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Norwegian Scientific Committee for Food and Environment

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2 Draft protocol for a risk-benefit assessment 3 of sunscreen

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

From the Norwegian Scientific Committee for Food and Environment (VKM) 2018
Draft 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
XX.XX.2018

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Draft protocol for a risk-benefit assessment of sunscreen

Preparation of the protocol

A project group prepared the draft protocol for a risk-benefit assessment of sunscreen. The project group consisted of three VKM members of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food, and Cosmetics and one employee of the VKM secretariat.

Assessed and approved

Members of the project group that contributed to the drafting of the protocol (in alphabetical order after chair of the project group):

Ellen Bruzell - Chair of the project group and member of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food, and Cosmetics. Affiliation: 1) VKM; 2) Nordic Institute of Dental Materials

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Trine Husøy – Member of the project group and member of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food, and Cosmetics. Affiliation: 1) VKM; 2) Norwegian Institute of Public Health

Gro Haarklou Mathisen – Member of the project group and project leader. Affiliation: VKM

Members of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food, and Cosmetics who contributed to and approved the draft protocol for public consultation:

In addition to Ellen Bruzell, Berit Granum and Trine Husøy, these were (in alphabetical order):

Jens Rohloff – Member of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food, and Cosmetics. Affiliation: 1) VKM; 2) Norwegian University of Science and Technology

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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

CIE - International Commission on Illumination

DALY - Disability-adjusted life-years

DU - Dobson units. A unit used for measurement of ozone in the atmosphere

EFSA - European Food Safety Authority

IARC - International Agency for Research on Cancer

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, 2009).

Benchmark dose: The minimum dose of a substance that produces a clear, low level health risk, usually in the range of a 1-10% change in a specific toxic effect such as cancer induction (https://www.efsa.europa.eu/en/glossary-taxonomy-terms).

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 (Guidance on Biological

Relevance, Jan Alexander and Nikolaos Georgiadis, EFSA. In presentation given to VKM 09.11.2017).

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 (modified from https://ec.europa.eu/growth/sectors/cosmetics/products/sunscreen_en).

No observed adverse effect level (NOAEL): The greatest concentration or amount of a substance at which no detectable adverse effects occur in an exposed population (https://www.efsa.europa.eu/en/glossary-taxonomy-terms).

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 (https://www.efsa.europa.eu/en/glossary-taxonomy-terms). The point of departure may be derived e.g. from the No-observed-adverse-effect level (NOAEL) or by using the benchmark dose (BMD) method. POD is also called 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, 2010). The proposed procedure for a risk-benefit assessment (EFSA, 2010) is illustrated in the table below.

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

1 Introduction

Sunscreens are cosmetic products used to reduce ultraviolet radiation (UVR) exposure to the skin. 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 2006/647/EC) (Figure 1-1). All sunscreen products must be safe under normal and reasonably foreseeable use conditions, as specified in the Cosmetic Products Regulation (EC, 2009). However, there are concerns whether some sunscreen ingredients pose risk to frequent users, e.g. allergic reactions or endocrine effects.

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 and immunomodulation. However, as formulated by the International Agency for Research on Cancer (IARC): "duration of sun exposure beyond skin capacity to form vitamin D will not further increase vitamin D, but will increase skin cancer risk" (IARC, 2008) (Figure 1-1).

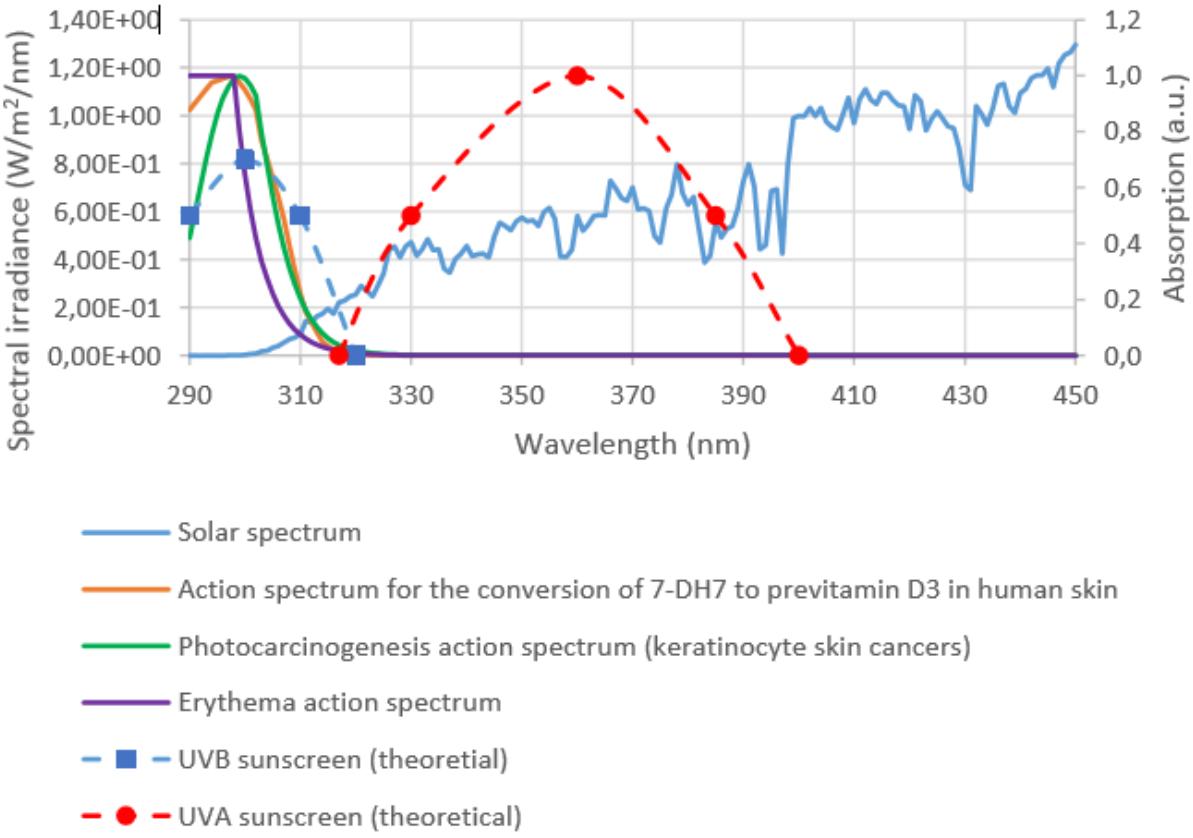

Figure 1-1: The wavelength dependent development of erythema (CIE, 1998) and keratinocyte (non-melanoma) skin cancers (ISO/CIE, 2016) peaks around 300 nm as does the conversion of 7-DH7 to provitamin D3 in skin (CIE, 2006). In the wavelength region 290-320 nm (UVB) the solar radiation

