Vitenskapskomiteen for mat og miljø
Norwegian Scientific Committee for Food and Environment

Revised protocol for a risk-benefit assessment of sunscreen

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

From the Norwegian Scientific Committee for Food and Environment (VKM)
Revised protocol for a risk-benefit assessment of sunscreen

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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Revised protocol for a risk-benefit assessment of sunscreen

Authors of the revised protocol

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The protocol has been assessed and approved by the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food, and Cosmetics. Members of the Panel that

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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.

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Abbreviations and definitions

Abbreviations

IARC	International Agency for Research on Cancer
CIE	International Commission on Illumination
CosIng	European Commission Cosmetic Ingredients Database
EFSA	European Food Safety Authority
NOAEL	no observed adverse effect level
POD	point of departure
RoB	risk of bias
SPF	sunscreen protection factor
UVA	ultraviolet radiation A. Denotes electromagnetic wavelengths in the range 320-400 nm
UVB	ultraviolet radiation B. Denotes electromagnetic wavelengths in the range 280-320 nm
UVR	ultraviolet radiation
WHO	World Health Organization
WoE	weight of evidence

Definitions

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 to compensate for additional stress or an increase in susceptibility to other influences" (WHO, 1994).

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 protocol a beneficial effect of sunscreen is further defined as follows: An effect of a sunscreen is considered beneficial when it reduces the dose of solar UVR to skin cells and thereby reduces the adverse health effects caused by UVR.

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.

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 illustrated in the table below (EFSA Scientific Committee, 2010).

Risk assessment	**Benefit assessment**
Hazard identification	Positive health effect/reduced adverse effect identification
Hazard characterisation (dose response assessment)	Positive health effect/reduced adverse effect characterisation (dose response assessment)
Exposure assessment	Exposure assessment
Risk characterisation	Benefit characterisation

Sunscreen (topical sunscreen): "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).

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).

1 Background

In Norway, the incidence of skin cancer is among the highest worldwide (Bray et al., 2018). The incidence rate of melanoma increased with >50% during the period 2000-2016 (Norwegian Cancer Registry). The mortality of malignant melanoma, the most severe form of skin cancers, is the highest in Europe (Sacchetto et al., 2018).

A direct link between solar ultraviolet radiation (UVR) and carcinogenicity has been made, and the International Agency for Research on Cancer (IARC) classified solar UVR as carcinogenic to humans (Wild et al., 2020).

Sunscreens are cosmetic products used to reduce UVR skin exposure. According to the EU Commission recommendations, sunscreen products should protect against both short-waved (UVB) and long-waved (UVA) UVR, because all UVR exposure is linked to increased risk of certain skin cancers (Commission Recommendation, 2006). Aside from induction of melanoma and keratinocyte skin cancers, UVR can induce other adverse effects such as sunburn, immunosuppression and cataract of the eye as well as beneficial effects such as vitamin D synthesis.

The spectral relationship between solar radiation wavelengths related to skin cancers and vitamin D synthesis and the theoretical absorption spectra of UVA and UVB filters is given in Figure 1-1.

