or Exanthem? or Hydroa Vacciniform* or (dermal adj (disease? or disorder? or inflammation?)) or dermatosis or dermatoses or epidermit#s or drug rash* or erythematous eruption? or erythematous rash* or erythemia? or cutaneous reaction? or dermatoxicity or prurigo or lupus or "erythematodes visceralis" or "libman sacks disease" or "libmansacks disease" or lupovisceritis or "sle rash*" or Porphyria? or ((porphyrin or porphyric) adj (disorder* or disease*)) or (deficienc* adj2 "uroporphyrinogen iii synthase") or "uros deficienc*" or "porphobilinogen deaminase deficiency syndrom*" or "ferrochelatase deficiency syndrom*" or ((gunther* or Guenther*) adj (syndrom* or disease*)) or "mckusick 26370" or "mckusick 17700" or "mckusick 12130" or protoporphyria? or protoporphyrinuria? or coproporphyria? or pseudoporphyria?).tw,kw.	909142
13	exp Simplexvirus/	34464
14	(((herpesvirus or "herpes virus") adj1 (homini? or human or "2" or "type 2" or "1" or "type 1" or "B" or simiae or Simian or platyrrhinae or platyrrhine or "T" or tamarinus or "saimiri 1" or "saimiri type 1" or marmoset or Platyrhinae or "Papio 2")) or Simplexvirus* or "simplex virus*" or "herpes homini?" or hsv or hsv1 or hsv2 or alphaherpesvirus or "HHV 1" or HHV1 or "HHV 2" or HHV2 or "Allerton virus*" or "bovine mammillitis virus*" or "Bovine ulcerative mammillitis virus*" or "BHM Virus*" or "Bovine Herpes Mammillitis Virus" or "herpes B virus*" or "herpes simiae virus*" or "Cercopithecine Herpesvirus 16" or "Cercopithecine Herpes virus 16" or "herpes T virus*" or "herpesT virus*" or "Herpes Labialis Virus*" or "Marmoset Virus*").tw,kw.	59968

1	**sunscreen/**	**10413**
15	or/7-14	14597453
16	6 and 15	17325
17	(1 or 2) and (effectiveness or effective or effect? or efficacy or benefi* or (evidence adj9 prevent*)).tw,kw.	5550
18	(3 or 4 or 5) and (effectiveness or effective or effect? or efficacy or benefi* or (evidence adj9 prevent*)).tw,kw. and (uv or ultraviolet or UVA or UVB or UVC).tw,kw.	2970
19	16 or 17 or 18	20124
20	limit 19 to (conference abstracts or embase)	16226
21	limit 20 to (danish or english or german or norwegian or swedish)	15719
22	limit 21 to "reviews (maximizes specificity)"	94
23	21 and (Meta-Analysis/ or "systematic review"/ or ((systematic* adj2 review*) or metaanal* or "meta anal*" or (review and ((structured or database* or systematic*) adj2 search*)) or "integrative review*" or (evidence adj2 review*)).tw,kw.)	183
24	22 or 23	183
25	limit 21 to "therapy (maximizes specificity)"	356
26	limit 21 to (randomized controlled trial or controlled clinical trial)	444
27	21 and (randomized or randomised or randomly or rct or placebo or trial or groups).tw,kw.	1733
28	25 or 26 or 27	1893
29	28 not 24	1842
30	21 not (24 or 29)	13694

Database: Web of Science
Date: 03.03.2020
Result: 31494 (166 reviews, 2619 RCTs, 28709 others)

# 10	**28,709**	**#6 NOT TS=(("systematic*" NEAR/1 "review*") or "metaanal*" or "meta anal*" or ("review" and (("structured" or "database*" or "systematic*") NEAR/1 "search*")) or "integrative review*" or ("evidence" NEAR/1 "review*") or ("randomized" or "randomised" or "randomly" or "rct" or "placebo" or "trial" or "groups"))** ***Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years***
# 9	2,619	#8 NOT TS=(("systematic*" NEAR/1 "review*") or "metaanal*" or "meta anal*" or ("review" and (("structured" or "database*" or "systematic*") NEAR/1 "search*")) or "integrative review*" or ("evidence" NEAR/1 "review*")) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*
# 8	2,660	#6 AND TS=(("randomized" or "randomised" or "randomly" or "rct" or "placebo" or "trial" or "groups")) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*
# 7	166	#6 AND TS=((("systematic*" NEAR/1 "review*") or "metaanal*" or "meta anal*" or ("review" and (("structured" or "database*" or "systematic*") NEAR/1 "search*")) or "integrative review*" or ("evidence" NEAR/1 "review*"))) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*
# 6	31,494	#5 OR #4 OR #3 *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*
# 5	9,478	TOPIC: ((("Butyl" NEAR/1 ("methoxydibenzoylmethane" or "methoxydibenzoyl methane")) or "avobenzone" or "butylmethoxydibenzoylmethane" or "butylmethoxydibenzoyl methane" or "parsol" or "Ethylhexyl salicylate" or "salicylic acid 2 ethylhexyl ester" or "Octyl Salicylate" or "octisalate" or "Bis ethylhexyloxyphenol methoxyphenyl triazine" or "Bisethylhexyloxyphenol methoxyphenyl triazine" or "Bemotrizinol" or "escalol s" or "tinosorb s" or "Octocrylene" or "octocrilene" or "uvinul n 539" or ("cyano" NEAR/2 ("diphenylacrylic" or "diphenylacrylate") NEAR/2 "ethylhexyl") or "Ethylhexyl triazone" or "Titanium dioxide" or "anatase" or "bayertitan rc k 20" or "rutile" or "titania" or "titanic dioxide" or "titanium oxide" or "titanox") and ("effectiveness" or "effective" or "effect$" or "efficacy" or "benefi*" or ("evidence" NEAR/8 "prevent*")) and ("ultraviolet" or "UV" or "UVA" or "UVB" OR "UVC")) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*
# 4	4,283	TOPIC: (("sunblock$" or "sun tan lotion$" or "suntan lotion$" or "sun screen$" or "sunscreen$" or "sunburn cream$" or "sun cream$" or "block out$" or (("ultraviolet" or "UV" or "UVA" or "UVB" OR "UVC") NEAR/1 "filter$")) AND ("effectiveness" or "effective" or "effect$" or "efficacy" or "benefi*" or ("evidence" NEAR/8 "prevent*"))) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*
# 3	22,733	#2 AND #1 *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*

# 2	13,439,302	TOPIC: (("risk*" or "safety" or "adverse" or "side effect$" or "sideeffect$" or "hazard*" or "harm*" or "negative" or "toxicity" or "toxic" or "association$" or "associate$" or "relationship" or "connection$" or "pertaining" or "induction$" or "cancer$" or "Neoplasm$" or "Neoplasia$" or "tumor*" or "tumour*" or "carcinoma*" or "Melanoma$" or "Melanotic Freckle$" or "Acanthoma$" or "carcinogenes$s" or "Cocarcinogenes$s" or "cocancerogenes$s" or "cocarcinogen$city" or "metastas$s" or ("maligna*" NEAR/0 "lentigo$") or "Neoplastic Cell Transformation$" or "epithelioma$" or "Adenocarcinoma$" or "Bowen* Disease" or "Rodent Ulcer$" or "basalioma$" or "basaloma$" or "nodular BCC" or "superficial BCC" or "paget$" or "hidradenocarcinoma$" or "porocarcinoma$" or "malignant eccrine poroma" or "Acanthoma$" or "Papilloma*" or "mutagen$city" or "mutagen testing" or "genotoxicity" or "carcinogen$city" or "carcinogen testing" or "cancerogen$city" or "oncogen$city" or "endocrine" or "reproductive" or "reproduction" or ("skin" NEAR/0 ("sensiti$ation" or "sensiti$ations" or "disease$" or "disorder$" or "manifestation$" or "discomfort$" or "irritation$" or "swelling$" or "rash" or "rashes" or "dryness" or "inflammation$" or "reaction$")) or "skin blood vessel disorder$" or "dry skin" or "drug eruption$" or "Drug Reaction$" or "dermatit$s" or "Dermatit$des" or "Neurodermatit$s" or "Neurodermatit$des" or "erythema$" or "erythroderma$" or "erythrodermia$" or "exanthema" or "photosensitivity disorder$" or "photodermatosis" or "Photodermatiti*" or "Photosensiti$ation" or "Photoallerg*" or "Phototoxic*" or "photocontact hypersensitivity" or "photocontact allerg*" or (("Polymorphic" or "polymorphous") NEAR/0 ("light* eruption$" or "light sensitive eruption$")) or "photodermopathy" or "pruritus" or "Pruritis" or "rosacea" or "Ichthyosis" or "xeroderma$" or "Urticaria$" or "Angioedema$" or "angioneurotic edema$" or "quincke* edema$" or "Acrodermatit$s" or "Acrodermatit$des" or "Eczema" or "Seborrhea" or "Exanthem$" or "Hydroa Vacciniform*" or ("dermal" NEAR/0 ("disease$" or "disorder$" or "inflammation$")) or "dermatosis" or "dermatoses" or "epidermit$s" or "drug rash*" or "erythematous eruption$" or "erythematous rash*" or "erythemia$" or "cutaneous reaction$" or "dermatoxicity" or "prurigo" or "lupus" or "erythematodes visceralis" or "libman sacks disease" or "libmansacks disease" or "lupovisceritis" or "sle rash*" or "Porphyria$" or (("porphyrin" or "porphyric") NEAR/0 ("disorder*" or "disease*")) or ("deficienc*" NEAR/1 "uroporphyrinogen iii synthase") or "uros deficienc*" or "porphobilinogen deaminase deficiency syndrom*" or "ferrochelatase deficiency syndrom*" or (("gunther*" or "Guenther*") NEAR/0 ("syndrom*" or "disease*")) or "mckusick 26370" or "mckusick 17700" or "mckusick 12130" or "protoporphyria$" or "protoporphyrinuria$" or "coproporphyria$" or "pseudoporphyria$" or (("herpesvirus" or "herpes virus") NEAR/0 ("homini$" or "human" or "2" or "type 2" or "1" or "type 1" or "B" or "simiae" or "Simian" or "platyrrhinae" or "platyrrhine" or "T" or "tamarinus" or "saimiri 1" or "saimiri type 1" or "marmoset" or "Platyrhinae" or "Papio 2")) or "Simplexvirus*" or "simplex virus*" or "herpes homini$" or "hsv" or "hsv1" or "hsv2" or "alphaherpesvirus" or "HHV 1" or "HHV1" or "HHV 2" or "HHV2" or "Allerton virus*" or "bovine mammillitis virus*" or "Bovine ulcerative mammillitis virus*" or "BHM Virus*" or "Bovine Herpes Mammillitis Virus" or "herpes B virus*" or "herpes simiae virus*" or "Cercopithecine Herpesvirus 16" or "Cercopithecine Herpes virus 16" or "herpes T virus*" or "herpesT virus*" or "Herpes Labialis Virus*" or "Marmoset Virus*")) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*
# 1	117,195	TOPIC: (("sunblock$" or "sun tan lotion$" or "suntan lotion$" or "sun screen$" or "sunscreen$" or "sunburn cream$" or "sun cream$" or "block out$" or (("ultraviolet" or "UV" or "UVA" or "UVB" OR "UVC") NEAR/1 "filter$") or

# 10	**28,709**	**#6 NOT TS=(("systematic*" NEAR/1 "review*") or "metaanal*" or "meta anal*" or ("review" and (("structured" or "database*" or "systematic*") NEAR/1 "search*")) or "integrative review*" or ("evidence" NEAR/1 "review*") or ("randomized" or "randomised" or "randomly" or "rct" or "placebo" or "trial" or "groups"))** ***Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years***
		("Butyl" NEAR/1 ("methoxydibenzoylmethane" or "methoxydibenzoyl methane")) or "avobenzone" or "butylmethoxydibenzoylmethane" or "butylmethoxydibenzoyl methane" or "parsol" or "Ethylhexyl salicylate" or "salicylic acid 2 ethylhexyl ester" or "Octyl Salicylate" or "octisalate" or "Bis ethylhexyloxyphenol methoxyphenyl triazine" or "Bisethylhexyloxyphenol methoxyphenyl triazine" or "Bemotrizinol" or "escalol s" or "tinosorb s" or "Octocrylene" or "octocrilene" or "uvinul n 539" or ("cyano" NEAR/2 ("diphenylacrylic" or "diphenylacrylate") NEAR/2 "ethylhexyl") or "Ethylhexyl triazone" or "Titanium dioxide" or "anatase" or "bayertitan rc k 20" or "rutile" or "titania" or "titanic dioxide" or "titanium oxide" or "titanox")) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*

17.1.1 Systematic reviews

17.1.1.1 Full-text assessed – excluded publications

An overview of the publications considered not to fulfil the eligibility criteria is given in Table 17.1.1.1-1.

Table 17.1.1.1-1. Publications considered not eligible.

Reference	Reason for exclusion
(Agin et al., 2009)	Study design
(Agin et al., 2008)	Exposure
(An et al., 2020)	Study design
(Bastuji-Garin and Diepgen, 2002)	Study design
(Bigby, 2004)	Study design
(Boas et al., 2009)	Study design
(Calzavara-Pinton et al., 2011)	Study design
(Cazenave et al., 2019)	Study design
(Chang et al., 2013)	Study design
(Charles et al., 2018)	Study design
Criado et al. (2012)	Study design
de Andrade Moreira et al. (2015)	Study design
de Maleissye et al. (2013)	Study design
Diffey (2005)	Study design
Diffey (2009)	Study design
Drozdowski et al. (2006)	Study design
Farmer and Naylor (1996)	Study design

Reference	Reason for exclusion
Fischer and Bartels (2009)	Study design
Gefeller and Pfahlberg (2002)	Study design
Ghazipura et al. (2017)	Study design
Gillie (2006)	Study design
Glanz and Mayer (2005)	Exposure
Gordon et al. (2009)	Study design
Gorham et al. (2007)	Study design
Guseva Canu et al. (2019)	Exposure
(Harvey, 1995)	Study design
Henrikson et al. (2018)	Exposure
Holman et al. (2014)	Study design
Howell et al. (2014)	Study design
Huncharek and Kupelnick (2000)	Study design
Huncharek and Kupelnick (2002)	Study design
Kasparian et al. (2009)	Outcome
Lin et al. (2011a)	Exposure
Lin et al. (2011b)	Exposure
Jeanmougin (1994)	Study design
Kabi (2015)	Study design
Kutting and Drexler (2010)	Study design
Lorenc et al. (2013)	Outcome
Lund and Timmins (2007)	Study design
Manriquez et al. (2008)	Outcome
Marshall et al. (2003)	Study design
Mazioti (2015)	Study design
Meurer and Jamieson (2006)	Study design
Moreno-Horn and Gebel (2014)	Study design
Mulliken et al. (2012)	Study design
Olsen et al. (2017)	Study design
Poon et al. (2015)	Study design
Rodrigues et al. (2013)	Exposure
Saraiya et al. (2004)	Outcome
Sober (2010)	Study design
Steiner et al. (2009)	Study design
Thanh et al. (2015)	Language
Trakatelli et al. (2016)	Outcome
Volkovova et al. (2012)	Study design
Waldman and Grant-Kels (2019)	Study design
Wang et al. (2016)	Study design
Warheit and Brown (2019)	Study design
Werner et al. (2013)	Outcome
Whiteman et al. (2019)	Study design
Wille et al. (1998)	Study design
Xie et al. (2015)	Study design
Zeeb and Greinert (2010)	Study design

17.1.1.2 Internal validity

The evaluation of internal validity in the eight eligible systematic reviews was as follows:

1. **Dennis et al. (2003)**

Review type: Aetiology

Phase 1: Assessing relevance		
Category (PICO equivalents)	Target question	Review being assessed
Patients/Population(s):	All age groups	Adults and children
Exposure(s) and comparator(s):	Sunscreen use compared to not using sunscreen	Sunscreen use compared to not using sunscreen
Outcome(s):	(Reduction of) Adverse health effects	Melanoma
Does the question addressed by the review match the question you are trying to answer?	Yes The questions match for all categories. The outcome addressed is considered to be an important adverse outcome.	
Phase 2: Identifying concerns with the review process		
Domain 1 – study eligibility criteria		
Signalling question	Rating	Reasoning
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Probably yes	The objective and study selection criteria were clearly described. There was no protocol, however, that was not expected as the study was published in 2003. It was good reason to believe that eligibility criteria were specified in advance and adhered to.
1.2 Were the eligibility criteria appropriate for the review question?	Yes	The eligibility criteria were appropriate for the review question with respect to age range, diagnosis, exposure agent and setting.
1.3 Were eligibility criteria unambiguous?	Probably yes	The type of study design and the exposure agent was clearly stated. For the outcome, an uncertainty was introduced: The authors stated "Because the diagnosis of melanoma is based on histologic examination, all studies were assumed to have included histologic confirmation, even if this was not explicitly stated". There was no mention of melanomas that were not induced by solar UVR.
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	Yes	The restrictions based on types of study design were clearly described and appeared to be appropriate.

Phase 1: Assessing relevance		
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	Probably yes	The literature search covered articles published from 1966. No justification for this restriction was provided.
Concerns regarding specification of study eligibility criteria	Low	All signaling questions were answered yes or probably yes, so no potential concerns about the study eligibility criteria were identified.
Domain 2: Identification and selection of studies		
Signalling question	Rating	Reasoning
2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports?	Yes	Medline and Cancerlit. As the study was published in 2003, this choice of databases was considered to be satisfactory.
2.2 Were methods additional to database searching used to identify relevant reports?	Yes	The references of identified articles, including bibliographies of the review articles, were checked for additional relevant studies. The authors reviewed articles from the first author's files that appeared to be related to melanoma and sunscreen use, sunburns, or sunlight. In addition, for one abstract and one unpublished study found in the references of reviews on sunscreen use but not on MEDLINE, the authors were contacted.
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Yes	The use of key words, text words and medical subject heading for melanoma and sunscreen agents appeared to be sensitive with no inappropriate restrictions. Note that search term criteria have become stricter and more advanced searches would be expected in newer publications.
2.4 Were restrictions based on date, publication format, or language appropriate?	Probably yes	No language restrictions were applied. The literature searches covered articles published from 1966, and no justification for this restriction was provided.
2.5 Were efforts made to minimise errors in selection of studies?	No information	The process for screening titles was acceptable. The process for evaluation of full text articles was not described.
Concerns regarding methods used to identify and/or select studies	Unclear	The signaling questions 2.1-2.4 were rated yes or probably yes. Due to insufficient information reported in signaling question 2.5, an overall judgement of concerns regarding methods used to identify and select studies cannot be made.
Domain 3: Data collection and study appraisal		
Signalling question	Rating	Reasoning

Phase 1: Assessing relevance		
3.1 Were efforts made to minimise error in data collection?	Yes	Reviewers were blinded to the authors, journal of publication, and introduction and discussion of each article. Two independent reviewers abstracted data from every article, and the 2 sets of results were compared for concordance and re-reviewed if necessary. Inconsistencies were re-reviewed until agreement was achieved. Third-party resolution of disagreements was sought when necessary. No data extraction form was used, however, that was not expected as the study was published in 2003.
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Yes	Detailed study characteristics and results tables were provided.
3.3 Were all relevant study results collected for use in the synthesis?	Probably yes	OR and variances when reported were used, otherwise these data were estimated (Data extraction and Results). Sub-group analyses were performed. It is a question whether it was relevant to include studies that received quality score ratings of zero.
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Probably yes	A quality-assessment scoring system was developed, and the criteria were appropriate, *e.g.* type of control, pretesting the questionnaire, blinding of interviews, etc.
3.5 Were efforts made to minimise error in risk of bias assessment?	Yes	Two investigators independently assessed study quality. In the publication year, 2003, it was not common to use RoB tools, but in newer publications it must be expected that quality scoring will impact the results and conclusions.
Concerns regarding methods used to collect data and appraise studies	Low	All signaling questions were rated yes or probably yes.
Domain 4: Synthesis and findings		
Signalling question	Rating	Reasoning
4.1 Did the synthesis include all studies that it should?	Yes	The authors identified 20 studies relevant to the review, of which 18 were included in the analysis. Detailed reasons for the exclusion of two studies were given.
4.2 Were all predefined analyses followed or departures explained?	Probably yes	No analyses were predefined in a protocol. However, from the text in the materials and methods Chapter, we have the impression that the analyses were predefined (method Chapter appears rigorous/all analyses mentioned were addressed in Results).

Phase 1: Assessing relevance		
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Probably yes	Random effects analyses were performed (takes the variability of effects into consideration) which is appropriate for a broad research question with large variations in PEO. Such a method enables the specification of sub-groups/sensitivity analyses in advance, which was not described, since a protocol was not available. It was probably not a strong relationship between study size and effect, which would have been inappropriate for a random-effect meta-analysis. It was not reported whether each study was weighted.
4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	Yes	Heterogeneity was addressed in the synthesis.
4.5 Were the findings robust, *e.g.* as demonstrated through funnel plot or sensitivity analyses?	Probably Yes	A sensitivity analysis was performed. A strength is that the sub-group analysis with the sun sensitive persons (n=9) has overlapping confidence intervals with the overall study (n=18) but goes in another direction. No funnel plot was presented (it could have indicated the presence of small studies with large standard errors)
4.6 Were biases in primary studies minimal or addressed in the synthesis?	No	The quality scores were not used in the quantitative analyses.
Concerns regarding methods used to synthesize results	Unclear	The signaling questions 4.1 to 4.5 were rated yes or probably yes. Due to lack of inclusion of the quality scores in the synthesis, an overall judgement of concerns regarding methods used to synthesize results cannot be made.
Phase 3: Judging risk of bias		
Signalling question	Rating	Reasoning
A. Did the interpretation of findings address all the concerns identified during the Phase 2 assessment?	Probably no	Unclear concerns identified during the phase 2 assessment: whether two reviewers performed full-text assessment and lack of inclusion of the quality scores in the synthesis
B. Was the relevance of identified studies to the review's research question appropriately considered	Probably yes	This is indicated by eligibility criteria and study characteristics as well as the thorough discussion which also included the bias of the included studies.
C. Did the reviewers avoid emphasizing results based on their statistical significance?	Yes	Both studies that demonstrated significantly statistical and non-statistical results were included and were part of the overall conclusion

Phase 1: Assessing relevance		
Risk of bias	Unclear	The phase 2 assessment identified concerns with the review process: full-text assessment and lack of inclusion in the quality scores. Some uncertainty is related to whether the studies are sufficiently similar, and a sensitivity analysis related to quality should have been performed.

2. Green and McBride (2014)

Review type: Intervention

Phase 1: Assessing relevance		
Category (PICO equivalents)	Target question	Review being assessed
Patients/Population(s):	All	Not specified
Intervention(s):	Sunscreen	Regular sunscreen
Comparator(s):	Not specified	Not specified
Outcome(s):	(Reduction in) adverse effects	Prevention of CSCC (incidence rates), SCC (mortality) and actinic (solar) keratosis (prevalence)
Does the question addressed by the review match the question you are trying to answer?	Partially The questions match for all categories except that population is not explicitly specified. The outcomes addressed are considered to be important adverse outcomes.	
Phase 2: Identifying concerns with the review process		
Domain 1 – study eligibility criteria		
Signalling question	Rating	Reasoning
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Probably no	The focused question lacks specifications on participants (Abstract and Questions). Some study selection criteria were described and exclusions were pre-specified (Methods). The Methods indicate that predefined criteria were set, but there is no mention of a protocol
1.2 Were the eligibility criteria appropriate for the review question?	Probably yes	The eligibility criteria reported were appropriate, but some details were lacking in particular in relation to the population

Phase 1: Assessing relevance		
1.3 Were eligibility criteria unambiguous?	Probably no	There were insufficient details about eligibility criteria. In particular, there were no details about which study populations or which study settings were eligible. Diagnosis criteria were lacking (although written in "definition"). Type of sunscreen was unclear (search terms included years prior to introduction of SPF)
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	Probably yes	The restrictions based on types of study design, study size, %follow-ups and blinding were clearly described and appeared to be appropriate (Methods). It is questionable whether restriction to RCT was appropriate due to the anticipated long time from onset of cellular damage to manifestation of (pre-)skin cancer. This may warrant other study designs than RCTs
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	Probably no	Restricted to English language.
Concerns regarding specification of study eligibility criteria	Unclear	There were insufficient details regarding study eligibility criteria to judge whether the appropriate studies were included in the review; in particular details on eligible participants, sunscreen type and diagnosis were lacking. Only RCTs in English were eligible
Domain 2: Identification and selection of studies		
Signalling question	Rating	Reasoning
2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports?	Yes	Medline, Embase, Cochrane DSR and additional searches in DARE and HTA.
2.2 Were methods additional to database searching used to identify relevant reports?	No information	There was no information about other methods to identify reports
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	No information	The full search strategy was not reported and there were no details of the search terms; there was therefore no information on which to base the assessment for this question.

Phase 1: Assessing relevance		
2.4 Were restrictions based on date, publication format, or language appropriate?	Probably no	The review was restricted to English language studies; there is therefore a potential for publication bias. Since Medline and Cochrane were searched from the beginning, so should Embase also have been (1974), however, it was searched from 1980.
2.5 Were efforts made to minimise errors in selection of studies?	No	Only one person conducted each sequence of the inclusion assessment.
Concerns regarding methods used to identify and/or select studies	High	There were concerns regarding restrictions to English language articles and the inclusion assessment that was conducted by only one person per sequence. Due to the lack of information on full search strategy we cannot judge whether the search strategy was fit for purpose.
Domain 3: Data collection and study appraisal		
Signalling question	Rating	Reasoning
3.1 Were efforts made to minimise error in data collection?	No	One person extracted all data relevant to the review. There is no mention of a data extraction form.
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Probably no	study characteristics and results tables were provided., but details on population characteristics were lacking
3.3 Were all relevant study results collected for use in the synthesis?	Probably yes	The number of people with the diagnosis in question with regular sunscreen use vs. discretionary/no sunscreen use were used to calculate RR or adjusted ratios. There was no detailed information in Methods to describe how results data that were not reported in the format required for synthesis were obtained; therefore, "probably yes" was chosen. Furthermore, results were presented narratively. Adverse effects did not undergo analysis.
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	No	No risk of bias was performed
3.5 Were efforts made to minimise error in risk of bias assessment?	Not applicable	No risk of bias was performed

Phase 1: Assessing relevance		
Concerns regarding methods used to collect data and appraise studies	High	Some bias may have been introduced through the data collection and risk of bias assessment processes since there is insufficient information on the number of reviewers and a data extraction form was not used.
Domain 4: Synthesis and findings		
Signalling question	Rating	Reasoning
4.1 Did the synthesis include all studies that it should?	Probably no	According to the abstract, five studies were identified and four were reported from in the synthesis (Refs. 12, 13, 17, 18) (Typing error?). Note: The SR included two other research questions (treatment-related), but no RCTs were found for these topics.
4.2 Were all predefined analyses followed or departures explained?	No information	No analyses were predefined in a protocol. There is no reference to the existence or absence of a protocol. No further information is provided in the text.
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Probably yes	Each category had only one or two (including follow-up) RCTs. With only one RCT per group, a meta-analysis was not feasible and a narrative synthesis was performed.
4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	No information	No detail was provided on statistical heterogeneity. A subgroup analysis was reported in one RCT within one category (sunscreen to prevent SCC). There were one (two) RCTs per category.
4.5 Were the findings robust, *e.g.* as demonstrated through funnel plot or sensitivity analyses?	Probably yes	The only subgroup analysis that was performed, did not change the conclusion (but addressed whether there was any difference in incidence between regular sunscreen users with or without a history of skin cancer, P= 0.42)
4.6 Were biases in primary studies minimal or addressed in the synthesis?	No	Risk of bias was not addressed
Concerns regarding methods used to synthesize results	High	The synthesis is likely to produce biased results because there were important inadequacies in the methodology
Phase 3: Judging risk of bias		
Signalling question	Rating	Reasoning
A. Did the interpretation of findings address all the concerns identified during the Phase 2 assessment?	No	Most of the limitations identified by the Phase 2 assessment were not identified as limitations by the review authors and so were not addressed in the interpretation of findings.

Phase 1: Assessing relevance		
B. Was the relevance of identified studies to the review's research question appropriately considered	Probably yes	Not explicitly, but each study was commented and study characteristics and sources of biases (regarding sunscreens) were mentioned.
C. Did the reviewers avoid emphasizing results based on their statistical significance?	Yes	The review conclusions reflect both the statistically significant and non-significant review findings.
Risk of bias	High	The Phase 2 assessment identified a number of areas of concern with the review process which were not addressed by the authors. These include eligible participants, possibility of missing studies, lack of formal quality assessment, and insufficient details on included studies.

3. Horsham et al. (2014)

Review type: Intervention

Phase 1: Assessing relevance		
Category (PICO equivalents)	Target question	Review being assessed
Patients/Population(s):	All	Outdoor workers
Intervention(s):	Sunscreen	Skin cancer intervention strategies to reduce sun exposure and/or its harmful effects, of which use of sunscreen could be one of them
Comparator(s):	Not specified	Partial or no intervention
Outcome(s):	(Reduction in) adverse effects	Sun protection behaviours and/or objective measures of skin cancer risks
Does the question addressed by the review match the question you are trying to answer?	Partial The questions partially match for population, intervention and outcome. Intervention is a broad term that may or may not include the use of sunscreen	
Phase 2: Identifying concerns with the review process		
Domain 1 – study eligibility criteria		
Signalling question	Rating	Reasoning
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Probably yes	The authors stated that the systematic review was an update of Saraiya et al. (2014) and that the inclusion criteria were adapted from this publication. No protocol was available.

