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A systematic risk-benefit assessment of sunscreen use in the Norwegian population in reply to mixed messages in risk communication

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Norway is among the countries with the highest incidence and mortality of skin cancer worldwide, yet consumer organizations pay less attention to cancer protection and more to unverified health and environmental hazards. This unnuanced communication may potentially lead to insecurity among consumers about sunscreen protection. Therefore, VKM performed an assessment of 1) the hazard of and dermal exposure to the six most frequently used ultraviolet (UV) filters in sunscreens in Norway: bis-ethyl-hexyloxyphenol methoxyphenyl triazine; butyl methoxydibenzoyl methane; 2-ethylhexyl salicylate; ethylhexyl triazone; octocrylene; and titanium dioxide in nanoform, 2) the hazard of sunscreen use, and 3) the protection of sunscreen against UV-induced adverse effects. Scientific publications and reports up to 2022 were retrieved in two searches to assess adverse and protective effects of sunscreen. Toxicological data of UV filters also came from a chemical agency's dossiers. Specific searches were made for data on concentrations and dermal absorption of UV filters and user amounts of sunscreens. We developed a systematic quality evaluation of the UV filter analysis methods. Probabilistic methods were used to estimate exposure to each UV filter. Health outcome studies were assessed for risk of bias and weight of evidence across outcomes was evaluated. The internal exposure to the individual UV filters were below the derived no-effect level. Thus, the risk of exposure to them was considered negligible. Hazards and risk conclusions associated with sunscreen use was precluded by insufficient evidence. The benefit conclusion was that sunscreens are presumed to protect against certain skin cancers and polymorphic light eruption. VKM concluded that for the general Norwegian population, sunscreen use is beneficial. This message should be communicated to the public by all relevant authorities.

Keywords: Sun protection, malignant melanoma, non-melanoma skin cancer, vitamin D synthesis, probabilistic exposure assessment, internal validity, confidence in evidence, uncertainty factor, consumer organization.

1. Introduction

In Norway, the incidence of skin cancer is among the highest worldwide (Ferlay et al. 2024). The incidence rate of malignant melanoma increased by more than 50% during the period 2000-2023 (Cancer Registry of Norway, 2024) and is accompanied by the highest mortality rate in Europe (ECIS, 2019). About 90% of skin cancers are expected to result from exposure to ultraviolet radiation (UVR). One of the protection measures against skin cancers is the use of sunscreen (WHO.org). Sunscreens are legally regulated as cosmetic products in the EU (Regulation (EC) No 1223/2009) which includes a positive list of 34 approved UV filters (Annex VI to the Cosmetics Regulation) that may be used in cosmetics up to the maximum allowed concentration. Sunscreen products usually contain combinations of several organic and inorganic UV filters, which both can protect against UVA and/or UVB radiation.

Consumer organizations often emphasize potential health hazards and environmental effects of sunscreen ingredients without taking the degree of exposure to these ingredients and the cancer risk of avoiding sunscreen use into account. For example, a Norwegian consumer right organization rated a sunscreen as "poor" due

to its content of the EU-approved UV filter 2-ethylhexyl salicylate (EHS). We present a short version of a comprehensive, systematic risk-benefit assessment of sunscreens and selected UV filters (VKM et al. 2022 and references therein) and protocol (VKM et al. 2020). The major study questions were: i) Is exposure to sunscreen and UV filters, combined or not with UVR, associated with adverse health effects? ii) Is dermal exposure to sunscreens associated with reduction of adverse effects that are caused by solar UVR? iii) What are the concentrations of the included UV filters used in sunscreens? (see VKM et al. 2020 for sub-questions).

2. Methods

2.1. *Delimitations*

2.1.1. *Selection of sunscreen ingredients*

We selected six of the most frequently occurring UV filters in 47 identified sunscreens on the Norwegian market from June to December 2017. These products are on the positive list of the EU Cosmetics Regulation per January 2025.

Table 1. Name and chemical identification of the ultraviolet (UV) filters selected for risk assessment.

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

2.1.2. *Sunscreen products*

Included sunscreen products were those that followed the EU regulation for UVR protection and which represented only dermal exposure (i.e. not lung or oral).