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 (ISO/CIE, 2016). No official action spectrum exists for the induction of melanoma skin cancer. Theoretical UVB and UVA sunscreen 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 DU (Dobson units) (Emde et al., 2016; Pierluissi and Peng, 1985; Ricchiazzi et al., 1998). Right y-axis: Relative magnitude of effect of action spectra or absorption of UVR in sunscreens.

In Norway, the incidence of skin cancer is among the highest worldwide (GLOBOCAN, 2012). The mortality of malignant melanoma, the most severe form of skin cancers, is highest in Europe (Sacchetto et al., 2018). The incidence rate of melanoma increased with >50% during the period 2000-2016 (Norwegian Cancer Registry, 2018).

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 suggested to perform a risk-benefit assessment of sunscreen use.

1.1 Terms of reference

The terms of reference is to develop a protocol of a risk-benefit assessment of sunscreen use. The target group for the assessment will be the Norwegian population, both sexes, and all age groups.

The purpose of the protocol is to ensure that the assessment will be efficient, transparent and methodologically rigorous.

The protocol shall address the following steps:

- The problem formulation (Chapter 2)
- The selection criteria for the sunscreens and sunscreen substances included in the assessment (Chapter 2)
- The hazard identification and characterisation (Chapter 3)
- The benefit identification and characterisation (Chapter 4)
- The exposure estimation (Chapter 5)
- The risk-benefit assessment (Chapter 6)

The protocol is a first step towards a risk-benefit assessment of sunscreens. The second step is to perform the risk-benefit assessment as described in the protocol. Following approval of the protocol, VKM will make the decision as to whether the assessment will be carried out.

2 Problem formulation

2.1 Objectives and sub-objectives of the assessment

The overall aim of the risk-benefit assessment is to weigh risks against benefits of using sunscreen as skin protection against ultraviolet radiation.

The sub-objectives are to:

- Identify and characterise adverse health effects related to sunscreen use, e.g. allergic reactions or endocrine effects
    - Evaluate the quality of the scientific evidence through a weight of evidence (WoE) approach
    - Identify and describe the uncertainty related to the outcome
- Identify and characterise beneficial health effects related to sunscreen use, i.e. the (indirect) positive effect of the sunscreen's ability to protect skin cells from solar UVR
    - Evaluate the quality of the scientific evidence through a WoE approach
    - Identify and describe the uncertainty related to the outcome
- Calculate the exposure to sunscreen using different scenarios
- Perform a risk-benefit analysis using the disability-adjusted-life years (DALY) method to quantify health losses or gains
- Identify and describe knowledge gaps

2.2 Target population

The target population is the Norwegian population, both sexes, and all age groups. The availability of data may limit inclusion of certain age groups.

2.3 Inclusion and exclusion of sunscreens and sunscreen ingredients

Sunscreens contain a large number of ingredients, 10-50 per product is a common range, and each sunscreen has its specific combination of ingredients. Sunscreen ingredients have a variety of functions and these may be divided into groups such as UV filters, preservatives and fragrances to mention a few. Therefore, to make a risk-benefit assessment feasible for VKM, only a limited number of ingredients and no effects of ingredient combinations will be included in the assessment. An overview of the criteria for including and excluding ingredients for the risk-benefit assessment is given in Table 2.3-1.

246 **Table 2.3-1**. Criteria for including and excluding sunscreens and ingredients.

	Inclusion	Reason	Exclusion	Reason
Sunscreens	Sunscreen products protecting against UVB and UVA and available on the Norwegian market	The assessment is for Norwegian conditions	Sunscreens protecting against any other wavelengths of the solar spectrum than UVA and UVB	
			Sunscreens that can be obtained only in web shops	Difficult to limit to the Norwegian market
			Sunscreen sprays from aerosol cans	To limit the assessment to dermal exposure excluding inhalation
			Sunscreen lip sticks	To limit the assessment, the intended use area is small, and to differentiate between skin cancer and lip and oral cancer
			Cosmetics containing UV-filters and preservatives but not marketed as sunscreens	These products are not mainly intended to block UVR
Ingredient groups	UV-filters and preservatives	UV-filters represent main purpose of the sunscreen		
			Other sunscreen ingredient groups than UV-filters and preservatives	To limit the assessment
		Consumer concern/media coverage about the health risk of preservatives in cosmetics		
Single substances	To be decided after all sunscreens are selected		To be decided after all sunscreens are selected	

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2.4 Literature searches and study selection

Separate literature searches will be performed to identify publications useful for answering the Terms of Reference. An information specialist will conduct the literature searches.

Literature searches will be conducted in several databases, and the result form each bibliographic database will be imported and combined in the bibliographic reference management software EndNote.

Articles will be screened based on inclusion and exclusion criteria specific for the hazard identification and characterisation, the benefit identification and characterisation, and the exposure estimation. Editorials, comments, letters to the editor, meeting's abstracts, posters and book chapters will be excluded.

For the selection of studies, VKM foresees a step-wise procedure as follows:

1. ***Screening of titles and abstracts:*** The screening of titles and abstract will be performed by two reviewers working independently. When in doubt about inclusion the paper will be considered as meeting the inclusion criteria.
2. ***Screening of full-text documents:*** For records passing the first screening based on titles and abstracts, the full text will undergo a second screening against the inclusion criteria by means of two reviewers working independently.

In case of disagreement, the two reviewers will discuss the paper in order to reach consensus. If the disagreement persists, the article will be brought to the attention of the Panel for discussion and agreement on a final decision.