Phase 1: Assessing relevance		
1.2 Were the eligibility criteria appropriate for the review question?	Probably yes	The eligibility criteria reported seemed appropriate.
1.3 Were eligibility criteria unambiguous?	Probably yes	There were some insufficient details about eligibility criteria such as study population (age, gender) and diagnosis (keratosis).
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	Yes	Restriction on date was appropriate since this was a follow-up.
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	Probably no	Language restriction was applied without justification. It is unclear if additional restriction criteria from Saraiya et al. (2004) were applied.
Concerns regarding specification of study eligibility criteria	Low	The overall concern was regarded to be low. We consider the language restriction to English not to represent a major bias.
Domain 2: Identification and selection of studies		
Signalling question	Rating	Reasoning
2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports?	Yes	MEDLINE, Cumulative Index to Nursing and Allied Health Literature, and PsycInfo.
2.2 Were methods additional to database searching used to identify relevant reports?	Yes	Reference lists of relevant papers were manually searched for further studies.
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Yes	The search terms and structure were considered appropriate to retrieve a wide range of relevant studies. The full search terms were referred to in Saraiya et al. (2004).
2.4 Were restrictions based on date, publication format, or language appropriate?	Probably no	No restrictions on publication format. Restrictions on date was appropriate. No justification for the language restriction was given.
2.5 Were efforts made to minimise errors in selection of studies?	Probably yes	The authors stated that "two independent reviewers screened the papers for eligibility for inclusion". It was not described in detail whether this task included both screening of titles/abstracts and assessment of full texts articles,

Phase 1: Assessing relevance		
Concerns regarding methods used to identify and/or select studies	Low	No concerns considered to be important for the identification and selection of studies were documented. The overall concerns were therefore considered to be low. We consider the language restriction to English not to represent a major bias.
Domain 3: Data collection and study appraisal		
Signalling question	Rating	Reasoning
3.1 Were efforts made to minimise error in data collection?	No information	It does not say explicitly whether two independent reviewers extracted data, whether a data extraction form was used and whether a piloting process was used.
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Probably no	Information was presented in a table and in the methods Chapters, but it was not detailed enough, especially with regard to sunscreen and objective outcome measures
3.3 Were all relevant study results collected for use in the synthesis?	Probably yes	Relevant results were collected. Quantitative data were not reported.
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	No	Quality grading system was not described and could not be interpreted. It was referred to a quality level in an accessible article (open access). This quality system did not include risk of bias rating.
3.5 Were efforts made to minimise error in risk of bias assessment?	Not applicable	As risk of bias evaluation was not performed, there is no information on the quality assessment process with respect to number of reviewers.
Concerns regarding methods used to collect data and appraise studies	High	Due to lack of information on the process for data collection and evaluation of risk of bias, the overall concern is regarded to be high.
Domain 4: Synthesis and findings		
Signalling question	Rating	Reasoning
4.1 Did the synthesis include all studies that it should?	Yes	All six included papers were present in the study characteristics table
4.2 Were all predefined analyses followed or departures explained?	No information	There was no way to check as no protocol was written and there were no predefined analyses
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Yes	A narrative approach was appropriate for the mixture of quantitative and qualitative results

Phase 1: Assessing relevance		
4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	Yes	The synthesis of results was narrative, *i.e.* heterogeneity was addressed by the fact that results were not combined.
4.5 Were the findings robust, *e.g.* as demonstrated through funnel plot or sensitivity analyses?	No information	The review authors did not address robustness.
4.6 Were biases in primary studies minimal or addressed in the synthesis?	No	Evaluation of risk of bias was not performed
Concerns regarding methods used to synthesize results	High	The overall concerns regarding methods used to synthesize results were high, as there was no information about predefined analyses and robustness evaluation and biases in primary studies were not addressed.
Phase 3: Judging risk of bias		
Signalling question	Rating	Reasoning
A. Did the interpretation of findings address all the concerns identified during the Phase 2 assessment?	No	None of the limitations identified in the Phase 2 assessment were identified as limitations by the review authors and were not addressed in the interpretation of the findings
B. Was the relevance of identified studies to the review's research question appropriately considered	Probably yes	The included studies seemed relevant although there was no specific consideration in the discussion or risk of bias assessment. Population characteristics were properly described in a table.
C. Did the reviewers avoid emphasizing results based on their statistical significance?	Yes	There was no overall calculated statistical significance. Both significant and no-significant results were reported
Risk of bias	High	The overall risk of bias was considered to be high as serious concerns identified in the Phase 2 assessment were not addressed by the study authors.

4. Neale et al. (2019)

Review type: Aetiology and intervention

Phase 1: Assessing relevance		
Category (PICO equivalents)	Target question	Review being assessed

Phase 1: Assessing relevance		
Patients/Population(s):	All age groups	All age groups
Intervention(s):	Sunscreen use compared to not using sunscreen	Sunscreen use compared to not using sunscreen
Comparator(s):	Adverse health effects	Reduction in vitamin D_3 or 25 hydroxyvitamin D [25(OH)D
Does the question addressed by the review match the question you are trying to answer?	Yes The questions match for all categories. Vitamin D deficiency is considered to be an adverse outcome	

Phase 2: Identifying concerns with the review process		
Domain 1 – study eligibility criteria		
Signalling question	Rating	Reasoning
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Probably yes	The aim and eligibility criteria were well described. No protocol was available.
1.2 Were the eligibility criteria appropriate for the review question?	Yes	The eligibility criteria were only for study design and seemed appropriate.
1.3 Were eligibility criteria unambiguous?	Yes	The eligibility criteria were clearly and sufficiently detailed described.
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	Probably yes	Restrictions based on study design were clearly described and appeared to be appropriate, although no justification was provided.
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	Yes	No such restrictions were applied.
Concerns regarding specification of study eligibility criteria	Low	All signaling questions were rated yes or probably yes, and the overall concerns were considered to be low.
Domain 2: Identification and selection of studies		
Signalling question	Rating	Reasoning
2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports?	Yes	The search was performed in MEDLINE, Embase and ISI Web of Science.
2.2 Were methods additional to database searching used to identify relevant reports?	Yes	The reference lists of retrieved studies were searched.

Phase 1: Assessing relevance		
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Yes	A wide range of search terms were used, including both MESH terms and text words. The searches, including the search terms, are shown in the supplementary material.
2.4 Were restrictions based on date, publication format, or language appropriate?	Probably no	Restrictions on language (English), publication period (from 1970 and later) and were applied. No justification was given. In addition, the search did not include abstracts and unpublished studies. No further restrictions on publication format were applied.
2.5 Were efforts made to minimise errors in selection of studies?	Yes	Two authors reviewed all potentially eligible manuscripts; any discrepancies were resolved by joint evaluation of the manuscript and further consultation with additional authors.
Concerns regarding methods used to identify and/or select studies	Low	The concerns regarding methods used to identify and select studies is considered to be low. We consider the restrictions based on date, publication format, and language not to represent a major bias. All other signaling questions were answered as "yes".
Domain 3: Data collection and study appraisal		
Signalling question	Rating	Reasoning
3.1 Were efforts made to minimise error in data collection?	Yes	Two authors extracted relevant information, with any discrepancies resolved through joint evaluation and consultation with two additional authors.
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Yes	Detailed information on study characteristics were reported.
3.3 Were all relevant study results collected for use in the synthesis?	Probably yes	Detailed information are included in tables, appropriately for a narrative synthesis. However, quantitative results such as difference in mean values or RR were not collected.
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	No	A quality assessment tool was used for the observational studies, however, it did not address biases. For the experimental studies and trials, quality scoring was not performed.
3.5 Were efforts made to minimise error in risk of bias assessment?	Not applicable	

Phase 1: Assessing relevance		
Concerns regarding methods used to collect data and appraise studies	High	As individual studies were not assessed for risk of bias, the concerns regarding methods used to collect and appraise studies were considered to be high.
Domain 4: Synthesis and findings		
Signalling question	Rating	Reasoning
4.1 Did the synthesis include all studies that it should?	Yes	All studies were included and described in tables.
4.2 Were all predefined analyses followed or departures explained?	No information	There was no way to check as no protocol was written and there were no predefined analyses
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Probably yes	A narrative synthesis approach was used for experimental, field studies and the observational studies, with the latter divided further into sub-groups due to large heterogeneity.
4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	Yes	Substantial heterogeneity in study populations and design and in reporting of results precluded meta-analysis of the observational studies. Instead, these studies were cross-classified into categories defined according to the results of unadjusted and adjusted analyses of the association between sunscreen use and 25(OH)D concentration or vitamin D status.
4.5 Were the findings robust, *e.g.* as demonstrated through funnel plot or sensitivity analyses?	No information	The review authors did not address robustness.
4.6 Were biases in primary studies minimal or addressed in the synthesis?	No	Risk of bias was not assessed.
Concerns regarding methods used to synthesize results	High	Concerns regarding methods used to synthesize results are considered to be high, as bias were not accounted for in the synthesis, robustness was not addressed, and there was no information on whether the analyses were predefined.
Phase 3: Judging risk of bias		
Signalling question	Rating	Reasoning
A. Did the interpretation of findings address all the concerns identified during the Phase 2 assessment?	No	None of the limitations identified by the Phase 2 assessment were identified as limitations by the review authors and so were not addressed in the interpretation of findings.

Phase 1: Assessing relevance		
B. Was the relevance of identified studies to the review's research question appropriately considered	Probably yes	The included studies seemed relevant although there was no specific consideration in the discussion.
C. Did the reviewers avoid emphasizing results based on their statistical significance?	Yes	Both studies that demonstrated significantly statistical and non-statistical results were included.
Risk of bias	High	The overall risk of bias was considered to be high as serious concerns identified in the Phase 2 assessment were not addressed by the study authors.

5. Rueegg et al. (2019)

Review type: Intervention

Phase 1: Assessing relevance		
Category (PICO equivalents)	Target question	Review being assessed
Patients/Population(s):	All age groups	General human population
Intervention(s):	Sunscreen	Sunscreen use: all versions of comparisons of sunscreen use: ever vs. never use; low vs. high use, and site of application
Comparator(s):	Not using sunscreen	Never/no use of sunscreen
Outcome(s):	Reduction of UVR induced adverse health effects	Cutanous melanoma The primary outcome is the effect of sunscreen use (ever/never use) on the risk of melanoma.
Does the question addressed by the review match the question you are trying to answer?	Yes The questions match for all categories. The outcome addressed is considered to be an important adverse outcome	
Phase 2: Identifying concerns with the review process		
Domain 1 – study eligibility criteria		
Signalling question	Rating	Reasoning
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Yes	A study protocol (PROSPERO ID:CRD4201706398049) written according to PRISMA-P was published in PROSPERO. Objective and eligibility criteria were clearly described.

Phase 1: Assessing relevance		
1.2 Were the eligibility criteria appropriate for the review question?	Yes	The inclusion and exclusion criteria were clearly described and seemed appropriate to answer the research question.
1.3 Were eligibility criteria unambiguous?	Yes	Properly described criteria addressing study type, population, exposure and outcome.
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	Yes	The restrictions based on types of study design were clearly described and appeared to be appropriate.
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	Yes	The only restriction was that the exposure should clearly proceed the outcome, and this was appropriate.
Concerns regarding specification of study eligibility criteria	Low	The eligibility criteria were predefined in a protocol and seems appropriate to answer the objectives. All signaling questions were rated yes.
Domain 2: Identification and selection of studies		
Signalling question	Rating	Reasoning
2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports?	Yes	Searches were performed in PubMed (including Medline), Embase and Cochrane Database of Systematic Reviews.
2.2 Were methods additional to database searching used to identify relevant reports?	Yes	The reference lists of relevant published reviews were searched. In addition, the protocol database PROSPERO was searched to identify relevant ongoing reviews and screen their reference lists.
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Yes	The search included terms for intervention, outcome and population, and no inappropriate restrictions were included. The use of key words, text words and medical subject heading for melanoma and sunscreen appeared to be sensitive. Search terms were adapted for each database.
2.4 Were restrictions based on date, publication format, or language appropriate?	Yes	The search included no such restrictions.
2.5 Were efforts made to minimise errors in selection of studies?	Yes	Both selection steps were performed independently by two reviewers. Discrepancies was discussed to find a consensus, if no consensus was reached, a third reviewer made a final decision.

Phase 1: Assessing relevance		
Concerns regarding methods used to identify and/or select studies	Low	All signaling questions were rated yes. The identification and selection of studies were performed according to the process of a systematic review and were appropriate.
Domain 3: Data collection and study appraisal		
Signalling question	Rating	Reasoning
3.1 Were efforts made to minimise error in data collection?	Yes	Data extraction was performed by one author and double-checked for errors by another author. Discrepancy were discussed among the authors until consensus was reached. A data extraction form was used.
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Yes	Detailed information from the included studies were presented. The data were presented in both overview tables and tables with more details regarding the outcome of the studies.
3.3 Were all relevant study results collected for use in the synthesis?	Yes	All relevant results from the included studies were collected.
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Yes	The Cochrance Collaboration's tool for assessing risk of bias (the Cochrane Handbook for Systematic Reviews of Interventions) was used.
3.5 Were efforts made to minimise error in risk of bias assessment?	Yes	Quality assessment was performed by one reviewer and double-checked for errors by to other authors. Disagreement was resolved by discussion within a subgroup of the authors
Concerns regarding methods used to collect data and appraise studies	Low	Data collection and study appraisal were done according to established well recognised methods. All signaling questions were rated yes.
Domain 4: Synthesis and findings		
Signalling question	Rating	Reasoning
4.1 Did the synthesis include all studies that it should?	Yes	All studies were included for the qualitative synthesis. For the meta-analysis, one study on melanoma in children was not included.
4.2 Were all predefined analyses followed or departures explained?	Yes	Analyses were performed according to the protocol.
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Yes	The synthesis seemed appropriate and well described.

Phase 1: Assessing relevance		
4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	Yes	The between-study variation was thoroughly addressed in the synthesis and showed that there was a considerable heterogeneity among the included studies.
4.5 Were the findings robust, *e.g.* as demonstrated through funnel plot or sensitivity analyses?	Yes/ probably yes	Publication bias and Egger's regression test was investigated using funnel plots, according to the author. The funnel plot was asymmetric indication a bias and heterogeneity between the studies.
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Yes/ probably yes	The level of bias were included in the level of heterogeneity in the meta-analysis.
Concerns regarding methods used to synthesize results	Low	The synthesis of the findings in the review seems very well presented using well recognized methods, including exploring the sources of heterogeneity and levels of bias. All signaling questions were rated yes/probably yes.
Phase 3: Judging risk of bias		
Signalling question	Rating	Reasoning
A. Did the interpretation of findings address all the concerns identified during the Phase 2 assessment?	Yes	The risk of bias was evaluated using well recognized methods and addressed according to the published protocol.
B. Was the relevance of identified studies to the review's research question appropriately considered	Yes	Relevant studies were included according to the eligibility criteria, and also shown in the synthesis of the results from these studies.
C. Did the reviewers avoid emphasizing results based on their statistical significance?	Yes	Both studies that showed an increased risk and reduced risk of sunscreen use and melanoma was included in the review
Risk of bias	**Low**	All parts of the review used methods approved for systematic review, resulting in a low risk of bias of the review.

6. Sanchez et al. (2016)

Review type: Intervention

Phase 1: Assessing relevance		
Category (PICO equivalents)	Target question	Review being assessed

Phase 1: Assessing relevance		
Patients/Population(s):	All	The general population (children and adults)
Intervention(s):	Sunscreen	Sun protection strategies (*i.e.* sunscreen and barrier methods)
Comparator(s):	Not specified	Not specified
Outcome(s):	(Reduction in) adverse effects	Prevention of keratinocyte cancer (basal cell carcinoma, cutaneous cell carcinoma of the skin) and adverse events
Does the question addressed by the review match the question you are trying to answer?	Yes The question matches for all categories	
Phase 2: Identifying concerns with the review process		
Domain 1 – study eligibility criteria		
Signalling question	Rating	Reasoning
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Yes	A clearly focused question is presented and a protocol was published (Sanchez, 2014) addressing, among others, study design, participants and types of intervention.
1.2 Were the eligibility criteria appropriate for the review question?	Yes	The details of studies eligible for inclusion provided in the article appeared appropriate to the review question.
1.3 Were eligibility criteria unambiguous?	Yes	The type of study design was clearly stated (RCT) as was population (general population) and outcomes (BCC and SCC confirmed with histopathology or clinically, adverse events and more). The authors excluded observational studies and trials focusing on special populations (e.g., people with actinic keratoses, organ transplant recipients, etc.). Sunscreens with any sun protection factor (SPF) were defined in types of intervention.
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	Probably no	The description of not including trials focused on educational strategies or and prevention in high-risk groups was appropriate. There were no restrictions on gender or age. There is a question whether the restriction to RCTs only is appropriate. The time from sun exposure to manifestation of (pre-)skin cancers may be from years to decades, and this may warrant other study designs than RCTs.
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	Yes	There was no other restrictions such as on language or publication status.

Phase 1: Assessing relevance		
Concerns regarding specification of study eligibility criteria	Unclear	No potential concerns about the specification of eligibility criteria were identified. The review question and objectives were clearly specified. Eligibility criteria were pre-specified in a detailed and published protocol (Cochrane). However, the restriction to RCTs may result in missing information and no rationale was given for this choice.
Domain 2: Identification and selection of studies		
Signalling question	Rating	Reasoning
2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports?	Yes	The following databases were searched: The Cochrane Skin Group Specialised Register; CENTRAL (Cochrane); MEDLINE; EMBASE; LILACS as well as trial registers: metaRegister of Controlled Trials; NIH ongoing trials Registers; Australian New Zealand Clinical Trials Registry; WHO International Clinical Registry Platform, EU Clinical Trials Register
2.2 Were methods additional to database searching used to identify relevant reports?	Yes	The authors checked the bibliographies of included studies for further references to relevant trials.
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Yes	A detailed search strategy was provided in the appendix for each database. Terms for intervention (sunscreen) and outcome were combined.
2.4 Were restrictions based on date, publication format, or language appropriate?	Yes	Databases were searched from inception, no language restrictions were applied, and no publication status.
2.5 Were efforts made to minimise errors in selection of studies?	Yes	Two review authors independently selected studies for eligibility using software (EROS) by checking titles and abstracts and assessing the full texts.
Concerns regarding methods used to identify and/or select studies	Low	No potential areas of bias were identified.
Domain 3: Data collection and study appraisal		
Signalling question	Rating	Reasoning
3.1 Were efforts made to minimise error in data collection?	Yes	Two review authors independently used predesigned data collections forms to retrieve information. The format was tested prior to extended use. Disagreements were solved by discussion with a third reviewer.

Phase 1: Assessing relevance		
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Yes	Detailed study characteristics and results tables were provided which reported sufficient information. Which data to be extracted was also described in the Method Chapter.
3.3 Were all relevant study results collected for use in the synthesis?	Yes	The Methods Chapter describes how results data were to be presented, both for dichotomous outcome (which was used for the only included study) and for continuous outcomes. It was not expected to find cross-over studies so unit of analysis issues were not expected.
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Yes	RoB was assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.
3.5 Were efforts made to minimise error in risk of bias assessment?	Yes	Two authors independently assessed risk of bias.
Concerns regarding methods used to collect data and appraise studies	Low	RoB was assessed using appropriate criteria, data extraction and RoB assessment involved two reviewers, and relevant study characteristics and results were extracted.
Domain 4: Synthesis and findings		
Signalling question	Rating	Reasoning
4.1 Did the synthesis include all studies that it should?	Yes	Flow chart reported one review as did the study characteristics table and risk of bias summary and summary of findings table.
4.2 Were all predefined analyses followed or departures explained?	Yes	The review followed a published and accessible protocol (Sanchez, 2014; Cochrane). Departures were described in detail in the Appendix.
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Yes	Since only one study was included, a narrative approach was appropriate for the synthesis.
4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	Yes	Assessment of heterogeneity was planned to be investigated by means of I^2 statistics, but was not relevant since only one study was included. Heterogeneity was planned if I^2 statistics was greater than 30%. In cases where I^2 statistics were more than 80%, the authors did not plan to present pooled results.

Phase 1: Assessing relevance		
4.5 Were the findings robust, *e.g.* as demonstrated through funnel plot or sensitivity analyses?	Not applicable	Only one study was included.
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Yes	Risk of bias was assessed and summarized in Fig. 2 and in detail in the table describing characteristics of studies. The assessment indicated a high risk of bias for incomplete outcome data (high loss of follow-up) regarding a secondary outcome and unclear bias regarding selective reporting and other bias. Other aspects were not of major concern.
Concerns regarding methods used to synthesize results	Low	Risk of bias was addressed and the authors had planned for heterogeneity if there had been more studies.
Phase 3: Judging risk of bias		
Signalling question	Rating	Reasoning
A. Did the interpretation of findings address all the concerns identified during the Phase 2 assessment?	Probably yes	The only concern regarding Phase 2 assessment was the restriction to RCT, and this was not discussed in the review. However, we do not consider this predefined choice to be a major issue compared with the thorough overall discussion that was presented.
B. Was the relevance of identified studies to the review's research question appropriately considered	Yes	Relevance was considered in the risk of bias assessment and in several sub-chapters of the discussion Chapter
C. Did the reviewers avoid emphasizing results based on their statistical significance?	Yes	The results were not statistically significant
Risk of bias	Low	The Phase 2 assessment identified no concerns with the review process. The potential limitations of the studies included in the review in terms of risk of bias were discussed in detail in the discussion. The review conclusions appropriately reflect the results of the review.

7. Silva et al. (2018)

Review type: Aetiology

Phase 1: Assessing relevance		
Category (PICO equivalents)	Target question	Review being assessed

Phase 1: Assessing relevance		
Patients/Population(s):	All age groups	Adults and children
Exposure(s) and comparator(s):	Sunscreen use	Sunscreen use, two or more categories of frequency of use
Outcome(s):	(Reduction of) adverse health effects	Risk of skin cancer (any type: melanoma, basal cell carcinoma, squamous cell carcinoma)
Does the question addressed by the review match the question you are trying to answer?	Yes The questions match for all categories. The outcomes addressed are considered to be important adverse outcomes.	

Phase 2: Identifying concerns with the review process		
Domain 1 – study eligibility criteria		
Signalling question	Rating	Reasoning
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Probably yes	The authors specified clearly in Abstract and Introduction that the objectives were to assess the association between risk of skin cancer and sunscreen use in adults and children. A protocol (PRISMA) was completed in 2015 and approved by a panel of experts, but it is not referenced or available as appendix, therefore this question was rated "probably yes".
1.2 Were the eligibility criteria appropriate for the review question?	yes	All are appropriate.
1.3 Were eligibility criteria unambiguous?	No	The review question addressed sunscreen use as exposure; however, "sunscreen" is a very broad term, and exposure should be limited to *e.g.* having an SPF or making sure that the product really reduced UV to skin cells (which was not the case for all of the earliest products prior to about 1980). It is not clear what the term "sunscreen" encompasses as articles studying sunscreens characterised as suntan lotion and sunburn cream were included. Skin cancer diagnosis methods are not addressed.
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	yes	Two search limits are described, but these are appropriate
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	yes	No restrictions on sources of information were described.

Phase 1: Assessing relevance		
Concerns regarding specification of study eligibility criteria	High	Studies including assessment of sunscreens that were not likely to prevent UV (prior to 1980'ies) were included and skin cancer diagnosis was not addressed.
Domain 2: Identification and selection of studies		
Signalling question	Rating	Reasoning
2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports?	Yes	PubMed, Google Scholar and BIREME were searched. The latter includes a large number of databases where also conference papers and reports can be found. Searches were done in two steps: from beginning to the protocol was written in 2015 and then from 2015 to 2017.
2.2 Were methods additional to database searching used to identify relevant reports?	Yes	Handsearching was performed by examining the reference list of the primary studies and systematic reviews.
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	No information	Search terms for skin cancer are not sufficient (synonyms are lacking) (full strategy was not available)
2.4 Were restrictions based on date, publication format, or language appropriate?	Yes	No restrictions were based on date, publication format or language.
2.5 Were efforts made to minimise errors in selection of studies?	Yes	Three review authors independently assessed the titles and abstracts and, although not stated explicitly, we assume all three assessed full-text articles of all citations identified in the searches.
Concerns regarding methods used to identify and/or select studies	Unclear	Overall, the concern is low; however, it is unclear how the limited search terms for cancer diagnoses will affect the identification of studies.
Domain 3: Data collection and study appraisal		
Signalling question	Rating	Reasoning
3.1 Were efforts made to minimise error in data collection?	Probably Yes	Two review authors independently extracted the data from each study using a standardised data extraction form.
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Yes	A table containing characteristics of the 30 included articles (29 studies) was presented.

Phase 1: Assessing relevance		
3.3 Were all relevant study results collected for use in the synthesis?	Yes	All association terms (OR, RR, HR+95%CI) along with study type were described in study characteristics table.
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Yes	The quality of each study was assessed according to quality assessment tools by the NIH. The grading was based on bias related to selection, information, measurement and confounding.
3.5 Were efforts made to minimise error in risk of bias assessment?	Yes	Two review authors independently assessed the quality of each study.
Concerns regarding methods used to collect data and appraise studies	Low	All signaling questions were rated "Yes" or "Probably yes". The review processes of data collection and study appraisal are unlikely to have introduced bias into the review.
Domain 4: Synthesis and findings		
Signalling question	Rating	Reasoning
4.1 Did the synthesis include all studies that it should?	Probably yes	30 articles reporting 29 studies were included (Results and Fig. 1) 30 studies are characterised in Table 1 and represented in a forest plot in Fig. 2. 32 estimates in funnel plot (Fig. 3)
4.2 Were all predefined analyses followed or departures explained?	Probably yes	Under methods, the authors write that a review protocol was completed and approved by a panel of experts, but there is no reference to it and it is not present as an appendix. However, the method Chapter is rigorous.
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Yes	A random-effects model was used for conventional and cumulative meta-analysis. The funnel plot (Fig. 3; Egger test) did not indicate small-study effects.
4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	Probably no	The heterogeneity was high (89.4%), and was addressed overall and for sub-group analyses. The high heterogeneity was not sufficiently explained.
4.5 Were the findings robust, *e.g.* as demonstrated through funnel plot or sensitivity analyses?	Yes	Funnel plot was symmetrical, heterogeneity was high, sensitivity analyses were performed that, with one exception, showed that all effects went in the same direction. The findings are robust as only one subgroup analysis factor changes the estimate.
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Yes	Quality of evidence was rated for each study in the synthesis (Table 1), and quality by subgroup analysis was investigated

Phase 1: Assessing relevance		
Concerns regarding methods used to synthesize results	Low	The high heterogeneity was not sufficiently explained and the protocol was not accessible. However, authors addressed heterogeneity in their analysis and explored subgroup analyses. Quality assessment of the individual studies was addressed.
Phase 3: Judging risk of bias		
Signalling question	Rating	Reasoning
A. Did the interpretation of findings address all the concerns identified during the Phase 2 assessment?	Probably no	The ambiguities related to type of sunscreen and diagnosis were not addressed.
B. Was the relevance of identified studies to the review's research question appropriately considered	No	Many aspects of the individual studies and the overall findings were discussed. However, the relevance of older studies with inappropriate (sunscreen) exposure was incompletely considered
C. Did the reviewers avoid emphasizing results based on their statistical significance?	Yes	The conclusion was based on the non-significant association between sunscreen and skin cancer.
Risk of bias	High	The concern regarding exposure during phase 2 was not appropriately addressed in the review conclusions and the conclusion did not consider the relevance of included studies with questionable sunscreen exposure/diagnosis to the review question.

8. Thoonen et al., 2020

Review type: Intervention

Phase 1: Assessing relevance		
Category (PICO equivalents)	Target question	Review being assessed
Patients/Population(s):	All age groups	Children and adolesents (0-18 år)
Intervention(s):	Sunscreen	Environmental interventions targeting sun protection behaviors
Comparator(s):	Not using sunscreen	Control group – no intervention
Outcome(s):	Reduction UVR induced adverse health effects	Effectiveness of interventions targeting sun protection behaviors as skin cancer prevention strategy

Phase 1: Assessing relevance		
Does the question addressed by the review match the question you are trying to answer?	Partial Effects of sunscreen is not the main focus, thus, the study is of limited relevance	
Phase 2: Identifying concerns with the review process		
Domain 1 – study eligibility criteria		
Signalling question	Rating	Reasoning
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Probably yes	The aim was clearly described, and the authors stated that prior formulated inclusion criteria were established. The criteria were presented in a table. A protocol was not available.
1.2 Were the eligibility criteria appropriate for the review question?	Yes	The criteria were suitable for the review question.
1.3 Were eligibility criteria unambiguous?	Yes	Population, intervention, comparison, outcomes and study design were clearly described.
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	Yes	Restrictions based on study characteristics were clearly presented and seemed appropriate.
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	Probably no	The language of the included articles was restricted to English, and the time period was limited to 1990. No reasoning was given.
Concerns regarding specification of study eligibility criteria	Low	The overall concern was regarded to be low. We consider the language and date restrictions not to represent a major bias.
Domain 2: Identification and selection of studies		
Signalling question	Rating	Reasoning
2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports?	Yes	Four databases, PubMed, PsycInfo, Cochrane, Web of Science, and Google Scholar were used. An updated search was also performed to ensure inclusion of recent studies.
2.2 Were methods additional to database searching used to identify relevant reports?	No information	There were no information on additional searching for relevant reports.

Phase 1: Assessing relevance		
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Probably no	A wide range of Mesh terms and text words were used. However, the included terms for specific interventions such as *e.g.* sunscreen were limited and relevant studies may therefore not have been identified.
2.4 Were restrictions based on date, publication format, or language appropriate?	Yes	No such restrictions were used in the search.
2.5 Were efforts made to minimise errors in selection of studies?	Yes	Two of the authors independently screened titles in the first round, abstracts in the second round and full-text articles in the third round. When no consensus about eligibility could be reached, a third researcher was consulted.
Concerns regarding methods used to identify and/or select studies	High	The overall with regard to identification and selection of studies was considered to be high, due to the lack of search terms for specific interventions.
Domain 3: Data collection and study appraisal		
Signalling question	Rating	Reasoning
3.1 Were efforts made to minimise error in data collection?	Yes	Data were extracted by two authors independently. A standardized data abstraction form was critically examined and altered regarding specific characteristics of the studies that were selected. Characteristics of the selected studies that were abstracted were predominantly formulated based on the PICOS framework. After entirely reading the first included study, study characteristics were further specified according to elaborate data that was present in this study.
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Yes	Detailed study characteristics were presented in a table, and outcomes and results were presented in a separate table. Information on statistical analyses that were conducted were also included.
3.3 Were all relevant study results collected for use in the synthesis?	Probably yes	Detailed information are included in tables, appropriately for a narrative synthesis. However, quantitative results such as difference in mean values or RR were not collected.

