Faglig vurdering af foreløbig SCCS vurdering for Homosalat

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Opgavebeskrivelse fra departementet

Departementet ønsker DTU Foods faglige vurdering, af den farevurdering som SCCS har foretaget af Homosalat, og som anvendes som baggrund for risikovurderingen. Særligt ønskes der en vurdering af, om der er en tærskelværdi for stoffet, eller om risikovurderingen af den grund burde være foretaget på et andet grundlag samt om der burde være taget højde for at der kan ske udsættelse for andre stoffer med samme virkningsmekanisme. Hvis muligt kom gerne med bud på, hvordan vurderingerne i givet fald så skulle være foretaget.

Hvis DTU Food ikke er enig med SCCS bedes udarbejdet kommentarer på engelsk, der kan anvendes som udgangspunkt for kommentarer til SCCS på Danmarks vegne. Disse må gerne indeholde bud på evt. andre parametre, som DTU Food mener er essentielle ved en vurdering.

SCCS har i oktober 2020 offentliggjort deres foreløbige vurdering af homosalat (SCCS 2020). Stoffet er mistænkt for at have hormonforstyrrende egenskaber og er på Kommissionens liste over hormonforstyrrende stoffer, der er prioriteret som gruppe A stoffer.

Kommissionen har anmodet SCCS om at vurdere om homosalat er sikkert, når det bruges som et UV-filter i kosmetiske produkter op til en maksimum koncentration på 10%, under hensyntagen til bekymringerne relateret til homosalats potentielle hormonforstyrrende egenskaber.

Herudover skal SCCS vurdere om der er en maksimal koncentration, der betragtes som sikker til brug af Homosalate som et UV-filter i kosmetiske produkter, samt om SCCS har yderligere videnskabelige bekymringer med hensyn til brugen af homosalat i kosmetiske produkter.

Besvarelse

DTU Food har evalueret farevurderingen, der danner baggrund for SCCS' risikovurdering af homosalat. Denne besvarelse har tre dele: den konkrete fare- og risikovurdering af homosalat, problematikken omkring tærskelværdi, samt problematikken omkring udsættelse for andre stoffer med samme virkningsmekanisme.

<u>De overordnede konklusioner er:</u>

- SCCS beregner en margin of safety (MoS) på 17 og da dette er meget lavere end 100, har SCCS konkluderet at homosalat ikke er sikkert at bruge som UV-filter i kosmetik ved koncentrationer op til 10%. De har på den baggrund anbefalet at sænke maksimum koncentrationen til 1.4% homosalate. DTU Food er enig i at en MoS på 17 er meget lavere end 100 og derfor ikke sikker. DTU Food mener dog ikke at denne sænkning fra 10% til 1.4% er tilstrækkeligt for at være sikker.

- Det datamateriale der er tilgængeligt for homosalat giver nogle indikationer for at stoffet har en hormonforstyrrende virkemåde. Det nuværende evidensniveau fra in vivo studier er imidlertid ikke stærkt nok til at vise at stoffet er hormonforstyrrende eller til at sætte et "*point of departure*" baseret på hormonforstyrrende egenskaber til anvendelse i human risikovurdering. Homosalat viser

hormonforstyrrende mekanisme *in vitro*, men er ikke undersøgt *in vivo* i studier der undersøger hormonfølsomme end points og dette bør føre til at man indfører en ekstra usikkerhedsfaktor i risikovurderingen.

- SCCS beregner en margin of safety (MoS) på 17 og da dette er meget lavere end 100, har SCCS konkluderet at homosalate ikke er sikkert at bruge som UV-filter i kosmetik ved koncentrationer op til 10%. De har på den baggrund anbefalet at sænke maksimum koncentrationen til 1.4% homosalate. DTU Food er enig i at en MoS på 17 er meget lavere end 100 og derfor ikke sikker. DTU Food mener dog ikke at denne sænkning fra 10% til 1.4% er tilstrækkeligt for at være sikker.