The results of the different steps of the study selection process will be reported separately for hazard identification and characterisation, the benefit identification and characterisation, and the exposure estimation, and the searches will be presented in the risk assessment opinion as separate flowcharts.

2.5 Data extraction from included studies

Pre-defined data extraction forms (modified from EFSA et al. (2017)) will be used to collect the data from the studies to be included in the assessment. Data extraction will be performed by one reviewer and checked for quality/consistency by a second reviewer.

3 Hazard identification and characterisation

3.1 Sub-questions to be answered in the hazard identification and characterisation steps

The sub-questions to be answered in the hazard identification and characterisation steps are presented in Table 3.1-1. A full systematic procedure will be applied to identify human and animal studies reporting on adverse health effects of UV-filters and preservatives in sunscreens. For studies on toxicokinetics and genotoxicity, the approach will be narrative.

Table 3.1-1. Sub-questions to be answered in the hazard identification and characterisation steps.

Risk assessment step	No	Sub-question	Approach
Hazard identification	1	Is exposure to the UV-filters alone or in combination with UVR related to adverse effects in humans? Identify target organs.	Systematic
Hazard identification	2	Is exposure to the preservatives alone or in combination with UVR related to adverse effect in humans? Identify target organs.	Systematic
Hazard identification	3	Is exposure to the UV-filters alone or in combination with UVR related to adverse effects in animals? Identify target organs.	Systematic
Hazard identification	4	Is exposure to the preservatives alone or in combination with UVR related to adverse effect in animals? Identify target organs.	Systematic
Hazard identification	5	Are UV-filters and/or preservatives alone or in combination with UVR associated with genotoxicity, skin irritation or sensitisation in *in vitro* experiments?	Narrative
Hazard characterisation	6	What is the nature of any dose-response relationships between UV-filters alone or in combination with UVR and relevant endpoints in the target organs in human and/or animal studies?	Systematic
Hazard characterisation	7	What is the nature of any dose-response relationships between preservatives alone or in combination with UVR and relevant endpoints in the target organs in human and/or animal studies?	Systematic
Hazard characterisation	8	What is the ADME* in humans and in different animal species/strains, and are there any differences?	Narrative
Hazard characterisation	9	Are the included human/animal studies biased according to the defined criteria?	Evaluation of risk of bias

*ADME - absorption, distribution, metabolism, excretion.

3.2 Literature search - Hazard

A literature search will be performed to identify publications useful for answering the hazard identification and characterisation sub-questions. The relevant endpoints are adverse health effects related to UV-filters and preservatives in sunscreens.

The literature search will be conducted in the following bibliographic databases:

- Ovid MEDLINE(R)
- Embase
- ISI Web of Science
- Scopus
- Cochrane Database of Systematic Reviews
- Epistemonikos

3.3 Methods for gathering evidence

Data from human and animal studies, identified using a systematic approach, will be collected using data extraction forms, and risk of bias will be evaluated (modified from EFSA et al. (2017)).

3.3.1 Inclusion/exclusion criteria for hazard identification and characterisation

Tables 3.3.1-1, 3.3.1-2 and 3.3.1-3 list criteria for inclusion or exclusion of human, animal and *in vitro* studies in the hazard identification and characterisation steps. For *in vitro* studies, studies addressing genotoxicity, skin irritation and skin sensitisation will be included in the hazard identification and characterisation steps.

Table 3.3.1-1. Inclusion/exclusion criteria for human studies in the hazard identification and characterisation.

Literature screening for data related to the following sub-questions to be answered in the hazard identification and characterisation 1: Is exposure to UV-filters alone or in combination with UVR related to adverse effects in humans? 2: Is exposure to preservatives alone or in combination with UVR related to adverse effects in humans? 6: What is the nature of any dose–response relationship between UV-filters alone or in combination with UVR and relevant endpoints in the target organs in human studies? 7: What is the nature of any dose–response relationship between preservatives alone or in combination with UVR and relevant endpoints in the target organs in human studies? 8: What is the ADME* in humans?		
Study design	In	Human studies, including cohort studies, case-control studies (prospective, retrospective and nested), toxicokinetic and biomonitoring studies
	Out	Animal studies and *in vitro/in silico* studies
Population	In	All age groups, males and females
Exposure	In	Dermal and oral**
	Out	Inhalation Studies where the examined agent is part of a substance mixture and not tested alone
Outcome of interest	In	All reported adverse health effects
	Out	Studies reporting exclusively preventive/beneficial effects on the target organs
Language of the full text	In	English, Norwegian, Swedish, Danish, German
Publication type	In	E.g. primary research studies, systematic reviews, meta-analyses and risk assessments
	Out	Editorials, letters to the editor, book chapters, meeting's abstracts and posters

*ADME - absorption, distribution, metabolism, excretion.

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

317 **Table 3.3.1-2:** Inclusion/exclusion criteria for animal studies for hazard identification and
318 characterisation

Literature screening for data related to the following sub-questions to be answered in the hazard identification and characterisation steps 3: Is exposure to UV-filters alone or in combination with UVR related to adverse effects in animals? 4: Is exposure to preservatives alone or in combination with UVR related to adverse effects in animals? 6: What is the nature of any dose–response relationship between UV-filters alone or in combination with UVR and relevant endpoints in the target organs in animal studies? 7: What is the nature of any dose–response relationship between preservatives alone or in combination with UVR and relevant endpoints in the target organs in animal studies? 8: What is the ADME* in animals and is it different from that of humans?		
Study design	In	*In vivo* studies on animals not examining genotoxicity Toxicokinetic studies (narrative approach)
	Out	Human studies and *in vitro*/*in silico* studies
Population	In	All mammalian animals
	Out	Non-mammalian animals
Exposure	In	Dermal and oral**
	Out	Inhalation Studies where the examined agent is part of a substance mixture and not tested alone
Outcome of interest	In	All reported adverse effects
	Out	Studies reporting exclusively preventive/beneficial effects
Language of the full text	In	English, Norwegian, Swedish, Danish, German
Publication type	In	E.g. primary research studies, systematic reviews, meta-analyses and risk assessments
	Out	Editorials, letters to the editor, book chapters, meeting's abstracts and posters

319 *ADME - absorption, distribution, metabolism, excretion.