Phase 1: Assessing relevance		
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Yes	The validated method for quality assessment "Quality Assessment Tool for Quantitative Studies" from the Effective Public Health Practice Project, was used.
3.5 Were efforts made to minimise error in risk of bias assessment?	Yes	The risk of bias assessment was performed by two authors independently.
Concerns regarding methods used to collect data and appraise studies	Low	Concerns regarding methods used to collect data and appraise studies were considered to be low as all signaling questions were rated "Probably yes" or "yes".
Domain 4: Synthesis and findings		
Signalling question	Rating	Reasoning
4.1 Did the synthesis include all studies that it should?	Yes	The authors identified 7 studies relevant to the review, and these were included in the qualitative synthesis
4.2 Were all predefined analyses followed or departures explained?	No information	There was no way to check as no protocol was written and there were no predefined analyses.
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Yes	Results were presented according to categories, and only studies addressing the specific category were included. The analysis performed was qualitative.
4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	Yes	Between-studies variations were described. Due to heterogeneity, no quantitative analysis was performed.
4.5 Were the findings robust, *e.g.* as demonstrated through funnel plot or sensitivity analyses?	No information	No such analyses were described.
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Probably no	Biases were assessed and discussed, however, not included in the data synthesis
Concerns regarding methods used to synthesize results	High	Concerns regarding methods used to synthesize results are considered to be high, as bias were not accounted for in the synthesis, robustness was not addressed, and there was no information on whether the analyses were predefined.
Phase 3: Judging risk of bias		

Phase 1: Assessing relevance		
Signalling question	Rating	Reasoning
A. Did the interpretation of findings address all the concerns identified during the Phase 2 assessment?	No	None of the limitations identified by the Phase 2 assessment were identified as limitations by the review authors and so were not addressed in the interpretation of findings.
B. Was the relevance of identified studies to the review's research question appropriately considered	Probably yes	
C. Did the reviewers avoid emphasizing results based on their statistical significance?	Yes	Both studies that demonstrated significantly statistical and non-statistical results were included and were part of the overall conclusions.
Risk of bias	High	

17.1.1.3 Data extraction

The data extraction forms for Rueegg et al. (2019), Sanchez et al. (2016) and Dennis et al. (2003):

Characteristics of the systematic review	
Title	Challenges in assessing the sunscreen-melanoma association
Author(s)	C. S. Rueegg, J. S. Stenehjem, M. Egger, R. Ghiasvand, E. Cho, E. Lund, E. Weiderpass, A. C. Green, M. B. Veierød
Year of publication	2019
Start and ending dates of the literature search	Articles published by 28.02.2018.
Country of origin (corresponding author)	Norway
Funding	FP7 People: Marie-Curie Actions (FP7-PEOPLE-2013-COFUND) to CSR; Grant numbers: 609020-Scientia Fellow, co-founded by the Institute of Basic Medical Sciences, University of Oslo; Grant sponsor: Norwegian Cancer Society; Grant numbers: 6823329, 2197685, 5829980; Grant sponsor: National Institutes of Health to EC; Grant numbers: CA198216.
Reported conflict of interest	No conflict of interest was reported for any of the authors.
What is the main objective of the review?	The main objective was to answer whether sunscreen use affects melanoma risk. The authors aimed to 1) systematically summarise the existing literature on sunscreen use and melanoma in humans; 2) investigate the effect of ever- vs. never-use on melanoma risk; 3) assess

Characteristics of the systematic review	
	the effect of different levels and patterns of sunscreen use; 4) identify sources of bias and between-study heterogeneity; and 5) describe the relationship between site of sunscreen application and site of melanoma.
Hypotheses tested	Not reported
Quality assessment tool(s)	Study quality was assessed based on the Cochrane Handbook's tool for assessing risk of bias and the Newcastle-Ottawa Scale for assessing the quality of non-randomised studies included in a systematic review and/or meta-analyses. The confidence in the cumulative evidence was assessed using GRADE (*i.e.* the 22 studies based on the "maximally adjusted estimate on ever- vs. never-use of sunscreen and melanoma risk".
Results of quality assessment	GRADE results (including risk of bias): For the hospital-based case-control studies (n=9) the risk of bias, the inconsistency, the indirectness and the imprecision were very serious, and publication bias was considered to be likely. The overall quality of evidence was considered to be very low. For the population-based case-control studies (n=8) the risk of bias and the indirectness were very serious, the inconsistency was serious, and publication bias was considered to be likely. The overall quality of evidence was considered to be very low. For the ecological study and the cohort studies (n=3) the risk of bias and the indirectness were serious, and the overall quality of evidence was considered to be very low. For the randomised controlled trial the imprecision was serious. The overall quality of evidence was considered to be moderate. Methodological quality: Case-control studies were heterogeneous while the ecological study, cohort study and RCT fulfilled almost all the methodological requirements. The method and detail of sunscreen use varied greatly between studies.
Data synthesis methodology	- All analyses were performed in STATA. - Ever- vs. never-use of sunscreen were analysed. If more than two categories of sunscreen use were reported, estimates were aggregated (*e.g.* "sometimes" and "often" were aggregated into ever-use). - For three-level, different patterns and high sunscreen use, all estimates with at least three categories on frequency of sunscreen use, SPF used, and duration of use were extracted. For each study, the lowest and highest categories were categorised as lowest and highest groups, respectively and all intermediate categories were aggregated. - For each three-level variable on sunscreen use, the intermediate was compared to the lowest level and the highest to the lowest level. - Heterogeneity between studies was tested with the Q-test. I^2 – index>50% and 75% were indicative of moderate and high heterogeneity, respectively. Sources of heterogeneity were explored by i) random-effects meta-analyses stratified by variables predefined in the protocol, and ii) univariable random-effects meta-regression

Characteristics of the systematic review	
	analyses, on the maximally adjusted ever- vs. never-use estimate. Tau-squared was used to estimate the remaining between-study variance in the meta-regression model. - Publication bias was investigated by the funnel plot and Egger's regression test for the maximally-adjusted ever-never estimates. - Contour-enhanced funnel plots were used to define regions of the plot in which a new study would have to be located to change the statistical significance of the meta-analysis and thereby assess the robustness of the current meta-analysis.
Data synthesis	*Ever- vs. never-use of sunscreen:* - The forest plot of minimally-adjusted estimates showed heterogeneity both within hospital-based (I^2 = 86%, p < 0.001) and population-based case–control studies (I^2 = 80%, p < 0.001), and between the different study designs. - The forest plot of maximally-adjusted estimates showed that adjustment moved most estimates toward a more reduced risk of melanoma among sunscreen users though substantial heterogeneity remained, especially within case–control studies (I^2 = 86%, p < 0.001 for hospital-based; 81%, p < 0.001 for population-based) but also between study designs. - Ever- vs. never-use of sunscreen was inversely associated with melanoma in hospital-based case–control studies (adjusted odds ratio (OR) = 0.57, 95% confidence interval (CI) 0.37–0.87, $p_{heterogeneity}$ < 0.001), the ecological study (rate ratio = 0.48, 95% CI 0.35–0.66), and the randomised controlled trial (hazard ratio (HR) = 0.49, 95% CI 0.24–1.01). Ever- vs. never-use of sunscreen and melanoma was not associated in the population-based case–control studies (OR = 1.17, 95% CI 0.90–1.51, $p_{heterogeneity}$ < 0.001). Ever- vs. never-use of sunscreen and melanoma was positively associated in the cohort studies (HR = 1.27, 95% CI 1.07–1.51, $p_{heterogeneity}$ = 0.236). The association differed by latitude, region, adjustment for naevi/freckling and proportion of never-sunscreen-users. Studies conducted in lower latitudes showed an inverse association between sunscreen use and melanoma (summary estimate = 0.64, 95%CI 0.47–0.89 for studies ≤42°N) but there was no association in studies from higher latitudes (summary estimate = 1.09, 95% CI 0.83–1.44, $p_{interaction}$ = 0.042). Statistically significant interactions were observed between the association of sunscreen use and 1) the region of the study ($p_{interaction}$ = 0.008); 2) adjustment for naevi and/or freckles (with an inverse association only in studies adjusting; $p_{interaction}$ = 0.035); and, 3) the proportion of sunscreen users in the study (with an inverse association of sunscreen use and melanoma only in studies where ≥55% of participants never used sunscreen; $p_{interaction}$ = 0.012). Remaining between-study variance was generally high after all stratifications (0.131 ≤ tau-squared ≤ 0.492). *Three-level estimates of sunscreen use and melanoma risk* The summary estimates comparing sometimes- to never-use were 1.07 (95% CI 0.80–1.42) in the hospital-based case–control studies, 1.13 (95% CI 0.98–1.30) in the population-based case–control studies, and 1.38

Characteristics of the systematic review					
	(95%CI 1.17–1.62) in the cohort studies. The summary estimates comparing often/always- to never-use were 1.01 (95% CI 0.38–2.67) in the hospital-based case–control studies, 1.01 (95% CI 0.67–1.52) in the population-based case–control studies, and 1.32 (95%CI 1.10–1.59) in the cohort studies *Meta bias* The funnel plot showed that all of the current studies were lying in the area where future studies (if lying in the same area) would change the current effect estimate toward a significantly positive association between sunscreen use and melanoma risk (significant effect estimate >1).				
Characteristics of the studies included in the systematic reviews					
Study design	23 case–control studies, 1 ecological study, 3 cohort studies and 1 randomised controlled trial.				
Country/countries where the study is conducted (n) and data collection period	*Study design*	*Country*	*Data collection period*	*Total no of participants/age range at diagnosis/% males*	*SPF*
	Hospital-based case-control studies	Austria	1993-1994	512/18-89/54	NR
		Brazil (2)	1995-1998; 2004-2008	309/20-84/NR; 424/15-79/50	SPF <8, SPF 8-15, SPF 15+; NR
		Czech Republic	2010-2011	518/NR (mean 54)/46	NR
		Greece	2000-2004	400/19-84/49	NR
		Italy	1992-1995	1080/NR/42	Never - minimal/medium SPF – high SPF
		Norway	1974-1975	209/>20/61	NR
		Spain (2)	1989-1993; 1990-1994	243/20-79/35; 351/21-87/47	NR; NR
		USA (2)	1974-1980; 1991-1992	420/NR/100; 1662/20-79/55	NR; NR
	Population-based case-control studies	Australia (3)	1980-1981; 1994; 1987-1994	1014/10-79/46; 208/3-14/NR; 406/15-19/50	NR; NR; NR

Characteristics of the systematic review					
		Denmark	1982-1985	1400/20-79/41	NR
		France	1989-2008	1219/NR (mean=57)/0	Sunscreen use since age 25: no protection, SPF <8, SPF 8-15, SPF >15
		France, Germany, Belgium	< 1990	856/NR/NR	NR
		Sweden (3)	1978-1983; 1988-1990; 1995-1997	1028/NR/45; 1040/15-75/49; 1449/16-80/50	NR; NR; no sunscreen, 1 to 10, >10
		USA (3)	1982-1983; not reported; 2004-2009	739/>18/100; 1382/25-59/0; 2268/25-59/40	NR; NR; 15+, never in both decades, inconsistent, frequent in both decades
	Prospective ecological study	Finland	1920-1985	11535/NR/47	NR
	Prospective cohort studies	Norway (2)	1991-2012; 1999-2012	143844/42-83/0; 1755/33-84/100	Sunscreen use in high/low latitude: never, SPF<15 inconsistently, SPF <15 consistently, sometimes SPF ≥15; NR
		USA	1976-2000	178155/NR (mean=53)/32	NR
	Randomised controlled trial	Australia	1992-2006	1621/NR/44	NR
Are hypotheses regarding our aim presented? If yes, quote	Not reported				
Substance(s) tested (sunscreen as such or sunscreen	Sunscreen as such, various use frequency and sun protection factors.				

Characteristics of the systematic review	
ingredient(s)) and sun protection factor	
List of outcomes considered	The outcome considered was the effect of sunscreen use on melanoma risk.
Key findings that relate to the research questions in Tables 3-1 and 4-1 in the protocol	- Ever- vs. never-use of sunscreen was inversely associated with melanoma in hospital-based case–control studies, the ecological study, and the randomised controlled trial. - Ever- vs. never-use of sunscreen and melanoma was not associated in the population-based case–control studies. - Ever- vs. never-use of sunscreen and melanoma was positively associated in the cohort studies
Comments:	

Characteristics of the systematic review	
Title	Sun protection for preventing basal cell and squamous cell skin cancers (Review)
Author(s)	G. Sánchez, J. Nova, A.E. Rodriguez-Hernandez, R.D. Medina, C. Solorzano-Restrepo, J. Gonzalez, M. Olmos, K. Godfrey, I. Arevalo-Rodriguez
Year of publication	2016
Start and ending dates of the literature search	Articles published up to May 2016.
Country of origin (corresponding author)	Colombia
Funding	Internal funding sources: Fundación Universitaria de Ciencias de la Salud, Colombia and Centro Dermatológico Federico Lleras Acosta, Colombia. External sources: Colombian Ministry of Health and Social Protection, Colombia, The National Institute for Health Research (NIHR), UK. The NIHR, UK, is the largest single funder of the Cochrane Skin Group
Reported conflict of interest	No reports of conflict of interest were disclosed.
What is the main objective of the review?	The main objective was to assess the effects of sun protection strategies (*i.e.* sunscreen and barrier methods) for preventing keratinocyte cancer (basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC) of the skin) in the general population.
Hypotheses tested	None reported
Quality assessment tool	The criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions was used to assess the risk of bias.

Characteristics of the systematic review	
	The guidelines of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group was used to assess the quality of the evidence.
Results of quality assessment	RoB: The following elements from six domains were considered to have low risk of bias: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of the following outcome assessments: histologically diagnosed BCC, cSCC, adverse events, actinic or solar keratosis, participant's compliance with preventive strategies; Incomplete outcome data for BCC, SCC, adverse events. High risk of bias: Incomplete outcome data for actinic keratoses. Unclear risk of bias: selective reporting and other bias (unclear assessment of sunscreen and beta-carotene; unclear impact of repeated significance testing; unclear impact of clinical vs. histological diagnosis of keratinocyte cancer) GRADE: The evidence used to address incidence of new BCC or new cSCC was of low quality. The assessment included consideration of risk of bias, heterogeneity, directness of the evidence, risk of publication bias, and precision of effect estimates.
Data synthesis methodology	Due to the low number of studies included, only one, the results were presented in a narrative way and most planned analyses were not performed. It was planned not to present a pooled result if a substantial heterogeneity was found (I^2> 80%) The results of dichotomous outcomes (such as number of participants developing BCC and/or cSCC) were presented as summary risk ratios (RR) with 95% confidence intervals as well as the number needed to treat for an additional harmful outcome (NNTH) as an absolute measure of harm, and NNTH as the reciprocal of risk differences (RD).
Data synthesis	One RCT was included. For the main analyses all participants were included, also those receiving beta-carotene. The incidence of new BCC was similar in the daily-application group (812 participants randomly assigned) compared with the discretionary-use group (809 participants randomly assigned) (RR 1.03; [0.74- 1.43] (95% CI)). This evidence was of low quality. The incidence of new cSCC was similar in the daily-application group (812 participants randomly assigned) compared with the discretionary-use group (809 participants randomly assigned) (RR 0.88; [0.50-1.54] (95% CI)). This evidence was of low quality. Analyses excluding the participants receiving beta-carotene was also performed, and the results were similar to the results including the groups receiving beta-carotene. It was narratively reported that main complaints made by the daily sunscreen use group were contact allergy (25/812) and skin oiliness (10/812). This evidence was of low quality.

<table>
<tr><th colspan="6">Characteristics of the systematic review</th></tr>
<tr><td></td><td colspan="5">There was no information about the number of self-reported sunburns or skin lesions, total hours of UVR exposure, total hours outdoors in peak exposure times, or Minimal Erythemal Dose. The rate of change in the total number of prevalent actinic keratosis between 1994 and 1996 was similar in the daily-application group and the discretionary-use group (RR 0.95; [0.75-1.20] (95% CI)).

It was narratively stated that: "75% of participants assigned to daily sunscreen use were applying sunscreen to their neck, arms and hands at least 3 to 4 days a week and those people not assigned to the sunscreen group were applying sunscreen to head, neck and arms not at all or no more than 1 or 2 days a week."

For the daily use group, the median daily weight of sunscreen applied on average throughout the trial was 1.5 g/d (range 0 to 7.4 g/d), but the median decreased as the trial progressed (1992 = 1.67 g and 1996 = 1.22 g).</td></tr>
<tr><th colspan="6">Characteristics of the studies included in the systematic reviews</th></tr>
<tr><td>Study design</td><td colspan="5">One trial</td></tr>
<tr><td rowspan="2">Country/countries where the study is conducted (n) and data collection period</td><td>Study design</td><td>Country</td><td>Data collection period</td><td>Total no of participants/age (range) participants</td><td>SPF</td></tr>
<tr><td>Randomised controlled trial</td><td>Australia</td><td>1992-1996</td><td>1061/ mean ages in groups: 48.1-49.8 years

(Provided no dropouts from previous study: 26-75 years)</td><td>16</td></tr>
<tr><td>Are hypotheses regarding our aim presented? If yes, quote</td><td colspan="5">Hypotheses were not reported.</td></tr>
<tr><td>Substance(s) tested (sunscreen as such or sunscreen ingredient(s)) and sun protection factor</td><td colspan="5">Daily application of sunscreen (SPF 16) was compared with discretional use of sunscreen (SPF 16), with or without beta-carotene administration.</td></tr>
<tr><td>List of outcomes considered</td><td colspan="5">Primary outcomes:

• Basal cell carcinoma confirmed clinically or histopathologically at any follow-up.
• Cutaneous squamous cell carcinoma confirmed clinically or histopathologically at any follow-up.
• Adverse events (e.g. dermatitis from sunscreens, acne secondary to the use of sunscreens, dermatitis from the use of hats and clothes,</td></tr>
</table>

Characteristics of the systematic review	
	vitamin D deficiency from lack of exposure to the sun, etc.) reported by a number of participants or individually. Secondary outcomes • Number of self-reported sunburns or skin lesions, defined by each study, at the end of follow-up. • Actinic or solar keratoses at any follow-up. • Total hours of ultraviolet radiation exposure at the end of follow-up. • Total hours outdoors in peak exposure times at the end of follow-up. • Minimal erythema dose at the end of follow-up. • Participant's compliance with preventive strategies at the end of the trial.
Key findings that relate to the research questions in Table 3-1 and 4-1	Comparing daily application of sunscreen with discretionary use, no difference in terms of the number of participants developing BCC or cSCC was found. Contact allergy was reported by 25 of 812 participants and skin oiliness by 10 of 812 participants. The evidence for these findings were of low quality. Side effects from the sunscreen used with or without the addition of beta-carotene (30 mg daily) included a low percentage of cases of contact allergy and skin irritation.
Comments:	

Characteristics of the systematic review	
Title	Sunscreen Use and the Risk for Melanoma: A Quantitative Review
Author(s)	L. K. Dennis, L. E. B. Freeman and M. J. VanBeek
Year of publication	2003
Start and ending dates of the literature search	Articles published from 1966 through April 2003.
Country of origin (corresponding author)	USA
Funding	The study was funded in part by the National Cancer Institute, grant number 1R03CA88834-01.
Reported conflict of interest	No reports of conflict of interest were disclosed.
What is the main objective of the review?	The main objective was to examine the strength and consistency of associations between melanoma and sunscreen use in the published literature.
Hypotheses tested	Hypotheses were not reported.

Characteristics of the systematic review	
Quality assessment tool	A quality-assessment scoring system was developed (highest possible score: 19 points). The method was not validated. A brief overview of the method: - The selection of the control group: hospital, cancer, or outpatient dermatology controls, 0 points; hospital visitors or other unclear group, 1 point; population controls, 2 points. - The questionnaire: For standardizing or pretesting the questionnaire in a sample similar to their study sample, 2 points; for using the same questions from a structured questionnaire, 1 point. - Interview/self-administration: interviewer-administered studies with an interviewer blinded to the status of the patient, 2 points; interviewer-administered studies with a not blinded interviewer, 1 point; studies in which questionnaires were self-administered, 0 points. - Detection bias: studies in which the control group had a skin examination, 1 point. - Confounding of sun sensitivity in the relationship between sunscreen and melanoma: studies that adjusted for skin color, skin type, ability to tan, and tendency to burn, 4 points; studies that adjusted only for hair color, eye color, or freckling, 2 points; adjustment for potential confounders of sunburn, 2 points; adjustment for other sun exposure, 2 points; partially adjustment for these confounders, 1 point. - Studies that adjusted for matched for sex and age, 2 points; studies were frequency-matched only, 1 point. - Examining sunscreen use: Reporting of more detail beyond ever use: studies that reported years of use, 2 points; frequency of use, 1 point.
Results of quality assessment	The scores ranged from 1 to 18. The scores (corresponding number of studies) of 20 studies: 1(1); 2(1); 3(1); 6(3); 8(2); 9(1); 10(4); 11(2); 12(1); 13(1); 14(1); 15(1); 18(1) The results of the quality scoring were presented to provide an overall sense of each study's quality, but were not used in any quantitative analyses.
Data synthesis methodology	- For dichotomous factors (ever use of sunscreen), fixed-effects and random-effects models were used to obtain pooled relative risk estimates. - Statistical tests of homogeneity were performed to assess the consistency of associations. To quantify the extent of heterogeneity among the studies, the between-study variance was estimated (H and I^2 statistic). - Odds ratios were pooled across studies using standard meta-analytic techniques. - Data were stratified by type of controls, adjustment for sun sensitivity, and sun sensitivity when available.

Characteristics of the systematic review	
	- For studies that did not report odds ratios and CIs, ever use was estimated on the basis of case and control distribution for frequency of sunscreen use. - For studies (n=3) that did not report case and control distribution, odds ratio and variance for ever use was estimated on the basis of an average of the odds ratios and variances reported for frequency of sunscreen use. - A fixed-effects dose–response method was used to evaluate possible linear relationships for multiple ordinal categories (frequency of sunscreen use and years of sunscreen use). The median number of years of each category range was used in calculating an overall linear β for each study. - A linear model that assumed equal distances between frequencies of sunscreen use categories was used.
Data synthesis	- Five studies reported odds ratios (ORs) and 95% CIs for "ever use" of sunscreen. ORs for the remaining 13 studies were estimated on the basis of frequency of sunscreen use. - The pooled OR for the 18 studies on ever use of sunscreen was 1.0 [0.8; 1.2] (95% CI) (P value for heterogeneity <0.001). - Heterogeneity was addressed by pooling data stratified by study design and by confounding factors that were adjusted for in the original articles. No difference in ORs was seen between type of control group. Pooling the 5 studies that adjusted for hair color only with the studies that adjusted for sun sensitivity, no association was seen (OR=1.0). The pooled OR for studies adjusted for sun sensitivity only (*i.e.* excluded studies for hair color), was 0.8 [0.6; 1.0] (CI)). - Four studies stratified participants by skin sensitivity. Among sun sensitive persons the association between sunscreen use and melanoma was homogeneous and non-significantly protective (OR=0.9 [0.7; 1.2] (95% CI); P value for heterogeneity=0.13). For sun-resistant persons OR varied: a null association between sunscreen use and melanoma (1 study; OR=1.17), increased associations (2 studies; ORs: 1.3 and 1.7), a significant protective effect (1 study; OR=0.6) (P value for heterogeneity=0.002). (The corresponding CIs are not stated). - Dose-response analyses of melanoma and frequency of sunscreen use (never, sometimes, or always) were performed. Pooling data from 12 case-control studies, there was no dose-response (OR=1.1, P=0.09). Excluding 4 studies that did not adjust for the confounding effects of sun sensitivity or adjusted only for hair color, the OR was 0.93 [0.81; 1.07] (CI). Excluding an additional 3 studies that did not adjust for the potential confounding effects of previous sunburns, and pooling data for the remaining 5 studies that adjusted for sun sensitivity and sunburns, a significant protective association was observed (OR=0.76 [0.65-0.90](CI)). However, the between-study variation was 84%. Pooling data from the 4 studies reporting years

<table>
<tr><td colspan="6">Characteristics of the systematic review</td></tr>
<tr><td></td><td colspan="5">of sunscreen use, there was no association with increasing years of sunscreen use and melanoma (P>0.2).

(Note that the quality scoring was not used in any quantitative analysis)</td></tr>
<tr><td colspan="6">Characteristics of the studies included in the systematic reviews</td></tr>
<tr><td>Study design</td><td colspan="5">Case–control studies (9 population-based case–control studies, 7 non–population-based studies and 2 case–control studies)</td></tr>
<tr><td rowspan="11">Country/countries where the study is conducted (n) and data collection period</td><td>Study design</td><td>Country</td><td>Data collection period</td><td>Age range participants (years) (Total no of participants)</td><td>Sunscreen protection factor*</td></tr>
<tr><td rowspan="4">Population-based case-control studies</td><td>Australia</td><td>1980-1981, 1987-1994, 1987-1994</td><td><80 (988)/; ≤15 (208); 15-19 (406)</td><td>Not reported</td></tr>
<tr><td>Denmark</td><td>1982-1985</td><td>20-79 (1400)</td><td>Not reported</td></tr>
<tr><td>Sweden</td><td>1978-1983, 1988-1990, 1995-1997</td><td>Not reported (1028); 15-75 (1040); 16-80 (1449)</td><td>Not reported</td></tr>
<tr><td>USA</td><td>1977-1979, 1981-1986</td><td>≥18 (739) (men); 25-59 (1382) (women)</td><td>Not reported</td></tr>
<tr><td rowspan="5">Non-population-based case-control studies</td><td>Austria</td><td>1993-1994</td><td>15-89 (512)</td><td>Not reported</td></tr>
<tr><td>Belgium, France, Germany</td><td>1991-1992</td><td>≥20 (856)</td><td>Not reported</td></tr>
<tr><td>Brazil</td><td>1995-1998</td><td>20-84 (309)</td><td>Not reported</td></tr>
<tr><td>Italy</td><td>1992-1995</td><td>Not reported (1080)</td><td>Not reported</td></tr>
<tr><td>Spain</td><td>1989-1993, 1990-1994</td><td>20-79 (243); 21-87 (351)</td><td>Not reported</td></tr>
<tr><td>USA</td><td>1974-1980</td><td>All (925)</td><td>Not reported</td></tr>
<tr><td>Case-control studies</td><td>USA</td><td>1987-1989, NR</td><td>Not reported (Not reported); Not reported (179)</td><td>Not reported</td></tr>
<tr><td>Are hypotheses regarding our aim presented? If yes, quote</td><td colspan="5">Hypotheses were not reported.</td></tr>
</table>

Characteristics of the systematic review	
Substance(s) tested (sunscreen as such or sunscreen ingredient(s)) and sun protection factor	Sunscreen not specified
List of outcomes considered	The outcomes considered was - Association between sunscreen use and melanoma. - The impact of frequency of sunscreen use (ever sunscreen use, always sunscreen use, or sunscreen use for more than 10 years) and confounding factors (sun sensitivity, phenotypes).
Key findings that relate to the research questions in Table 3-1 and 4-1 in the protocol	This meta-analysis found no association between melanoma and sunscreen use. Several studies did not account for patients' sensitivity to sunlight, which could increase both sunscreen use and melanoma. A few studies found protective relationships between sunscreen use and melanoma.
Comments: ***Studies that were reviewed did not evaluate newer sunscreens with a sun protection factor greater than 15, protection particularly against ultraviolet A radiation, or water resistance.** **All studies reporting on melanoma were assumed to have included histologic confirmation of the diagnosis, even if this was not explicitly stated.**	

17.1.2 Randomised controlled trials

17.1.2.1 Full-text assessed – excluded publications

An overview of the publications considered not to fulfil the eligibility criteria is given in Table 17.1.2.1-1.

Table 17.1.2.1-1. Publications considered not eligible.

Reference	Reason for exclusion
(2000) (no author name given)	Language
Abarca et al. (1987)	Language
Abbott et al. (1970)	Exposure
Anonymous (2018)	Language
Appa and Ouyang (2011)	Study design
Autier (2001)	Language
Autier et al. (2011)	Study design
Avenel-Audran et al. (2010)	Study design

Bauer et al. (2005)	Exposure
Berwick (2007)	Study design
Bigby and Kim (2011)	Study design
Buller et al. (2005)	Exposure
Carli et al. (2008)	Exposure
Crane et al. (2006)	Exposure
Crane et al. (2012)	Exposure
Cockburn et al. (1997)	Study design
Ctri (2018)	Study design
DeLeo et al. (2009a)	Study design
Duteil et al. (2002)	Study design
Einspahr et al. (2006)	Exposure
English et al. (2005)	Study design
Faurschou et al. (2011)	Study design
Glanz et al. (2015)	Outcome
Green et al. (1994)	Outcome
Green and Williams (2007)	Study design
Harrison et al. (2005)	Exposure
Hughes et al. (2013)	Outcome
Janjua et al. (2007)	Exposure
Jeanmougin et al. (1994)	Language
Jeanmougin et al. (2006)	Language
Jost and Dummer (1999)	Study design
Jprn (2014)	Study design
Jprn (2016a)	Study design
Jprn (2016b)	Study design
Katz (1970)	Exposure
Khan et al. (2018)	Exposure
Kim et al. (2017)	Study design
Kohli et al. (2019)	Study design
Kunimoto et al. (2016)	Study design
Lacour and Beani (2007)	Language
Libon et al. (2017b)	Study design
Liardet et al. (2001)	Study design
Lindstrom et al. (2019)	Study design
Ling et al. (2001)	Study design
McCollum et al. (2010)	Study design
Mizuno et al. (2016)	Study design
Moyal et al. (1997)	Study design
Narbutt et al. (2019)	Study design
Naylor and Robinson (2005)	Study design
Nct (2007)	Study design
Oncology Cooperative Group Of The Italian Group For Epidemiologic Research In (2003)	Study design
Pereira et al. (2019)	Study design
Prow (2018)	Study design

Robinson (2005)	Study design
Singh et al. (2019)	Study design
Scalini et al. (2014)	Study design
Schwartzmann Solon et al. (1990)	Study design
Stege et al. (2012)	Study design
Tripp et al. (2016)	Study design
Van Der Pols et al. (2010)	Study design
Vazquez and Sanchez (1983)	Exposure
Veronese et al. (2019)	Study design
Weinstock (2001)	Study design
Williams et al. (2017a)	Study design
Williams et al. (2017b)	Study design
Wolf et al. (2019)	Exposure
Wollina et al. (2014)	Exposure

17.1.2.2 Studies addressing UVR-induced outcomes of limited importance

The aim of the studies addressing UVR-induced outcomes considered to be of limited importance is shown in Table 17.1.2.2-1.

Table 17.1.2.2-1. Studies addressing UVR-induced outcomes of limited importance.

Reference	Aim	Outcome
Dupuy et al. (2005)	High-protection sunscreens have been suspected to prompt people to increase sun-exposure, and thus to increase skin cancer risk. We tested the influence of both the actual protection (sun protection factor) and the information about protection (label) on sun-exposure behavior.	Secondary outcomes were occurrence of sunburns and amount of sunscreen used.
Gallagher et al. (2000)	Determine whether use of broad-spectrum, high–sun protection factor sunscreen attenuates development of nevi in white children.	Number of new nevi acquired.
Granger et al. (2019a)	Test sunscreens in outdoor conditions (very high to extreme ultraviolet radiation) approximating real-life solar exposure while maintaining scientific standards and acceptable conditions.	Erythema and sunburn.
Granger et al. (2019b)	Test a sunscreen (SPF 50+) in conditions more representative of real-life solar exposure, to confirm its reported laboratory efficacy.	Erythema and sunburn.