- Homosalat omdannes til bl.a. salicylsyre (DK EPA, 2015), som er identificeret som et hormonforstyrrende stof og er på den nye ED liste[1] og dette bør tydeliggøres i den reviderede opinion.

- Det er ikke muligt at bevise eller modbevise tilstedeværelse af tærskel for hormonforstyrrende effekt af homosalat, men hvis der tages udgangspunkt i, at der ikke eksisterer en tærskel, vil det være nødvendigt at bruge en alternativ og forbedret tilgang til risikovurdering, fx lineær ekstrapolation til 10^{-5} eller anvendelse af ekstra *assessment* faktorer i størrelsesorden 10-100 (jf. CEHOS 2019).

- For Homosalat vil en ekstra "*mixture assessment faktor*" på f.eks. 10 kunne anvendes for at tage højde for mulige bidrag fra andre stoffer med samme virkemåde. En sådan ekstra faktor vil betyde, at MoS skal være over 1000 for at kunne betragtes som sikkert, i modsætning til default værdi på 100. Dermed vil en MoS på 17 som beregnet for Homosalat være en del under den ønskede MoS og yderligere understøtte konklusionen om at brugen af Homosalat ikke er sikker, og at koncentrationen bør nedsættes endnu mere end de forslåede 1.4%.

The overall conclusions are:

- SCCS calculates a margin of safety (MoS) of 17 and as this is much lower than 100, SCCS has concluded that homosalate is not safe to use as a UV filter in cosmetics at concentrations up to 10%. On this background, they have recommended lowering the maximum concentration to 1.4%. DTU Food agrees that a MoS of 17 is much lower than 100 and therefore not safe. However, DTU Food does not find that this reduction from 10% to 1.4% is sufficient to be safe.

- The data material available for Homosalate gives some indications that the substance shows endocrine disrupting activity. However, the current level of evidence from *in vivo* studies is not strong enough to show that the substance is actually endocrine disrupting or to set a "point of departure" based on endocrine disrupting properties for use in human risk assessment. Homosalate shows endocrine disrupting mechanism *in vitro*, but has not been studied *in vivo* in studies examining endocrine sensitive endpoints and this should lead to the introduction of an additional uncertainty factor in the risk assessment.

- Homosalat is metabolized to e.g. salicylic acid (DK EPA 2015), which has been identified as an endocrine disruptor and is on the new ED list and this should be clarified in the revised opinion from SCCS.

- For homosalate, it is not possible to prove or disprove the existence of a toxicological threshold for endocrine disrupting effect. It is possible that the available data on homosalate are sufficient to identify this substance as an ED. Also, by taking into account that homosalate can metabolize to salicylic acid,

[1] https://edlists.org/substance/salicylic-acid baseret på CEHOS 2018 ED liste rapport evaluering af salicylsyre

which is earlier evaluated to be an ED[2]. However, if no safe threshold exists for the effects of homosalate on the reproductive system, it could be argued that linear extrapolation to 10^{-5} incidence or inclusion of additional ED specific assessment factors of 10-100 would be improve protection of human health (cf. CEHOS 2019).

- For Homosalate, an extra "mixture assessment factor" of e.g. 10 could be used to take into account possible contributions from other substances with the same mode of action. Such an additional factor would mean that the MoS must be above 1000 in order to be considered safe, as opposed to the default value of 100. This would further substantiate the conclusion by SCCS that the use of the substance is not considered safe and that the reduction of concentration from 10% to 1.4% is not sufficient to ensure consumer safety.

Background: Hazard- and risk assessment of Homosalate by SCCS

The SCCS concludes the following (answers to questions below):