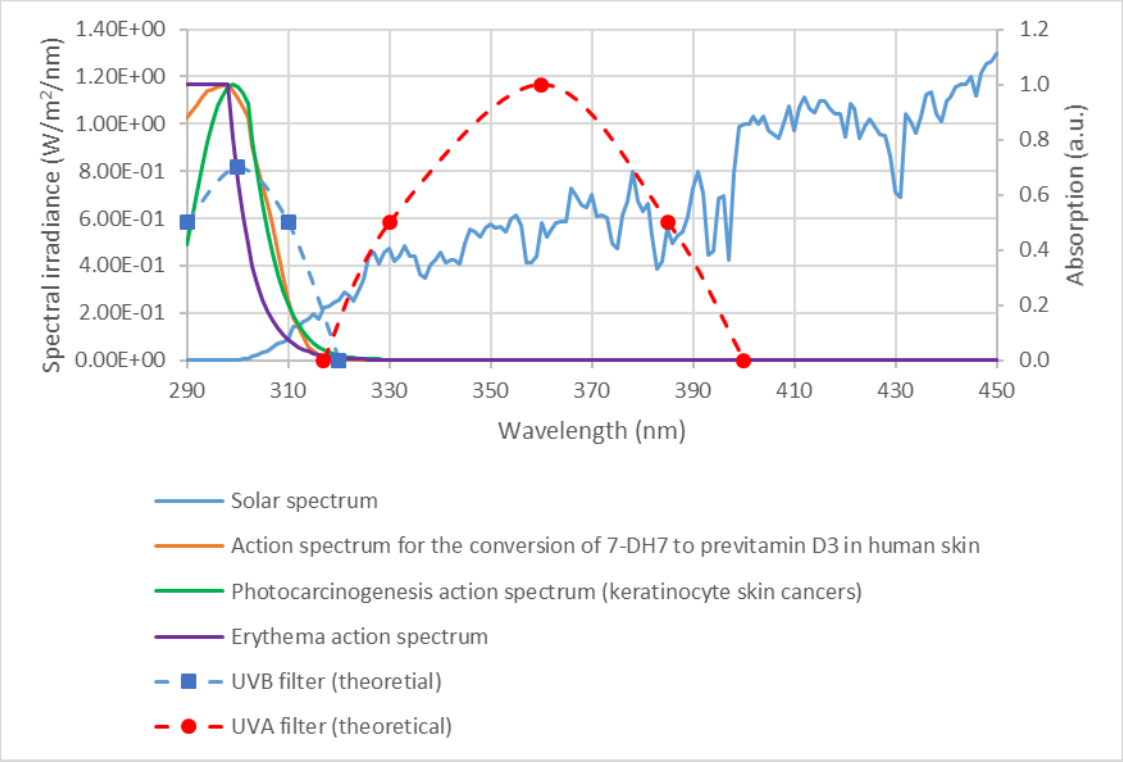

Figure 1-1. Overview of "intensity"- and wavelength dependency of solar radiation and its related health effects as well as UV filter absorption. The wavelength dependent development of erythema (International Commission on Illumination (CIE), 1998) and keratinocyte (non-melanoma) skin cancers (International Organization for Standardization (ISO)/International Commission on Illumination (CIE)) peaks around 300 nm as does the conversion of 7-DH7 to provitamin D3 in skin (International Commission on Illumination (CIE), 2006). In the wavelength region 290-320 nm (UVB) the solar radiation irradiance is lower than in the 320-400 nm (UVA) region; however, UVB photons have higher energy than UVA photons. Other effects of UVR induction are not shown. Experimental data are not sufficient for specifying effectiveness of keratinocyte skin cancers above 400 nm (International Organization for Standardization (ISO)/International Commission on Illumination (CIE)). No official action spectrum exists for the induction of melanoma skin cancer. Theoretical UVB and UVA filter absorption spectra are shown for illustration. Left y-axis: Spectral irradiance of the sun estimated for the following conditions: Norway in the summer at noon, solar zenith angle 40° and 340 Dobson units (DU) (Emde et al., 2016; Pierluissi and Peng, 1985; Ricchiazzi et al., 1998). Right y-axis: Relative magnitude of effect of action spectra or (theoretical) absorption of UVR in sunscreen filters.

All sunscreen products must be safe under normal and reasonably foreseeable use conditions, as specified in the Cosmetic Products Regulation (European Commission, 2009). However, there are concerns whether some sunscreen ingredients pose risk to frequent users, e.g. allergic reactions or endocrine disruptive effects.

On this background, the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food, and Cosmetics of the Norwegian Scientific Committee for Food and Environment (VKM) has self-initiated a risk-benefit assessment of sunscreen. In the risk-benefit assessment we aim to characterise potential adverse health effects related to exposure to sunscreens and/or sunscreen ingredients (risks), and potential reduction of solar UVR-induced adverse health effects related to use of sunscreen (benefits) as solar UVR protection. The risks and benefits will be discussed and, if possible, compared.

An overview of the steps in a risk-benefit assessment is given in Figure 1-2.