Reference	Aim	Outcome
Josse et al. (2018)	Measure lentigines' pigmentation over a long period of time and evaluate if summer over- pigmentation can be avoided by the use a SPF30 day skin cream.	Lentigines/ overpigmentation.
Kaidbey (1990)	Compare sunscreens with regard to their ability to prevent sunburn cell formation after the exposure of human skin to a standardized dose of solar-simulated radiation.	Sunburn.
Kerr et al. (2009)	Determine the frequency of irritant reactions to 19 organic sunscreen filters in current use.	Irritant reactions.
Seite and Fourtanier (2008)Seite and Fourtanier (2008)Seite and Fourtanier (2008)Seite and Fourtanier (2008)Seite and Fourtanier (2008)Seite and Fourtanier (2008)Seite and Fourtanier (2008)Seite and Fourtanier (2008)	Assess the effect of sunscreen use on nevus development by anatomic sites and by nevi of different sizes for white schoolchildren in a randomized trial.	Nevi count
Manganoni et al. (2012)	Investigate the clinical, dermoscopic, histological and immunohistochemical changes in acquired melanocytic nevi (AMN) exposed to repeated equally sub-erythemogenic UVB and UVA radiation.	Melanocytic nevi.
Naldi et al. (2007)	Evaluate the effect of an educational intervention to reduce sunburn rates (primary outcome) and improve sun-protection behavior (secondary outcome). In a subgroup (44% of the total sample), melanocytic nevi were also counted.	Sunburn and melanocytic nevi.
Nichols et al. (1998)	Examine the effects of different ingredients found in sunscreen on facial cutaneous irritancy in patients with rosacea.	Cutaneous irritation.
Odio et al. (1994b)	Develop a method to evaluate the efficacy of various regimens of sunscreen reapplication in children, under conditions of unrestricted behavior and exposure to ambient sunlight.	Erythema.

Reference	Aim	Outcome
Pearse and Marks (1983)	Determine whether, following irradiation with UVR, two frequently used sunscreens prevented the epidermal response in humans as effectively as they protected against the production of erythema.	Erythema and epidermal response.
Phillips et al. (2000)	Determine the effectiveness of a sunscreen product with a sunscreen protection factor (SPF) of 15 applied daily in preventing UV-induced histologic damage in human skin compared with the protection afforded by sunscreens with equal or higher SPF applied intermittently.	Histologic damage.

17.1.2.3 Evaluation of internal validity

The OHAT (2015) criteria for evaluation of internal validity was slightly modified as show in Table 17.1.2.3-1.

Table 17.1.2.3-1. The criteria used for the evaluation of internal validity (modified from OHAT, 2015).

1	Definitely low risk of bias	There is direct evidence that subjects were allocated to any study group including controls using a method with a random component. Acceptable methods of randomization include: referring to a random number table, using a computer random number generator, coin tossing, shuffling cards or envelopes, throwing dice, or drawing of lots. Restricted randomization (*e.g.*, blocked randomization) to ensure particular allocation ratios will be considered low risk of bias. Similarly, stratified randomization and minimization approaches that attempt to minimize imbalance between groups on important prognostic factors (*e.g.*, body weight) will be considered acceptable.
	Probably low risk of bias	There is indirect evidence that subjects were allocated to study groups using a method with a random component (*i.e.*, authors state that allocation was random, without description of the method used), OR it is deemed that allocation without a clearly random component during the study would not appreciably bias results. For example, approaches such as biased coin or urn randomization, replacement randomization, mixed randomization, and maximal randomization may require consultation with a statistician to determine risk-of-bias rating.
	Probably high risk of bias	There is indirect evidence that subjects were allocated to study groups using a method with a non-random component, OR there is insufficient information provided about how subjects were allocated to study groups (record "NR" as basis for answer). Note: Non-random allocation methods may be systematic, but have the potential to allow participants or researchers to anticipate the allocation to study groups. Such "quasi-random" methods include alternation, assignment based on date of birth, case record number, or date of presentation to study.
	Definitely high risk of bias	There is direct evidence that subjects were allocated to study groups using a non-random method including judgment of the clinician, preference of the participant, the results of a laboratory test or a series of tests, or availability of the intervention.
2	Definitely low risk of bias	There is direct evidence that at the time of recruitment the research personnel and subjects did not know what study group subjects were allocated to, and it is unlikely that they could have broken the blinding of allocation until after recruitment was complete and irrevocable. Acceptable methods used to ensure allocation concealment include central allocation (including telephone, web-based and pharmacy-controlled randomization); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes; or equivalent methods
	Probably low risk of bias	There is indirect evidence that the research personnel and subjects did not know what study group subjects were allocated to and it is unlikely that they could have broken the blinding of allocation until after recruitment was complete and irrevocable, OR it is deemed that lack of adequate allocation concealment would not appreciably bias results.

	Probably high risk of bias	There is indirect evidence that at the time of recruitment it was possible for the research personnel and subjects to know what study group subjects were allocated to, or it is likely that they could have broken the blinding of allocation before recruitment was complete and irrevocable, OR there is insufficient information provided about allocation to study groups (record "NR" as basis for answer). Note: Inadequate methods include using an open random allocation schedule (*e.g.*, a list of random numbers); assignment envelopes used without appropriate safeguards (*e.g.*, if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; or any other explicitly unconcealed procedure. For example, if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.
	Definitely high risk of bias	There is direct evidence that at the time of recruitment it was possible for the research personnel and subjects to know what study group subjects were allocated to, or it is likely that they could have broken the blinding of allocation before recruitment was complete and irrevocable.
3	Definitely low risk of bias	There is direct evidence that the subjects and research personnel were adequately blinded to study group, and it is unlikely that they could have broken the blinding during the study. Methods used to ensure blinding include central allocation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes; or equivalent methods.
	Probably low risk of bias	There is indirect evidence that the research personnel and subjects were adequately blinded to study group, and it is unlikely that they could have broken the blinding during the study, OR it is deemed that lack of adequate blinding during the study would not appreciably bias results.
	Probably high risk of bias	There is indirect evidence that it was possible for research personnel or subjects to infer the study group, OR there is insufficient information provided about blinding to study group during the study (record "NR" as basis for answer). Note: Inadequate methods include using an open random allocation schedule (*e.g.*, a list of random numbers), assignment envelopes used without appropriate safeguards (*e.g.*, if envelopes were unsealed or non-opaque or not sequentially numbered), alternation or rotation; date of birth; case record number; or any other explicitly unconcealed procedure. For example, if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.
	Definitely high risk of bias	There is direct evidence for lack of adequate blinding of the study group including no blinding or incomplete blinding of research personnel and subjects. For some treatments, such as behavioral interventions, allocation to study groups cannot be concealed.

4	Definitely low risk of bias	There is direct evidence that there was no loss of subjects during the study and outcome data were complete, OR loss of subjects (*i.e.*, incomplete outcome data) was adequately addressed and reasons were documented when human subjects were removed from a study or analyses. Review authors should be confident that the participants included in the analysis are exactly those who were randomised into the trial. Acceptable handling of subject attrition includes: very little missing outcome data (less than 10% in each group); reasons for missing subjects unlikely to be related to outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across study groups, with similar reasons for missing data across groups, OR analyses (such as intention-to-treat analysis) in which missing data have been imputed using appropriate methods (insuring that the characteristics of subjects lost to follow up or with unavailable records are described in identical way and are not significantly different from those of the study participants). Note: Participants randomized but subsequently found not to be eligible need not always be considered as having missing outcome data
	Probably low risk of bias	There is indirect evidence that loss of subjects (*i.e.*, incomplete outcome data) was adequately addressed and reasons were documented when human subjects were removed from a study, OR it is deemed that the proportion lost to follow-up would not appreciably bias results (less than 20% in each group). This would include reports of no statistical differences in characteristics of subjects lost to follow up or with unavailable records from those of the study participants. Generally, the higher the ratio of participants with missing data to participants with events, the greater potential there is for bias. For studies with a long duration of follow-up, some withdrawals for such reasons are inevitable.
	Probably high risk of bias	There is indirect evidence that loss of subjects (*i.e.*, incomplete outcome data) was unacceptably large (greater than 20% in each group) and not adequately addressed, OR there is insufficient information provided about numbers of subjects lost to follow-up (record "NR" as basis for answer).
	Definitely high risk of bias	There is direct evidence that loss of subjects (*i.e.*, incomplete outcome data) was unacceptably large and not adequately addressed. Unacceptable handling of subject attrition includes: reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across study groups; or potentially inappropriate application of imputation.

5	Definitely low risk of bias	1) For sunscreens reported to consist of one or more UV filters: The concentration of each UV filter is reported, it is likely that UV filters were intact (optimal stability is considered to be less than one year), and that the appropriate UV filter was present in the sunscreen (*e.g.*, UVA filter for UVA exposure), AND that sunscreen was consistently applied (*i.e.*, with the same method, time-frame, amount and frequency) across treatment groups. 2) For single UV filters: There is direct evidence that the exposure (including purity and stability of the test substance) was independently characterized and purity confirmed generally as ≥99% for single substance or non-mixture evaluations, AND that exposure was consistently administered (*i.e.*, with the same method, time-frame, amount and frequency) across treatment groups.
	Probably low risk of bias	1) For sunscreens reported to consist of one or more UV filters: There is uncertainty about one of the following three parameters: the concentration of each UV filter, whether UV filters were intact (optimal stability is considered to be less than one year), and whether the appropriate UV filter was present in the sunscreen (*e.g.* UVA filter for UVA exposure), AND there is indirect evidence that sunscreen was consistently applied (*i.e.*, with the same method, time-frame, amount and frequency) across treatment groups 2) For single UV filters: There is indirect evidence that the exposure (including purity and stability of the test substance) was independently characterized and purity confirmed generally as ≥99% (*i.e.*, the supplier of the chemical provides documentation of the purity of the chemical) OR direct evidence that purity of each UV-filter was independently confirmed as ≥98% it is deemed that impurities of up to 2% would not appreciably bias results AND there is indirect evidence that exposure was consistently administered (*i.e.*, with the same method, time-frame, amount and frequency) across treatment groups.
	Probably high risk of bias	1) For sunscreens consisting of one or more UV filters: There is uncertainty about two of the following three parameters: the concentration of each UV filter, whether UV filters were intact (optimal stability is considered to be less than one year), and whether the appropriate UV filter was present in the sunscreen (*e.g.* UVA filter for UVA exposure), AND there is uncertainty about whether sunscreen was consistently applied (*i.e.*, with the same method, time-frame, amount and frequency) across treatment groups OR there is insufficient information (including which filters the sunscreen contained, but no evidence for concern (record "NR" as basis for answer). 2) For single UV filters: There is indirect evidence that the exposure (including purity and stability of the test substance) was assessed using poorly validated methods OR there is insufficient information provided about the validity of the exposure assessment method, but no evidence for concern (record "NR" as basis for answer).

	Definitely high risk of bias	1) For sunscreens consisting of one or more UV filters: The concentration of each UV filter is not reported, it is unlikely that UV filters were intact, and that the appropriate UV filter was present in the sunscreen (*e.g.*, UVA filter for UVA exposure), AND unlikely that sunscreen was consistently applied (*i.e.*, with the same method, time-frame, amount and frequency) across treatment groups OR UV-filters were not described. 2) For single UV filters: There is direct evidence that the exposure (including purity and stability of the test substance) was assessed using poorly validated methods.
6	Definitely low risk of bias	There is direct evidence that the outcome was assessed using well-established methods AND subjects had been followed for the same length of time in all study groups. Acceptable assessment methods will depend on the outcome, but examples of such methods may include objectively measured with diagnostic methods, measured by trained interviewers, obtained from registries, AND there is direct evidence that the outcome assessors (including study subjects, if outcomes were self-reported) were adequately blinded to the study group, and it is unlikely that they could have broken the blinding prior to reporting outcomes.
	Probably low risk of bias	There is indirect evidence that the outcome was assessed using acceptable methods (*i.e.*, deemed valid and reliable but not the gold standard) (*e.g.*, validity and reliability ≥0.40), AND subjects had been followed for the same length of time in all study groups, OR it is deemed that the outcome assessment methods used would not appreciably bias results, AND there is indirect evidence that the outcome assessors (including study subjects, if outcomes were self-reported) were adequately blinded to the study group, AND it is unlikely that they could have broken the blinding prior to reporting outcomes, OR it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results, which is more likely to apply to objective outcome measures.

	Probably high risk of bias	There is indirect evidence that the outcome assessment method is an insensitive instrument (*e.g.*, a questionnaire used to assess outcomes with no information on validation), OR the length of follow up differed by study group, OR there is indirect evidence that it was possible for outcome assessors (including study subjects if outcomes were self-reported) to infer the study group prior to reporting outcomes, OR there is insufficient information provided about blinding of outcome assessors (record "NR" as basis for answer).
	Definitely high risk of bias	There is direct evidence that the outcome assessment method is an insensitive instrument, OR the length of follow up differed by study group, OR there is direct evidence for lack of adequate blinding of outcome assessors (including study subjects if outcomes were self-reported), including no blinding or incomplete blinding.
7	Definitely low risk of bias	There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported. This would include outcomes reported with sufficient detail to be included in meta-analysis or fully tabulated during data extraction and analyses had been planned in advance.
	Probably low risk of bias	There is indirect evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported, OR analyses that had not been planned in advance (*i.e.*, retrospective unplanned subgroup analyses) are clearly indicated as such and it is deemed that the unplanned analyses were appropriate and selective reporting would not appreciably bias results (*e.g.*, appropriate analyses of an unexpected effect). This would include outcomes reported with insufficient detail such as only reporting that results were statistically significant (or not).

	Probably high risk of bias	There is indirect evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported, OR and there is indirect evidence that unplanned analyses were included that may appreciably bias results, OR there is insufficient information provided about selective outcome reporting (record "NR" as basis for answer).
	Definitely high risk of bias	There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have not been reported. In addition to not reporting outcomes, this would include reporting outcomes based on composite score without individual outcome components or outcomes reported using measurements, analysis methods or subsets of the data (*e.g.*, subscales) that were not pre-specified or reporting outcomes not pre-specified, or that unplanned analyses were included that would appreciably bias results.
8	Definitely low risk of bias	There is direct evidence that statistical methods, including power calculations, were appropriate AND that UV exposure was controlled for and was similar across study groups
	Probably low risk of bias	There is indirect evidence that statistical methods were appropriate AND that UV exposure was controlled for and was similar across study.
	Probably high risk of bias	There is indirect evidence that statistical methods were not appropriate OR that UV exposure was not controlled for or was different across study groups.
	Definitely high risk of bias	There is direct evidence that statistical methods, including power calculations, were not appropriate OR that UV exposure was not controlled for or was different across study groups.

The evaluation of internal validity was as follows:

Actinic keratoses

Darlington et al. (2003)

Type of bias	Question	Risk of bias evaluation	Risk of bias rating
Selection bias	Was administered dose or exposure level adequately randomized?	A customized randomization computer program was used.	++
	Was allocation to study groups adequately concealed?	The allocation concealment was poorly described. From personal communication with Green, it was informed that the nursing staff who co-ordinated the distribution of sunscreen knew the allocation groups. However, the dermatologists, pathologists and investigators were unaware of the allocation. It is deemed that using a customized randomization computer program combined with a centralised service to distribute the sunscreen, it is unlikely selection bias would have been introduced.	++
Performance bias	Were the research personnel and human subjects blinded to the study group during the study?	The subjects and nursing staff who co-ordinated the distribution of sunscreen were not blinded. Dermatologists, pathologists and investigators were blinded. It is deemed that lack of adequate blinding of the subjects would not appreciably bias the results.	+
Attrition/exclusion bias	Were outcome data complete without attrition or exclusion from analysis?	Seventy-four percent (1195) of the recruited participant completed the study. Of these, 79 participants were excluded. Either exclusion or loss to follow-up resulted in differences between the intervention and control group. Reasons to loss to follow-up were not reported.	+
Detection bias	Can we be confident in the exposure characterisation?	The type and concentration of each filter were not reported for the intervention sunscreen. The participants in the intervention group were instructed to apply	-

		sunscreen every day. Compliance with instructions concerning applications was measured by weighing the bottles every 3 months and participants were asked to report frequency of use. The control group used sunscreen at their own discretion.	
	Can we be confident in the outcome assessment?	Outcome was assessed using acceptable methods, and subjects had been followed for the same length of time in all study groups. Dermatologists, pathologists and investigators were blinded. Since the subjects were not blinded, the blinding could have been broken during the examination with the dermatologists. However, it is deemed that this would not appreciably bias the results. From personal communication with Green, it was informed that the statistician had access to the randomization code but did not refer to this information.	+
Selective reporting bias	Were all measured outcomes reported?	All of the study's measured outcomes outlined in the methods were reported.	++
Other sources of bias	Were there no other potential threats to internal validity (*e.g.* statistical methods were appropriate and researchers adhered to the study protocol)?	No protocol available, however, thoroughly description of the study in previous publications. Statistical methods seem appropriate.	+

Naylor et al. (1995)

Type of bias	**Question**	**Risk of bias evaluation**	**Risk of bias rating**
Selection bias	Was administered dose or exposure level adequately randomized?	authors state that allocation was random, without description of the method use	+

	Was allocation to study groups adequately concealed?	Reported that study was double-blind which would make it difficult to know to which study group subjects were allocated, concealment not described, but preparations had identical packaging	-
Performance bias	Were the research personnel and human subjects blinded to the study group during the study?	Report that study was double-blind, but not whether this applied to all	+
Attrition/exclusion bias	Were outcome data complete without attrition or exclusion from analysis?	Loss of subjects was above 20%. 50 participants were included in the analyses, but 37 came for the final visit after 2 yrs. Reasons for drop-out were adequately addressed and reasons were documented when human subjects were removed from a study or analyses. Performed a test that indicated that subjects who withdrew were not different from those who completed the study.	+
Detection bias	Can we be confident in the exposure characterisation?	Commercial, named sunscreen with reported ingredients, supplied from the manufacturer (assume sufficient stability). Concentrations not reported. Control was placebo: sunscreen base. Uncertainty about consistency of application (each participant used own routines and applied the preparation liberally	-
	Can we be confident in the outcome assessment?	Little information about the criteria for lesions identified clinically actinic keratoses.	+
Selective reporting bias	Were all measured outcomes reported?	All measured outcomes were reported.	++
Other sources of bias	Were there no other potential threats to internal validity (*e.g.* statistical methods were appropriate and researchers adhered to the study protocol)?	No priori protocol. Power analysis may have revealed that a higher number of participants was needed, but was not performed. Statistical methods seem appropriate. UV exposure was not controlled for or was different across study groups.	-

Thompson et al. (1993)

Type of bias	Question	Risk of bias evaluation	Risk of bias rating
Selection bias	Was administered dose or exposure level adequately randomized?	Stratified randomisation was done, but there is not information about the method.	+
	Was allocation to study groups adequately concealed?	Not reported.	-
Performance bias	Were the research personnel and human subjects blinded to the study group during the study?	The subjects were blinded and although it is not explicit mentioned that the research personnel were blinded, it is reported that the physician who did the examination was unaware of the results from the baseline examination.	+
Attrition/exclusion bias	Were outcome data complete without attrition or exclusion from analysis?	Of the 588 participants that were enrolled in the study, 431 completed the study. Drop-out was addressed adequately and was similar between the intervention and control group.	++
Detection bias	Can we be confident in the exposure characterisation?	The concentration of each UV filter is reported. There is information about amount and frequency of application, due to self-reporting and weighing of the cream tubes. The control group applied a cream with the same consistency, but without UV-filters.	++
	Can we be confident in the outcome assessment?	It is reported that the physician who did the examination was unaware of the results from the baseline examination. However, it is not explicit specified that the examiner was blinded. Ninety-six percent of the participants were examined by the same examiner at baseline and at the end of the study.	+
Selective reporting bias	Were all measured outcomes reported?	Yes	++

Other sources of bias	Were there no other potential threats to internal validity (*e.g.* statistical methods were appropriate and researchers adhered to the study protocol)?	No power analysis was performed. Statistical methods seems appropriate. All participants were told to avoid the sun around the middle of the day, and to wear hats and clothing where appropriate.	+

Basal cell carcinoma

Green et al. (1999)

Type of bias	**Question**	**Risk of bias evaluation**	**Risk of bias rating**
Selection bias	Was administered dose or exposure level adequately randomized?	A customized randomization computer program was used.	++
	Was allocation to study groups adequately concealed?	The allocation concealment was poorly described. From personal communication with Green, it was informed that the nursing staff who co-ordinated the distribution of sunscreen knew the allocation groups. However, the dermatologists, pathologists and investigators were unaware of the allocation. It is deemed that using a customized randomization computer program combined with a centralised service to distribute the sunscreen, it is unlikely selection bias would have been introduced.	++
Performance bias	Were the research personnel and human subjects blinded to the study group during the study?	The subjects and nursing staff who co-ordinated the distribution of sunscreen were not blinded. Dermatologists, pathologists and investigators were blinded. It is deemed that lack of adequate blinding of the subjects would not appreciably bias the results.	+

Attrition/exclusion bias	Were outcome data complete without attrition or exclusion from analysis?	Reasons for withdrawal was described. After 12 months, 128 (8%) participants had withdrawn with no subsequent follow-up. By 36 months there were another 88 withdrawals and at the end of the study in year 5, 238 (15%) participants had withdrawn without a complete skin examination by a dermatologist in the follow-up period.	-
Detection bias	Can we be confident in the exposure characterisation?	There was not sufficient information about exposure in the control group (*e.g.* type of sunscreen, amounts used).	-
	Can we be confident in the outcome assessment?	Dermatologists, pathologists and investigators were blinded. Since the subjects were not blinded, the blinding could have been broken during the examination with the dermatologists. However, it is deemed that this would not appreciably bias the results. From personal communication with Green, it was informed that the statistician had access to the randomization code but did not refer to this information. All skin cancers clinically diagnosed during these follow-up surveys were examined histologically by a single dermatopathologist.	+
Selective reporting bias	Were all measured outcomes reported?	Yes	++
Other sources of bias	Were there no other potential threats to internal validity (*e.g.* statistical methods were appropriate and researchers adhered to the study protocol)?	The statistics seemed appropriate. No protocol available.	+

Pandeya et al. (2005)

Type of bias	**Question**	**Risk of bias evaluation**	**Risk of bias rating**

Selection bias	Was administered dose or exposure level adequately randomized?	A customized randomization computer program was used.	++
	Was allocation to study groups adequately concealed?	The allocation concealment was poorly described. From personal communication with Green, it was informed that the nursing staff who co-ordinated the distribution of sunscreen knew the allocation groups. However, the dermatologists, pathologists and investigators were unaware of the allocation. It is deemed that using a customized randomization computer program combined with a centralised service to distribute the sunscreen, it is unlikely selection bias would have been introduced	+ +
Performance bias	Were the research personnel and human subjects blinded to the study group during the study?	The subjects and nursing staff who co-ordinated the distribution of sunscreen were not blinded. Dermatologists, pathologists and investigators were blinded. It is deemed that lack of adequate blinding of the subjects would not appreciably bias the results.	+
Attrition/exclusion bias	Were outcome data complete without attrition or exclusion from analysis?	The loss of subjects was adequately addressed.	++
Detection bias	Can we be confident in the exposure characterisation?	There was not sufficient information about exposure in the control group (*e.g.* type of sunscreen, amounts used).	-
	Can we be confident in the outcome assessment?	Dermatologists, pathologists and investigators were blinded. Since the subjects were not blinded, the blinding could have been broken during the examination with the dermatologists. However, it is deemed that this would not appreciably bias the results. From personal communication with Green, it was informed that the statistician had access to the randomization code but did not refer to this information.	+

		A specialist dermatologists carried out full-body skin examinations of trial participants, and all skin cancers were recorded. Any tumors clinically diagnosed as keratinocytic skin cancers were biopsied, and a single histopathologist reviewed all specimens. Between these examinations, participants reported any skin lesions treated by their physicians, and medical and pathology records were reviewed to validate all such reports. Linkage with the databases of all local pathology companies ensured that no histologically diagnosed skin cancers were overlooked.	
Selective reporting bias	Were all measured outcomes reported?	All of the study's measured outcomes outlined in the methods were reported.	++
Other sources of bias	Were there no other potential threats to internal validity (*e.g.* statistical methods were appropriate and researchers adhered to the study protocol)?	No protocol available, however, thoroughly description of the study in previous publications.	+

van der Pols et al. (2006)

Type of bias	**Question**	**Risk of bias evaluation**	**Risk of bias rating**
Selection bias	Was administered dose or exposure level adequately randomized?	A customized randomization computer program was used.	++
	Was allocation to study groups adequately concealed?	Dermatologists, pathologists and investigators were blinded. Since the subjects were not blinded, the blinding could have been broken during the examination with the dermatologists. However, it is deemed that this would not appreciably bias the results. From personal communication with Green, it was informed that the	++

		statistician had access to the randomization code but did not refer to this information.	
Performance bias	Were the research personnel and human subjects blinded to the study group during the study?	The subjects and nursing staff who co-ordinated the distribution of sunscreen were not blinded. Dermatologists, pathologists and investigators were blinded. It is deemed that lack of adequate blinding of the subjects would not appreciably bias the results.	+
Attrition/exclusion bias	Were outcome data complete without attrition or exclusion from analysis?	The loss of subjects was adequately addressed.	++
Detection bias	Can we be confident in the exposure characterisation?	There was not sufficient information about exposure in the control group (*e.g.* type of sunscreen, amounts used).	-
	Can we be confident in the outcome assessment?	The outcome was addressed using well established methods. Skin cancer diagnoses was verified by physicians. Dermatologists, pathologists and investigators were blinded. Since the subjects were not blinded, the blinding could have been broken during the examination with the dermatologists. However, it is deemed that this would not appreciably bias the results. From personal communication with Green, it was informed that the statistician had access to the randomization code but did not refer to this information.	+
Selective reporting bias	Were all measured outcomes reported?	All of the study's measured outcomes outlined in the methods were reported.	++
Other sources of bias	Were there no other potential threats to internal validity (*e.g.* statistical methods were appropriate and researchers adhered to the study protocol)?	The statistics were adequate. No protocol available.	+

Immunosuppression

Moyal and Fourtanier (2001)

Type of bias	Question	Risk of bias evaluation	Risk of bias rating
Selection bias	Was administered dose or exposure level adequately randomized?	Randomized assembling into treatment groups after initial Multitest on the back and then randomized according to initial reaction on the Multitest. The method for randomisation was not reported.	+
	Was allocation to study groups adequately concealed?	NR; there is insufficient information provided about allocation to study groups	-
Performance bias	Were the research personnel and human subjects blinded to the study group during the study?	NR; there is insufficient information provided about blinding to study group during the study	-
Attrition/exclusion bias	Were outcome data complete without attrition or exclusion from analysis?	Seventy-five subjects were recruited for the indoor studies. Three of them dropped out for personal reasons without any relation to the treatment. For the outdoor study, 32 subjects were included and all completed.	++
Detection bias	Can we be confident in the exposure characterisation?	The sunscreen was prepared for this study, and the UV-filters used (in %) are described. The amount sunscreen applied were reported. As the study did not last for several days, it is likely that the filters were intact, not degraded. No cream was administered to the controls.	+
	Can we be confident in the outcome assessment?	Not reported, there is insufficient information provided about blinding of outcome assessors	-
Selective reporting bias	Were all measured outcomes reported?	All of the study's measured outcomes outlined in the methods were reported.	++

Other sources of bias	Were there no other potential threats to internal validity (*e.g.* statistical methods were appropriate and researchers adhered to the study protocol)?	There is indirect evidence that statistical methods, including power calculations, were appropriate and that UV exposure was controlled for and was similar across study groups.	+

Moyal and Fourtanier (2003)

Type of bias	**Question**	**Risk of bias evaluation**	**Risk of bias rating**
Selection bias	Was administered dose or exposure level adequately randomized?	The participants were not randomised.	-
	Was allocation to study groups adequately concealed?	No information . .	-
Performance bias	Were the research personnel and human subjects blinded to the study group during the study?	The products were labelled O or L; it is not described whether the participants or the assessors were blinded. Lack of blinding could possibly have affected the results.	-
Attrition/exclusion bias	Were outcome data complete without attrition or exclusion from analysis?	Insufficient information provided about numbers of subjects lost to follow-up.	-
Detection bias	Can we be confident in the exposure characterisation?	The concentration of each UV filter is not reported.	+

	Can we be confident in the outcome assessment?	There is no information whether the assessors were blinded or not and it is possible that lack of blinding could affect the outcome assessment.	-
Selective reporting bias	Were all measured outcomes reported?	Insufficient information of the results. N is not stated.	-
Other sources of bias	Were there no other potential threats to internal validity (*e.g.* statistical methods were appropriate and researchers adhered to the study protocol)?	No power analysis and few subjects (<20) in each group.	-

Neale et al. (1997)

Type of bias	**Question**	**Risk of bias evaluation**	**Risk of bias rating**
Selection bias	Was administered dose or exposure level adequately randomized?	A customized randomization computer program was used.	++
	Was allocation to study groups adequately concealed?	The allocation concealment was poorly described. From personal communication with Green, it was informed that the nursing staff who co-ordinated the distribution of sunscreen knew the allocation groups. However, the dermatologists, pathologists and investigators were unaware of the allocation. It is deemed that using a customized randomization computer program combined with a centralised service to distribute the sunscreen, it is unlikely selection bias would have been introduced.	++

Performance bias	Were the research personnel and human subjects blinded to the study group during the study?	The subjects and nursing staff who co-ordinated the distribution of sunscreen were not blinded. Dermatologists, pathologists and investigators were blinded. It is deemed that lack of adequate blinding of the subjects would not appreciably bias the results.	+
Attrition/exclusion bias	Were outcome data complete without attrition or exclusion from analysis?	Exclusion was described sufficiently, and it is deemed that the proportion lost to follow-up would not appreciably bias results	++
Detection bias	Can we be confident in the exposure characterisation?	The participants had a prospective sun exposure diary for 2 weeks, in which daily records were made of the number of hours spent outside and in the sun, the clothing worn and weather conditions during these exposure periods and the times and sites of sunscreen application. The UV-filters in the sunscreen used by the intervention group was described, and the content of the filters were given as percent wt/wt. There was not sufficient information about exposure in the control group (*e.g.* type of sunscreen, amounts used).	-
	Can we be confident in the outcome assessment?	Manual counting of Langerhans cells. Dermatologists, pathologists and investigators were blinded. Since the subjects were not blinded, the blinding could have been broken during the examination with the dermatologists. However, it is deemed that this would not appreciably bias the results. From personal communication with Green, it was informed that the statistician had access to the randomization code but did not refer to this information.	+
Selective reporting bias	Were all measured outcomes reported?	All of the study's measured outcomes outlined in the methods were reported.	++
Other sources of bias	Were there no other potential threats to internal validity (*e.g.* statistical methods were appropriate and researchers adhered to the study protocol)?	No power analysis was performed. Statistical methods seem appropriate.	+