1. In light of the data provided and taking under consideration the concerns related to potential endocrine disrupting properties of homosalate, does the SCCS consider homosalate safe when used as a UV-filter in cosmetic products up to a maximum concentration of 10 %?
    - *On the basis of safety assessment of homosalate, and considering the concerns related to potential endocrine disrupting properties, the SCCS has concluded that homosalate is not safe when used as a UV-filter in cosmetic products at concentrations of up to 10%.*
2. Alternatively, what is according to the SCCS, the maximum concentration considered safe for use of homosalate as a UV-filter in cosmetic products?
    - *In the SCCS's opinion, the use of homosalate as a UV filter in cosmetic products is safe for the consumer up to a maximum concentration of 1.4% homosalate in the final product.*
3. Does the SCCS have any further scientific concerns with regard to the use of homosalate in cosmetic products?
    - *It needs to be noted that the SCCS has regarded the currently available evidence for endocrine disrupting properties of homosalate as inconclusive, and at best equivocal. This applies to all of the available data derived from in silico modelling, in vitro tests and in vivo studies, when considered individually or taken together. The SCCS considers that, whilst there are indications from some studies to suggest that homosalate may have endocrine effects, the evidence is not conclusive enough at present to enable deriving a specific endocrine-related toxicological point of departure for use in safety assessment. Exposure to homosalate from other products than those in this Opinion has not been considered. Inhalation toxicity of homosalate was not assessed in this Opinion because no data were provided.*

For the homosalate risk assessment, the SCCS used a threshold approach and selected a LOAEL of 60 mg/kg bw/d, based on the Combined Repeated Dose Toxicity Study with the reproduction/Developmental Toxicity Screening Test (OECD Guideline 422) was used. This LOAEL was based on increased infertility reported without dose-response relationship at control, 60, 120, 300 and 750 mg/kg bw/day with 8, 4, 5, 7 and 3 pregnant females in each group. Since the point of departure is based on a LOAEL, an assessment factor of 3 was added (NOAEL =20). Furthermore, due to lack of information or oral bioavailability, 50% of the administered dose was used as the default oral absorption value, resulting in an adjusted NOAEL of 10 mg/kg bw/day. By comparing with calculated human exposure from the selected cosmetic products

[2] https://edlists.org/substance/salicylic-acid based on CEHOS 2018 ED list report evaluation of salicylic acid https://edlists.org/sites/edlists.org/files/media/document/Salicylic%20acid.pdf

(UV-filter in sunscreens) in question, they calculated a margin of safety (MoS) of 17 (NOAEL (10)/SED (systemic exposure dose) (0.6). Based on this MoS that is much lower than 100, SCCS has concluded that homosalate is not safe when used as a UV-filter in cosmetic products at concentrations of up to 10%. They has lowered the maximum concentration to 1.4% homosalate in the final product.

Other reports on Homosalate

In cosmetic products, the ingredient homosalate (CAS No 118-56-9, EC No 204-260-8) with the chemical names Benzoic acid, 2-hydroxy-, 3,3,5-trimethylcyclohexyl ester and (3,3,5-trimethylcyclohexyl) 2-hydroxybenzoate is currently regulated as a UV-filter in sunscreen products in a concentration up to 10 %. Homosalate is an organic compound that belongs to a class of chemicals called salicylates. Salicylates prevent direct skin exposure to the sun's harmful rays by absorbing ultraviolet (UV) light (Sambandan et al. 2011).

A report by CEHOS (Danish Centre on Endocrine Disrupters) in 2013 entitled "Assessment of the endocrine disrupting potential of 23 UV-filters"[3] previously evaluated the endocrine potential of Homosalate. In vitro data indicating possible endocrine disrupting potential are present, however no adverse effects have been seen in vivo in uterotrophic assays (CEHOS 2013).

In the CEHOS report; "List of Endocrine Disrupting Chemicals" it is concluded that there is solid scientific evidence that salicylic acid is an endocrine disruptor. DTU FOOD finds that; it should be more clearly stated in an update of the SCCS opinion that homosalate is hydrolyzed into salicylic acid (DK EPA, 2015). In the first literature screening in the CEHOS 2018 project Homosalate was excluded from being thorough evaluated, based on only some in vitro data on ED, some environmental relevant literature, and two negative in vivo studies (same studies as the 2013 report). Moreover, the substance was in an ongoing REACH substance evaluation at the time ED list report was written (CEHOS 2018).