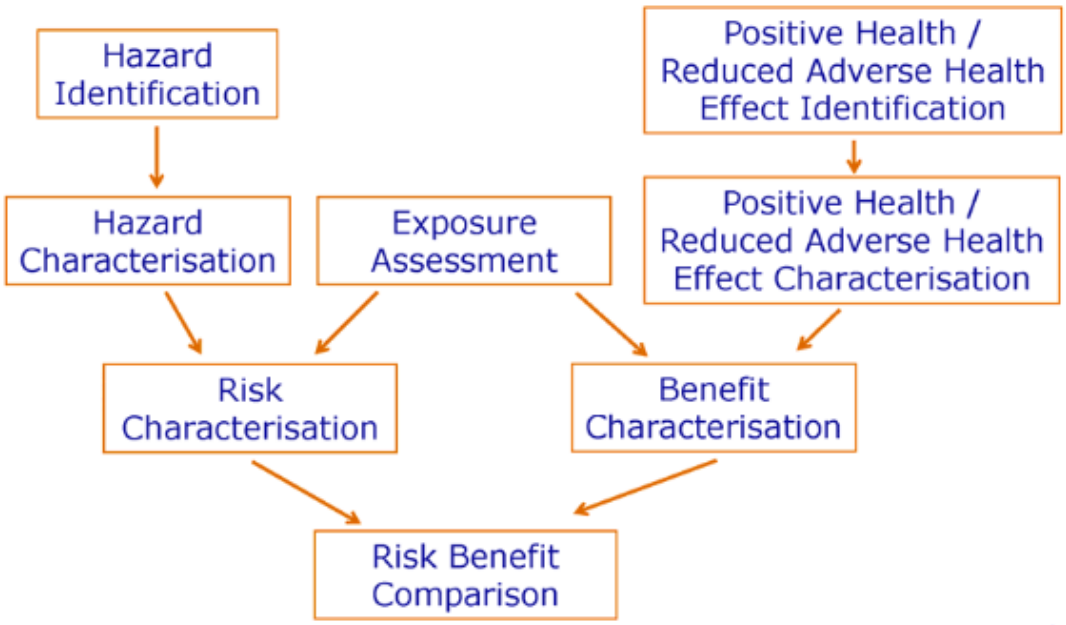

Figure 1-2. The individual steps in a risk-benefit assessment (EFSA Scientific Committee, 2010).

2 Objective and aims

The overall objective is to address the following issue when sunscreens are used as solar UVR protection: Identify and compare any adverse health effects caused by sunscreen products/sunscreen ingredients with any reduction in solar UVR-induced adverse health effects.

The assessment will be made for the Norwegian population, both sexes and all age groups. The availability of data may exclude certain groups.

Both commercially available sunscreen products as such and sunscreen ingredients will be included. Sunscreen ingredients include e.g. UV filters, preservatives, emulsifiers, emollients, thickeners, film formers and fragrances, and each sunscreen has its specific combination of ingredients. As UV filters represent the main purpose of sunscreens, a selection of chemical and physical filters specified in the EU regulation Annex VI will be included (European Commission, 2009). We aim to identify and include UV filters frequently used in sunscreens in Norway and/or other Scandinavian countries. Other ingredients may be included.

Aims:

- Identify and characterise adverse health effects related to use of sunscreens/sunscreen ingredients
    - Evaluate the confidence in the evidence for adverse health effects
    - Identify and describe dose-response and point of departure (POD), and describe uncertainty related to the POD(s)
- Identify and characterise reduction of solar UVR-induced adverse health effects associated with the use of sunscreens
    - Evaluate the confidence in the evidence for reduction of adverse health effects
    - Describe the degree of reduction of solar UVR-induced adverse health effects, and describe factors contributing to uncertainty
- Estimate the exposure to sunscreen ingredients when used as solar UVR protection
    - Identify and describe patterns of use for sunscreens in the Norwegian population
    - Identify ingredients and their concentration in sunscreens on the Norwegian market
    - Identify and describe uncertainty associated with the outcome of the exposure estimation of sunscreen ingredients
- Characterise health risks associated with sunscreen/sunscreen ingredients when sunscreen is used as protection against solar UVR
- Characterise health benefits related to sunscreen used as protection against solar UVR

- Compare risks and benefits related to sunscreens used as protection against solar UVR
- Identify and describe main knowledge gaps that may have an impact on the conclusions

3 Methods for hazard identification and characterisation

The hazard identification and characterisation steps will be performed for sunscreens as such and sunscreen ingredients in sunscreens, both for dermal application. Which sunscreen ingredients to be included are not yet decided. The number and types of sunscreen ingredients to be included will be selected according to available resources. The ingredients will be characteristic for sunscreens on the Scandinavian market.