Serre et al. (1997)

Type of bias	Question	Risk of bias evaluation	Risk of bias rating
Selection bias	Was administered dose or exposure level adequately randomized?	There is indirect evidence that subjects were allocated to study groups using a method with a random component. The method was not described.	+
	Was allocation to study groups adequately concealed?	Not reported, there is insufficient information provided about allocation to study groups.	-
Performance bias	Were the research personnel and human subjects blinded to the study group during the study?	Not reported, there is insufficient information provided about blinding to study group during the study.	-
Attrition/exclusion bias	Were outcome data complete without attrition or exclusion from analysis?	There was no loss of subjects during the study and outcome data were complete.	++
Detection bias	Can we be confident in the exposure characterisation?	Controlled UVR. The concentration of each UV filter was reported, it is likely that UV filters were intact (not degraded), and the appropriate UV filter was present in the sunscreen. The amount sunscreen applied was reported. No cream was administered to the controls.	+
	Can we be confident in the outcome assessment?	Not reported, there was insufficient information provided about blinding of outcome assessors.	-
Selective reporting bias	Were all measured outcomes reported?	All of the study's measured outcomes were reported, however, the detail level was insufficient.	+

Other sources of bias	Were there no other potential threats to internal validity (*e.g.* statistical methods were appropriate and researchers adhered to the study protocol)?	Statistical analysis performed and normality test checked. Similar exposure in all the groups (solar simulation). None of the participants had experienced sun exposure for at least 4 weeks prior to the study	++

Polymorphic light eruption

DeLeo et al. (2009)

Type of bias	**Question**	**Risk of bias evaluation**	**Risk of bias rating**
Selection bias	Was administered dose or exposure level adequately randomized?	At baseline, participants were randomised to either treatment group, and treatment was randomised to either side of the body. The method for randomisation was not reported.	+
	Was allocation to study groups adequately concealed?	Participant demographics and baseline characteristics was similar for the groups. No specific information on concealment of allocation. However, this is considered not to bias the results, as every participants was its own control.	+
Performance bias	Were the research personnel and human subjects blinded to the study group during the study?	The authors state that the study was double-blind. The method was not reported.	+
Attrition/exclusion bias	Were outcome data complete without attrition or exclusion from analysis?	The loss of subjects during the study was <10%. We consider the loss of participants not to be unacceptably large, and that is was adequately addressed.	++
Detection bias	Can we be confident in the exposure characterisation?	Each participant was treated on all exposed body areas other than the face and hands by a specifically trained study nurse. The amount sunscreen used is not described, however, the sunscreen was applied by a trained nurse. Purity of the	+

		substances was not described. The amount of the UV-filters in the sunscreen was given (in %). The control cream was applied by the same study nurse.	
	Can we be confident in the outcome assessment?	Clear criteria for the outcome assessment were described. The exposure time was similar for all participants, and the global severity scale was used for the evaluation of PMLE. It is unclear who performed the scoring, and if it was one or more persons.	+
Selective reporting bias	Were all measured outcomes reported?	All of the study's measured outcomes outlined in the methods were reported.	++
Other sources of bias	Were there no other potential threats to internal validity (*e.g.* statistical methods were appropriate and researchers adhered to the study protocol)?	The study was reviewed and approved by institutional review boards. The protocol is not available, therefore we cannot know if the study was performed as stated in the protocol. A power analysis was performed, and the statistics were appropriate. Exposure to significant UVR within 3 months before the start of the study was an exclusion criteria. UV radiation doses were measured and participants were exposed to the sunlight to receive an equal amount of sunlight on both sides.	+

Moyal et al. (1999)

Type of bias	**Question**	**Risk of bias evaluation**	**Risk of bias rating**
Selection bias	Was administered dose or exposure level adequately randomized?	The test (intervention and control) creams were applied to each side of the neck in a randomised manner. Randomisation method was not described.	+
	Was allocation to study groups adequately concealed?	Allocation is not described. However, this is considered as of low importance as each subject functions as its own control.	+

Performance bias	Were the research personnel and human subjects blinded to the study group during the study?	It is reported that the study is double-blinded. No further information on the blinding were reported.	+
Attrition/exclusion bias	Were outcome data complete without attrition or exclusion from analysis?	Outcome data were complete.	++
Detection bias	Can we be confident in the exposure characterisation?	The concentration of each UV filter and the amount applied was reported. The UV-exposure was controlled. There is insufficient information about the stability of the filters, however, as the study was of short duration, we assume that the UV-filters were not degraded. A control cream was applied to the control side of the neck.	++
	Can we be confident in the outcome assessment?	Little information on how the scoring was performed; manually or automatically.	-
Selective reporting bias	Were all measured outcomes reported?	All of the study's measured outcomes outlined in the methods were reported.	++
Other sources of bias	Were there no other potential threats to internal validity (*e.g.* statistical methods were appropriate and researchers adhered to the study protocol)?	A protocol was approved before initiation of the study. No statistical analyses were performed. Exposure to natural or artificial sunlight was avoided over the 3 months preceding the study, and the UV-exposure was controlled.	-

Schleyer et al. (2008)

Type of bias	**Question**	**Risk of bias evaluation**	**Risk of bias rating**

Selection bias	Was administered dose or exposure level adequately randomized?	Participants were randomized.	-
	Was allocation to study groups adequately concealed?	Not reported, however, it is deemed that lack of adequate allocation concealment would not appreciably bias results as all participants received the same treatment, and served as their own control.	+
Performance bias	Were the research personnel and human subjects blinded to the study group during the study?	There is insufficient information provided about blinding to study group during the study.	-
Attrition/exclusion bias	Were outcome data complete without attrition or exclusion from analysis?	Loss of subjects was adequately addressed and reasons were documented.	++
Detection bias	Can we be confident in the exposure characterisation?	The UV-filters in the sunscreen used were specified, the concentration of the filters was not reported. The amount sunscreen applied was according to the COLIPA instructions. As the study did not last for several days, it is likely that the filters were intact, not degraded. A cream without several of the ingredients in the sunscreen (including the UV-filters) were applied to the control areas.	+
	Can we be confident in the outcome assessment?	Not reported, however, lack of adequate blinding of outcome assessors were deemed not to appreciably bias results as the results were pronounced/distinct.	+
Selective reporting bias	Were all measured outcomes reported?	All of the study's measured outcomes outlined in the methods were reported.	++
Other sources of bias	Were there no other potential threats to internal validity (e.g. statistical methods were appropriate and researchers adhered to the study protocol)?	There were no other potential threats to internal validity.	++

Other reversible skin reactions

Naylor et al. (1995)

Type of bias	Question	Risk of bias evaluation	Risk of bias rating
Selection bias	Was administered dose or exposure level adequately randomized?	Authors state that allocation was random, without description of the method use.	+
	Was allocation to study groups adequately concealed?	Insufficient information about allocation to study groups.	-
Performance bias	Were the research personnel and human subjects blinded to the study group during the study?	Report that study was double-blind, but not whether this applied to all.	+
Attrition/exclusion bias	Were outcome data complete without attrition or exclusion from analysis?	Loss of subjects was adequately addressed and reasons were documented when human subjects were removed from a study or analyses. Performed a test that indicated that subjects who withdrew were not different from those who completed the study. Long duration of study (2 years) can explain the loss>20%.	+
Detection bias	Can we be confident in the exposure characterisation?	Commercial, named sunscreen with reported ingredients, supplied from the manufacturer (assume sufficient stability). Concentrations not reported. Control was placebo: sunscreen base. Uncertainty about consistency of application (each participant used own routines and applied the preparation liberally.	-
	Can we be confident in the outcome assessment?	Other adverse effects were self-reported. There was no information on how this was reported.	-

Selective reporting bias	Were all measured outcomes reported?	All measured "other negative effects" were reported.	+
Other sources of bias	Were there no other potential threats to internal validity (*e.g.* statistical methods were appropriate and researchers adhered to the study protocol)?	Statistical methods were not performed for assessment of adverse effects. Power analysis may have revealed that a higher number of participants was needed, but was not performed. UV exposure was similar between the groups at enrolment, but no data reported during study time.	-

Squamous cell carcinoma

Green et al. (1999)

Type of bias	**Question**	**Risk of bias evaluation**	**Risk of bias rating**
Selection bias	Was administered dose or exposure level adequately randomized?	A customized randomization computer program was used.	++
	Was allocation to study groups adequately concealed?	The allocation concealment was poorly described. From personal communication with Green, it was informed that the nursing staff who co-ordinated the distribution of sunscreen knew the allocation groups. However, the dermatologists, pathologists and investigators were unaware of the allocation. It is deemed that using a customized randomization computer program combined with a centralised service to distribute the sunscreen, it is unlikely selection bias would have been introduced.	++

Performance bias	Were the research personnel and human subjects blinded to the study group during the study?	The subjects and nursing staff who co-ordinated the distribution of sunscreen were not blinded. Dermatologists, pathologists and investigators were blinded. It is deemed that lack of adequate blinding of the subjects would not appreciably bias the results.	+
Attrition/exclusion bias	Were outcome data complete without attrition or exclusion from analysis?	Reasons for withdrawal was described. After 12 months, 128 (8%) participants had withdrawn with no subsequent follow-up. By 36 months there were another 88 withdrawals and at the end of the study in year 5, 238 (15%) participants had withdrawn without a complete skin examination by a dermatologist in the follow-up period.	-
Detection bias	Can we be confident in the exposure characterisation?	There was not sufficient information about exposure in the control group (*e.g.* type of sunscreen, amounts used).	-
	Can we be confident in the outcome assessment?	Dermatologists, pathologists and investigators were blinded. Since the subjects were not blinded, the blinding could have been broken during the examination with the dermatologists. However, it is deemed that this would not appreciably bias the results. From personal communication with Green, it was informed that the statistician had access to the randomization code but did not refer to this information. All skin cancers clinically diagnosed during these follow-up surveys were examined histologically by a single dermatopathologist.	+
Selective reporting bias	Were all measured outcomes reported?	Yes	++
Other sources of bias	Were there no other potential threats to internal validity (*e.g.* statistical methods were appropriate and researchers adhered to the study protocol)?	The statistics seemed appropriate. No protocol available.	+

van der Pols et al. (2006)

Type of bias	Question	Risk of bias evaluation	Risk of bias rating
Selection bias	Was administered dose or exposure level adequately randomized?	A customized randomization computer program was used.	++
	Was allocation to study groups adequately concealed?	Dermatologists, pathologists and investigators were blinded. Since the subjects were not blinded, the blinding could have been broken during the examination with the dermatologists. However, it is deemed that this would not appreciably bias the results. From personal communication with Green, it was informed that the statistician had access to the randomization code but did not refer to this information.	++
Performance bias	Were the research personnel and human subjects blinded to the study group during the study?	The subjects and nursing staff who co-ordinated the distribution of sunscreen were not blinded. Dermatologists, pathologists and investigators were blinded. It is deemed that lack of adequate blinding of the subjects would not appreciably bias the results.	+
Attrition/exclusion bias	Were outcome data complete without attrition or exclusion from analysis?	The loss of subjects was adequately addressed.	++
Detection bias	Can we be confident in the exposure characterisation?	There was not sufficient information about exposure in the control group (*e.g.* type of sunscreen, amounts used).	-
	Can we be confident in the outcome assessment?	The outcome was addressed using well established methods. Skin cancer diagnoses was verified by physicians. Dermatologists, pathologists and investigators were blinded. Since the subjects were not blinded, the blinding could have been broken during the examination with the dermatologists. However, it is deemed that this would not appreciably bias the results. From personal communication with Green, it was informed that the statistician had access to the randomization code but did not refer to this information.	+

Selective reporting bias	Were all measured outcomes reported?	All of the study's measured outcomes outlined in the methods were reported.	++
Other sources of bias	Were there no other potential threats to internal validity (*e.g.* statistical methods were appropriate and researchers adhered to the study protocol)?	The statistics were adequate. No protocol available.	+

Vitamin D production

Faurschou et al. (2012)

Type of bias	Question	Risk of bias evaluation	Risk of bias rating
Selection bias	Was administered dose or exposure level adequately randomized?	The participants were randomized by drawing opaque sealed envelopes with a computer-generated randomization list to receive sunscreen.	++
	Was allocation to study groups adequately concealed?	There is direct evidence that at the time of recruitment the research personnel and subjects did not know what study group subjects were allocated to, and it is unlikely that they could have broken the blinding of allocation until after recruitment was complete and irrevocable.	++
Performance bias	Were the research personnel and human subjects blinded to the study group during the study?	It is deemed that lack of adequate blinding during the study would not appreciably bias results.	+

Attrition/exclusion bias	Were outcome data complete without attrition or exclusion from analysis?	Outcome data were complete.	++
Detection bias	Can we be confident in the exposure characterisation?	The UV-filter in the sunscreen was reported. The concentration of the UV-filter was not reported. The amount applied was reported. As the study duration was short, we consider it likely that the UV-filter was not degraded.	_
	Can we be confident in the outcome assessment?	There is direct evidence that the outcome was assessed using well-established methods, and that subjects had been followed for the same length of time in all study groups.	++
Selective reporting bias	Were all measured outcomes reported?	All of the study's measured outcomes outlined in the methods were reported.	++
Other sources of bias	Were there no other potential threats to internal validity (*e.g.* statistical methods were appropriate and researchers adhered to the study protocol)?	There were no other potential threats to internal validity.	++

Libon et al. (2017a)

Type of bias	**Question**	**Risk of bias evaluation**	**Risk of bias rating**
Selection bias	Was administered dose or exposure level adequately randomized?	Subjects were allocated to study groups using a method with a random component without description of the method used.	+
	Was allocation to study groups adequately concealed?	Not reported.	-

Performance bias	Were the research personnel and human subjects blinded to the study group during the study?	No information, however, it is deemed that lack of adequate blinding during the study would not appreciably bias results.	+
Attrition/exclusion bias	Were outcome data complete without attrition or exclusion from analysis?	There is indirect evidence that the outcome data were complete.	++
Detection bias	Can we be confident in the exposure characterisation?	Controlled UVR. A commercially available sunscreen with a sunprotection factor 50+. The UV-filter in the sunscreen was reported. The concentration of the UV-filter was not reported. The amount applied was reported. As the study duration was short, we consider it likely that the UV-filter was not degraded. No information on application of cream/lotion on the control groups.	-
	Can we be confident in the outcome assessment?	Outcome was assessed using well-established methods, subjects had been followed for the same length of time in all study groups, and the outcome assessors were adequately blinded to the study group.	++
Selective reporting bias	Were all measured outcomes reported?	All of the study's measured outcomes outlined in the methods were reported.	++
Other sources of bias	Were there no other potential threats to internal validity (*e.g.* statistical methods were appropriate and researchers adhered to the study protocol)?	There were there no other potential threats to internal validity. UV exposure not sufficiently controlled.	+

Marks et al. (1995)

Type of bias	**Question**	**Risk of bias evaluation**	**Risk of bias rating**

Selection bias	Was administered dose or exposure level adequately randomized?	Authors report that the study was randomised.	+
	Was allocation to study groups adequately concealed?	Not reported.	-
Performance bias	Were the research personnel and human subjects blinded to the study group during the study?	The placebo cream was the base cream of the sunscreen made up to the same consistency as the sunscreen cream. Both creams were in identical 500 g containers. No further information on blinding was reported. It is deemed that lack of blinding of personnel or participants would not appreciably bias results.	+
Attrition/exclusion bias	Were outcome data complete without attrition or exclusion from analysis?	Loss of 27 subjects throughout the study was not adequately addressed (17%), reasons for missing subjects unlikely to be related to outcome.	+
Detection bias	Can we be confident in the exposure characterisation?	Sunscreen ingredients and % UV filter were reported; UVB in sunscreen; sunscreen weighed; participants were given written instructions on how to apply the cream, as well as watching a video produced to show visually the manner in which it should be applied. They were given diaries in which they were asked to record the frequency and time of application of the cream on a daily basis. The control group received a cream without UV-filters. The sunscreen was not consistently applied as different amounts used was reported in the diaries.	+
	Can we be confident in the outcome assessment?	The outcome was assessed using well-established methods, and subjects had been followed for the same length of time in all study groups.	++
Selective reporting bias	Were all measured outcomes reported?	All of the study's measured outcomes outlined in the methods were reported.	++

Other sources of bias	Were there no other potential threats to internal validity (*e.g.* statistical methods were appropriate and researchers adhered to the study protocol)?	The statistics were appropriate. In an attempt to control the UVR, participants were told to avoid sun exposure in the middle of the day, and to wear cloths and hats where appropriate. The time spent out in the sun was reported in a diary.	+

Matsuoka et al. (1990)

Type of bias	**Question**	**Risk of bias evaluation**	**Risk of bias rating**
Selection bias	Was administered dose or exposure level adequately randomized?	Subjects were allocated to study groups using a method with a random component without description of the method used.	+
	Was allocation to study groups adequately concealed?	There is insufficient information provided about allocation to study groups.	-
Performance bias	Were the research personnel and human subjects blinded to the study group during the study?	It is deemed that lack of adequate blinding during the study would not appreciably bias results.	+
Attrition/exclusion bias	Were outcome data complete without attrition or exclusion from analysis?	There was no loss of subjects during the study and outcome data were complete.	++
Detection bias	Can we be confident in the exposure characterisation?	Controlled UVR. It is not described which UV-filters the sunscreen contains, the concentration of the UV-filters, and there is insufficient information about the amount sunscreen used. There is no information on use of cream/lotion by the control group.	--

	Can we be confident in the outcome assessment?	The outcome was assessed using acceptable methods, and it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results, which is more likely to apply to objective outcome measures.	+
Selective reporting bias	Were all measured outcomes reported?	All of the study's measured outcomes outlined in the methods were reported.	++
Other sources of bias	Were there no other potential threats to internal validity (*e.g.* statistical methods were appropriate and researchers adhered to the study protocol)?	All participants were asked to minimize direct solar exposure for the duration of the study (24 hours).	-

17.1.2.4 Data extraction

Data extraction forms for the RCTs are available below.

Study characteristics	Title	A Randomized Controlled Trial to Assess SunscreenApplication and Beta Carotene Supplementationin the Prevention of Solar Keratoses
	Author(s)	**Steven Darlington,** Gail Williams, Rachel Neale, Christine Frost, Adele Gree**n**
	Year of publication	**2003**
	Country	Australia
	Funding	The study was supported by the Public Health Research and Development Committee of the National Health and Medical Research Council of Australia. Sunscreen was supplied by Ross Cosmetics Australia, Melbourne, Australia, and Woolworths Limited, Sydney, Australia. Betacarotene supplements and placebo were supplied by Roche Vitamins and Fine Chemicals, Nutley, NJ, USA.

	Reported conflict of interest	Not reported
Methods/ intervention	Study design	RCT
	Blinding	Only the investigator who generated the treatment code and the two people who packaged the tablets (beta-carotene supplementation; co-exposure not assessed in the current opinion) for distribution knew the treatment code. None of these people had contact with participants. The participants in the control group were not blinded.
	Method for randomisation	A customised randomisation computer program was used.
	Intervention design (sunscreen/included SPF/controls, presence of UVR, frequency of application)	Background study: 2x2 factorial field trial (sunscreen and beta-carotene). The current study: The intervention group: application of a broad-spectrum SPF 15 sunscreen to head, neck, arms, and hands every morning (supplied by Woolworths Limited, Sydney, Australias under the brand Auscreen Ultrablock Lotion SPF 15+, Ross Cosmetics, Melbourne, Australia). Reapplication was advised after heavy sweating, bathing, or long sun exposure. Control group: use of sunscreen at their usual, discretionary frequency, including no use.
	Concentration of ingredient(s), amount applied, substance purity. UVR exposure (source, irradiance, dose)	The study sunscreen contained 8% (by weight) 2-ethylhexyl-p-methoxycinnamate and 2% (by weight) 4-tert-butyl–4'-methoxy-4-dibenzoylmethane, rated as water resistant with sun protection factor 16 according to Australian Standard 2604. The treatment protocol involved self-application of a layer to all exposed sites on the head, neck, arms, and hands every morning. Participants received one or more 250 mL bottles of sunscreen every 3 months. UV exposure was determined in the two groups (daily vs. discretionary use) through interviews. Exposure site: Nambour, Queensland, Australia: latitude 26°S.
	Duration of study	4.5 years
Participants	Number of participants and completion rate (invited, accepted, drop out, included in follow-up if applicable)	Invited=3850; attending baseline survey=1647; randomized=1621, assigned to daily sunscreen and placebo=408 of which 338 were examined for skin cancer; assigned no daily sunscreen or placebo=393 of which 334 were examined for skin cancer.

	Inclusion/exclusion criteria for participants	Study participants were originally randomly chosen residents of Nambour, who were aged between 20 and 69 years when they took part in a skin-cancer survey in 1986. To be eligible for the current study, the original survey participants had to attend a second survey in 1992, undergo a complete skin examination by a dermatologist with removal of all diagnosed skin cancers, and give written consent to take part in this randomised trial until 1996.
	Country/countries of origin of the study subjects	Australia
	Country/countries where the study is conducted	Australia
	Gender	Of the 1621 randomised at inclusion in 1992: Daily sunscreen: F: 458; M: 354. Discretionary sunscreen: F: 455; M: 354. Total F: 913; total M: 708
	Age	Between 20 and 69 years in 1986. In 1992, mean age (SD) sunscreen intervention users (+/- beta carotene): 48.5 (12.9)(+); 48.7 (13.6) (-); mean age (SD) discretionary sunscreen users: 48.1 (13.6)(+); 49.8 (12.7)(-).
	Ethnicity and skin type classification (Fitzpatrick, 1988)	Baseline characteristics (no difference between those who dropped out and those who did not): 55% of the participants assessed themselves as having fair skin while the vast majority (89%) reported that they would usually sunburn on acute sun exposure, with (68%) or without (21%) subsequent tanning. Skin colours reported (of 1433 participants): fair (62.6%), medium (42.7%), olive (7.6%)
	Number of exposed/non-exposed	Sunscreen intervention: 404; Discretionary sunscreen use: 393.
	Confounders and other variables as reported	At trial entry (the original trial), there were 917 women (56%) and 709 men overall in the study sample, reflecting the oversampling of women (at lower risk of skin cancer than men) in the skin cancer prevalence survey. 454 (28%) of the participants were under the age of 40 years.
	Health and socioeconomic status of participants	• 430 participants (26%) reported a prior diagnosis of skin cancer • Solar keratosis at baseline were diagnosed by a dermatologist in 788 participants, and 15% had more than ten keratosis. Approximately 75% reported ever having used sunscreen

	Other (*e.g.* selection bias and representativeness for the general Norwegian population)	Nambour is a subtropical town, at latitude 26°S and 8.7 m above sea level. This latitude and the UV irradiation are representative for typical holiday destinations for the Norwegian population (Canary Islands). The reported skin types, with a majority of the fair type, are also representative.
Results	Parameters measured, methods used, and measurement time points	Main Outcome Measure:Change in the prevalentnumber of solar keratoses in the intervention group relative to change in the control group.
	Reported outcome (including measures of variance)	The ratio of SK counts in 1994 relative to 1992 was lower in people randomized to daily sunscreen use (1.20; 95% confidence interval, 1.04-1.39) than in those randomized to discretionary sunscreen use (1.57; 95% confidence interval, 1.35-1.84). A reduction in the rate of change of solar keratosis prevalence was also seen in the sunscreen intervention group relative to the discretionary sunscreen group between 1994 and 1996, but it was not significant.
Statistical analysis	Power analysis	
	Statistical test	
Comments		There was no mention of sunbed use. The control group was also using sunscreen.

Study characteristics	Title	Reduction of solar keratoses by regular sunscreen use
	Author(s)	**S.C. Thompson**, D. Jolley, R. Marks
	Year of publication	**1993**
	Country	Australia

	Funding	Grants from the Victorian Health Promotion Foundation, Melbourne; the Skin and Cancer Foundation, Sydney; the Skin and Psoriasis Foundation, Melbourne; the Lloyd Williams Trust, Maryborough; the Sydney Melanoma Foundation; and the Australasian College of Dermatologists.
	Reported conflict of interest	Not reported
Methods/ intervention	Study design	Randomised controlled trial
	Blinding	The subjects were blinded, and it was reported that the physician who did the final examination was unaware of the results from the baseline examination.
	Method for randomisation	The randomisation of the 588 subjects who enrolled in the study was stratified according to sex and self-rated skin type. Randomisation method was not described.
	Intervention design (sunscreen/included SPF/controls, presence of UVR, frequency of application)	The participants applied daily either a broad-spectrum sunscreen cream with SPF 17 or the base cream without the active ingredients of the sunscreen to the head, neck, forearms, and hands. The sunscreen was rated according to the Australian Standard 2604 (1986) (94% reduction in the wavelength range 290-320 nm) and rated as a broad-spectrum filter (90% UVA reduction in the wavelength range 320-360 nm). UVR exposure was ambient solar radiation. All subjects were told not to rely entirely on the cream, but also to avoid the sun around the middle of the day and to wear hats and clothing where appropriate. They were asked not to use other sunscreen products during the study.
	Concentration of ingredient(s), amount applied, substance purity. UVR exposure (source, irradiance, dose)	The sunscreen cream contained 8% (wt/wt) 2-ethylhexyl p-methoxycinnamate and 2% (wt/wt) 4-tert-butyl-4-methoxy-4-dibenzoylmethane. The participants were instructed to (but determined their own level) apply minimum 4.5 ml of the sunscreen per day distributed as follows: 1.5 ml to the head and neck and the same amount to each forearm and hand once every morning. Participants were encouraged to reapply if necessary, during the day. Ambient UVR conditions: Maryborough, Victoria (about 37°S), September 1991 to March 1992. Sun avoidance measures were encouraged.
	Duration of study	Seven months (one summer: September 1991 to March 1992)

Participants	Number of participants and completion rate (invited, accepted, drop out, included in follow-up if applicable)	Of the 588 participants enrolled, 431 completed the study. Number of dropouts was similar between the intervention and control group, and there was no significant difference in the baseline demographic characteristics or study variables (including side effects of treatment) between those who completed the study and those who did not.
	Inclusion/exclusion criteria for participants	Persons 40 years of age or older with 1 to 30 solar keratoses were invited to participate.
	Country/countries of origin of the study subjects	Maryborough and surrounding districts in the state of Victoria, Australia
	Country/countries where the study is conducted	Australia
	Gender	Of the 431 subjects who completed the study, 180 (42%) were men and 251 (58%) were women.
	Age	Mean age [±SD]: 63 ±11. Age range: 40 to 93 years.
	Ethnicity and skin type classification (Fitzpatrick, 1988)	"White" subjects with self-rated skin types described as: burn only and never tan, burn first and then tan, or tan only and never burn.
	Number of exposed/non-exposed	There were 221 subjects (89 men and 132 women) in the base-cream group and 210 subjects (91 men and 119 women) in the sunscreen group.
	Confounders and other variables as reported	Not reported
	Health and socioeconomic status of participants	Not reported

	Other (*e.g.* selection bias and representativeness for the general Norwegian population)	The fair skin types reported are representative for a large part of the Norwegian population. The latitude is representative for typical holiday destinations for Norwegians, although UV irradiance in summer may be 50% higher in the southern than northern hemisphere
Results	Parameters measured, methods used, and measurement time points	Three outcome variables were identified for each subject: the number of solar keratoses at the end of the trial, the number of new lesions appearing during the study (incident lesions), and the number of remissions, expressed as a proportion of the number of base-line lesions. Initially, a skin cancer screening was performed (head, neck, hands and forearms) by a medical officer with interest in skin cancer. After randomisation to groups, diagnosis was performed, based on clinical appearance. A randomised sub-sample of subjects was selected for biopsy of a lesion from the hands and forearms. If the solar keratosis chosen for biopsy was no longer present at follow-up, the disappearance was termed a remission; this occurred in some but not all lesions chosen for biopsy. Any lesion treated by a doctor during the course of the study was excluded from analysis. Follow-up examinations were performed on three occasions during seven months, the time of maximal daily sunlight in southern Australia (from spring until autumn); the last examination was in March 1992. At each examination, the total number of solar keratoses, remissions, and new lesions were recorded, the diaries were examined, and the bottles of cream were weighed. Any untoward reactions to the creams were recorded. Subjects who withdrew from the study were contacted to determine the reasons. Of the 431 subjects who completed the study, 413 (96 percent) were examined by the same physician at the beginning and end of the study. The remaining 4% were seen by different examiners. The results of the final examination were recorded on a new grid map, so that the examiner was unaware of the results of previous examinations. The subjects kept daily diaries in which they recorded the time of application of the cream.
	Reported outcome (including measures of variance)	The mean (+/- SD) number of solar keratoses increased by 1.0 (+/- 0.3) per subject in the base-cream group and decreased by 0.6 (+/-0.3) per subject in the sunscreen group (difference, 1.53; 95 % confidence interval (CI), 0.81 to 2.25).