DTU FOOD evaluation of SCCS report

The SCCS was asked to consider whether homosalate is viewed as safe when used as a UV-filter in cosmetic products up to a maximum concentration of 10%. The SCCS concluded that Homosalate is not safe at concentrations of up to 10% and lowered the maximum concentration to 1.4% homosalate. It is noted that DTU FOOD did not evaluate the exposure assessment. DTU Food agrees that a MoS of 17 is much lower than 100 and therefore not safe. However, DTU Food does not find that this reduction from 10% to 1.4% is sufficient to be safe.

DTU FOOD finds that for the hazard identification the SCCS has performed a thorough evaluation of all the available information on the ED properties of Homosalate. The overall conclusion on ED effects of homosalate from SCCS is based on details of the data[4] on different levels 1-5 of the conceptual framework (OECD, 2018).

At Level 1(non-testing methods) QSAR gives some indications that homosalate can activate the oestrogen receptor α and act as an antagonist of androgen receptor. At Level 2 (in vitro assays) anti-androgenic and estrogenic activities are reported in *in vitro* studies. Furthermore, some contradictory interactions were

[3] http://www.cend.dk/files/UV-filter-rapport-28022013_40s388pi.pdf

[4] ANSES (January 2018)- Analysis of the most appropriate risk management option (RMOA) for homosalate EC n° 204-260-8 https://echa.europa.eu/documents/10162/ ccaa4d83-f34c-ebe5-1939-b9a4e4536738

seen with the progesterone signaling pathway. At Level 3(*in vivo* assays with data regarding MoA) negative results have been reported from uterotrophic assays performed up to 1000 mg/kg bw/d. However, this assay is only based on an assessment of uterus weight and such a test cannot allow a firm conclusion on all possible estrogenic modes of action. Although this assay has a good sensitivity for strong estrogenic compounds, the sensitivity is lower for weaker estrogenic compounds. Negative results have also been reported in transgenic zebrafish, but this study is not appropriate for drawing a firm conclusion on the mode of action of homosalate. At Level 4: (in vivo assays with data regarding adverse effects) two in vivo studies are available. A 14 day range-finding study is considered inadequate to assess ED-related properties as it investigated limited parameters. The other study is only available to SCCS as a summary of the original study report (OECD TG 422) and is considered to be of limited value to conclude on ED-related properties because the animals were under constant light conditions, which might have affected the reliability of the reported effects. This study has reported some findings that could be linked to an endocrine mediated mode of action. However, no clear trend could be identified in the hormonal fluctuations and there was no effect reported from histopathological examination of the reproductive organs. In addition, possible effects on fertility (increased infertility, sperm changes), development (higher post-implantation) and thyroid (hypertrophy of the follicular epithelium) were identified (only summary in report).

DTU FOOD wants to draw the attention to the fact that this TG 422 study was not performed according to the new version the guideline. Therefore it did not include additional ED endpoints added in the enhanced version of the TG, such as assessment of Anogenital distance, Nipple retention and Thyroid hormones (OECD, 2016). Moreover, no level 5 test (such as EOGRTS, OECD TG 443) have yet been performed for Homosalate (see below in relation to the REACH process).

Overall, the RMOA has indicated that the available data from level 1 and 2 information and the inadequate *in vivo* studies provides indications for an ED potential of homosalate, whereas the available level 3 studies are of limited relevance and do not indicate the potential for ED concern. Despite the poor quality of the *in vivo* studies, findings that could be linked to an endocrine disruption were identified, in particular fluctuations of hormones, sperm changes and effects on the thyroid. These effects raised some concerns regarding ED properties of homosalate.

The SCCS agrees with the conclusions drawn in the French RMOA document that from the currently available dataset, no conclusion can be drawn on the endocrine potential of homosalate. The available data on homosalate provide some indications for potential endocrine effects. However, the current level of evidence is not sufficient to conclusively regard it as an endocrine disrupting substance, or to derive a toxicological point of departure based on endocrine disrupting properties for use in human health risk assessment.