2.1.3. *Priority of outcomes induced by UVR*

The rating of importance of identified UVR-induced adverse effects was performed according to GRADE (Schünemann et al. 2013) and included expert judgement. “Critical” and “Important but not critical” adverse health effects and mechanistic effects of UVR were prioritised. Adverse effects evaluated to be “Of limited importance” were not included in the evidence profile (see VKM et al. 2022).

2.2. *PECO and aims*

PECO statements were the following:

Participants (P): All age groups, males and females; Exposure (E): Dermal application. The tested substances were sunscreen products and UV filters; Comparator (C): Sunscreen controls are not specified use, no sunscreen, placebo, excipients without UV filters; UV filter controls are no UV-filter, UV filter solvent; Outcomes (O): Protective health effects of sunscreen use when exposed to UVR. Adverse health effects of sunscreen products and UV filters.

The overall risk-benefit assessment aims were to:

i) Characterise health risks related to sunscreen products and selected ingredients (i.e. UV filters) when used as protection against solar UVR

ii) Characterise health benefits related to sunscreen products when used as protection against solar UVR

iii) Compare risks and benefits of sunscreen products when used as protection against solar UVR.

2.3. *Systematic review (SR) methodology*

We followed the Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration (OHAT 2015, 2019) with amendments and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement criteria (Tricco et al. 2018). The publication selection was performed by calibrated pairs of reviewers (one reviewer for exposure data), while for data extraction, one reviewer extracted data and another independently checked them. Authors independently assessed risk of bias (RoB) and weight of evidence in pairs of two. In case of

conflicts, consensus was reached by including a third reviewer or the project group.

2.4. *Data sources*

The databases MEDLINE (Ovid), Embase (Ovid), and Web of Science were searched for adverse and protective effects from inception to 03.03.2020. A specific search, not included in the protocol, was performed to identify other human studies addressing skin irritation and skin sensitisation. The search was updated for SRs and randomized controlled trials (RCTs) addressing health effects 24.08.2022. All literature searches were limited to studies published in English, Norwegian, Swedish, Danish, and German. The UV filters OC and NP-TiO_2 were not included in the first search as recent published opinion by the Scientific Committee on Consumer Safety (SCCS) were considered sufficient to evaluate adverse effects. Toxicological data of all the selected UV filters were obtained from registration dossiers of the European Chemicals Agency (ECHA) (ECHA 2021) throughout the assessment period. Data on UV filter concentrations were searched for in Cochrane Database of Systematic Reviews, The Centre for Reviews and Dissemination, and Epistemonikos. Studies addressing dermal absorption (factors) were obtained from ECHA's registration dossiers, the OECD QSAR Toolbox (4.3.1, 2019) chemical database, SCCS opinions, and PubMed. Retention factors were obtained from SCCS (2021). PubMed was searched for studies reporting on amounts of sunscreen used, in absence of national surveys on pattern of use and amount of applied sunscreen. (For search terms and search strategy, see VKM et al. 2022).

2.5. *Study selection*

The study selection was based on predefined eligibility criteria (VKM et al. 2020). In short, studies were selected to answer the research questions while adhering to the PECO statements (2.3). Publication types were scientific publications, reports, and risk assessments. Studies on (health) effects were prioritised in the following order: 1) human (SR > RCT > observational), 2) experimental animal. *In vitro* studies were not included due to lack of consensus as to which tools were appropriate for evaluation of e.g. internal validity. Specific inclusion/exclusion criteria were set for data on exposure (VKM et al. 2020). Scandinavian and other European data on concentration were prioritised before other geographical areas.

2.6. *Data extraction*

Separate data extraction forms were developed for SRs, RCTs and other human studies, animal studies, and studies on exposure (see VKM et al. 2022).

2.7. *Internal validity*

2.7.1. *Risk of bias (RoB) in studies*

The ROBIS tool (Whiting et al. 2016) was used to evaluate RoB in SRs in levels of low, unclear, and high and the OHAT tool for primary studies in tier 1 (low), tier 2 (moderate), and tier 3 (high). Publications rated as having high RoB were not included as evidence.