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

322

323 **Table 3.3.1-3:** Inclusion/exclusion criteria for *in vitro* studies.

Literature screening for data related to the following hazard identification and characterisation sub-question 5: Are UV-filters and/or preservatives alone or in combination with UVR associated with genotoxicity*, skin irritation or skin sensitisation?		
Study design/test systems	In	*In vitro* and *in vivo* studies on genotoxicity and *in vitro* studies on skin irritation and skin sensitisation
	Out	Test systems: *Drosophila melanogaster*, *Vicia faba*, *Allium cepa*, fish.
	In	Route of exposure for animal *in vivo* studies: dermal, oral, subcutaneous, intraperitoneal

Exposure	Out	Other exposure routes
Outcome of interest	In	• 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
Language of the full text	In	English, Norwegian, Swedish, Danish, German
Publication type	In	E.g. primary research studies, systematic reviews, meta-analyses and risk assessments
	Out	Editorials, letters to the editor, book chapters, meeting's abstracts and posters

*Genotoxicity includes mutagenicity in this assessment.

3.3.2 Data extraction and evaluation of risk of bias

3.3.2.1 Data extraction

Data from the included human studies will be extracted using Table 3.3.2.1-1.

Table 3.3.2.1-1: Data extraction form for human studies (modified from EFSA *et al.* (2017)).

Study ID	**Reference:**
	Study name and acronym (if applicable):
Funding	Funding source: Public/private:
Study design	Study type:
	Type of blinding:
	Year the study was conducted (start):
	Duration/length of follow-up:
	Method for randomisation:
	Dates of sampling and data acquisition (when relevant):
	Dates for analyses of levels of UV-filters/preservatives, their related metabolites, (photo-)degradation products or skin effects:
Subjects	Number of participants in the study:
	Participation rate:
	Number of subjects with measured levels of UV-filters/preservatives, their related metabolites, (photo-)degradation products or skin effects:
	Number of exposed/non-exposed subjects:

	Follow-up rates by group (%):
	Ethnicity: Skin type classification (e.g. Fitzpatrick (1988)):
	Sex (male/female):
	Geography (country, region, state, etc.) of subjects:
	Age at exposure:
	Socioeconomic background:
	Confounders and other variables as reported:
	Inclusion and exclusion criteria:
Intervention/exposure	Measured levels of UV-filters/preservatives (and metabolites, degradation products) from chemical exposure, photoproducts, degradation products and UV (repair-) biomarkers from UV co-exposure in human biological samples (e.g. breast milk, blood, urine, skin) as well as erythema detection in skin. Methods used (validation of the method, measures to avoid contamination of samples, calibration, etc.):
Methods for endpoint assessment	Parameters measured, estimated or calculated (units of measure, measures of central tendency and dispersion, confidence interval, approximations):
	Diagnostics or methods to measure health outcome (including self-reporting):
Results and statistical analysis	Outcome assessment (e.g. mean, median, measures of variance as presented in paper such as standard deviation, standard error of the mean, 75th/90th/95th percentile, minimum/maximum):
	Measures of effect and all statistics at each exposure level as reported in the paper, and for each sub-group and end-point when applicable:
	Predefinition of sub-group analyses (yes/no, including justification):
	Treatment of variables (continuous, transformed, or categorical):
	Statistical test used, modifying factors and other potential sources of bias:
Other comments	

329 Data from the included animal studies will be extracted using Table 3.3.2.1-2.

330 **Table 3.3.2.1-2:** Data extraction form for experimental animal studies (modified from EFSA *et al.*
331 2017).

Study ID	**Reference:**
	Year the study was conducted (start, if available):
Funding	Funding source: Public/private:
Type of study and guideline	Good laboratory practice (yes/no): Guideline study (if yes, specify):
	Type of study:
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):
Exposure	UV-filter/preservative provider:
	Compound purity:
	Vehicle used:
	UVB/UVA-filter:
	Dose regimen (dose level or concentration of preservatives and dose level, concentration, SPF and/or layer thickness of UV-filter per group, and frequency):
	Route of administration:
	Period of exposure (pre-mating, mating, gestation, lactation, adult):
	Exposure duration of the UV-filter/preservative:
	Level of test compounds and their degradation products and metabolites, photo(degradation-)products in tissue or blood and co-exposure radiation effects in skin (e.g. erythema):
	Optical radiation* source (e.g. sun simulator) and manufacturer:
	Duration of the optical radiation co-exposure:
	Optical radiation spectrum and dose (e.g. radiant exposure, standard erythemal dose, minimal erythemal dose):
Study design	Sex and age of the initially exposed animals:
	Number of groups/ number of animals per group:
	Randomisation procedures at start of the study:
	Reducing (culling) of litters and method:
	Number of pups per litter for next generation and methodology:
	Number of pups per litter/animals for certain measurements and methodology:
	Time of measurement/observation period (premating, mating, gestation, lactation, adult):
	Endpoints measured:
	Methods to measure endpoint:
	Dates of sampling, skin change determination (when relevant):
	Anaesthesia/analgesia and possible interaction with optical radiation
Statistical analysis	Statistical methods:
Results	Documentation of details for dose conversion when conducted:
	Results per dose or concentration (e.g. mean, median, frequency, measures of precision or variance):
	Observed effect level:
	Shape of dose-response if reported by the authors:
Other comments	

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

3.3.2.2 Evaluation of risk of bias

In the assessment, the evaluation of risk of bias includes the following considerations:

- Aspects that introduce a systematic difference between the control and the exposed group only (e.g. non-randomised allocation of animals to study groups).
- Aspects potentially affecting, to the same extent, control and exposed study groups (e.g. the reliability of the method used to test the outcome).

The questions addressed to assess the risk of bias in the human and animal studies are presented in Table 3.3.2.2-1 and Table 3.3.2.2-2, respectively (NTP, 2015). For each question in Table 3.3.2.2-1 and Table 3.3.2.2-2, the response options (Table 3.3.2.2-3) are "Definitely low risk of bias (++)", "Probably low risk of bias (+)", "Probably high risk of bias (-)", "Definitely high risk of bias (--)". Whenever an element to be evaluated is not reported, this will by default be judged as "Probably high risk of bias".

Table 3.3.2.2-1. Evaluation of risk of bias in human studies (modified from EFSA et al. (2017)).