Among the outcomes to be addressed are mutagenicity/genotoxicity, carcinogenicity, endocrine effects, reproductive toxicity, repeated dose toxicity, skin sensitisation and skin irritation.

The research questions for the hazard identification and characterisation steps are presented in Table 3-1.

Table 3-1. Hazard: Research questions.

Hazard	No	Research questions
Identification	1	Is exposure to sunscreen/sunscreen ingredients, alone or in combination with UVR, associated with adverse health effects?
Characterisation	2	What is the dose-response relationships between exposure to sunscreen/sunscreen ingredients, alone or in combination with UVR, and the adverse effects?
	3	Can a POD* be identified for sunscreen ingredients?

* POD – the dose-response point that marks the beginning of a low-dose extrapolation (for threshold and non-threshold compounds).

3.1 Literature search and publication selection

Literature searches will be performed to identify relevant publications for answering the hazard identification and characterisation research questions (Table 3-1). The study design will determine the priority sequence of the publications as follows: Systematic reviews have the highest priority. Human studies will be prioritised over animal and *in vitro* studies, and RCTs will be prioritised over observational studies. Animal and *in vitro* studies will be included only when additional evidence is needed.

An experienced research librarian will be involved in the planning of the search and conduct the search. The retrieved literature will be screened based on the criteria presented in Tables 3.1-1 to 3.1-3.

Screening of titles and abstracts

To ensure reviewer calibration, all reviewers will first screen a sample of the retrieved titles and abstracts. Then, the reviewers will meet to check consistent application of the inclusion criteria. Following calibration, pairs of reviewers will screen titles and abstracts independently. A publication should be included, when there is doubt about whether the publication meets the inclusion criteria.

Screening of full texts

A sample of the full text publications that have passed the initial screening (title and abstract), will be screened by all reviewers to ensure calibration between them. Following calibration, pairs of reviewers will screen the full text publications independently. In case of disagreement, the two reviewers will discuss the paper to reach consensus. If the disagreement persists, the Panel will reach a final decision.

Table 3.1-1. Hazard: inclusion criteria for human studies.

Study design	In prioritised order: 1. Systematic reviews 2. Human studies (RCTs are prioritised over observational studies)
Population	All age groups, males and females
Exposure	Dermal application The substances tested are sunscreens/sunscreen ingredients tested alone
Outcome of interest	Any adverse health effect related to sunscreen/sunscreen ingredients
Language of the full text	English, Norwegian, Swedish, Danish, German
Publication type	Scientific publications, reports and risk assessments

Table 3.1-2. Hazard: inclusion criteria for animal studies.

Study design	Animal studies testing more than one dose of a given sunscreen/sunscreen ingredient
Time of publication	Published before March 2013
Animal models	Mammalian animals
Exposure	Dermal application and oral intake* The substances tested are sunscreen ingredients alone or in combination with UVR
Outcome of interest	Any adverse health effect associated with sunscreen ingredients
Language of the full text	English, Norwegian, Swedish, Danish, German
Publication type	Scientific publications, reports and risk assessments

***** Information from toxicological studies based on oral exposure may be of value for dermal hazard characterisation.

Table 3.1-3. Hazard: inclusion/exclusion criteria for *in vitro* studies.

Study design/test systems	*In vitro* studies of sunscreen ingredients
Outcome of interest	• Gene (point) mutation • Structural and numerical chromosomal aberrations • Micronuclei • Endoreduplication, polyploidy • Sister chromatid exchange (SCE) • Unscheduled DNA synthesis (UDS)/DNA repair • Cell transformation • Skin irritation • Skin sensitisation • Phototoxicity
Language of the full text	English, Norwegian, Swedish, Danish, German
Publication type	Scientific publications

An overview of the results of the study selection will be presented in flowcharts.

3.2 Data extraction

An overview of data items to be extracted is given in Tables 3.2-1-3.2-3.

Table 3.2-1. Data items to be extracted from systematic reviews.