2.7.2. *Evaluation of reliability in dossier studies*

The reliability of the evidence for toxicological effects of UV filters retrieved from the ECHA database was evaluated by ECHA using the Klimisch scoring system (Klimisch et al. 1997).

2.7.3. *Quality methodology for exposure data*

The quality of the studies on dermal absorption was evaluated based on existing guidelines for *in vitro* dermal absorption and the SCCS Notes of Guidance. The quality of the methods used in the analysis of UV filters concentrations was scored for type of sample extraction, type of analytical method, validation of methods, and data presentation. Only studies with a score above a predefined limit were included for the exposure assessment. Only studies on amount of sunscreen use that clearly described the method used and reported the amount per use or per day as individual data or summary data were included in the amount data used for the exposure assessment.

2.8. *Weight of evidence across studies*

Confidence in evidence evaluations in SRs were taken into consideration. For outcomes across primary studies, initial rating was followed by evaluation of elements that could trigger downgrading (RoB, unexplained inconsistency, indirectness, imprecision) or upgrading (large effect, dose-response relationship, consistency). The resulting confidence in the body of evidence for each outcome was classified as high,

moderate, low, or very low/no evidence identified.

The confidence in the body of evidence was translated into levels of evidence for an association between the substance in question and the health outcome(s): For identified health effect(s), the levels of evidence corresponding to confidence ratings above were high, moderate, low, or inadequate, respectively. In the absence of health effect(s), the corresponding terms were no health effect or inadequate (all lower ratings than high), respectively.

2.9. *Hazard characterisation and evidence integration*

The hazard characterisation of adverse health effects associated with the investigated UV filters was based on evidence identified from the literature searches and data in ECHA registration dossiers. For each line of evidence from such studies, animal or human, conclusions of evidence for health effects were reached together with the identification of a no observed adverse effect level (NOAEL) as a point of departure (PoD) when possible. Systemic and local toxic effects were considered separately. In declining order of level of evidence (of integrated evidence lines from human and animal studies), when a health effect was observed, the hazard conclusions for human health were termed (level of evidence): Known (high); presumed (moderate); suspected (moderate); not classifiable (low or inadequate). In the absence of health effect(s) or when deemed of minor importance, the corresponding conclusion was: Not identified. The justification for the final hazard conclusion was based on scientific judgement of the overall evidence (OHAT 2019).

The hazard conclusions of the animal dossier data were the derived level of chemical exposure above which humans should not be exposed, i.e. the derived no-effect level (DNEL). The DNEL was obtained by dividing the PoD by the overall uncertainty factor (UF) (EFSA 2012, ECHA 2012). UFs were applied on a case-by case basis and justified.

2.10. *Characterisation and evidence integration of health protective effects*

In all included studies, the intervention was the use of sunscreen containing one or more UV filters with concurrent exposure to UVR. Conclusions on health protection of sunscreen were reached by applying the same method as for hazard conclusions (2.10).

2.11. *Exposure estimation method*

Estimations of a realistic dermal exposure to individual UV filters for sunscreen use in the Norwegian population, were performed as follows. In brief, (see VKM et al. 2022), the exposure was estimated for chronic, daily use of sunscreen by including all data of sufficient quality (2.7.3). A probabilistic exposure estimate was performed using Monte-Carlo simulation (1000 iterations), i.e. all qualified data for concentrations, amounts, and % dermal absorptions were implemented. The resulting exposure estimate was a distribution of probable exposures to each UV filter. The internal exposure (Exp_i) to each UV filter expressed as amount (mg) per day was estimated according to the following equation (Eq. (1)):

$$Exp_i = C \times m \times RF \times \frac{abs}{100} \quad (1)$$

where C is UV filter concentration in sunscreen, m is the amount of sunscreen used per day, RF is the retention factor of the sunscreen product on the skin (=1), and abs is the dermal absorption value of the UV filter. The external exposure is expressed as in Eq. (1) for $abs = 0$. For details, see VKM et al. 2022. For dataset and R- codes see https://doi.org/10.5281/zenodo.6414372

2.12. *Risk characterisation*

For each UV filter, the risk for systemic toxicity was calculated as the ratio of the median (P50) and high consumer exposures (P95) to the DNEL. A risk characterisation ratio <1 was considered not to represent a risk for adverse health effects, whereas a ratio ≥1 might represent a risk for adverse health effects. For sunscreens the risk was assessed narratively.