DTU FOOD agrees to these overall conclusions, and the fact that the dossier on homosalate contains no robust data on ED. However, DTU FOOD wants to specify that there for homosalate is *in vitro* studies showing ED MoA. A lack of studies with exposure during sensitive windows (in development), limited sensitivity of the level 3 tests with regard to relevant ED endpoints addressed and power/robustness of study (CEHOS 2019). This needs to be taken into account in the risk assessment with inclusion of additional assessment factors. Moreover, DTU FOOD finds that; it should be more clearly stated in an update of the SCCS opinion that homosalate is hydrolyzed into salicylic acid.

SCCS notes that, in the context of a compliance check process under REACH, the European Chemicals Agency adopted in March 2018 a decision requesting a sub-chronic toxicity study (OECD TG 408), a prenatal developmental toxicity study (OECD TG 414), an extended one-generation reproductive toxicity

study (OECD TG 443), and the identification of degradation products (ECHA decision 50 CCH-D-2114386909-26-01/F).

Moreover, an appeal was filed against this decision (Notice of appeal in Case No. A-009-2018) and a decision was adopted by the ECHA Board of Appeal on 18 August 2020. The Board of Appeal dismissed the appeal and decided that the information required by the Contested Decision must be provided by 25 February 2024. The Board of Appeal found that the REACH Regulation requires registrants to perform studies on vertebrate animals even if the substance is used exclusively as an ingredient in cosmetic products.

SCCS mentioned in the draft opinion that in view of the above-mentioned requests, new data may become available after finalization of this SCCS Opinion and may trigger a new request for SCCS assessment. DTU FOOD agrees to this as the above mentioned studies in animals will provide assessment of more sensitive endpoints for ED. This is especially in relation to the EOGRTS (OECD TG 443) which is the preferable test for detecting endocrine disruption because it provides an evaluation of a number of endocrine endpoints in the juvenile and adult F1, which are not included in the two-generation study (OECD TG 416) adopted in 2001 (OECD, 2018). Also the TG 414 guideline have in 2018 been enhanced with more ED sensitive endpoints (Thyroid hormones in dams and Anogenital distance in all fetuses).

Considerations on potential lack of threshold for endocrine disrupting chemicals

For the homosalate risk assessment, the SCCS used a threshold approach and selected a LOAEL of 60 mg/kg bw/d, based on the Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OECD Guideline 422) was used. Since the point of departure is based on a LOAEL, an assessment factor of 3 was added (NOAEL =20). Furthermore, due to lack of information or oral bioavailability, 50% of the administered dose was used as the default oral absorption value, resulting in an adjusted NOAEL of 10 mg/kg bw/day. By comparing with calculated human exposure from the selected cosmetic products (UV-filter in sunscreens) in question, they calculated a margin of safety (MoS) of 17 (NOAEL (10)/SED(0.6).

There are however a number of recent scientific and regulatory reports suggesting that risk-assessment of endocrine disrupting chemicals should be done differently than most other chemicals (CEHOS 2019, Demenix et al 2020). In 2019, ED researchers and risk assessors from European authorities drew up recommendations on uncertainties related to the setting of acceptable levels of ED substances. Recommendations include 1) the use of additional uncertainty factors for EDs, and 2) use a non-threshold approach when evaluating ED substances when no knowledge on presence or absence of a threshold is present (CEHOS 2019).

Re.1: Additional uncertainty factors for EDs could be included to better account for lack of exposure during sensitive periods, lack of endocrine sensitive endpoints in the performed studies, irreversible and delayed effects of exposure occurs during critical developmental windows.

For homosalate, DTU FOOD proposes that the issue of including additional uncertainty factors should be addressed by SCCS in the final opinion for the studies where effects were not seen with exposure in critical developmental windows or when sensitive endpoints for ED was not added. This should be done while waiting for the above-mentioned requests of *in vivo* studies in the REACH process.