Characteristics of the systematic review
• Title • Author(s) • Year of publication • Year included in the literature search • Country of origin • Funding • Reported conflict of interest • What is the main objective of the review? • Hypotheses tested • Quality assessment tool • Data synthesis

Characteristics of the studies included in the systematic reviews • Study design • Country/countries of origin of the study subjects • Country/countries where the study is conducted • Are hypotheses regarding our aim presented? If yes, quote • Substance(s) tested (sunscreen as such or sunscreen ingredient(s)) and sun protection factor • List of outcomes considered • Key findings that relate to the research questions in Table 3-1
Comments

Table 3.2-2. Data items to be extracted from human studies. Note that not all data extraction information listed is relevant for all study designs.

Study characteristics • Title • Author(s) • Year of publication • Country/countries of origin (author(s)) • Funding • Reported conflict of interest
Methods/intervention • Study design (e.g. RCT, cohort, etc.) • Type of blinding • Method for randomisation • Intervention (sunscreen (included SPF)/ingredient/controls, presence of UVR) • Concentration of ingredient(s), amount applied, substance purity. UVR exposure (source, irradiance, dose) • Intervention design (frequency of application, duration of study) • Biomonitoring

Participants • Number of participants and completion rate (invited, accepted, drop out, included in follow-up if applicable) • Inclusion/exclusion criteria for participants • Gender • Country/countries of origin of the study subjects • Country/countries where the study is conducted • Age • Ethnicity and skin type classification (Fitzpatrick, 1988) • Number of exposed/non-exposed • Confounders and other variables as reported • Health and socioeconomic status of participants • Other (e.g. selection bias and representativeness for the general Norwegian population)
Results • Reported outcome (including measures of variance) • Parameters measured and methods used • Measurement time points
Statistical analysis • Power analysis • Statistical test
Comments

Table 3.2-3. Data items to be extracted from animal studies.

Study characteristics • Title • Author(s) • Year • Country • Funding source(s) • Reported conflict of interest
Type of study • Good laboratory practice (yes/no) • Guideline study (yes/no; if yes, specify) • Study design (including number of groups/ number of animals per group)

Animal model • Species/(sub)strain/line • Disease models (e.g. allergy) • Skin/fur pigmentation
Housing condition • Housing condition (including cages, bottles, bedding • Diet name and source • Background levels of phytoestrogens in the diet (type and levels) • Background levels of potential photosensitisers (e.g. riboflavin) in the diet (type and levels) • Background level and type of lighting (potential UVR or visible radiation)
Study design and exposure • Sex and age • Test substance(s) • Compound purity • Vehicle used • Dose regimen (dose/concentration, amount applied for dermal exposure, frequency) • Route of administration • Period of exposure (e.g. pre-mating, mating, gestation, lactation, adult) • Exposure duration • Optical radiation (UV and visible) source*, spectrum and dose (e.g. radiant exposure, standard erythemal dose, minimal erythemal dose)
Results and statistical analysis • Main outcome(s) • Period of outcome assessment (premating, mating, gestation, lactation, adult) • Parameters measured and methods used (biotransformation; level of test compounds and their (photo-) degradation products and metabolites) • Dates of sampling • Statistical test • Results per dose or concentration (e.g. mean, median, frequency, measures of precision or variance)
Comments

*Optical radiation (UV, visible and infra-red). Other wavelength ranges than UV may influence on outcomes.

3.3 Evaluation of methodological quality of included studies

3.3.1 Systematic reviews

The identification of systematic reviews will be based on criteria developed by the Cochrane collaboration (Higgins et al., 2019). In short, the publications will be considered as systematic reviews if they have described or presented 1) a specific research question and clear criteria for relevant studies to be included, 2) a systematic literature search, and 3) a quality assessment of the included studies.

We will assess the quality of systematic reviews using a commonly used quality assessment tool.

3.3.2 Original studies: internal validity

All the included original studies will be divided between pairs of reviewers for evaluation of internal validity/risk of bias (RoB) as described in "Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration" (OHAT, 2019). The criteria for the response options are specified in the handbook. These may be modified to enable adequate assessment, e.g. bias related to exposure. When information is inadequate or not available, the response will be "not reported" (NR). Response options and symbols (in parentheses) are:

- Definitely low risk of bias (++)
- Probably low risk of bias (+)
- Probably high risk of bias/not reported (NR) (–)
- Definitely high risk of bias (– –)

The questions raised to determine internal validity will be rated as key or non-key questions according to relevance. Based on the level of bias, each study will be classified in tiers 1 to 3 corresponding to decreasing levels of internal validity/increasing RoB.