		The relative change in the total number of solar keratoses in the sunscreen group, with the relative change in the base-cream group used as a reference, was 0.83 (95% CI, 0.78 to 0.89). There was a sex-based difference in the change in the number of lesions during the study (smaller change in women compared to men) (rate ratio, 0.87; 95% CI, 0.80 to 0.94). The sunscreen group had 1.6 new mean lesions per subject, whereas the base-cream group had 2.3. The difference in the mean number of new lesions per subject between the groups was 0.72 (95% CI, 0.15 to 1.28; P= 0.014). The sunscreen group had fewer new lesions (rate ratio, 0.62; 95% CI, 0.54 to 0.71) and more remissions (odds ratio, 1.53; 95 % CI, 1.29 to 1.80) than the base-cream group. Remission (mean) throughout the study was 28% in the sunscreen group vs. 20% in the base-cream group (difference of 8%; 95% CI, 2 to 13%). There was a dose-response relation: the amount of sunscreen cream used was related to both the development of new lesions and the remission of existing ones. Number of new lesions and the probability of remission were affected by the amount of cream used (X^2=6.3, P = 0.04 for new lesions; X^2=13.3, P = 0.001 for remissions).
Statistical analysis	Power analysis	Not reported
	Statistical test	Multiplicative Poisson models were used to analyse the total number of solar keratoses and the number of new solar keratoses. A binomial logistic model was assumed for remission probabilities. The logarithm of the number of each subject's lesions at baseline was included in each of the three models, with a fixed coefficient of 1.0 (as an offset) in the case of the total number of lesions. For all models, treatment effects were assessed for significance by comparing changes in model deviance with the chi-square distribution. Effect estimates were obtained from model coefficients, and two-sided confidence intervals were calculated from the unscaled matrix of coefficient covariance.
Comments		

Study characteristics	Title	Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomised controlled trial
	Author(s)	**Adèle Green,** Gail Williams, Rachel Neale, Veronica Hart, David Leslie, Peter Parsons, Geoffrey C Marks, Philip Gaffney, Diana Battistutta, Christine Frost, Carolyn Lang, Anne Russell.
	Year of publication	**1999**
	Country	Australia
	Funding	The study was supported by the Public Health Research and Development Committee of the National Health and Medical Research Council of Australia. Sunscreen was supplied by Ross Cosmetics Australia, Melbourne, Australia, and Woolworths Limited, Sydney, Australia. Betacarotene supplements and placebo were supplied by Roche Vitamins and Fine Chemicals, Nutley, NJ, USA.
	Reported conflict of interest	Not reported
Methods/ intervention	Study design	RCT
	Blinding	Only the investigator who generated the treatment code and the two people who packaged the tablets (beta-carotene supplementation; co-exposure not assessed in the current opinion) for distribution knew the treatment code. None of these people had contact with participants. The participants in the control group were not blinded.
	Method for randomisation	A customised randomisation computer program was used.
	Intervention design (sunscreen/included SPF/controls, presence of UVR, frequency of application)	Background study: 2x2 factorial field trial (sunscreen and beta-carotene). The current study: analysis of time to multiple occurrences of basal cell carcinoma data in the period 1992-1996 (4.5 years). The intervention group: application of a broad-spectrum SPF 15 sunscreen to head, neck, arms, and hands every morning (supplied by Woolworths Limited, Sydney, Australias under the brand Auscreen Ultrablock Lotion SPF 15+, Ross Cosmetics, Melbourne, Australia). Reapplication was advised after heavy sweating, bathing, or long sun exposure. Control group: use of sunscreen at their usual, discretionary frequency, including no use.

	Concentration of ingredient(s), amount applied, substance purity. UVR exposure (source, irradiance, dose)	The study sunscreen contained 8% (by weight) 2-ethylhexyl-p-methoxycinnamate and 2% (by weight) 4-tert-butyl–4'-methoxy-4-dibenzoylmethane, rated as water resistant with sun protection factor 16 according to Australian Standard 2604. The treatment protocol involved self-application of a layer to all exposed sites on the head, neck, arms, and hands every morning. Participants received one or more 250 mL bottles of sunscreen every 3 months. UV exposure was determined in the two groups (daily vs. discretionary use) through interviews. Exposure site: Nambour, Queensland, Australia: latitude 26°S.
	Duration of study	4.5 years
Participants	Number of participants and completion rate (invited, accepted, drop out, included in follow-up if applicable)	Invited=3850; attending baseline survey=1647; randomized=1621, assigned to daily sunscreen and placebo=408 of which 338 were examined for skin cancer; assigned no daily sunscreen or placebo=393 of which 334 were examined for skin cancer.
	Inclusion/exclusion criteria for participants	Study participants were originally randomly chosen residents of Nambour, who were aged between 20 and 69 years when they took part in a skin-cancer survey in 1986. To be eligible for the current study, the original survey participants had to attend a second survey in 1992, undergo a complete skin examination by a dermatologist with removal of all diagnosed skin cancers, and give written consent to take part in this randomised trial until 1996.
	Country/countries of origin of the study subjects	Australia
	Country/countries where the study is conducted	Australia
	Gender	Of the 1621 randomised at inclusion in 1992: Daily sunscreen: F: 458; M: 354. Discretionary sunscreen: F: 455; M: 354. Total F: 913; total M: 708
	Age	Between 20 and 69 years in 1986. In 1992, mean age (SD) sunscreen intervention users (+/- beta carotene): 48.5 (12.9)(+); 48.7 (13.6) (-); mean age (SD) discretionary sunscreen users: 48.1 (13.6)(+); 49.8 (12.7)(-).

	Ethnicity and skin type classification (Fitzpatrick, 1988)	Baseline characteristics (no difference between those who dropped out and those who did not): 55% of the participants assessed themselves as having fair skin while the vast majority (89%) reported that they would usually sunburn on acute sun exposure, with (68%) or without (21%) subsequent tanning. Skin colours reported (of 1433 participants): fair (62.6%), medium (42.7%), olive (7.6%)
	Number of exposed/non-exposed	Sunscreen intervention: 404; Discretionary sunscreen use: 393.
	Confounders and other variables as reported	At trial entry (the original trial), there were 917 women (56%) and 709 men overall in the study sample, reflecting the oversampling of women (at lower risk of skin cancer than men) in the skin cancer prevalence survey. 454 (28%) of the participants were under the age of 40 years.
	Health and socioeconomic status of participants	• 430 participants (26%) reported a prior diagnosis of skin cancer • Solar keratosis at baseline were diagnosed by a dermatologist in 788 participants, and 15% had more than ten keratosis. • Approximately 75% reported ever having used sunscreen
	Other (*e.g.* selection bias and representativeness for the general Norwegian population)	Nambour is a subtropical town, at latitude 26°S and 8.7 m above sea level. This latitude and the UV irradiation are representative for typical holiday destinations for the Norwegian population (Canary Islands). The reported skin types, with a majority of the fair type, are also representative.
Results	Parameters measured, methods used, and measurement time points	Analysis of the effect of sunscreen was based only on skin cancers that developed on sites of daily application.
	Reported outcome (including measures of variance)	There was no harmful effect of daily use of sunscreen in this medium-term study. Cutaneous squamous-cell carcinoma, but not basal-cell carcinoma seems to be amenable to prevention through the routine use of sunscreen by adults for 4.5 years. 1383 participants underwent full skin examination by a dermatologist in the follow-up period. 250 of them developed 758 new skin cancers during the follow-up period. There were no significant differences in the incidence of first new skin cancers between groups randomly assigned daily sunscreen and no daily sunscreen (basal-cell carcinoma 2588 vs 2509 per 100 000; rate ratio 1.03 [95% CI 0.73–1.46]; squamous-cell carcinoma 876 vs 996 per 100 000; rate ratio 0.88[0.50–1.56]). Similarly, there was no

		significant difference between the betacarotene and placebo groups in incidence of either cancer (basal-cell carcinoma 3954 vs 3806 per 100 000; 1.04 [0.73–1.27]; squamous-cell carcinoma 1508 vs 1146 per 100 000; 1.35 [0.84–2.19]). In terms of the number of tumours, there was no effect on incidence of basal-cell carcinoma by sunscreen use or by betacarotene but the incidence of squamous-cell carcinoma was significantly lower in the sunscreen group than in the no daily sunscreen group (1115 vs 1832 per 100 000; 0.61 [0.46–0.81]).
Statistical analysis	Power analysis	Based on a cohort of 1,626, the power of the study was calculated to be 83% to detect a 40% reduction in skin cancer incidence of BCC and SCC combined and 55% to detect a 30% reduction in skin cancer incidence at the 5% level of significance.
	Statistical test	Intention-to-treat analysis was carried out separately for all histologically confirmed BCCs and SCCs occurring on the head, neck, arms, and hands between 1993 and 2004 (cancers diagnosed in the first year of intervention were excluded). Treatment effect on cancer incidence rates was assessed using Poisson and negative binomial regression applied to persons affected and tumor counts, respectively. Treatment effectiveness was assessed overall in trial and follow-up periods combined (1993-2004) and separately in the total follow-up period (September 1996 to December 2004) and late follow-up period (January 2001 to December 2004). The analyses presented were performed using the PHREG procedure in SAS/STAT statistical software. The proportional hazard assumption test was done using the cox.zph command in R software.
Comments		There was no mention of sunbed use. The control group was also using sunscreen.

Study characteristics	Title	Repeated Occurrence of Basal Cell Carcinoma of the Skin and Multifailure Survival Analysis: Follow-up Data from the Nambour Skin Cancer Prevention Trial
	Author(s)	**N. Pandeya,** D.M. Purdie, A. Green, G. Williams

	Year of publication	**2005**
	Country	Australia
	Funding	Not reported. The study is based on data from Green et al. 1994, in which funding was reported from the Public Health Research and Development Committee of the National Health and Medical Research Council of Australia, and in part by the Prevent Blindness Foundation.
	Reported conflict of interest	Not reported
Methods/ intervention	Study design	Randomised controlled trial (Green et al. 1994)
	Blinding	Only the investigator who generated the treatment code and the two people who packaged the tablets (beta-carotene supplementation; co-exposure not assessed in the current opinion) for distribution knew the treatment code. None of these people had contact with participants. The participants in the control group were not blinded.
	Method for randomisation	A customised randomisation computer program was used.
	Intervention design (sunscreen/included SPF/controls, presence of UVR, frequency of application)	Background study: 2x2 factorial field trial (sunscreen and beta-carotene). The current study: analysis of time to multiple occurrences of basal cell carcinoma data in the period 1992-1996 (4.5 years). The intervention group: application of a broad-spectrum SPF 16 sunscreen to head, neck, arms, and hands every morning (supplied by Woolworths Limited, Sydney, Australias under the brand Auscreen Ultrablock Lotion SPF 15+, Ross Cosmetics, Melbourne, Australia). Reapplication was advised after heavy sweating, bathing, or long sun exposure. Control group: use of sunscreen at their usual, discretionary frequency, including no use.
	Concentration of ingredient(s), amount applied, substance purity. UVR exposure (source, irradiance, dose)	The study sunscreen contained 8% (by weight) 2-ethylhexyl-p-methoxycinnamate and 2% (by weight) 4-tert-butyl–4'-methoxy-4-dibenzoylmethane, rated as water resistant with sun protection factor 16 according to Australian Standard 2604. The treatment protocol involved self-application of a layer to all exposed sites on the head, neck, arms, and hands every morning. Participants received one or more 250 mL bottles of sunscreen every 3 months. UV exposure was determined in the two groups (daily vs. discretionary use) through interviews. In Green et al., 1999 it is

		stated that: "no changes in outdoor behaviour of participants were observed in the follow-up period that could have influenced outcomes within randomised groups". (Exposure site: Nambour, Queensland, Australia: latitude 26°S).
	Duration of study	Follow-up of a previously 4.5-year randomised controlled trial with study start in 1992.
Participants	Number of participants and completion rate (invited, accepted, drop out, included in follow-up if applicable)	3,000 adults in 1992 were invited to take part in the Skin Cancer Prevention Trial. 1,621 persons enrolled in the trial, 137 died during the follow-up period, leaving 1,484 (92%) followed to the end of 2004.
	Inclusion/exclusion criteria for participants	Study participants were originally randomly chosen residents of Nambour, who were aged between 20 and 69 years when they took part in a skin-cancer survey in 1986. To be eligible for the current study, the original survey participants had to attend a second survey in 1992, undergo a complete skin examination by a dermatologist with removal of all diagnosed skin cancers, and give written consent to take part in this randomised trial until 1996.
	Country/countries of origin of the study subjects	Australia
	Country/countries where the study is conducted	Australia
	Gender	Of the 1621 randomised at inclusion in 1992: Daily sunscreen: F: 458; M: 354. Discretionary sunscreen: F: 455; M: 354. Total F: 913; total M: 708
	Age	Between 20 and 69 years in 1986. In 1992, mean age (SD) sunscreen intervention users (+/- beta carotene): 48.5 (12.9)(+); 48.7 (13.6) (-); mean age (SD) discretionary sunscreen users: 48.1 (13.6)(+); 49.8 (12.7)(-).
	Ethnicity and skin type classification (Fitzpatrick, 1988)	Baseline characteristics (no difference between those who dropped out and those who did not): 55% of the participants assessed themselves as having fair skin while the vast majority (89%) reported that they would usually sunburn on acute sun exposure, with (68%) or without (21%) subsequent tanning. Skin colours reported (of 1433 participants): fair (62.6%), medium (42.7%), olive (7.6%)

	Number of exposed/non-exposed	Sunscreen intervention: 404; Discretionary sunscreen use: 393.
	Confounders and other variables as reported	At trial entry (the original trial), there were 917 women (56%) and 709 men overall in the study sample, reflecting the oversampling of women (at lower risk of skin cancer than men) in the skin cancer prevalence survey. 454 (28%) of the participants were under the age of 40 years.
	Health and socioeconomic status of participants	• 430 participants (26%) reported a prior diagnosis of skin cancer • Solar keratosis at baseline were diagnosed by a dermatologist in 788 participants, and 15% had more than ten keratosis • Approximately 75% reported ever having used sunscreen
	Other (*e.g.* selection bias and representativeness for the general Norwegian population)	Nambour is a subtropical town, at latitude 26°S and 8.7 m above sea level. This latitude and the UV irradiation are representative for typical holiday destinations for the Norwegian population (Canary Islands). The reported skin types, with a majority of the fair type, are also representative.
Results	Parameters measured, methods used, and measurement time points	The Cox proportional hazard model was applied, using the time to diagnosis of first BCC as an outcome. Three different approaches of time to ordered multiple events were applied and compared: the Andersen-Gill, Wei-Lin-Weissfeld, and Prentice-Williams-Peterson models. Robust variance estimation approaches were used for all multifailure survival models.
	Reported outcome (including measures of variance)	Sunscreen treatment was not associated with time to first occurrence of a BCC (hazard ratio =1.04, 95% confidence interval (CI): 0.79, 1.45). Time to subsequent BCC tumors using the Andersen-Gill model resulted in a lower estimated hazard among the daily sunscreen application group, although statistical significance was not reached (hazard ratio =0.82, 95% confidence interval: 0.59, 1.15). Similarly, both the Wei-Lin-Weissfeld marginal-hazards and the Prentice-Williams-Peterson gap-time models revealed trends toward a lower risk of subsequent BCC tumors among the sunscreen intervention group. Hazard ratios (crude); 95% CI; p-value for the combined effect of sunscreen intervention on repeated occurrences of BCC: Time to first episode: 1.03; 0.77, 1.38; 0.83. Andersen-Gill model: 0.90; 066, 1.23; 0.49. Wei-Lin Weissfeld model: 0.89; 0.65, 1.24; 0.50. Prentice-Williams-Peterson: 0.91; 0.72, 1.15; 0.42.
Statistical analysis	Power analysis	Based on a cohort of 1,626, the power of the study was calculated to be 83% to detect a 40% reduction in skin cancer incidence of BCC and SCC combined and 55% to detect a 30% reduction

		in skin cancer incidence at the 5% level of significance. "The correlation among the tumor occurrences within individuals resulted in inflated standard errors and, combined with the small number of events, the analysis lacked the power to provide a statistically significant result."
	Statistical test	Intention-to-treat analysis was carried out separately for all histologically confirmed BCCs and SCCs occurring on the head, neck, arms, and hands between 1993 and 2004 (cancers diagnosed in the first year of intervention were excluded). Treatment effect on cancer incidence rates was assessed using Poisson and negative binomial regression applied to persons affected and tumor counts, respectively. Treatment effectiveness was assessed overall in trial and follow-up periods combined (1993-2004) and separately in the total follow-up period (September 1996 to December 2004) and late follow-up period (January 2001 to December 2004). The analyses presented were performed using the PHREG procedure in SAS/STAT statistical software. The proportional hazard assumption test was done using the cox.zph command in R software.
Comments		There was no mention of sunbed use. The control group was also using sunscreen.

Study characteristics	Title	Prolonged Prevention of Squamous Cell Carcinoma of the Skin by Regular Sunscreen Use
	Author(s)	**J.C. van der Pols,** G. M. Williams, N. Pandeya, V. Logan, A.C. Green
	Year of publication	**2006**
	Country	Australia
	Funding	National Health and Medical Research Council of Australia, National Health and Medical Research Council Capacity Building Grant in Population Health Research, and Department of Health and Ageing, Australia.

	Reported conflict of interest	No information available
Methods/ intervention	Study design	Randomised controlled trial (Green et al. 1994)
	Blinding	Only the investigator who generated the treatment code and the two people who packaged the beta-carotene tablets (co-treatment in the original study) for distribution knew the treatment code. None of these people had contact with participants. The participants in the control group were not blinded.
	Method for randomisation	A customised randomisation computer program was used.
	Intervention design (sunscreen/included SPF/controls, presence of UVR, frequency of application)	Background study: 2x2 factorial field trial (sunscreen and beta-carotene), RCT lasting for 4.5 years. Current study: Follow-up of the participants for a further 8 years to evaluate possible latency of preventive effect on BCCs and SCCs. The intervention group: application of a broad-spectrum SPF 16 sunscreen to head, neck, arms, and hands every morning. Reapplication was advised after heavy sweating, bathing, or long sun exposure. Control group: use of sunscreen at their usual, discretionary frequency, including no use. UVR exposure was ambient.
	Concentration of ingredient(s), amount applied, substance purity. UVR exposure (source, irradiance, dose)	The study sunscreen (Auscreen Ultrablock Lotion SPF 15-plus, Ross Cosmetics, Melbourne, Australia) was a standard cream containing 8% (by weight) 2-ethylhexyl-p-methoxycinnamate and 2% (by weight) 4-tert-butyl–4′-methoxy-4-dibenzoylmethane, rated as water resistant with sun protection factor 16 according to Australian Standard 2604. The treatment protocol involved self-application of a layer to all exposed sites on the head, neck, arms, and hands every morning. Participants received one or more 250 mL bottles of sunscreen every 3 months. UV exposure was determined in the two groups (daily vs. discretionary use) through interviews. In Green et al., 1999 it is stated that: "no changes in outdoor behaviour of participants were observed in the follow-up period that could have influenced outcomes within randomised groups". (Exposure site: Nambour, Queensland, Australia: latitude 26°S)
	Duration of study	Follow-up of a previously 4.5-year randomised controlled trial, with study start in 1992, for a period of eight years (1996-2004).

Participants	Number of participants and completion rate (invited, accepted, drop out, included in follow-up if applicable)	In December 1986, a prevalence survey of skin cancer and actinic eye damage was conducted among a random sample of 2095 adult residents of Nambour (drawn from the electoral roll, originally from 3000 invited (Pandeya et al., 2005). All persons in the original 1986 study who were able to be contacted in 1992 were invited to take part in the Skin Cancer Prevention Trial. 1621 persons enrolled in the trial and were randomised, 137 died during the follow-up period, leaving 1484 (92%) followed to the end of 2004.
	Inclusion/exclusion criteria for participants	Study participants were originally randomly chosen residents of Nambour, who were aged between 20 and 69 years when they took part in a skin-cancer survey in 1986. To be eligible for the 1992-1996 study, the original survey participants had to attend a second survey in 1992, undergo a complete skin examination by a dermatologist with removal of all diagnosed skin cancers, and give written consent to take part in this randomised trial until 1996.
	Country/countries of origin of the study subjects	Australia
	Country/countries where the study is conducted	Australia
	Gender	Of the 1621 randomised at inclusion in 1992: Daily sunscreen: F: 458; M: 354. Discretionary sunscreen: F: 455; M: 354. Total F: 913; total M: 708. The gender distribution of the 1484 participants followed to end of 2004 was not reported.
	Age	Between 20 and 69 years in 1986. In 1992, mean age (SD) sunscreen intervention users (+/- beta carotene): 48.5 (12.9)(+); 48.7 (13.6)(-); mean age (SD) discretionary sunscreen users: 48.1 (13.6)(+); 49.8 (12.7)(-).
	Ethnicity and skin type classification (Fitzpatrick, 1988)	Australians, no difference in treatment allocation by skin color. Baseline characteristics (no difference between those who dropped out and those who did not): 55% of the participants assessed themselves as having fair skin while the vast majority (89%) reported that they would usually sunburn on acute sun exposure, with (68%) or without (21%) subsequent tanning. Skin colours reported (of 1433 participants): fair (62.6%), medium (42.7%), olive (7.6%) (Pandeya et al., 2005).

	Number of exposed/non-exposed	Intervention: 744; control: 740
	Confounders and other variables as reported	At trial entry (the original trial), there were 917 women (56%) and 709 men overall in the study sample, reflecting the oversampling of women (at lower risk of skin cancer than men) in the skin cancer prevalence survey. 454 (28%) of the participants were under the age of 40 years.
	Health and socioeconomic status of participants	• 430 participants (26%) reported a prior diagnosis of skin cancer • Solar keratosis at baseline were diagnosed by a dermatologist in 788 participants, and 15% had more than ten keratosis • Approximately 75% reported ever having used sunscreen
	Other (*e.g.* selection bias and representativeness for the general Norwegian population)	Nambour is a subtropical town, at latitude 26°S and 8.7 m above sea level. The UV irradiance at this latitude is representative of typical holiday destinations for the Norwegian population (*e.g.* Canary Islands). The reported skin types, with a majority of the fair type, are also representative
Results	Parameters measured, methods used, and measurement time points	Participants received full skin examinations by dermatologists unaware of treatment allocation at the start (1992), midway (1994), and at the finish (1996), and physicians verified skin cancer diagnoses. After the trial ended in 1996, all participants, including those who withdrew from active follow-up, consented to have subsequently diagnosed skin cancers notified to the investigators by regional pathology laboratories in Queensland. In addition, active participants completed 6-monthly questionnaires with information about any new skin cancers treated, as well as the amount of time spent outdoors on weekdays and weekends, and sunscreen use. In 2000, participants were offered a further full skin examination by a dermatologically trained physician, with histologic confirmation of suspected skin cancers. In the current study, the authors evaluated possible latency of sunscreen intervention on BCC and SCC among trial participants for 8 years after the trial had ceased using the statistical methods outlined below (Statistical analysis)
	Reported outcome (including measures of variance)	Regular application of sunscreen had prolonged preventive effects on SCC but with no clear benefit in reducing BCC. BCC tumor rates tended to decrease but not significantly in people formerly randomised to daily sunscreen use compared with those not applying sunscreen daily.

		SCC tumor rates were significantly decreased by almost 40% during the entire follow-up period (rate ratio, 0.62; 95% confidence interval, 0.38-0.99). In the same period the corresponding rate ratio for BCC was 0.89; 95% CI, 0.64-1.25. Ratio ratios for persons affected during the entire follow-up period were 0.65; 95% CI, 0.43-0.98 and 1.02; 95% CI, 0.75-1.37 for SCC and BCC, respectively.
Statistical analysis	Power analysis	Based on a cohort of 1,626, the power of the study was calculated to be 83% to detect a 40% reduction in skin cancer incidence of BCC and SCC combined and 55% to detect a 30% reduction in skin cancer incidence at the 5% level of significance.
	Statistical test	Intention-to-treat analysis was carried out separately for all histologically confirmed BCCs and SCCs occurring on the head, neck, arms, and hands between 1993 and 2004 (cancers diagnosed in the first year of intervention were excluded). Treatment effect on cancer incidence rates was assessed using Poisson and negative binomial regression applied to persons affected and tumor counts, respectively. Treatment effectiveness was assessed overall in trial and follow-up periods combined (1993-2004) and separately in the total follow-up period (September 1996 to December 2004) and late follow-up period (January 2001 to December 2004).
Comments		

Study characteristics	Title	Sun Exposure, Sunscreen and Their Effects on Epidermal Langerhans Cells
	Author(s)	**Rachel Neale,** Anne Russelli, H. Konrad Muller and Adele Green
	Year of publication	**1997**
	Country	Australia

	Funding	National Health and Medical Research Council of Australia, National Health and Medical Research Council Capacity Building Grant in Population Health Research, and Department of Health and Ageing, Australia.
	Reported conflict of interest	No information available
Methods/ intervention	Study design	Randomised controlled trial (Green et al. 1994)
	Blinding	Only the investigator who generated the treatment code and the two people who packaged the beta-carotene tablets (co-treatment in the original study) for distribution knew the treatment code. None of these people had contact with participants. The participants in the control group were not blinded.
	Method for randomisation	A customised randomisation computer program was used.
	Intervention design (sunscreen/included SPF/controls, presence of UVR, frequency of application)	Background study: 2x2 factorial field trial (sunscreen and beta-carotene), RCT lasting for 4.5 years. Current study: The intervention group: application of a broad-spectrum SPF 16 sunscreen to head, neck, arms, and hands every morning. Reapplication was advised after heavy sweating, bathing, or long sun exposure. Control group: use of sunscreen at their usual, discretionary frequency, including no use. UVR exposure was ambient.
	Concentration of ingredient(s), amount applied, substance purity. UVR exposure (source, irradiance, dose)	The study sunscreen (Auscreen Ultrablock Lotion SPF 15-plus, Ross Cosmetics, Melbourne, Australia) was a standard cream containing 8% (by weight) 2-ethylhexyl-p-methoxycinnamate and 2% (by weight) 4-tert-butyl–4'-methoxy-4-dibenzoylmethane, rated as water resistant with sun protection factor 16 according to Australian Standard 2604. The treatment protocol involved self-application of a layer to all exposed sites on the head, neck, arms, and hands every morning. Participants received one or more 250 mL bottles of sunscreen every 3 months. UV exposure was determined in the two groups (daily vs. discretionary use) through interviews. In Green et al., 1999 it is stated that: "no changes in outdoor behaviour of participants were observed in the follow-up period that could have influenced outcomes within randomised groups". (Exposure site: Nambour, Queensland, Australia: latitude 26°S)

	Duration of study	Follow-up of a previously 4.5-year randomised controlled trial, with study start in 1992, for a period of eight years (1996-2004).
Participants	Number of participants and completion rate (invited, accepted, drop out, included in follow-up if applicable)	In December 1986, a prevalence survey of skin cancer and actinic eye damage was conducted among a random sample of 2095 adult residents of Nambour (drawn from the electoral roll, originally from 3000 invited (Pandeya et al., 2005). All persons in the original 1986 study who were able to be contacted in 1992 were invited to take part in the Skin Cancer Prevention Trial. 1621 persons enrolled in the trial and were randomised, 137 died during the follow-up period, leaving 1484 (92%) followed to the end of 2004.
	Inclusion/exclusion criteria for participants	Study participants were originally randomly chosen residents of Nambour, who were aged between 20 and 69 years when they took part in a skin-cancer survey in 1986. To be eligible for the 1992-1996 study, the original survey participants had to attend a second survey in 1992, undergo a complete skin examination by a dermatologist with removal of all diagnosed skin cancers, and give written consent to take part in this randomised trial until 1996.
	Country/countries of origin of the study subjects	Australia
	Country/countries where the study is conducted	Australia
	Gender	Of the 1621 randomised at inclusion in 1992: Daily sunscreen: F: 458; M: 354. Discretionary sunscreen: F: 455; M: 354. Total F: 913; total M: 708. The gender distribution of the 1484 participants followed to end of 2004 was not reported.
	Age	Between 20 and 69 years in 1986. In 1992, mean age (SD) sunscreen intervention users (+/- beta carotene): 48.5 (12.9)(+); 48.7 (13.6)(-); mean age (SD) discretionary sunscreen users: 48.1 (13.6)(+); 49.8 (12.7)(-).
	Ethnicity and skin type classification (Fitzpatrick, 1988)	Australians, no difference in treatment allocation by skin color. Baseline characteristics (no difference between those who dropped out and those who did not): 55% of the participants assessed themselves as having fair skin while the vast majority (89%) reported that they would usually sunburn on acute sun

		exposure, with (68%) or without (21%) subsequent tanning. Skin colours reported (of 1433 participants): fair (62.6%), medium (42.7%), olive (7.6%) (Pandeya et al., 2005).
	Number of exposed/non-exposed	Intervention: 744; control: 740
	Confounders and other variables as reported	At trial entry (the original trial), there were 917 women (56%) and 709 men overall in the study sample, reflecting the oversampling of women (at lower risk of skin cancer than men) in the skin cancer prevalence survey. 454 (28%) of the participants were under the age of 40 years.
	Health and socioeconomic status of participants	• 430 participants (26%) reported a prior diagnosis of skin cancer • Solar keratosis at baseline were diagnosed by a dermatologist in 788 participants, and 15% had more than ten keratosis Approximately 75% reported ever having used sunscreen
	Other (*e.g.* selection bias and representativeness for the general Norwegian population)	Nambour is a subtropical town, at latitude 26°S and 8.7 m above sea level. The UV irradiance at this latitude is representative of typical holiday destinations for the Norwegian population (*e.g.* Canary Islands). The reported skin types, with a majority of the fair type, are also representative
Results	Parameters measured, methods used, and measurement time points	Number of Langerhans cells
	Reported outcome (including measures of variance)	There were significantly fewer Langerhans cells on the exposed (463 cells/mm2) than on the unexposed forearm (528 cells/mm2) (P = 0.0001).
Statistical analysis	Power analysis	
	Statistical test	The difference be- tween dorsal and ventral cell numbers was assessed using a paired t-test, and Student's f-test or ANOVA was used for comparisons of the mean cell numbers within categories of age, sex, indices of oc- cupational UVR exposure and skin cancer.
Comments		

Study characteristics	Title	A New Ecamsule-Containing SPF 40 Sunscreen Cream for the Prevention of Polymorphous Light Eruption: A Double-blind, Randomized, Controlled Study in Maximized Outdoor Conditions
	Author(s)	**V.A. DeLeo**, S. Clark, J. Fowler, M. Poncet, C. Loesche, P. Soto
	Year of publication	**2009**
	Country	Country affiliation of corresponding author is USA.
	Funding	The study was funded by L'Oréal, USA.
	Reported conflict of interest	Dr. DeLeo is a consultant for Johnson & Johnson Consumer Products, Inc; L'Oréal USA; and Schering-Plough. Dr. Clark is a consultant and investigator for Galderma Laboratories, LP. Dr. Fowler received a research grant from Galderma Laboratories, LP. Mr. Poncet, Dr. Loesche, and Ms. Soto are employees of Galderma R&D.
Methods/ intervention	Study design	Randomised controlled trial.
	Blinding	The authors report that the study was double-blind. The method was not reported.
	Method for randomisation	The method for randomisation was not reported.
	Intervention design (sunscreen/included SPF/controls, presence of UVR, frequency of application)	At least 15 min prior to every sun exposure, each participant was treated on all exposed body areas other than the face and hands by a specifically trained study nurse who applied an SPF 40 sunscreen cream (ecamsule, octocrylene, avobenzone, titanium dioxide; tetrad) to one side of the body; the other side received either an ecamsule-deprived (triad-E) or avobenzone-deprived (triad-A) cream.