No.	Question	Domain	Rating (++, +, -, --)
1	Did selection of study participants result in appropriate comparison groups?	Selection	
2	Can we be confident in the exposure characterisation?	Detection	
3	Can we be confident in the outcome assessment?	Detection	
4	Did the study design or analysis account for important confounding and modifying variables?	Confounding	
5	Do the statistical methods seem appropriate?	Other sources of bias	

Table 3.3.2.2-2. Evaluation of risk of bias in animal studies (modified from EFSA et al. (2017)).

No.	Question	Domain	Rating (++, +, -, --)
1	Were experimental conditions identical across study groups?	Performance	
2	Were outcome data completely reported without attrition or exclusion from analysis?	Attrition	
3	Can we be confident in the exposure characterisation?	Detection	
4	Can we be confident in the outcome assessment?	Detection	
5	Were the statistical methods and the number of animals per dose group appropriate?	Other sources of bias	

Table 3.3.2.2-3. Response options for evaluation of risk of bias (modified from EFSA et al. (2017)).

Rating	Response to the question	Description
++	**Definitely low** risk of bias	There is direct evidence of low risk of bias practices.
+	**Probably low risk** of bias	There is indirect evidence of low risk of bias practices, or it is deemed that deviations from low risk of bias practices for these criteria during the study would not appreciably bias results. This includes consideration of direction and magnitude of bias.
-/not reported	**Probably high** risk of bias	There is indirect evidence of high risk of bias practices, or there is insufficient information provided about the relevant risk of bias practices.
--	**Definitely high** risk of bias	There is direct evidence of high risk of bias practices.

The ratings of the questions (++, +, -, --) will be integrated to classify the studies in tiers from 1 to 4 corresponding to decreasing levels of risk of bias. Two reviewers will perform each evaluation independently. In case of disagreement, the reviewers will discuss until consensus is reached or the Panel will reach a final decision.

3.4 Evaluation of relevance of the endpoints for the target population

For the animal studies, the relevance of the specific endpoints studied for the human target population will be evaluated (EFSA Scientific Committee et al., 2017). The evaluation will be performed by two reviewers independently. In case of disagreement, the reviewers will discuss until consensus is reached or the Panel will reach a final decision.

3.5 Weighing the body of evidence

All studies reporting on a given endpoint will be grouped, and the evidence will be weighed using a modified version from EFSA et al. (2017) downgrading or upgrading the confidence in the evidence. Several elements will be considered for downgrading or upgrading the confidence in the evidence:

Elements that may cause downgrading of the confidence in the evidence are:

- Risk of bias
- Relevance of endpoints (for animal studies only)
- Unexplained inconsistency
- Imprecision

Elements that may cause upgrading of the confidence in the evidence are:

- Large effect (e.g. incidence, degrees of severity)
- Dose-response relationship
- Consistency, across study design type, dissimilar populations, animal models, species or gender, and in direction of effect
- Confounding, if all relevant confounders are described and taken into account

Table 3.5.-1 will be used for the downgrading/upgrading of the evidence. One table will be used per endpoint. After the downgrading/upgrading of the evidence, the terms used for the overall confidence in the evidence are:

- **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.

393 **Table 3.5-1.** Grading confidence in the body of evidence per endpoint (modified from *EFSA et al.* (2017)).

Endpoint [describe]									
	Elements triggering downgrading				**Elements triggering upgrading**				
Reference	Risk of bias	Relevance of endpoint (animal studies only)	Unexplained inconsistency	Imprecision	Large effect	Dose-response relationship	Consistency	Confounding	Confidence level
Reference 1	Describe identified risks	Discuss use of endpoints or models with less relevance to humans	Describe results in terms of consistency Explain apparent inconsistency (if it can be explained)	Discuss ability to distinguish treatment from control Describe confidence intervals	Describe magnitude of response	Outline evidence for or against dose response	Describe cross-species, model, or population consistency	Address whether there is evidence that confounding would bias toward null	Confidence level
Reference 2									
Reference 3 etc.									
Overall conclusion on confidence									Overall confidence interval

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To decide if each endpoint represents an adverse health effect or not will be based on the overall confidence in the body of evidence. The Panel emphasises that the likelihood assessed by the WoE approach refers specifically to hazard identification, i.e. it refers to the likelihood of an association between UV-filters and/or preservatives and the effect under consideration. It does *not* refer to the likelihood or frequency of the effect actually occurring in humans, which depend on additional factors. Such factors include e.g. the dose-response relationship for the effect (considered in hazard characterisation) and the levels of human exposure to UV filters and/or preservatives (see Chapter 5).

3.6 Method for performing hazard characterisation

For the hazard characterisation, the overall confidence in the evidence for each endpoint will be transformed to likelihood of an association between the agent in question and the adverse effect represented by the endpoint (Table 3.6-1).

Table 3.6-1. Terms used to transform the overall confidence interval in the evidence per endpoint to overall likelihood.

Overall confidence level range *	Likelihood of an association between UV filters/preservatives and the adverse effect under consideration
++++	Very likely
From ++++ to +++	Likely
From +++ to ++	As likely as not
From ++ to +	Unlikely
+	Very unlikely

*This table is only used for endpoints described in more than one article. Endpoints that are described in one article only will be evaluated by expert judgement.

Dose-response analysis will be performed for "Very likely" and "Likely" effects using human and/or experimental animal studies showing adverse health effects relevant to humans. Given the broad number of endpoints examined, the adversity of a specific effect and the critical effect size (benchmark response) will be evaluated case-by-case based on expert judgement. A justification will be provided.

3.7 Uncertainty in hazard identification and characterisation

The uncertainty evaluation of hazard identification and characterisation will be described qualitatively, and an overview is given in Table 3.7-1. The symbols + and – indicate overestimation and underestimation, respectively, and the scales from + to +++ and from – to --- indicate the magnitude. When possible, the size of the uncertainty will be calculated quantitatively.

Table 3.7-1. Form used for qualitative evaluation of influences of uncertainties in the hazard identification and characterisation. The symbols + and – indicate overestimation and underestimation, respectively, and the scales from + to +++ and from – to --- indicate the magnitude. Examples are provided.