2.13. *Benefit characterisation*

The benefit characterisation was performed by narrative assessment of data of UV exposure and amounts of sunscreen used. Amount of sunscreen used in other European countries than Norway was considered representative for the Norwegian population.

3. Results

3.1. *Data retrieved from searches*

Titles and abstracts of 365 records of SRs and 4193 records of RCTs of human health effects of sunscreen products and UV filters were screened prior to assessment of 70 and 105 full text articles, respectively. Eight SR publications and 37 RCTs fulfilled the eligibility criteria. After excluding studies deemed "of limited importance" (2.1.3) and those lacking appropriate controls, 15 RCTs remained. Titles and abstracts of 1000 records of other human studies, animal studies and *in vitro* studies were screened prior to assessment of 68 full-text articles. Thirteen human studies on patch tests, two animal studies, and 13 in vitro studies fulfilled the eligibility criteria. Included studies were published from 1986 to 2020.

The following number of studies were identified and found relevant for dermal absorption of UV filters: BEMT; three; BMDBM: four; EHS: three; EHT: three; OC: two; NP-TiO_2: two.

For identification of concentration of UV filters, titles and abstracts of 877 records were screened and 104 full text articles were assessed. Forty publications fulfilled the eligibility criteria, and 28 studies included analysis of UV filter concentration in sunscreens.

Seven publications (surveys) described the amount of sunscreen used in Danish and other European populations, and these data were considered representative also for the Norwegian population.

In the updated search, 220 titles and abstracts of SRs as well as 2259 titles and abstracts of RCTs of human health protective effects of sunscreen products and UV filters were screened prior to assessment of 9 and 14 full text articles of SRs and RCTs, respectively. One SR and seven RCTs fulfilled the eligibility criteria.

3.2. *Internal validity evaluation*

3.2.1. *Risk of bias of health effect outcomes*

RoB was rated low/unclear in three SRs and tiers 1 and 2 in 15 primary studies (Table 2). RoB was rated high in five SRs and as tier 3 in seven RCTs, seven other human studies (photopatch) and in two animal studies. Studies in which RoB was high or tier 3 were not included in weight of evidence assessment (for details, see VKM et al. 2022). Data from ECHA registration dossiers were included if evaluated as reliable without restriction (score 1) or reliable with restrictions (score 2) (see 2.7.2). From the updated search, RoB was low in the one eligible RCT (Duteil et al. 2022). RoB was not assessed in Green et al. (2011) as this study was included in a SR.

Table 2. RoB ratings by study, study type, and outcomes classified as low, unclear, tier 1, or tier 2 for eligible studies. AK: actinic keratosis, BCC: basal cell carcinoma; SCC: squamous cell carcinoma; Immune: immunosuppression; Vit. D: reduction in vitamin D synthesis; PA: photoallergy; AICD: allergic (irritant) contact dermatitis; CT: human controlled study (photopatch); PLE: polymorphic light eruption

Study (et al.)	Study type	RoB	Outcome
Rueegg 2019	SR	Low	Melanoma
Dennis 2003	SR	Unclear	Melanoma
Sanchez 2016	SR	Low	BCC, SCC
Darlington 2003	RCT	1	AK
Thompson 1993	RCT	2	AK
Green 1999	RCT	2	BCC, SCC
Pandeya 2005	RCT	2	BCC
van der Pols2006	RCT	2	BCC, SCC
Neale 1997	RCT	2	Immune
Faurschou 2012	RCT	2	Vit. D
Marks 1995	RCT	2	Vit. D
Bryden et al. 2006	CT	1	PA/AICD
Haylett 2014	CT	1	PA/AICD
Katsarou-Katsari 2008	CT	1	PA/ACD
Kerr 2012	CT	1	PA/AICD
Subiabre-Ferrer 2019	CT	1	PA/ACD
Valbuena Mesa 2016	CT	1	PA/AICD
Duteil 2022	RCT	1	PLE

3.2.2 *Quality of data on exposure*

Expert judgement of one reviewer who followed predefined criteria, resulted in inclusion of dermal absorption data of UV filters from the following studies and data sources (substance in parentheses): ECHA 2021 (BEMT); Chatelain et al. 2003; Montenegro et al. 2013, ECHA 2021 (BMDBM); Chatelain et al. 2003; Walters et al. 1997; ECHA 2021 (EHS); Potard et al. 1999; Hojerova et al. 2017; Souza et al. 2017 (EHT);

SCCS 2021; OECD QSAR Toolbox (OC); ECHA 2021; SCCS 2013 (NP-TiO_2).