		To elicit polymorphic light eruption (PMLE) flares, participants were exposed to incremental doses of sunlight, reported as doses of UVA, for up to 6 days (once on the first day and twice daily thereafter); assessments were done twice on the first day and 3 times daily thereafter: before the morning exposure, and before and after the afternoon exposure at approximately 1 to 3 hours after the end of the previous sun exposure. UVA radiation doses were measured and participants were exposed to the sunlight to receive an equal amount of sunlight on both sides. Participants were withdrawn from the study when a clear-cut diagnosis of PMLE flare on both sides of the body was made. If only one side reacted, irradiation continued on the other side and the involved side was covered with protective towels. Participants were randomized to either treatment group, and treatment was randomized to either side of the body.
	Concentration of ingredient(s), amount applied, substance purity. UVR exposure (source, irradiance, dose)	1. Tetrad sunscreen cream (SPF 42.5; UVA-PF, 23.2): ecamsule 3%, octocrylene 10%, avobenzone 2%, and titanium dioxide 5%. 2. Triad-E sunscreen: ecamsule-deprived (SPF 28.5; UVA-PF, 15.3) 3. Triad-A sunscreen: avobenzone-deprived (SPF 38.7; UVA-PF, 13.2) Sunlight exposure (reported as UVA): Incremental doses from day 1 to day 6: 20; 30; 45; 50; 55; 60 J/cm ^{2}
	Duration of study	Six days
Participants	Number of participants and completion rate (invited, accepted, drop out, included in follow-up if applicable)	A total of 150 participants were randomized, of which 144 received study drug (tetrad/triad-E treatment group, 73; tetrad/triad-A treatment group, 71). Participant disposition was similar between the treatment groups. Among the 144 participants who received the study drug, 140 completed the study (tetrad/triad-E treatment group, 69; tetrad/triad-A treatment group, 71). Four participants discontinued due to adverse events, of which none were considered to be related to study drugs.
	Inclusion/exclusion criteria for participants	Men and women, 18 years and older, previously diagnosed with PMLE, had negative serum anti-nuclear and serum anti-Ro antibodies test results, and had no concomitant photosensitive-causing medications were included.

		Participants with a history of skin cancer and/or uncontrolled systemic disease, known sensitivity to any ingredients of the study preparations, exposure to significant UVR within 3 months before the start of the study sun exposure, history of photodermatoses or other photosensitive diseases/conditions other than PML, and use of study medications that would interfere with interpretation of study results, were excluded.
	Country/countries of origin of the study subjects	Participants were recruited from across the United States.
	Country/countries where the study is conducted	The study was conducted at one site (Puerto Rico).
	Gender	Females: 118; males: 26.
	Age	Mean age: 40.3 years, minimum age: 18 years, maximum age: 73 years.
	Ethnicity and skin type classification (Fitzpatrick, 1988)	Participants: White: 141; Black: 1; Hispanic: 2. Fitzpatrick skin types: I: 32; II: 72: III: 35; IV: 5.
	Number of exposed/non-exposed	Tetrad/triad-E treatment group, 73 participants; tetrad/triad-A treatment group, 71 participants.
	Confounders and other variables as reported	Not reported. Pigmentation is a potential confounder which was not controlled for
	Health and socioeconomic status of participants	Not stated other than exclusion criteria
	Other (*e.g.* selection bias and representativeness for the general Norwegian population)	Representative for the Norwegian population (81.9% female; 72.2% skin types I-II)

Results	Parameters measured, methods used, and measurement time points	Polymorphous light eruption was declared when a score of 2 or more was reached on the global severity scale. The primary efficacy assessment was a composite success rate with 3 components. Success of the tetrad relative to either of the triads was defined as follows for each participant: • PMLE flare occurred on the triad-treated side at any time and not on the tetrad-treated side. • PMLE flare occurred later on the tetrad-treated side than on the triad-treated side. • PMLE flare occurred on both sides at the same time with a global severity score on the triad-treated side that was at least 2 grades higher than the tetrad-treated side. The success of the triad relative to the tetrad was defined in a similar way. Secondary criteria included the time and cumulative UVA doses to the onset of PMLE flares, global severity of the PMLE flare, as well as symptoms of erythema, pruritus, and burning/stinging, and lesion counts (papules, vesicles, plaques, total lesions) at the visit when PMLE flare was first observed (end point). Efficacy end point assessments, including primary and secondary assessments, were performed at the time of a PMLE flare. The last evaluation visit was used as end point if PMLE flares did not develop on either side of the body.
	Reported outcome (including measures of variance)	Of the 144 participants enrolled and randomized, 22 did not experience PMLE during the study duration. A significantly greater number of successes were detected on the tetrad-treated side compared with either triad: 41 of 73 participants (56%) versus 8 of 73 participants (11%) in the triad-E treatment group and 26 of 71 participants (36%) versus 11 of 71 participants (16%) in the triad-A treatment group. PMLE appeared later with the tetrad than with either triad. The global severity of the PMLE flares was significantly lower with the tetrad than with both triads at end. The tetrad sunscreen cream prevented PMLE flares significantly better than similar formulations with only one of the UVA filters.
Statistical analysis	Power analysis	Using a 2-sided sign test, a sample size of 66 evaluable participants per group was deemed appropriate to detect, with 90% power, a significant difference in success rates between the tetrad and each triad. To account for unevaluable participants, 75 participants per group were planned to be randomized.

	Statistical test	Statistical hypotheses were to test if there were differences in relative success rates between the tetrad and each triad within each parallel group using the sign (binomial) test in the intention-to-treat population. Global severity scores of PMLE, lesion counts, and PMLE symptoms of erythema, pruritus, and burning/stinging at end were compared using the Wilcoxon signed rank test. All tests were 2-sided, performed at the .05 nominal probability level (α level).
Comments		Controls without sunscreen and without UV-exposure were missing. UVB exposure, that can elicit PMLE and can be absorbed by the UV filters used, was not reported. Amount of sunscreen applied was not reported. Regarding representativeness: Prevalence up to 20% in European countries (Gruber-Wackernagel et al., 2014). PLE affects mostly women, and a prevalence of 33.4% in females of skin type I was reported by Rhodes et al. (2010) in Europe.

Study characteristics	Title	Indoor simulation of polymorphic light eruption using a UVA/UVB solar simulator and prevention by a well-balanced UVA/UVB sunscreen
	Author(s)	**D. Moyal**, M. Verschoore, O. Binet
	Year of publication	**1999**
	Country	France
	Funding	No information
	Reported conflict of interest	No information
	Study design	Randomised controlled trial

Methods/ intervention	Blinding	It was reported that the study was double-blinded. No further information on the blinding was available.
	Method for randomisation	Method for randomisation was not described.
	Intervention design (sunscreen/included SPF/controls, presence of UVR, frequency of application)	The test product was a UVA-UVB sunscreen containing Parsol 1789, Eusolex 6300 and Mexoryl SX with micronized titanium dioxide (Heliobloc Forte Cream, Galderma Laboratories, France). The positive control used in this study was a UVB photoprotection sunscreen containing Parsol MCX, Eusolex 6300 and homosalate. The SPFs were 60 for the UVA-UVB sunscreen and 18 for the positive control. The UVA protection factors determined by the method of persistent pigment darkening were 15 for the UVA-UVB sunscreen and 1.2 for the positive control. Each morning, creams (2 mg/cm^2) were applied to the right or left half of the front of the neck in a randomized manner. Each subject's neckline was then exposed to UV irradiation.
	Concentration of ingredient(s), amount applied, substance purity. UVR exposure (source, irradiance, dose)	The concentration of UV filters in the UVA-UVB sunscreen: Parsol 1789: 3.5%, Eusolex 6300: 5%, Mexoryl SX: 3.25%, micronized titanium dioxide: 5%. The positive control used contained Parsol MCX (10%), Eusolex 6300 (5%) and homosalate (4.5%). UVA and UVB doses were increased progressively each day. The highest UVA and UVB dose was equivalent to a 2-h exposure to the midday sun. If polymorphic light eruption (PMLE) occurred, the half of the neckline involved was not exposed to further UV radiation. The UV radiation source was a metal halide Supersun 5000 lamp (Mutzhas Trading, Munich), with UVA dose regulation and cut-off filters. This system produced UV radiation within the 290-390 nm spectrum with a UVA:UVB ratio of approximately 18.5: 1 (similar to the UVA-UVB ratio of standard sun radiation). UVA and UVB doses were increased progressively each day. The highest UVA and UVB dose was equivalent to a 2-h exposure to the midday sun. Cumulative UVA dose: 89 J/cm^2; cumulative UVB dose: 4815 mJ/cm^2
	Duration of study	Five days

Participants	Number of participants and completion rate (invited, accepted, drop out, included in follow-up if applicable)	18 participants were included and completed.
	Inclusion/exclusion criteria for participants	A diagnosis of systemic lupus erythematosus was excluded by confirming the absence of antinuclear antibodies in the participants' serum prior to study entry. No medication was permitted during the study. Medication and exposure to natural or artificial sunlight was also avoided over the 3 months preceding the study.
	Country/countries of origin of the study subjects	France
	Country/countries where the study is conducted	France
	Gender	Females
	Age	20-48 years
	Ethnicity and skin type classification (Fitzpatrick, 1988)	Phototype II and III
	Number of exposed/non-exposed	All participants were both exposed and non-exposed (intervention and control creams were applied to each side of the neck).
	Confounders and other variables as reported	
	Health and socioeconomic status of participants	Participants were diagnosed with PMLE.

	Other (*e.g.* selection bias and representativeness for the general Norwegian population)	The participants are representative for parts of the Norwegian population with respect to phototype. PMLE occurs mostly in women.
Results	Parameters measured, methods used, and measurement time points	Evaluations were performed approximately 6 hours after UV exposure from the 2nd day onwards. Objective signs (erythema, papules and oedema) and subjective symptoms (burning and pruritus) were rated on a four-point scale of severity (0 to 3) during and after exposure. Photographs were taken of any eruptions. PMLE was considered to have been reproduced when at least three characteristic signs were rated with a score of at least 1 in severity.
	Reported outcome (including measures of variance)	After five exposures which mimicked a natural outdoor sun exposure, all subjects developed typical PMLE symptoms in the positive control areas, whereas only one subject developed symptoms in the area protected by a UVA-UVB sunscreen (94% effective): • Day one, after one UV exposure, no subject developed clinical signs of photodermatosis. • Day two, 14 of the 18 subjects (78%) developed the first signs of PMLE on the side of the neckline protected by the positive control product. No signs of MPLE were detected on the side protected by the combined UVA and UVB sunscreen at this time. • Day three, 12 of the 18 volunteers developed clear-cut clinical symptoms of PMLE and 5 volunteers developed early signs of PMLE on the side protected by the positive control sunscreen. • Day four, all volunteers exhibited signs of PMLE on the side protected by the positive control product.
Statistical analysis	Power analysis	Not reported
	Statistical test	Not reported
Comments		Two authors are affiliated with the sunscreen manufacturers.

Study characteristics	Title	The relation between sunscreen layer thickness and vitamin D production after ultraviolet B exposure: a randomized clinical trial
	Author(s)	**A. Faurschou**, D.M. Beyer, A. Schmedes, M.K. Bogh, P.A. Philipsen, H.C. Wulf
	Year of publication	**2012**
	Country	Denmark
	Funding	None
	Reported conflict of interest	None declared
Methods/ intervention	Study design	Randomised controlled trial
	Blinding	Neither the participant nor the investigator knew in advance which sunscreen layer thickness to be given.
	Method for randomisation	The participants were randomized by drawing opaque sealed envelopes with a computer-generated randomization list
	Intervention design (sunscreen/included SPF/controls, presence of UVR, frequency of application)	Each participant was treated with sunscreen on the back and front of the upper body, approximately 25% of the body area. A commercially available inorganic sunscreen labelled SPF 8 (Matas, Allerød, Denmark) containing the inorganic filter titanium dioxide, was used. The areas of the back and the front of the upper body were measured and divided into four subareas, which had sunscreen applied separately to secure even application. All participants were UVB irradiated with a fixed UVB dose 20 min after sunscreen application. This procedure was repeated four times with a 2- to 3-day interval. To secure a solid control group, more participants were included in the group not treated with sunscreen.
	Concentration of ingredient(s), amount applied, substance purity. UVR exposure (source, irradiance, dose)	The concentration and purity of the UV-filter were not reported. The exact amount of sunscreen was weighed and applied.in layer thickness of 0 mg cm^2, 0.5 mg cm^2, 1 mg cm^2, 1.5 mg cm^2, or

		2 mg cm^2. The rest of the body was covered with UV-impermeable fabric and the face was shielded. Irradiation: 3 standard erythema doses (SED) were obtained with six Waldman UV fluorescent tubes (Herbert Waldmann GmbH & Co. KG, Vilingen-Schwenningen, Germany) emitting broadband UVB (290-360 nm; peak emission 320 nm). The UVB dose was chosen to induce vitamin D production without inducing erythema according to the findings in a previous study. Irradiance was measured and equipment calibrated. UV doses were quantified in SED: 100 J/m^2 at 298 nm. Skin pigmentation was measured as control at baseline and before every treatment. The study was conducted in January to March 2008 in Denmark, 56°N. At that time of year, the ambient UVB radiation is negligible.
	Duration of study	The procedure was repeated four times with a 2 to 3-day interval, thus, the total duration of the study could be from 8 to 12 days.
Participants	Number of participants and completion rate (invited, accepted, drop out, included in follow-up if applicable)	37 healthy volunteers participated and completed.
	Inclusion/exclusion criteria for participants	Healthy volunteers, with Fitzpatrick skin types I–III, were included. Exposure to sun or sunbeds and vitamin D supplementation were not permitted 3 months before and during the study. Exclusion criteria were skin disease, intake of photosensitizing or cholesterol lowering medicine, inability to complete the study, pregnancy and breast-feeding.
	Country/countries of origin of the study subjects	Denmark
	Country/countries where the study is conducted	Denmark
	Gender	20 women and 17 men

	Age	Age range was 18–49 years
	Ethnicity and skin type classification (Fitzpatrick, 1988)	Fitzpatrick skin types I–III
	Number of exposed/non-exposed	Controls: n=10; intervention: n=27
	Confounders and other variables as reported	Pigmentation was controlled
	Health and socioeconomic status of participants	"Healthy" volunteers
	Other (*e.g.* selection bias and representativeness for the general Norwegian population)	Similar ethnicity and genetic variations (in vitamin D metabolism?) as well as Fitzpatrick skin types (I-III)
Results	Parameters measured, methods used, and measurement time points	At baseline and 3 days after the last irradiation, blood samples were collected and analysed for serum 25-hydroxyvitamin D_3. Method: The blood samples were taken by venepuncture and were centrifuged (5,000 g in 10 minutes) within 2 hours of sampling. The serum samples for 25-hydroxyvitamin D_3 analysis were frozen, stored at 80 °C, and sent on dry ice to the biochemical laboratory for 25-hydroxyvitamin D_3 analysis by liquid chromatography-tandem mass spectrometry. To minimize the variance of 25-hydroxyvitamin D_3, two serum samples from each subject were included and each 25-hydroxyvitamin D_3 analysis was performed twice.
	Reported outcome (including measures of variance)	The vitamin D serum level increased in an exponential manner with decreasing thickness of sunscreen layer in response to UVB exposure. For all thicknesses of sunscreen, the level of 25-hydroxyvitamin D_3 increased significantly after irradiation, except for the group treated with 2 mg cm^2, in which the increase in 25-hydroxyvitamin D_3 was not statistically significant. Mean increase in 25-hydroxyvitamin D_3 measured 2-3 days after the final irradiation for layer thickness 0.0; 0.5; 1.0; 1.5; 2.0 mg/cm^2 (SD; p-value indicating difference from vitamin D level before irradiation; p-value indicating difference from the vitamin D level in the UV-irradiated group without sunscreen) were: 25.8 (12.0; 0.0001; not applicable); 12.5 (7.8; 0.0059; 0.007); 11.5 (5.1;

		0.0009; 0.004); 10.2 (5.6; 0,0028; 0.002); 6.4 (9.5; 0.16; 0.0003), respectively. The vitamin D increase was adjusted for baseline and the SD in the various sunscreen groups.
Statistical analysis	Power analysis	The correlation coefficient of 0.46 between sunscreen layer thickness and vitamin D serum level was used for sample size calculation (data from previous study). The power was set to 0.8 and the associated type I error probability was 0.05. As a result, 31 persons needed to be included.
	Statistical test	Descriptive data were reported as the mean and SD. $P < 0.05$ was considered statistically significant. Commercially available software was used to analyse these data.
Comments		25(OH)D analysis method was referred to a previous publication.

Study characteristics	Title	The Effect of Regular Sunscreen Use on Vitamin D Levels in an Australian Population. Results of a Randomized Controlled Trial
	Author(s)	**R. Marks**, P.A. Foley, D. Jolley, K.R. Knight, J. Harrison, S.C. Thompson
	Year of publication	**1995**
	Country	Australia
	Funding	Grants from the Victorian Health Promotion Foundation; The Skin and Psoriasis Foundation, Victoria; The Skin and Cancer Foundation, Sydney; The Australasian College of Dermatologists; The Sydney Melanoma Foundation; and the Lloyd Williams Trust, Maryborough.
	Reported conflict of interest	Not reported
	Study design	Randomised controlled trial

Methods/ intervention	Blinding	The sunscreen and the placebo cream had the same consistency, and were in identical 500 g containers. The authors reported that the study was double-blind. No further information on blinding was reported.
	Method for randomisation	Method for randomization was not described.
	Intervention design (sunscreen/included SPF/controls, presence of UVR, frequency of application)	A broad-spectrum sunscreen (SPF 17; Australian standard; 94% reduction in the UVB (290-320 nm); 90% reduction in UVA (320-360 nm)) and a placebo cream (base cream of the sunscreen made up to the same consistency by adding 10% wt/wt mineral oil) were tested. The placebo cream was without UV-filters. Participants were given written instructions on how to apply the cream, as well as watching a video produced to show how the cream should be applied. The participants were instructed to apply sunscreen to the head, neck and each forearm and hand once every morning. They were given diaries in which they were asked to record the frequency and time of application of the cream on a daily basis. UVR exposure was from solar radiation. Participants were told to avoid sun exposure in the middle of the day, and to wear clothes and hats where appropriate.
	Concentration of ingredient(s), amount applied, substance purity. UVR exposure (source, irradiance, dose)	The sunscreen contained 8% (wt/wt) 2-ethylhexyl p-methoxycinnamate and 2% (wt/wt) 4-tert-butyl-4-methoxy-4-dibenzoylmethane. Application amount: approximately 1.5 ml to the head and neck and the same amount to each forearm and hand once every morning. Reapplication if necessary, during the day. Containers of cream were weighed to determine the amount used. The time spent out in the sun was reported in a diary. Latitude of study place was 37°3´S (Maryborough, Australia). In the last week of the study, a subsample of the participants wore one polysulfone film badge every day, until sunset, attached to the outside of their clothing on the right shoulder. At the same time, a series of badges were placed on a level surface for the period of the study to determine the ambient irradiation received during that time. These were analysed for UVR in the range 285-315 nm (J/m)[probably meant J/m^2].
	Duration of study	Seven months, summer (September 1991 to March 1992)

Participants	Number of participants and completion rate (invited, accepted, drop out, included in follow-up if applicable)	A random subsample of participants enrolled in a solar keratosis study (Thompson et al., 1993) were invited to participate. 153 participants were recruited. 27 failed to complete the study for reasons unrelated to vitamin D levels. Of the 126 people who completed the study, 13 were excluded from the analysis because of unmatched or insufficient sample (n=5), abnormally elevated serum calcium levels (n=4), elevated serum urea and creatinine levels (n=3), or elevated serum alkaline phosphatase levels (n=l), leaving 113 subjects for study.
	Inclusion/exclusion criteria for participants	Criteria of the solar keratosis study from which the participants were enrolled (Thompson et al 1993): Persons with 1 to 30 solar keratoses recruited from a population of people aged >40 years were invited to participate. Sampling particularly of people >70 years.
	Country/countries of origin of the study subjects	Maryborough and surrounding districts in the state of Victoria, Australia.
	Country/countries where the study is conducted	Australia
	Gender	46 men and 67 women
	Age	59 were aged 40-70 years and 54 were aged 70 years and above (no exact maximum age was given).
	Ethnicity and skin type classification (Fitzpatrick, 1988)	Skin type were self-reported as burn only and never tan (n=31), burn first and then tan (n=56), or tan only and never burn (n=26) (from Thompson et al., 1993)
	Number of exposed/non-exposed	Fifty-eight participants used the sunscreen cream and 55 the placebo cream.
	Confounders and other variables as reported	All crude effects were examined for possible confounding. Little evidence of age confounding.

	Health and socioeconomic status of participants	Not reported
	Other (*e.g.* selection bias and representativeness for the general Norwegian population)	The study was conducted in the central Victorian city of Maryborough, 100 km north of Melbourne, at a latitude of 37°3' south. The UV irradiance at this coordinate may 50% higher that of the north, which includes typical holiday destinations for the Norwegian population (southern Europe). The distribution of self-reported skin types is comparable to a large degree.
Results	Parameters measured, methods used, and measurement time points	Ten milliliters of blood were collected by venipuncture at the initial interview in 1991 and at the final interview in 1992. Serum samples were analyzed for 25-hydroxyvitamin D_3 and 1,25-dihydroxyvitamin D_3 by competitive binding protein assay. All serum samples were subjected to routine biochemical analysis for creatinine, urea, calcium, phosphate, and serum alkaline phosphatase. UV irradiation: see details under Methods
	Reported outcome (including measures of variance)	Mean levels of 25-hydroxyvitamin D_3 increased significantly by the same amount in both groups over the period of the study (placebo, +12.8 nmol/L (95% CI, 8.4-17.1); sunscreen, + 11.8 nmol/L (95% CI, 7.6-15.9)). Mean levels of 1,25-dihydroxyvitamin D_3 increased significantly in the placebo group only (placebo, +10.8 pmol/L (95% CI 6.7-14.8); sunscreen, +1.3 pmol/L (95% CI –2.3 - 4.9)). For no subject in either group was the level of 1,25-dihydroxyvitamin D_3 outside the reference range either at the start or at the end of the study. There were no significant differences by age, sex, or skin type in the change in 25-hydroxyvitamin D_3 or 1,25-dihydroxyvitamin D_3 over the study period. Across all subjects, the mean 25-hydroxyvitamin D_3 level was 54.2 nmol/L (95% CI, 50.9 to 57.5 nmol/L) and for 1,25-dihydroxyvitamin D_3 it was 88.5 pmol/L (95% CI, 84.7 to 92.3 pmol/L). No difference in mean levels of 25-hydroxyvitamin D_3 was evident, except for persons with skin type 1 (burn only) whose mean level was lower than for persons with other skin types (9.5 nmol/L (95% CI, 2.3 to 16.7 nmol/L)). There was no heterogeneity between subgroups in their mean levels of 1,25-dihydroxyvitamin D_3 before the study began. Laboratory reference

		range: 30 to 125 nmol/L for 25-hydroxyvitamin D_3; 35 to 125 pmol/L for 1,25-dihydroxyvitamin D_3. UV-irradiation: Weighted geometric mean daily UV irradiation exposure levels were 137.9J/m^2 (95% CI, 62.6 to 304.0J/m^2) in the sunscreen cream group and 138.7 J/m^2 (95% CI, 60.8 to 316.6 J/m^2) in the placebo cream group. There was no detectable difference in UV exposure between the two groups (P=.99). The subjects received on average between 5% and 8% of the ambient irradiation at ground level during the week of the study period. Other biochemical analysis data were not reported except if levels were elevated, in which case the participants were excluded from analysis.
Statistical analysis	Power analysis	Not reported
	Statistical test	As histograms and probability plots of results of both vitamin D assays showed no serious departures from the expected normal distributions, standard methods for the analysis of continuous data were used. Within-person differences were computed to assess temporal changes, and treatment effects were estimated by differences in mean within-person changes across the study period. Because sampling was stratified by age, all crude effects were examined for possible confounding using multiple regression.
Comments		

17.2 Literature search: other human studies, animal and *in vitro* studies

17.2.1 Search strategy

Database: Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions® <1946 to November 24, 2020>

Date:	25.11.2020 Result: 396	
1	((Butyl adj2 (methoxydibenzoylmethane or "methoxydibenzoyl methane")) or avobenzone or butylmethoxydibenzoylmethane or "butylmethoxydibenzoyl methane" or "parsol 1789" or parsol1789 or "BMDBM cpd").tw,kf.	277
2	("Ethylhexyl salicylate" or "2ethylhexyl salicylate" or "salicylic acid 2 ethylhexyl ester" or "salicylic acid 2ethylhexyl ester" or "Octyl Salicylate" or octisalate or octylsalicylate or "ethyl hexyl salicylate" or "trans 2 hexenyl salicylate" or "trans2hexenyl salicylate" or "trans2 hexenyl salicylate" or "trans 2hexenyl salicylate").tw,kf.	120
3	limit 2 to yr="1996 -Current"	116
4	("Bis ethylhexyloxyphenol methoxyphenyl triazine" or "Bisethylhexyloxyphenol methoxyphenyl triazine" or Bemotrizinol or "escalol s" or "tinosorb s").tw,kf.	33
5	limit 4 to yr="1999 -Current"	33
6	("Ethylhexyl triazone" or "octyl triazone").tw,kf.	34
7	limit 6 to yr="1997 -Current"	32
8	1 or 3 or 5 or 7	396
9	8 not (comment or editorial or letter).pt.	396

Database: Embase 1974 to 2020 November 24

Date:	25.11.2020 Result: 759

1	avobenzone/ or 70356-09-1.rn.	688
2	((Butyl adj2 (methoxydibenzoylmethane or "methoxydibenzoyl methane")) or avobenzone or butylmethoxydibenzoylmethane or "butylmethoxydibenzoyl methane" or "parsol 1789" or parsol1789 or "BMDBM cpd").tw,kw.	429
3	1 or 2	755
4	octisalate/ or 118-60-5.rn.	123
5	("Ethylhexyl salicylate" or "2ethylhexyl salicylate" or "salicylic acid 2 ethylhexyl ester" or "salicylic acid 2ethylhexyl ester" or "Octyl Salicylate" or octisalate or octylsalicylate or "ethyl hexyl salicylate" or "trans 2 hexenyl salicylate" or "trans2hexenyl salicylate" or "trans2 hexenyl salicylate" or "trans 2hexenyl salicylate").tw,kw.	132
6	4 or 5	211
7	limit 6 to yr="1996 -Current"	206
8	Bemotrizinol/ or 187393-00-6.rn.	51
9	("Bis ethylhexyloxyphenol methoxyphenyl triazine" or "Bisethylhexyloxyphenol methoxyphenyl triazine" or Bemotrizinol or "escalol s" or "tinosorb s").tw,kw.	68
10	8 or 9	90
11	limit 10 to yr="1999 -Current"	90
12	("Ethylhexyl triazone" or "octyl triazone").tw,kw.	44
13	limit 12 to yr="1997 -Current"	42
14	3 or 7 or 11 or 13	927
15	14 not (Conference Abstract or Letter or Editorial).pt.	858

16	limit 15 to embase	759

Database: Web of Science

Date:	25.11.2020 Result: 506	
# 9	506	#7 OR #5 OR #3 OR #1 Refined by: [excluding] DOCUMENT TYPES: (PROCEEDINGS PAPER OR EDITORIAL MATERIAL OR MEETING ABSTRACT) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*
# 8	538	#7 OR #5 OR #3 OR #1 *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*
# 7	38	TS=("Ethylhexyl triazone" or "octyl triazone") *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=1997-2020*
# 6	39	TOPIC: ("Ethylhexyl triazone" or "octyl triazone") *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*
# 5	35	TS=("Bis ethylhexyloxyphenol methoxyphenyl triazine" or "Bisethylhexyloxyphenol methoxyphenyl triazine" or "Bemotrizinol" or "escalol s" or "tinosorb s") *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=1999-2020*
# 4	35	TOPIC: ("Bis ethylhexyloxyphenol methoxyphenyl triazine" or "Bisethylhexyloxyphenol methoxyphenyl triazine" or "Bemotrizinol" or "escalol s" or "tinosorb s") *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*
# 3	134	TS=("Ethylhexyl salicylate" or "2ethylhexyl salicylate" or "salicylic acid 2 ethylhexyl ester" or "salicylic acid 2ethylhexyl ester" or "Octyl Salicylate" or "octisalate" or "octylsalicylate" or "ethyl hexyl salicylate" or "trans 2 hexenyl salicylate" or "trans2hexenyl salicylate" or "trans2 hexenyl salicylate" or "trans 2hexenyl salicylate") *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=1996-2020*

# 2	136	TOPIC: ("Ethylhexyl salicylate" or "2ethylhexyl salicylate" or "salicylic acid 2 ethylhexyl ester" or "salicylic acid 2ethylhexyl ester" or "Octyl Salicylate" or "octisalate" or "octylsalicylate" or "ethyl hexyl salicylate" or "trans 2 hexenyl salicylate" or "trans2hexenyl salicylate" or "trans2 hexenyl salicylate" or "trans 2hexenyl salicylate") *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*
# 1	392	TOPIC: (("Butyl" NEAR/1 ("methoxydibenzoylmethane" or "methoxydibenzoyl methane")) or "avobenzone" or "butylmethoxydibenzoylmethane" or "butylmethoxydibenzoyl methane" or "parsol 1789" or "parsol1789" or "BMDBM cpd") *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*

17.2.2 Full text assessed – excluded publications

An overview of the publications considered not to fulfil the eligibility criteria is given in Table 17.2.2-1.

Table 17.2.2-1. Publications considered not eligible.