Re.2: Despite further discussions in recent years there is still no consensus in the scientific community on whether the toxicological principle of a ‘safe threshold’, (i.e. a dose below which no adverse effect is expected to occur) is applicable in assessing the safety of EDs (EC 2020b). In 2019, the European

Parliament has passed a non-binding resolution asking the European Commission for a more coherent regulations of endocrine disruptors in the EU. One of the points adapted in this regulation called on the Commission to: *draw up legislative proposals no later than June 2020 to insert specific provisions on EDCs into Directive 2009/48/EC, similar to those on CMR substances but without any reference to thresholds of classification, as such thresholds are not applicable for EDCs* **(**Parliament, 2019**)**. The issue of toxicological threshold is mentioned in the Commission Staff working document on the *fitness check* on Endocrine disrupters (EC 2020b). Here, the different opinions among authorities and experts about the ability to demonstrate safe or unsafe uses of EDs using available methods in a risk assessment are discussed. It is noted that at EU level, agencies and scientific committees may in principle conclude on a level below which no risk is identified, if the evidence for a specific substance allows a threshold to be established (EC 2020a**).**

In the report by CEHOS 2019, one of two approaches for the derivation of references levels (DMEL) are recommended, i.e. 1) linear extrapolation (to e.g. 10^{-5} or 10^{-6} incidence) or 2) derivation of a reference dose using additional factors covering specific uncertainties related to assessment of ED including also as default an additional ED assessment factor of 10-100. Both approaches have strengths and limitations that include non-scientific issues (e.g. feasibility and risk level considered tolerable by risk managers).

For homosalate, it is not possible to prove or disprove the existence of a toxicological threshold. It is possible that the available data on homosalate are sufficient to identify this substance as an ED. Also, by taking into account that homosalate can metabolize to salicylic acid, which is earlier evaluated to be an ED[5]. However, if no safe threshold exists for the effects of homosalate on the reproductive system, it could be argued that linear extrapolation to 10^{-5} incidence or inclusion of additional ED specific assessment factors of 10-100 would be improve protection of human health.

Mixture risk assessment

SCCS mentions in the opinion that even though homosalate is mainly reported to be used as a UV filter in sunscreen product, use in other cosmetic products has been reported to occur occasionally. Therefore, the SCCS has also calculated safety of homosalate from combined use in sunscreen products, hand cream and face cream.

DTU FOOD finds this insufficient and propose that risk assessment of Homosalate should also take into account the exposure from other sources and to other compounds having similar MoA as the substances evaluated. A key concern is the cumulative effects that endocrine disruptors could have when mixed in consumer products.

In the European Commission communication on a new Chemicals Strategy of October 2020, it is stated that scientific consensus is emerging that the effect of chemical mixtures needs to be integrated more generally into chemical risk assessments. Therefore, the possibility of using a mixture assessment factor (MAF) is introduced (EC 2020a).

The MAF concept was discussed at a workshop in October 2020[6] concluding that a single, generic MAF would be a pragmatic, effective and feasible way forward under REACH and should be pursued. A MAF will be lowering the overall chemical pressure, which is a fundamental aspect of this approach. Introducing a MAF (in REACH or other legislations) will be a political decision, but an Impact

[5] https://edlists.org/substance/salicylic-acid

[6] 2nd Workshop on a pragmatic approach to address the risk from combined exposure to non-intentional mixtures of chemicals – REACH as an example, 27-28 October 2020, https://www.chemischestoffengoedgeregeld.nl/content/2nd-workshop-pragmatic-approach-address-risk-combined-exposure-non-intentional-mixtures

Assessment will provide a solid basis for deciding the magnitude of the MAF. In the absence of a political decision on the magnitude of the MAF, it is not currently possible to carry out risk assessment of single chemicals while taking into account the contribution of other substances with similar mode of action.

In an attempt to take into account the contribution of other substances before such a MAF has been decided, we propose – as an additional consumer protection – to include a provisional MAF (pMAF) of 10. The number 10 is arbitrary, but might be considered sufficient for consumer protection in many cases until further scientific evidence has been evaluated.

For Homosalate the use of an additional factor of 10 would lead to a conclusion that the MoS must be above 1000 in order to be considered safe, as opposed to the default value of 100. This would further substantiate the conclusion by SCCS that the use of the substance is not considered safe and that the reduction of concentration from 10% to 1.4% is not sufficient to ensure consumer safety.

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