Twenty-five studies reporting concentration data of UV filters received a score equal to or above the pre-defined quality limit. Included studies are listed in VKM et al. 2022.

Three studies addressing amount of sunscreen used, fulfilled the criteria (Autier (2001); Ficheux et al. (2016); The Danish Environmental Protection Agency (2016).

3.3. *Study characteristics*

3.3.1. *Health effects*

The following adverse effects due to sunscreen use were reported (Table 2): Increase in melanoma, reduction in vitamin D synthesis photoallergic and allergic contact dermatitis, and irritant contact dermatitis.

Toxicology data reports of the selected UV filters from ECHA registration dossiers included evaluation of the following systemic effects: acute (all), sub-acute (MBDBM, OC), sub-chronic (BEMT, BMDBM, EHT, OC), and chronic toxicity (BEMT, EHS), carcinogenicity (BEMT) and genotoxic effects (all), and reproductive and developmental toxicity (all). Local toxicological effects were skin irritation and skin sensitisation (all). Only skin irritation and skin sensitisation were evaluated for NP-TiO_2.

The following protective effects of sunscreens, i.e. reduced adverse effect in humans, were reported: melanoma (Green et al. 2011 in addition to studies in Table 2), basal cell carcinoma (BCC), squamous cell carcinoma (SCC), actinic keratosis BCC, immunosuppression, and polymorphic light eruption (PLE).

3.3.2. *Exposure parameters*

The following dermal absorption values (in %) were used in the exposure estimations: BEMT: 0.01 and 0.06; BMDBM: 0.1, 0.8, 1.8, 4.5, and 7.3; EHS: 0.2, 1, and 3; EHT: 0.1, 4.1, 6.5, and 10.4; OC: 0.1 and 0.33; NP-TiO_2: 0. Since negligible absorption of NP-TiO_2 occurs through the skin (ECHA 2021, SCCS 2021), systemic exposure resulting from dermal application was not estimated. Reported concentration values in mg/g (number of values) were in the ranges 10-71 (5) for BEMT, 0 - 63 (68) for BMDBM, 0 - 52 (30) for EHS, 21 (1) for EHT, 0 - 108 (58) for OC, and 0-213 (39) for NP-TiO_2. Sunscreen use amount per day was 12.2 g (SD: 12.7).

3.3.3. *Estimated internal exposure*

The estimated Exp_i to selected UV filters (see Table 1) expressed as mean, 50^{th} (P50) and 95^{th} (P95) percentiles obtained probabilistically is shown in Table 3.

Table 3. Estimated internal exposure (Exp_i) to UV filters (mg/kg bw per day) resulting from chronic, daily use of sunscreens. Full names in Table 1.

UV filter[1]	Mean (SD)	P50	P95
BEMT	0.0019 (0.0013)	0.0019	0.0032
BMDBM	0.0875 (0.0803)	0.0547	0.2219
EHS	0.0535 (0.0442)	0.0383	0.1149
EHT	0.0746 (0.0528)	0.0585	0.1483
OC	0.0003 (0.0002)	0.0005	0.0005

[1] Dermal absorption of NP-TiO_2 was considered negligible.

3.4. *Hazard characterisation and evidence integration (adverse outcomes)*

3.4.1. *Sunscreens*

Evidence was insufficient to assess whether sunscreen use was associated with the adverse outcomes: increase in melanoma and reduction in vitamin D synthesis. The hazard to humans was rated “not classifiable”.