Endpoint	Source of uncertainty	Direction
e.g. biomarker x	Incorrect biological sample analysis	-
e.g. skin adverse effect	Radiation spectrum included infrared in addition to UV in animal exposure	+
Etc.		

- : uncertainty likely to cause under-estimation of the consequence.
+: uncertainty likely to cause over-estimation of the consequence.

4 Benefit identification and characterisation

4.1 Identification of sub-questions for the benefit assessment

The sub-questions to be answered by the benefit identification and characterisation are presented in Table 4.1-1. A full systematic procedure will be applied to identify studies reporting on beneficial health effects of UV-filters and preservatives in sunscreens.

Table 4.1-1. Sub-questions to be answered in the benefit identification and characterisation.

Benefit assessment step	No.	Sub-question	Approach
Benefit identification	1	Is dermal exposure to UV-filters alone or in combination with UVR related to beneficial effects in humans? Identify target organs.	Systematic
Benefit identification	2	Is dermal exposure to preservatives alone or in combination with UVR related to beneficial effects in humans? Identify target organs.	Systematic
Benefit identification	3	Is dermal exposure to UV-filters alone or in combination with UVR related to beneficial effects in animals? Identify target organs.	Systematic
Benefit identification	4	Is exposure to preservatives alone or in combination with UVR related to beneficial effects in animals? Identify target organs.	Systematic
Benefit characterisation	5	What is the nature of any dose–response relationships between UV-filters alone or in combination with UVR and beneficial effects in the target organs in human and/or animal studies?	Systematic
Benefit characterisation	6	What is the nature of any dose–response relationships between preservatives alone or in combination with UVR and beneficial effects in the target organs in human and/or animal studies?	Systematic
Benefit characterisation	7	Are the included human/animal studies biased according to the defined criteria?	Risk of bias evaluation

4.2 Literature search - Benefit

A literature search will be performed to identify publications on beneficial health effects related to UV-filters and preservatives in sunscreens alone or in combination with solar UVR.

The literature search will be conducted in the following bibliographic databases:

- Ovid MEDLINE(R)
- Embase
- ISI Web of Science
- Scopus
- Cochrane Database of Systematic Reviews
- Epistemonikos

4.3 Methods for gathering evidence

4.3.1 Inclusion/exclusion criteria for the benefit identification and characterisation steps

Tables 4.3.1-1 and 4.3.1-2 schematically list criteria for inclusion and exclusion of human and animal studies, respectively.

Table 4.3.1-1: Inclusion/exclusion criteria for human studies in the benefit identification and characterisation.

Literature screening for data related to the following sub-questions to be answered in the benefit identification and characterisation steps 1: Is dermal exposure to UV-filters alone or in combination with UVR related to beneficial effects in humans? Identify target organs. 2: Is dermal exposure to preservatives alone or in combination with UVR related to beneficial effects in humans? Identify target organs. 5: What is the nature of any dose–response relationships between UV-filters alone or in combination with UVR and beneficial effects in the target organs in human studies? 6: What is the nature of any dose–response relationships between preservatives alone or in combination with UVR and beneficial effects in the target organs in human studies?		
Study design	In	Human studies, including cohort studies, case-control studies (prospective, retrospective and nested)
	Out	Animal studies and *in vitro/in silico* studies
Population	In	All age groups, male and females
Exposure	In	Dermal exposure
	Out	Oral and inhalation Studies where the examined agent is part of a substance mixture and not tested alone
	In	All reported beneficial effects

Outcome of interest	Out	Studies reporting exclusively adverse health effects
Language of the full text	In	English, Norwegian, Swedish, Danish, German
Publication type	In	E.g. primary research studies, systematic reviews, meta-analyses and risk assessments
	Out	Editorials, letters to the editor, book chapters, meeting's abstracts and posters

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458 **Table 4.3.1-2:** Inclusion/exclusion criteria for animal studies in the benefit identification and
459 characterisation steps.

Literature screening for data related to the following sub-questions to be answered in the benefit identification and characterisation steps 3: Is dermal exposure to UV-filters alone or in combination with UVR related to beneficial effects in animals? Identify target organs. 4: Is dermal exposure to preservatives alone or in combination with UVR related to beneficial effects in animals? Identify target organs. 5: What is the nature of any dose–response relationships between UV-filters alone or in combination with UVR and beneficial effects in the target organs in animal studies? 6: What is the nature of any dose–response relationships between preservatives alone or in combination with UVR and beneficial effects in the target organs in animal studies?		
Study design	In	*In vivo* studies on animals
	Out	Human studies and *in vitro/in silico* studies
Population	In	All mammalian animals
	Out	Non-mammalian animals
Exposure	In	Dermal
	Out	Oral and inhalation Studies where the examined agent is part of a substance mixture and not tested alone
Outcome of interest	In	All reported beneficial effects
	Out	Studies reporting exclusively adverse health effects
Language of the full text	In	English, Norwegian, Swedish, Danish, German
Publication type	In	E.g. primary research studies, systematic reviews, meta-analyses and risk assessments
	Out	Editorials, letters to the editor, book chapters, meeting's abstracts and posters

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461 4.3.2 Data extraction and evaluation of risk of bias

462 Data from the included human and animal studies will be extracted using Tables 4.3.2-1 and
463 4.3.2-2, respectively.

464 **Table 4.3.2-1**: Data extraction form for human studies (modified from EFSA et al. (2017)).