3.4 Evidence synthesis and rating of confidence in evidence

3.4.1 Evidence synthesis

The main results on adverse health outcomes will be presented in summary of findings tables. Factors to be reported include UVR exposure, usage of sunscreen (amounts, frequencies, etc.), as well as relevant results in terms of odds-ratios, risk-ratios or response-functions.

3.4.2 Rating confidence in evidence

All original studies reporting on a given outcome will be grouped.

3.4.2.1 Initial level of confidence in evidence

For each study, an initial confidence rating will be determined by the ability of the study design to ensure that exposure preceded and was associated with the outcome. The following four study design features will be evaluated to determine the initial level of confidence for each study (OHAT, 2019):

"

- the exposure to the substance is experimentally controlled
- the exposure assessment demonstrates that exposures occurred prior to the development of the outcome (or concurrent with aggravation/amplification of an existing condition)
- the outcome is assessed on the individual level (i.e., not through population aggregate data)
- an appropriate comparison group is included in the study"

Fulfilment of all features will receive an initial rating of high confidence (++++). Lower ratings, i.e. moderate (+++), low (++) or very low (+), correspond to the number of features fulfilled. Studies rated high or moderate will be included for further analysis. Studies rated low or very low will be excluded.

3.4.2.2 Overall confidence in evidence

Factors that may downgrade or upgrade the initial level of confidence in evidence will be evaluated for each study. Factors that may downgrade the initial level of confidence are:

- Internal validity/risk of bias
- Bias related to funding/conflict of interest
- Unexplained inconsistency
- Imprecision

Factors that may upgrade the initial level of confidence are:

- Large magnitude of effect (e.g. incidence, degrees of severity)
- The presence of a dose-response relationship
- Residual confounding (if a study reports an effect or association despite the presence of residual confounding, confidence in the association is increased)
- Consistency across study design type/dissimilar populations for the relevant studies combined

Following downgrading and upgrading, for each study the confidence in the evidence for a given effect will be determined using the following terms (OHAT, 2019):

"

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

Next, all studies addressing a given outcome will be grouped, and the overall level of confidence in evidence across all studies will be determined using the same rating terms as for single studies.

3.5 Level of evidence for health effect

The confidence ratings (3.4.2.2) will be translated into level of evidence for health effect according to OHAT (2019). Five descriptors are used to categorise the level of evidence: "high," "moderate," "low," "evidence of no health effect," and "inadequate evidence". The definition of the descriptors, as given by OHAT (2019) is as follows:

"

- High Level of Evidence. There is high confidence in the body of evidence for an association between exposure to the substance and the health outcome(s).
- Moderate Level of Evidence. There is moderate confidence in the body of evidence for an association between exposure to the substance and the health outcome(s).
- Low Level of Evidence. There is low confidence in the body of evidence for an association between exposure to the substance and the health outcome(s), or no data are available.
- 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).
- Inadequate Evidence. There is insufficient evidence available to assess if the exposure to the substance is associated with the health outcome(s)".

3.6 Uncertainty in the hazard identification and characterisation

Factors that may cause under- or overestimation of the point of departure for adverse health effects will be identified and described qualitatively.

4 Methods for identification and characterisation of reduction of solar UVR-induced adverse health effects

The identification and characterisation of reduction of solar UVR-induced adverse health effects will be performed for sunscreens as such for dermal application.

Solar UVR-induced adverse health effects may be e.g. sunburns, skin (pre-)cancers, and "sun allergy". The research questions are presented in Table 4-1.

Table 4-1. Reduction of solar UVR-induced adverse effects: Research questions.

Reduced adverse health effect	No.	Research question
Identification	1	Is dermal exposure to sunscreens associated with reduction of adverse effects caused by solar UVR?
Characterisation	2	What are the relationships between sunscreen use and reduction of adverse effects caused by solar UVR?