3.4.2. *UV filters*

Local effects (skin irritation and sensitization): Effects in humans were either not reported or occurred in low frequency. No studies of OC or NP-TiO_2 were included for assessment. No irritant or sensitising potential were reported in animal studies of any of the UV filters. The integrated hazard conclusion for all UV filters was “not identified as a hazard to humans”.

Systemic effects: Overall hazard conclusions for systemic toxicity were expressed as DNEL values for the critical endpoint (see 2.10) (mg/kg bw per day): 2.50; 1.13; 2.40; 0.50; and 0.38 for BEMT; BMDBM; EHS; EHT; and OC, respectively. A DNEL value was not derived for NP-TiO_2 (negligible dermal absorption).

3.5. *Conclusions on health protective effects of sunscreens and benefit characterisation*

Health protective effects were present for all outcomes except BCC (little to no effect). The

confidence levels for evidence of health effects and benefit conclusions for the outcomes were as follows: Melanoma: Low, "not classifiable as health protective in humans". Actinic keratosis: moderate, "presumed to be health protective in humans". BCC: Moderate, "not classifiable as health protective in humans". SCC: Moderate, "presumed to be health protective in humans". Immunosuppression: Low, "not classifiable as health protective in humans". PLE: Moderate, "presumed to be health protective in humans", (a single study with a low number of participants).

The overall hazard conclusion for (pre-) skin cancers is: Due to the few, but well-designed and -conducted studies with relatively large populations and a consistent pattern of effect for all skin (pre-) cancers, except BCC, the hazard conclusion was denoted as "presumed". Therefore, VKM concludes that sunscreen use is presumed to protect against certain skin (pre-)cancers. The protection is larger for squamous cell carcinoma and actinic keratosis than for melanoma.

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

Sunscreen and UVR (e.g. from the sun) exposure data were considered uncertain and were not quantified. Only amounts of sunscreen used (3.3.2.) were included.

Sunscreen use is presumed to be beneficial as protection against PLE and certain skin (pre-)cancers. The benefit is larger for SCC and actinic keratosis than for melanoma. There is probably no benefit of sunscreen in protection against BCC.

3.6. *Risk characterisation*

Sunscreens: Since the evidence was insufficient for associations between sunscreen use and increased melanoma and reduction in vitamin D synthesis, the potential risk of these outcomes was not determined.

UV filters: The median (P50) Exp_i was considered to better represent exposure than the mean due to a right-skewed exposure estimate distribution. The 95th percentile was chosen as a representative estimate for high exposure. The risk characterisation ratio (Exp_i/DNEL) was less than 1 for all UV filters both for P50 and P95 (Table 3) (DNEL values: see 3.4.2). Exp_i to NP-TiO_2 did not represent a risk due to negligible absorption. Thus, VKM concluded that the selected UV filters represent little to no risk for adverse health effects.

Table 4. Risk characterisation ratios of the selected UV filters (except NP-TiO_2). Exp_i/DNEL.P50: 50th percentile; P95: 95th percentile.

UV filter	P50/ DNEL	P95/ DNEL
BEMT	0.00	0.00
BMDBM	0.05	0.20
EHS	0.02	0.05
EHT	0.12	0.30
OC	0.00	0.00

3.8. *Risk-benefit conclusion*

VKM concludes that the risk of exposure to the six selected UV filters is negligible since the actual use of these substances is several-fold lower than the amounts that may cause any adverse health effect. The evidence for harmful effects of sunscreens is insufficient to determine risk. Sunscreen use is likely to protect against PLE and certain skin cancers and is beneficial for the general Norwegian population.

4. Data gaps and discussion

More data on UV filter concentrations, their dermal absorption and amounts of sunscreen applied in the population of interest would reduce the uncertainty in the exposure estimate. *In vitro* studies could have contributed to support of a health effect conclusion had validated methods for evaluation been available. Hazards due to other UV filters than those selected in the current assessment could have been different. However, the selected filters were among the ten most frequently used in sunscreens at the time of investigation. Internal exposure to EHS, despite expressed concern by a consumer right organization, did not represent a risk for adverse effects even at the 95th percentile internal exposure.

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Due to the large number of references, only key references (3.5, 3.6) and those not included in VKM et al. 2022 are listed below.

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