Reference	Reason for exclusion
Abranches et al. (2013)	Outcome
Ahn et al. (2019)	Outcome
Anonymous (2007)	Study design
Anonymous (2013)	Study design
Benevenuto et al. (2015)	Exposure
Billek (1984)	Study design
Bora et al. (2017)	Exposure
Bruynzeel et al. (2004)	Study design
Chew et al. (2010)	Exposure
Chiang et al. (2005)	Outcome
Collaris and Frank (2008)	Study design
Damiani et al. (2000)	Outcome

Reference	Reason for exclusion
De Groot et al. (1987)	Exposure
Foti et al. (2009)	Publication type
Fotiades et al. (1995)	Outcome
Goncalo et al. (2013)	Publication type
Goncalo et al. (1995)	Exposure
Guarrera et al. (2003)	Exposure
Guesmi et al. (2020)	Outcome
Hayden et al. (2005)	Outcome
Hiller et al. (2019b)	Outcome
Julian et al. (2015)	Publication type
Kaimal and Abraham (2011)	Publication type
Kawakami and Gaspar (2015)	Outcome
Kawakami et al. (2017)	Outcome
Kockler et al. (2013b)	Publication type
Lecha and Ortiz De Frutos (2003)	Publication type
Lenique et al. (1992)	Exposure
Li et al. (2017)	Outcome
Ma et al. (2003)	Outcome
Matta et al. (2020b)	Outcome
Matta et al. (2019b)	Outcome
Miralles et al. (2015)	Study design
Mortz et al. (2010)	Study design
Neumann and Lehmann (2003)	Outcome
Ouchene et al. (2019)	Publication type
Rehfeld et al. (2018a)	Outcome
Schauder (1991a)	Publication type
Schauder (1991b)	Study design
Schauder and Ippen (1997)	Publication type

Reference	Reason for exclusion
Schieszer (2019)	Publication type
Shaath (2010)	Publication type
uco et al. (2018)	Exposure
Xu and Parsons (1999)	Exposure

17.2.3 Internal validity

Bryden et al. (2006)

Type of bias	Question	Risk of bias evaluation	Risk of bias rating
Confounding bias	Did the study design or analysis account for important confounding and modifying variables?	Patients using potential interacting medication were excluded. Patients with active skin disease were excluded.	++
Detection bias	Can we be confident in the exposure characterisation?	Dose of 5 J /cm^2 fluorescent UVA (Philips R-UVA), test lamp was measured and calibrated. Non-irradiated controls and white soft paraffin as substance control. The UVA- dose tolerated by patient was checked prior to photopatch test. The doses were reported. The name of the UV-filters tested and the concentrations used, and the control, was reported.	++
	Can we be confident in the outcome assessment?	No information with regard to blinding of outcome assessors. It is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results. Reactions were scored using the International Contact Dermatitis Research Group visual scoring system. The clinical relevance of an allergic reaction was recorded using the COADEX system	+
Selective reporting bias	Were all measured outcomes reported?	All outcomes were reported in sufficient detail.	++

Other sources of bias	Were there no other potential threats to internal validity (*e.g.*, statistical methods were appropriate and researchers adhered to the study protocol)?		na

Cook et al. (2001)

Type of bias	Question	Risk of bias evaluation	Risk of bias rating
Confounding bias	Did the study design or analysis account for important confounding and modifying variables?	No exclusion criteria due to, or mention of, skin disease or medications.	--
Detection bias	Can we be confident in the exposure characterisation?	Dose: 5 J/cm2 UVA. A VS48A UVA unit with an output of 8 mW/cm2 measured with an IL442 phototherapy radiometer (Wayne Electronics, Sydney, NSW, Australia) will most likely cover absorption spectrum of BMDBM; however, spectrum cannot be found. Photopatch chemicals were applied in duplicate. Vehicle was reported. Pretest of patients' UV sensitivity was not reported	+
	Can we be confident in the outcome assessment?	No information with regard to blinding of outcome assessors. It is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results. Reactions were scored using the International Contact Dermatitis Research Group visual scoring system.	+
Selective reporting bias	Were all measured outcomes reported?	Yes	++
Other sources of bias	Were there no other potential threats to internal validity (*e.g.*, statistical methods were		na

	appropriate and researchers adhered to the study protocol)?		

Darvay et al. (2001)

Type of bias	Question	Risk of bias evaluation	Risk of bias rating
Confounding bias	Did the study design or analysis account for important confounding and modifying variables?	No information on exclusion of patients on sensitizing medication or active disease.	--
Detection bias	Can we be confident in the exposure characterisation? Jeg synes også at vi bør kreve, under eksponering, at navn på produsent og type av UV-kilden er oppgitt, slik at man kan finne ut hvilket spektrum den har. Noen spektra er smale og vil ikke dekke noe av f.eks. et UVB-filter, mens andre er bredere og dekker sannsynligvis akkurat nok til å kunne gi en reaksjon.	Standard methodology. 5 J /cm^2 of broadband UVA, Philips TL 44D 25\09N fluorescent tubes. Photoallergen in petrolatum, controls were used. Lower doses UVA used in some patients	++
	Can we be confident in the outcome assessment?	No information with regard to blinding of outcome assessors. It is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results. Reactions were scored using the International Contact Dermatitis Research Group visual scoring system.	+
Selective reporting bias	Were all measured outcomes reported?	Yes	++
Other sources of bias	Were there no other potential threats to internal validity (*e.g.*,		na

	statistical methods were appropriate and researchers adhered to the study protocol)?		

English et al. (1987)

Type of bias	Question	Risk of bias evaluation	Risk of bias rating
Confounding bias	Did the study design or analysis account for important confounding and modifying variables?	No information on exclusion of patients on sensitizing medication or active disease.	--
Detection bias	Can we be confident in the exposure characterisation?	Standard methodology. The duplicate light series was exposed to UVA 1 J/cm^2 from Philips TL 44D 25/09 fluorescent tubes. This is a fifth of current doses. Pretests to check for UV sensitivity was not reported. No report of controls	-
	Can we be confident in the outcome assessment?	No information with regard to blinding of outcome assessors. It is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results. No information on scoring of the reactions.	-
Selective reporting bias	Were all measured outcomes reported?	Outcomes not reported with specification of year and disease (changed during the study) "In recent months, our criteria for testing with these allergens has broadened to include patients with cheilitis and patients suspected of having a cosmetic dermatitis".	-
Other sources of bias	Were there no other potential threats to internal validity (*e.g.*, statistical methods were appropriate and researchers adhered to the study protocol)?		na

Greenspoon et al. (2013)

Type of bias	Question	Risk of bias evaluation	Risk of bias rating
Confounding bias	Did the study design or analysis account for important confounding and modifying variables?	No information on exclusion of patients on sensitizing medication or active disease.	--
Detection bias	Can we be confident in the exposure characterisation?	Standard methodology. Pretest with UVA and UVB. Dose of 5 J/cm^2 UVA. Non-UV controls. Name and manufacturer of irradiation source was not reported.	-
	Can we be confident in the outcome assessment?	No information with regard to blinding of outcome assessors. It is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results. Trained evaluators. A reaction was considered positive if there was a well-demarcated area of erythema filling the borders of the allergen patch. Reactions were rated either +/-, 1+, 2+, or 3+, where +/- is faint erythema, not filling the entire exposed area, 1+ is positive (nonvesicular macular erythema), 2+ is strong (erythema and edema), and 3+ is an extreme reaction (spreading, bullous, and ulcerative erythema).	+
Selective reporting bias	Were all measured outcomes reported?	Yes	++
Other sources of bias	Were there no other potential threats to internal validity (*e.g.*, statistical methods were appropriate and researchers adhered to the study protocol)?		na

Haylett et al. (2014)

Type of bias	Question	Risk of bias evaluation	Risk of bias rating
Confounding bias	Did the study design or analysis account for important confounding and modifying variables?	Photopatch testing was conducted according to the European consensus methodology (exclusion criteria described)	++
Detection bias	Can we be confident in the exposure characterisation?	Standard methodology. Pretesting with UVA and UVB (and also visible light in those aged > 11 years), broadband UV radiation provocation testing, and photopatch testing with control patch testing to sunscreen agents. broadband UVA (5 J cm^2, 310–400 nm, Waldmann UVAL 801; Herbert Waldmann GmbH & Co. KG, Villingen Schwenningen, Germany), non-irradiated controls.	++
	Can we be confident in the outcome assessment?	No information with regard to blinding of outcome assessors. It is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results. The response grading system was well described. Prior to 2009: Predefined grading; after 2009: according to International Contact Dermatitis Research Group grading scale.	+
Selective reporting bias	Were all measured outcomes reported?	Yes	++
Other sources of bias	Were there no other potential threats to internal validity (*e.g.*, statistical methods were appropriate and researchers adhered to the study protocol)?		na

Katsarou-Katsari et al. (2008)

Type of bias	Question	Risk of bias evaluation	Risk of bias rating

Confounding bias	Did the study design or analysis account for important confounding and modifying variables?	Tests were performed according to current international recommendations: The European Taskforce for Photopatch Testing. Photopatch testing: a consensus methodology for Europe.	++
Detection bias	Can we be confident in the exposure characterisation?	Standard methodology. 5J /cm^2 of fluorescent UVA. The light source was a Waldmann 800-A UVA lamp and non-irradiated controls. No pretest for UV sensitivity	+
	Can we be confident in the outcome assessment?	No information with regard to blinding of outcome assessors. It is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results. Reactions were scored using the International Contact Dermatitis Research Group visual scoring system.	+
Selective reporting bias	Were all measured outcomes reported?	Photopatch results were reported.	+
Other sources of bias	Were there no other potential threats to internal validity (*e.g.*, statistical methods were appropriate and researchers adhered to the study protocol)?		na

Kerr et al. (2012)

Type of bias	Question	Risk of bias evaluation	Risk of bias rating
Confounding bias	Did the study design or analysis account for important confounding and modifying variables?	Exlusion criteria reported, and these included topical steroid and active skin disease (+ systemic antidepressants)	++
Detection bias	Can we be confident in the exposure characterisation?	Standard methodology. A dose of 5 J /cm^2 UVA (or less if UVA minimal erythemal dose testing revealed objective photosensitivity) and non-UV-irradiated controls. Lamps were monitored and meters calibrated at	+

		accredited laboratory. Since this was a multi-centre study, several irradiation sources were used, and the spectra were measured. However, no data are given in the publication	
	Can we be confident in the outcome assessment?	No information with regard to blinding of outcome assessors. It is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results. Reactions were scored using the International Contact Dermatitis Research Group visual scoring system. Investigators were asked to assign relevance to any positive reactions seen whenever possible using the COADEX system	+
Selective reporting bias	Were all measured outcomes reported?	Yes	++
Other sources of bias	Were there no other potential threats to internal validity (*e.g.*, statistical methods were appropriate and researchers adhered to the study protocol)?		na

Schauder and Ippen (1986)

Type of bias	Question	Risk of bias evaluation	Risk of bias rating
Confounding bias	Did the study design or analysis account for important confounding and modifying variables?	No information on exclusion of patients on sensitizing medication or active disease.	--
Detection bias	Can we be confident in the exposure characterisation?	Standard methodology. 5 J / cm^2 from fluorescent tubes, Waldmann PUVA 180 Comby radiation unit. Sylvania tubes F8T5/BL emitted UVA with a peak energy output at 350 nm. The radiation intensity was measured with a Waldmann PUVA-Meter. Before irradiation with a UVA dose of 5 J/cm2 the UVA sensitivity was tested. The MED for UVA was higher than 5 J/cm^2. Non-UVA-irradiated controls included.	++

	Can we be confident in the outcome assessment?	No information with regard to blinding of outcome assessors. It is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results. Method for scoring of reactions were reported. Rating criteria described: from – to 3+. Only 2+ and 3+ were considered photoallergic. Photopatch tests were only performed on patient who had no reaction after plain patch tests.	-
Selective reporting bias	Were all measured outcomes reported?	Yes	++
Other sources of bias	Were there no other potential threats to internal validity (*e.g.*, statistical methods were appropriate and researchers adhered to the study protocol)?		na

Schauder and Ippen (1986)

Type of bias	Question	Risk of bias evaluation	Risk of bias rating
Confounding bias	Did the study design or analysis account for important confounding and modifying variables?	No information on exclusion of patients on sensitizing medication or active disease.	--
Detection bias	Can we be confident in the exposure characterisation?	Standard methodology. Prior to 1986: 5 J/cm^2 Sylvania F8 T5/BL (UVA); After 1986: 10 J/cm^2 Philips TL-K 40W/09N (UVA) (both wavelength max at 360 nm). Measured emission. Non-irradiated controls used	++
	Can we be confident in the outcome assessment?	No information with regard to blinding of outcome assessors. It is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results. Method for scoring of reactions were reported. Reaction assessment was probably pre-defined, but no protocol/consenus reported	-

Selective reporting bias	Were all measured outcomes reported?	Yes	++
Other sources of bias	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?		na

Shaw et al. (2010)

Type of bias	**Question**	**Risk of bias evaluation**	**Risk of bias rating**
Confounding bias	Did the study design or analysis account for important confounding and modifying variables?	No information on exclusion of patients on sensitizing medication or active disease.	--
Detection bias	Can we be confident in the exposure characterisation?	Standard methodology. Prestesting with UVA and UVB. A dose of 10 J/cm^2 used as none had abnormal MEDs. No name or manufacturer of lamp was described	-
	Can we be confident in the outcome assessment?	No information with regard to blinding of outcome assessors. It is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results. Reactions were self-reported. No test criteria were described.	--
Selective reporting bias	Were all measured outcomes reported?	Yes, patch and photopatch test results and onset of reaction of 11 patients	++
Other sources of bias	Were there no other potential threats to internal validity (*e.g.*, statistical methods were appropriate and researchers adhered to the study protocol)?		na

Subiabre Ferrer et al. (2019)

Type of bias	Question	Risk of bias evaluation	Risk of bias rating
Confounding bias	Did the study design or analysis account for important confounding and modifying variables?	Testing in accordance with European consensus methodology: " As with patch testing, this investigation should not be undertaken when the skin test area is active. To avoid the effects of the angry back syndrome it is recommended that testing be conducted on skin that has been clinically normal for the previous 2 weeks.	+
Detection bias	Can we be confident in the exposure characterisation?	Standard methodology. UVA (5 J/cm^2, 310-400 nm, Waldmann UVAL 801; Herbert Waldmann, Villingen-Schwenningen, Germany). European consensus methodology: Controls included	++
	Can we be confident in the outcome assessment?	No information with regard to blinding of outcome assessors. It is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results. Method for scoring of reactions were reported. Reactions graded according to ESCD/ICDRG. Relevance of positive test reaction was considered	+
Selective reporting bias	Were all measured outcomes reported?	Yes	++
Other sources of bias	Were there no other potential threats to internal validity (*e.g.*, statistical methods were appropriate and researchers adhered to the study protocol)?		na

Valbuena Mesa et al. (2016)

Type of bias	Question	Risk of bias evaluation	Risk of bias rating
Confounding bias	Did the study design or analysis account for important	Patients were excluded if they had certain light sensitive diseases or used steroids/immunosuppressive drugs in advance of the test	++

	confounding and modifying variables?		
Detection bias	Can we be confident in the exposure characterisation?	Standard methodology. Photopatch tests were done following the European consensus methodology. 5 J/cm2 UVA light in a Daavlin phototherapy unit 305-350 calibrated with an IL-1700 research radiometer and a UVB sensor (International Light Technologies Inc, Peabody, MA) with an irradiance of 9.2 J/cm2, which provided a 320-400 nm spectrum.	++
	Can we be confident in the outcome assessment?	No information with regard to blinding of outcome assessors. It is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results. Method for scoring of reactions were reported. Reactions were evaluated in accordance with ICDRG recommendations. The results relevance was evaluated using the COADEX system	+
Selective reporting bias	Were all measured outcomes reported?	Yes	++
Other sources of bias	Were there no other potential threats to internal validity (*e.g.*, statistical methods were appropriate and researchers adhered to the study protocol)?		na

18 Appendix IV. Literature reporting concentrations of UV-filters in commercially available sunscreens

18.1 Literature search

Database: Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions® <1946 to March 13, 2020>
Date: 16.03.2020
Result: 427

1	**Sunscreening Agents/**	**5493**
2	(sunblock? or "sun block?" or "sun tan lotion?" or "suntan lotion?" or "sun screen?" or "sunscreen?" or "sunburn cream?" or "sun burn cream?" or "sun cream?" or "block out?" or ((ultraviolet or ultra violet or UV or UVA or UVB or UVC) adj2 filter?)).tw,kf.	6700
3	1 or 2	8682
4	((Butyl adj2 (methoxydibenzoylmethane or "methoxydibenzoyl methane")) or avobenzone or butylmethoxydibenzoylmethane or "butylmethoxydibenzoyl methane" or parsol or "Ethylhexyl salicylate" or "salicylic acid 2 ethylhexyl ester" or "Octyl Salicylate" or octisalate or "Bis ethylhexyloxyphenol methoxyphenyl triazine" or "Bisethylhexyloxyphenol methoxyphenyl triazine" or Bemotrizinol or "escalol s" or "tinosorb s" or Octocrylene or octocrilene or "uvinul n 539" or (cyano adj3 (diphenylacrylic or diphenylacrylate) adj3 ethylhexyl) or "Ethylhexyl triazone" or "Titanium dioxide" or anatase or "bayertitan rc k 20" or rutile or titania or "titanic dioxide" or "titanium oxide" or titanox).tw,kf.	17168
5	(Concentration? or occurrence? or occurence? or content? or composition? or analysis or analyses or amount? or (Weight adj2 percent)).tw,kf.	6804368
6	3 and 4 and 5	411
7	4 and Sunscreening Agents/an [Analysis]	97
8	6 or 7	427

Database: Embase 1974 to 2020 March 13
Date: 16.03.2020
Result: 552

1	**sunscreen/**	**10426**
2	(sunblock? or "sun block?" or "sun tan lotion?" or "suntan lotion?" or "sun screen?" or "sunscreen?" or "sunburn cream?" or "sun burn cream?" or "sun cream?" or "block out?" or ((ultraviolet or ultra violet or UV or UVA or UVB or UVC) adj2 filter?)).tw,kw.	9130
3	1 or 2	13432
4	avobenzone/ or octisalate/ or Bemotrizinol/ or Octocrylene/ or Titanium dioxide/	25374
5	((Butyl adj2 (methoxydibenzoylmethane or "methoxydibenzoyl methane")) or avobenzone or butylmethoxydibenzoylmethane or "butylmethoxydibenzoyl methane" or parsol or "Ethylhexyl salicylate" or "salicylic acid 2 ethylhexyl ester" or "Octyl Salicylate" or octisalate or "Bis ethylhexyloxyphenol methoxyphenyl triazine" or "Bisethylhexyloxyphenol methoxyphenyl triazine" or Bemotrizinol or "escalol s" or "tinosorb s" or Octocrylene or octocrilene or "uvinul n 539" or (cyano adj3 (diphenylacrylic or diphenylacrylate) adj3 ethylhexyl) or "Ethylhexyl triazone" or "Titanium dioxide" or anatase or "bayertitan rc k 20" or rutile or titania or "titanic dioxide" or "titanium oxide" or titanox).tw,kw.	16863
6	(70356-09-1 or 118-60-5 or 187393-00-6 or 6197-30-4 or 88122-99-0 or 13463-67-7 or 1317-70-0 or 1317-80-2).rn.	21418
7	4 or 5 or 6	29379
8	(Concentration? or occurrence? or occurence? or content? or composition? or analysis or analyses or amount? or (Weight adj2 percent)).tw,kw.	9246343
9	3 and 7 and 8	644
10	limit 9 to (conference abstracts or embase)	552

Database: Web of Science

Date:	16.03.2020 Result: 621

# 4	**621**	**#3 AND #2 AND #1** ***Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=2019-2020***
# 3	12,330,130	TOPIC: ("Concentration$" or "occurrence$" or "occurence$" or "content$" or "composition$" or "analysis" or "analyses" or "amount$" or ("Weight" NEAR/1 "percent")) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*
# 2	109,143	TOPIC: (("Butyl" NEAR/1 ("methoxydibenzoylmethane" or "methoxydibenzoyl methane")) or "avobenzone" or "butylmethoxydibenzoylmethane" or "butylmethoxydibenzoyl methane" or "parsol" or "Ethylhexyl salicylate" or "salicylic acid 2 ethylhexyl ester" or "Octyl Salicylate" or "octisalate" or "Bis ethylhexyloxyphenol methoxyphenyl triazine" or "Bisethylhexyloxyphenol methoxyphenyl triazine" or "Bemotrizinol" or "escalol s" or "tinosorb s" or "Octocrylene" or "octocrilene" or "uvinul n 539" or ("cyano" NEAR/2 ("diphenylacrylic" or "diphenylacrylate") NEAR/2 "ethylhexyl") or "Ethylhexyl triazone" or "Titanium dioxide" or "anatase" or "bayertitan rc k 20" or "rutile" or "titania" or "titanic dioxide" or "titanium oxide" or "titanox") *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*
# 1	9,542	TOPIC: ("sunblock$" or "sun block$" or "sun tan lotion$" or "suntan lotion$" or "sun screen$" or "sunscreen$" or "sunburn cream$" or "sun burn cream$" or "sun cream$" or "block out$" or (("ultraviolet" or "ultra violet" or "UV" or "UVA" or "UVB" OR "UVC") NEAR/1 "filter$")) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*

Database: Cochrane Database of Systematic Reviews: Issue 3 of 12, March 2020, Central Register of Controlled trials: Issue 3 of 12, March 2020
Date: 16.03.2020
Result: 8 (from Trials)

ID	Search	Hits
#1	[mh ^"Sunscreening Agents"]	319
#2	(sunblock? or "sun block?" or "sun tan lotion?" or "suntan lotion?" or "sun screen?" or "sunscreen?" or "sunburn cream?" or "sun burn cream?" or "sun cream?" or "block out?" or ((ultraviolet or "ultra violet" or UV or UVA or UVB or UVC) NEAR/2 filter?)):ti,ab	704
#3	#1 OR #2	802
#4	((Butyl NEAR/2 (methoxydibenzoylmethane or "methoxydibenzoyl methane")) or avobenzone or butylmethoxydibenzoylmethane or "butylmethoxydibenzoyl methane" or parsol or "Ethylhexyl salicylate" or "salicylic acid 2 ethylhexyl ester" or "Octyl Salicylate" or octisalate or "Bis ethylhexyloxyphenol methoxyphenyl triazine" or "Bisethylhexyloxyphenol methoxyphenyl triazine" or Bemotrizinol or "escalol s" or "tinosorb s" or Octocrylene or octocrilene or "uvinul n 539" or (cyano NEAR/3 (diphenylacrylic or diphenylacrylate) NEAR/3 ethylhexyl) or "Ethylhexyl triazone" or "Titanium dioxide" or anatase or "bayertitan rc k 20" or rutile or titania or "titanic dioxide" or "titanium oxide" or titanox):ti,ab	107
#5	(Concentration? or occurrence? or occurence? or content? or composition? or analysis or analyses or amount? or (Weight NEAR/2 percent)):ti,ab	461881
#6	#3 AND #4 AND #5	8

Database: CRD - The Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED) and HTA

Date: 16.03.2020
Result: 0

1	MeSH DESCRIPTOR Sunscreening Agents	15
2	((sunblock? or "sun block?" or "sun tan lotion?" or "suntan lotion?" or "sun screen?" or "sunscreen?" or "sunburn cream?" or "sun burn cream?" or "sun cream?" or "block out?" or ((ultraviolet or ultra violet or UV or UVA or UVB or UVC) NEAR1 filter?) or (filter? NEAR1 (ultraviolet or ultra violet or UV or UVA or UVB or UVC))))	18
3	#1 OR #2	24
4	(((Butyl NEAR1 (methoxydibenzoylmethane or "methoxydibenzoyl methane")) or ((methoxydibenzoylmethane or "methoxydibenzoyl methane") NEAR1 Butyl) or avobenzone or butylmethoxydibenzoylmethane or "butylmethoxydibenzoyl methane" or parsol or "Ethylhexyl salicylate" or "salicylic acid 2 ethylhexyl ester" or "Octyl Salicylate" or octisalate or "Bis ethylhexyloxyphenol methoxyphenyl triazine" or "Bisethylhexyloxyphenol methoxyphenyl triazine" or Bemotrizinol or "escalol s" or "tinosorb s" or Octocrylene or octocrilene or "uvinul n 539" or (cyano AND (diphenylacrylic or diphenylacrylate) AND ethylhexyl) or "Ethylhexyl triazone" or "Titanium dioxide" or anatase or "bayertitan rc k 20" or rutile or titania or "titanic dioxide" or "titanium oxide" or titanox))	2
5	(Concentration? or occurrence? or occurence? or content? or composition? or analysis or analyses or amount? or (Weight NEAR1 percent) or (percent NEAR1 weight))	51345
6	#3 AND #4 AND #5	0

Database: Epistemonikos
Date: 16.03.2020
Result: 0

(sunblock* or "sun block*" or "sun tan lotion" or "sun tan lotions" or "suntan lotion" or "suntan lotions" or "sun screen" or "sun screens" or sunscreen* or "sunburn cream" or "sunburn creams" or "sun burn cream" or "sun burn creams" or "sun cream" or "sun creams" or "block out" or "block outs" or "ultraviolet filter" or "ultraviolet filters" or "ultra violet filter" or "ultra violet filters" or "UV filter" or "UVA filter" or "UVB filter" or "UVC filter" or "UV A filter" or "UV B filter" or "UV C filter" or "UV filters" or "UVA filters" or "UVB filters" or "UVC filters" or "UV A filters" or "UV B filters" or "UV C filters") AND (avobenzone or butylmethoxydibenzoylmethane or "butylmethoxydibenzoyl methane" or parsol or "Ethylhexyl salicylate" or "salicylic acid 2 ethylhexyl ester" or "Octyl Salicylate" or octisalate or "Bis ethylhexyloxyphenol methoxyphenyl triazine" or "Bisethylhexyloxyphenol methoxyphenyl triazine" or Bemotrizinol or "escalol s" or "tinosorb s" or Octocrylene or octocrilene or "uvinul n 539" or "Ethylhexyl triazone" or "Titanium dioxide" or anatase or "bayertitan rc k 20" or rutile or titania or "titanic dioxide" or "titanium oxide" or titanox) AND (Concentration* or occurrence* or occurence* or content* or composition* or analysis or analyses or amount* or "Weight percent") = 0 records identified

(cyano AND (diphenylacrylic or diphenylacrylate) AND ethylhexyl) = 0 records identified
(Butyl AND (methoxydibenzoylmethane or "methoxydibenzoyl methane")) = 0 records identified

18.2 Assessment of full-text articles – excluded publications

An overview of the publications considered not to fulfil the eligibility criteria is given in Table 18.2-1. An overview of the biomonitoring studies is given in Table 18.2-2.

Table18.2-1. Publications considered not eligible.

Reference	Reason for exclusion
Abdel-Ghany et al. (2015)	Study design
Abdel-Ghany et al. (2018)	Study design
Agin and Edmonds (2002)	Study design
Al Alamein et al. (2019)	Study design
Bairi et al. (2017)	Study design
(Bairi et al., 2016)	UV filter (TiO_2, not nano)
Barnard (2010)	Study design
Bhuva et al. (2012)	Study design
(Bunhu et al., 2011)	UV filter (TiO_2, not nano)
Ceresole et al. (2013)	Study design
Chang and Chang (2001)	Study design
Chisvert et al. (2012)	Study design
Choquenet et al. (2008)	Study design
(Contado and Pagnoni, 2008)	UV filter (TiO_2, not nano)
Cosmetic Ingredient Review Expert (2003)	Study design
Couteau et al. (2016)	Study design
(Cuddy et al., 2016)	UV filter (TiO_2, not nano)
(de la Calle et al., 2018)	UV filter (TiO_2, not nano)
(de la Calle et al., 2017)	UV filter (TiO_2, not nano)
Dencausse et al. (2008)	Study design
(Ferreira et al., 2019)	UV filter (TiO_2, not nano)
Freitas et al. (2015)	Study design
Gu et al. (2019)	Study design
Gulson et al. (2012)	Study design
Harrison et al. (1991)	Study design
Hsiao et al. (2015)	Study design
Huang et al. (2014)	Language
Ikarashi et al. (2007b)	Language
Imamovic et al. (2009)	Study design
Jiang et al. (1996)	Study design
Jou and Tomecki (2014)	Study design
Kale et al. (2014)	Study design
Kerr (2011)	Study design
Khalikova et al. (2018a)	Study design
Kim et al. (2012)	Study design

Reference	Reason for exclusion
Kim et al. (2006)	Publication type
Klotz et al. (2019)	Study design
Kockler et al. (2013a)	Study design
Lademann et al. (2000)	Study design
Lee et al. (2008)	Publication type
Lu et al. (2015)	Study design
Lu et al. (2018)	Study design
Manova et al. (2013)	Study design
(Melquiades et al., 2008)	UV filter (TiO_2, not nano)
Melquiades et al. (2010)	Language
Montenegro and Puglisi (2013b)	Study design
Muller et al. (2016)	Study design
Nyeborg et al. (2010)	Study design
Oh et al. (2010)	Study design
Ohba et al. (1991)	Language
(Quinones et al., 2016)	Study design
Rastogi and Jensen (1998)	Study design
Salvador et al. (2003)	Study design
Scalia (2000)	Study design
Schakel et al. (2004)	Study design
Smyrniotakis and Archontaki (2004)	Study design
(Sobanska and Pyzowski, 2012a)	Study design
(Sobanska and Pyzowski, 2012b)	Study design
Tyner et al. (2009)	Study design
Uter et al. (2014)	Study design
Wharton et al. (2011)	Study design
Whiteman et al. (2003)	Study design

Table18.2-2. Biomonitoring studies.

Reference	Reason for exclusion
(Bury et al., 2018)	Biomonitoring, not analysis of concentration in sunscreen
(Bury et al., 2019a)	Biomonitoring, not analysis of concentration in sunscreen
(Bury et al., 2019c)	Biomonitoring, not analysis of concentration in sunscreen
(Bury et al., 2019b)	Biomonitoring, not analysis of concentration in sunscreen
(Charalambides et al., 2019)	Biomonitoring, not analysis of concentration in sunscreen
(Gulson et al., 2010)	Biomonitoring, not analysis of concentration in sunscreen
(Gustavsson Gonzalez et al., 2002)	Biomonitoring, not analysis of concentration in sunscreen
(Hiller et al., 2019a)	Biomonitoring, not analysis of concentration in sunscreen
(Hiller et al., 2019b)	Biomonitoring, not analysis of concentration in sunscreen
(Huang et al., 2019)	Biomonitoring, not analysis of concentration in sunscreen
(Matta et al., 2020a)	Biomonitoring, not analysis of concentration in sunscreen
(Matta et al., 2019a)	Biomonitoring, not analysis of concentration in sunscreen

18.3 Methodological quality

An overview of the publications considered not to fulfil quality criteria is given in Table 18.3-1.

Table 18.3-1. Publications not fulfilling the quality criteria.

Reference	Question 1	Question 2	Question 3	Total score
(Moyal et al., 2000)	na	na	na	-
(Oladepo and Loppnow, 2008)	4.0	3.5	3.0	3.3
(Weir et al., 2012)	3.25	3.0	2.0	2.5

19 Appendix VI. Deviations from the protocol

Data from ECHA registration dossiers were used for the hazard identification and characterisation.