4.1 Literature search and publication

Literature searches will be performed to identify publications useful for answering the research questions in Table 4-1. The study design will determine the priority sequence of the publications as follows: Systematic reviews have the highest priority. Human studies will be prioritised over animal and in vitro studies, and RCTs will be prioritised over observational studies. Animal and in vitro studies will be included only when additional evidence is needed.

An experienced research librarian will be involved in the planning of the search and will also conduct the search. The retrieved literature will be screened based on the criteria presented in Table 4.1-1.

Screening of titles and abstracts

To ensure reviewer calibration, all reviewers will first screen a sample of the retrieved titles and abstracts. Then, the reviewers will meet to check consistent application of the inclusion criteria. Following calibration, pairs of reviewers will screen titles and abstracts independently. A publication should be included, when there is doubt about whether the publication meets the inclusion criteria.

Screening of full texts

A sample of the full text publications that have passed the initial screening (title and abstract), will be screened by all reviewers to ensure calibration between them. Following calibration, pairs of reviewers will screen the full text publications independently. In case of disagreement, the two reviewers will discuss the paper to reach consensus. If the disagreement persists, the Panel will reach a final decision.

Table 4.1-1. Reduction of adverse health effects: inclusion/exclusion criteria.

Study design	In prioritised order: 1. Systematic reviews 2. Human studies (RCTs are prioritised over observational studies)
Population	All age groups, male and females
Exposure	Dermal exposure
Outcome of interest	Reduction of solar UVR-induced adverse health effects related to sunscreen use
Language of the full text	English, Norwegian, Swedish, Danish, German
Publication type	Scientific articles, reports and risk assessments

An overview of the results of the study selection will be presented in flowcharts.

4.2 Data extraction

Data items related to sunscreen as such, not sunscreen ingredients, will be extracted. An overview is given in Tables 3.2-1 and 3.2-2.

4.3 Evaluation of methodological quality of included studies

4.3.1 Systematic reviews

The method is mentioned in 3.3.1.

4.3.2 Original studies: internal validity

The method is described in 3.3.2.

4.4 Evidence synthesis and rating of confidence in evidence

4.4.1 Evidence synthesis

The main results on reduction of adverse health effects will be presented in summary of findings tables. Factors to be reported include UVR exposure, usage of sunscreen products

(amounts, frequencies, etc.), as well as relevant results in terms of odds-ratios, risk-ratios or response-functions.

4.4.2 Rating of confidence in evidence

The methods are described in 3.4.2.1 and 3.4.2.2.

4.5 Level of evidence for health effect

The methods are described in 3.5.

4.6 Uncertainty in identification and characterisation of reduction of solar UVR-induced adverse health effects

Factors that may cause under- or overestimation of the reduction of solar UVR-induced adverse health effects will be identified and described qualitatively.

5 Exposure assessment for sunscreen ingredients

The research questions are presented in Table 5-1.

Table 5-1. Exposure: Research questions.

Exposure	No	Research questions
Occurrence	1	What are the concentrations of the included ingredients used in sunscreens?
Use	2	What are the patterns of use for 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 sunscreen ingredients?
	4	What is the internal exposure to sunscreen ingredients?

The exposure will be estimated for dermal application of sunscreens. The exposure estimates (research question 4) will be based on:

- Concentration data for included sunscreen ingredients (research question 1) will be obtained from literature and/or manufacturers. When more data are available, the prioritisation of concentration data will be as follows: Scandinavian>rest of Europe>rest of the world.
- National surveys/studies/data will be used to identify pattern of use (research question 2).
- Dermal absorption factors (research question 3) for sunscreen ingredients will be obtained from literature.
- Fraction of sunscreen available for uptake after application (retention factor) will be obtained from the SCCS (Scientific Committee on Consumer Safety) (2018) guidance.

5.1 Literature search and publication selection

Literature searches will be performed to identify relevant publications for answering research question 1 in Table 5-1. An experienced research librarian will be involved in the planning of the search and conduct the search. The literature retrieved will be screened based on the criteria presented in Table 5.1-1.

Screening of titles and abstracts

To ensure reviewer calibration, all reviewers will first screen a sample of the retrieved titles and abstracts. Then, the reviewers will meet to check consistent application of the inclusion criteria. Following calibration, pairs of reviewers will screen titles and abstracts independently. A publication should be included, when there is doubt about whether the publication meets the inclusion criteria.