Study ID	**Reference:**
	Study name and acronym (if applicable):
Funding	Funding source: Public/private:
Study design	Study type:
	Type of blinding:
	Year the study was conducted (start):
	Duration/length of follow-up:
	Dates of sampling and data acquisition (when relevant):
	Dates for analyses of levels of UV-filters/preservatives, their related metabolites, (photo-)degradation products or skin effects:
Subjects	Number of participants in the study:
	Participation rate:
	Number of subjects with measured levels of UV-filters/preservatives, their related metabolites, (photo-)degradation products or skin effect:
	Number of exposed/non-exposed subjects:
	Follow-up rates by group (%):
	Ethnicity and skin type classification (e.g. Fitzpatrick (1988)):
	Sex (male/female):
	Geography (country, region, state, etc.) of subjects:
	Age at exposure:
	Socioeconomic background:
	Confounders and other variables as reported:
	Inclusion and exclusion criteria:
Intervention/exposure	Measured levels of UV-filters/preservatives (and metabolites, degradation products) from chemical exposure and photoproducts, degradation products and UV (repair-) biomarkers from UV co-exposure in human biological samples (e.g. breast milk, blood, urine, skin) as well as erythema detection in skin. Methods used (validation of the method, measures to avoid contamination of samples, calibration, etc.):
Methods for endpoint assessment	Parameters measured, estimated or calculated (units of measure, measures of central tendency and dispersion, confidence interval, approximations):
	Diagnostics or methods to measure health outcome (including self-reporting):
Results and statistical analysis	Outcome assessment (e.g. mean, median, measures of variance as presented in paper such as standard deviation, standard error of the mean, 75th/90th/95th percentile, minimum/maximum):
	Measures of effect and all statistics at each exposure level as reported in the paper, and for each sub-group and endpoint when applicable:
	Predefinition of sub-group analyses (yes/no, including justification):
	Treatment of variables (continuous, transformed, or categorical):

	Statistical test used, modifying factors, estimation uncertainty and other potential sources of bias:
Other comments	

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466 **Table 4.3.2-2.** Data extraction form for animal studies (modified from EFSA et al. (2017)).

Study ID	**Reference:**
	Year the study was conducted (start, if available):
Funding	Funding source: Public/private:
Type of study and guideline	Good laboratory practice (yes/no): Guideline study (if yes specify):
	Type of study:
Animal model	Species/(sub-)strain/line:
	Disease models (e.g. cancer, allergy):
	Skin/fur pigmentation:
Housing condition	Housing conditions (including cages, bottles, bedding):
	Diet name and source:
	Anaesthesia/analgesia and possible interaction with optical radiation:
	Background levels of phytoestrogens in the diet (type and levels):
	Background levels of potential photosensitisers (e.g. riboflavin) in the diet (type and levels):
Exposure	UV-filter/preservative provider:
	Compound purity:
	Vehicle used:
	UVB/UVA-filter:
	Dose regimen (dose level or concentration of preservatives and dose level, concentration, SPF and/or layer thickness of UV-filter per group, and frequency):
	Route of administration:
	Period of exposure (pre-mating, mating, gestation, lactation, adult):
	Exposure duration of the UV-filter/preservative:
	Optical radiation* source (e.g. sun simulator) and manufacturer:
	Duration of the optical radiation co-exposure:
	Optical radiation spectrum and dose (e.g. radiant exposure; standard erythemal dose; minimal erythemal dose):
Study design	Sex and age of the initially exposed animals:
	Number of groups/number of animals per group:
	Randomisation procedures at start of the study:
	Reducing (culling) of litters and method:
	Number of pups per litter for next generation and methodology:
	Number of pups per litter/animals for certain measurements and methodology:
	Time of measurement/observation period (premating, mating, gestation, lactation, adult):
	Endpoints measured:

	Methods to measure endpoints:
	Dates of sampling, skin change determination (when relevant):
Results and statistical analysis	Statistical methods:
	Documentation of details for dose conversion when conducted:
	Level of test compounds and their degradation products and metabolites, photo(degradation-)products in tissue or blood and co-exposure radiation effects in skin (e.g. erythema):
	Results per dose or concentration (e.g. mean, median, frequency, measures of precision or variance):
	Observed effect level:
	Shape of dose-response if reported by the authors:
Other comments	

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

4.4 Evaluation of relevance of the endpoints for the target population

For the animal studies, the relevance of the specific endpoints studied for the human target population will be evaluated (EFSA Scientific Committee et al., 2017). The evaluation will be performed by two reviewers independently. In case of disagreement, the reviewers will discuss until consensus is reached or the Panel will reach a final decision.

4.5 Weighing the body of evidence

Please see section 3.5.

The Panel emphasises that the likelihood assessed by the WoE approach refers specifically to benefit identification, i.e. it refers to the likelihood of an association between UV-filters and/or preservatives and the (reduction of the) effect under consideration. It does *not* refer to the likelihood or frequency of the effect actually occurring in humans, which depends on additional factors including the dose-response relationship for the effect (considered in benefit characterisation) and the levels of human exposure to UV-filters and/or preservatives (considered in exposure estimation).

4.6 Method for performing benefit characterisation

For the benefit characterisation, the overall confidence in the evidence of each endpoint is transformed to likelihood (Table 4.6-1).

Table 4.6-1. Terms used to transform the overall confidence interval per endpoint to overall likelihood.

Overall confidence level range*	Likelihood of an association between UV filters/preservatives and the adverse effect under consideration
++++	Very likely
From ++++ to +++	Likely
From +++ to ++	As likely as not
From ++ to +	Unlikely
+	Very unlikely

*This table is only used for endpoints described in more than one article. Endpoints that are described in one article only will be evaluated by expert judgement.

Dose-response analysis will be performed for "Very likely" and "Likely" effects using human and/or experimental animal studies showing adverse health effects relevant to humans. Given the broad number of endpoints examined, the benefit of a specific effect and the critical effect size (benchmark response) will be evaluated case-by-case based on expert judgement. A justification will be provided.

4.7 Uncertainty in benefit identification and characterisation

The uncertainty evaluation of benefit identification and characterisation will be described in the same way as uncertainty in the hazard identification and characterisation (see Table 3.7-1).

5 Exposure

For all exposure estimations, the route of exposure is dermal. Inhalation of sunscreen particles, aerosols etc. is possible when aerosol can spray products are used. However, such products will not be included (please see section 2.3).

5.1 Sub-questions to be answered in the exposure assessment step

An overview of the sub-questions to be answered in the exposure assessment is given in Table 5.1-1.

Table 5.1-1. Sub-questions to be answered in the exposure assessment.

Risk assessment step	No.	Sub-question	Approach
Exposure estimation	1	Using sunscreen products to protect against solar UVR, what is the exposure to UV-filters?	Systematic
Exposure estimation	2	Using sunscreen products to protect against solar UVR, what is the exposure to preservatives?	Systematic

A full systematic approach will be applied to identify studies reporting on concentrations of the included UV-filters and preservatives in sunscreens and on sunscreen use.

5.2 Literature search - Exposure

A literature search will be performed to identify publications on concentration of the included UV-filters and preservatives in sunscreens, and publications on sunscreen use.

The literature search will be conducted in the following bibliographic databases:

- Ovid MEDLINE(R)
- Embase
- ISI Web of Science
- Scopus
- Cochrane Database of Systematic Reviews
- Epistemonikos

5.3 Method for gathering evidence

5.3.1 Inclusion/exclusion criteria

Tables 5.3.1-1 and 5.3.1-2 list criteria for including or excluding studies in the exposure assessment step.

Table 5.3.1-1. Inclusion/exclusion criteria for studies on concentration of the included UV-filters and preservatives in sunscreens.

Literature screening for data on concentrations of the included UV-filters and preservatives in sunscreens		
Study design	In	All publications that address analyses of concentrations of the included UV-filters and preservatives in sunscreens
Study characteristics	In	Studies presenting analytical data and/or biomonitoring data
Analytical method	In	All methods
	Out	-
Outcome of interest	In	Concentration of UV-filter in sunscreens Concentration of preservative in sunscreens
	Out	Concentration of UV-filters and preservatives in other cosmetics than sunscreens and in sunscreen lipsticks/aerosol can sprays Concentration data for other sunscreen ingredients Studies reporting exclusively on toxicity or preventive/beneficial effects
Language of the full text	In	English, German, Norwegian, Swedish and Danish
Publication type	In	Primary research articles Risk assessments and reports
	Out	Editorials, letters to the editor, book chapters, meeting's abstracts and posters

Table 5.3.1-2. Inclusion/exclusion criteria for studies on sunscreen use.

Literature screening for data on realistic sunscreen use		
Study design	In	All publications addressing application/user amounts of sunscreen
Exposure	In	Dermal
	Out	All other exposures
Outcome of interest	In	Data on application/use of sunscreen
	out	Data on application/use of sunscreen lipsticks/aerosol can sprays and other cosmetics not marketed primarily as sunscreen
Language of the full text	In	English, German, Norwegian, Swedish and Danish

Publication type	In	Primary research articles Risk assessments and reports
	Out	Editorials, letters to the editor, book chapters, meeting's abstracts and posters

5.4 Data extraction

Data from the included studies will be extracted using Table 5.4-1.

Table 5.4-1. Data extraction form for included studies.

Study ID	**Reference:**
	Year the study was conducted:
Funding	Funding source: Public/private:
Aim of the study	Analysis:
	Exposure:
Methods for analysis	Sample extraction:
	Calibration:
	Limit of detection/limit of quantification:
	Recovery data:
	Instrument/detector:
Results	Number of samples:
	Concentration of UV-filter/preservative:
	Amount of sunscreen used and skin area covered:
	Statistical methods used:

5.5 Exposure estimation – scenarios and methods

Different scenarios will be used for the exposure calculations.

Exposure estimation will be based on concentrations of the included UV-filters and preservatives in sunscreens, and realistic user amounts of sunscreen product. If the sunscreen manufacturer does not specify the concentration of the substance in question, the maximally approved amount will be considered (EC, 2009). "Realistic user amount" is the sunscreen amount as specified in the literature or decided by expert judgement.

An overview of exposure parameters relevant for the exposure assessment is given in Table 5.5-1.

Table 5.5-1. An overview of parameters relevant for the exposure assessment.

Descriptor	Input parameter
Amount of sunscreen applied	• "Realistic" use – here defined as the amount of sunscreen as specified in the literature or decided by expert judgement
Absorption through skin	• As specified in the literature
Concentration of substance (UV-filter or preservative) in sunscreen	• Given by the producer or specified in the literature • If no data exist, the maximum approved concentration will be considered

5.6 Uncertainty in the exposure estimation

The uncertainty evaluation of the exposure estimation will be described qualitatively (see Table 3.7-1). When possible, the size of the uncertainty will be calculated quantitatively.

6 Risk-benefit assessment

6.1 Risk-benefit analysis

To weigh the probability of adverse health effects against the probability of benefit of sunscreen use as skin protection against UVR, the Panel will perform a risk-benefit assessment using a common scale of measurement. The outline below is adapted from Hoekstra et al. (2008).

From the hazard and benefit identification the population of interest will be selected. A population at risk can be e.g. people with allergy to any of the sunscreen ingredients to be assessed. A benefiting population can be e.g. the people who are the most exposed to solar UVR or people in age groups with high incidence of skin cancer.

Dose-response relationships may be established, depending on the available data, for each health effect expressed as the exposure to the selected sunscreen ingredients (UV-filters and/or preservatives) versus the probability to develop a disease. This quantitative procedure will be performed both for adverse and positive, i.e. reduced adverse, health effects.

The use distribution of sunscreen ingredient will be estimated and calculated at population level. The next step will be to calculate the incidence of disease for each health effect and for each sunscreen ingredient. The incidence can be expressed as the integral of the dose-response function obtained as described above and the probability density function of the sunscreen ingredient exposure distribution over the range of all exposures.

The burden of disease in the population caused by adverse effects of sunscreen ingredients and the reduction in the burden of disease for beneficial effects of sunscreen ingredients, will be estimated. Health losses or gains will be quantified with the disability-adjusted life-years method (DALY) (Murray, 1994) (see definition below). The disability weights for adverse and beneficial health effects of sunscreen (ingredient) use will be identified and DALYs for the sum of beneficial effects will be compared to DALYs for the sum of adverse effects of sunscreen (ingredient) use.

DALY = YLL + (wt) YLD

- DALY is the number of healthy years of life lost due to premature death and/or disability
- YLL is years of life lost
- wt is disability weight
- YLD is the years lived with disability (incidence of the disease times the duration)

A disability weight is a weight factor that reflects the severity of the disease on a scale from 0 (perfect health) to 1 (equivalent to death) (Murray, 1994). Disability weights in Salomon et al. (2015) will be used where applicable. A document from WHO gives disability weights for melanoma and other malignant skin cancers (WHO, 2004) and disability weights for various skin diseases can be found in Murray et al. (2012) and Hollestein and Nijsten (2014). If these references prove insufficient, a literature search will be performed.

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