Screening of full texts

A sample of the full text publications that have passed the initial screening (title and abstract), will be screened by all reviewers to ensure calibration between them. Following calibration, pairs of reviewers will screen the full text publications independently. In case of disagreement, the two reviewers will discuss the paper to reach consensus. If the disagreement persists, the Panel will reach a final decision.

Table 5.1-1. Exposure: inclusion (in)/exclusion (out) criteria.

Literature screening (research question 1)		
Study design	In	Analytical studies on concentrations of sunscreen ingredients. Biomonitoring studies on concentration of sunscreen ingredients in blood and/or urine samples.
Analytical method	In	All methods
Outcome of interest	In	Concentration data and biomonitoring data for sunscreen ingredients.
	Out	Concentration data for sunscreen ingredients 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	English, German, Norwegian, Swedish and Danish
Publication type	In	Scientific publications, reports and risk assessments

An overview of the results of the study selection will be presented in flowcharts.

5.2 Evaluation of methodological quality and data extraction

The methods used for the concentration analysis of all the included studies will be evaluated by two reviewers independently. An overview of the questions that will be addressed for the evaluation of methodological quality is given in Table 5.2-1. The evaluation includes scoring of the sample extraction method, the instrumental analysis, and the validation of the method and the data presentation. The score will be deduced according to a scale of scores from 1 (lowest quality) to 5 (highest quality). To obtain the total score, the individual scores are weighted as follows: 1/5 from sample extraction, 1/5 from instrumental analysis, and 3/5 from validation and data presentation. Only studies with a total score of ≥ 3.5 will be used for the exposure assessment.

Table 5.2-1. Table for evaluation of the analytical method used.

No.	**Question**	**Rating (1-5)**
1	How appropriate was the solvent used for the extraction method?	
2	Which instrumental analysis was used?	

No.	Question	Rating (1-5)
3	Which validation method was used, and was LOD/LOQ, internal/external calibration, number of samples described?	
	Total score (1/5 x sample extraction+1/5 x instrumental analysis+3/5 x validation and data presentation)	

An overview of data items to be extracted from the included studies is given in Table 5.2-2.

Table 5.2-2. Data items to be extracted.

Study characteristics • Title • Author(s) • Year • Country • Funding • Reported conflict of interest
Methods for analyses • Sample extraction • Calibration • Limit of detection/limit of quantification • Recovery data • Instrument/detector
Results (for studies with a total score of ≥3.5; see Table 5.2-1)) • Number of samples • Concentration data for sunscreen ingredients (Table 2.3-1) • Biomonitoring data for sunscreen ingredients (Table 2.3-1)
Comments

5.2.1 Uncertainty in the exposure estimation

Factors that may cause under- or overestimation of the exposure will be identified and described qualitatively.

6 Risk characterisation

The risk characterisation will be based on the point of departure for toxicity and the estimated exposure to sunscreen ingredients.

7 Benefit characterisation

The benefit characterisation will be based on the reduction of adverse health effects using sunscreen as protection against solar UVR.

8 Risk and benefit comparison and discussion

Risks and benefits related to sunscreens and/or sunscreen ingredients when used as skin protection against UVR will be compared in a step-wise approach. This procedure broadly corresponds to the steps outlined in EFSA's guidance on human health risk-benefit assessment of foods (EFSA Scientific Committee, 2010).

Step 1: The Panel evaluates whether or not the benefit clearly outweighs the risk (or vice versa) with no further quantitative evaluation than the risk and benefit characterisation from chapters 6 and 7. If the risks and benefits do not clearly outweigh each other, move to step 2.

Step 2: A refined risk-benefit assessment aims to provide, depending on the availability of data, semi-quantitative or quantitative estimates of risks and benefits at relevant exposures from chapter 5. A semi-quantitative comparison compares exposures to health-based guidance values and usually presents probabilities of exceeding such guidance values for the risk(s). For sunscreens and sunscreen ingredients it is unlikely that such guidance values exist, and a quantitative approach will be attempted. A quantitative approach summarises risks and benefits using common metrics, such as incidence or mortality. The reduction and/or increase in incidence and/or mortality associated with usage of sunscreen will be quantified if sufficient data are found.

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