Faglig vurdering af foreløbig SCCS vurdering for resorcinol

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Opgavebeskrivelse

Departementet ønsker DTU Foods faglige vurdering, af den farevurdering som SCCS har foretaget, 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 gerne med bud på, hvordan vurderingerne i givet fald så skulle være foretaget. Hvis DTU Food ikke er enig med SCCS bedes udarbejdes 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 resorcinol. 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 Resorcinol er sikkert, når det bruges som et oxidativt hårfarve i produkter beregnet til hår og øjenvipper op til 1,25% og op til 0,5% i hårcremer og shampoo.
I et alternativt spørgsmål til SCCS bedes de vurdere om der er en maksimal koncentration, der kan betragtes som sikker ved brug af Resorcinol som et oxidativt hårfarve i produkter beregnet til hår og øjenvipper og til hårcremer og shampoo.
Ydermere bliver SCCS bedt om at svare på om de har yderligere videnskabelige bekymringer med hensyn til brugen af Resorcinol i kosmetiske produkter.

Besvarelse

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

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

- DTU FOOD vurderer at resorcinol er thyreoidea-hormonforstyrrende, hvilket også konkluderes af SCCS. NOAEL værdien for thyreoidea-forstyrrelser bliver af SCCS vurderet til at være 173 mg/kg bw/dag. Ved denne dosis ses nogle få signifikante effekter på thyroid hormonsystemet, hvorfor DTU FOOD vurderer at den lavere dosis på ca. 60 mg/kg burde blive betragtet som NOAEL for thyreoidea effekter.

-Ved udregning af MoS (Margin of Safety) bruger SCCS en NOAEL på 80 mg bw/kg/dag, ud fra skadelige effekter set i repeated dose studier samt prænatal toksicitets studier. Ved brug af denne

NOAEL vurderes MoS at være 4000. Ud fra traditionelle toksikologiske principper (MOS>100 = sikker eksponering), ville den ovenfor nævnte brug af resorcinol ikke udgøre en risiko.

- DTU FOOD sætter dog spørgsmål ved, om det for resorcinol er retvisende at anvende en NOAEL fra et oralt studie, idet den humane eksponeringen i overvejende grad er dermal, og resorcinols metabolisme og effekter ser ud til at blive markant påvirket af eksponeringsvejen.

- Ved risikovurdering af hormonforstyrrende stoffer er det anbefalet at tage ekstra sikkerhedsfaktorer i brug. Det er ikke muligt at bevise eller modbevise tilstedeværelse af tærskel for hormonforstyrrende effekt af resorcinol, 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). Det betyder, at MoS skal være over 1000-10.000 for at anvendelsen af stoffet kan betragtes som sikker. I resorcinols tilfælde betyder dette, at brugen ikke kan betragtes som sikker ved det højeste beskyttelsesniveau, idet den beregnede MoS på 4000 er mindre end 10.000.

- Mange stoffer i vores miljø kan påvirke thyreoidea-hormonsystemet. For resorcinol vil en ekstra "mixture assessment faktor" (MAF) på fx 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. For resorcinol vil en MoS på 4000 stadig blive betragtet som sikker når man medregner co-eksponering for andre stoffer med samme virkningsmekanisme.

- Hvis der i risikovurderingen af resorcinol både tages højde for eksponering for andre stoffer med thyreoidea-hormonforstyrrende mekanisme ved at inkludere en MAF, samt inkluderes ekstra usikkerhedsfaktorer grundet resorcinols hormonforstyrrende egenskaber, er den beregnede MoS værdi på 4000 ikke længere ensbetydende med manglende human risiko.

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 Resorcinol, does the SCCS consider Resorcinol safe when used as an oxidative hair dye in products intended for hair and eyelashes up to 1.25 % and up to 0.5 % in hair lotions and shampoos? *Keeping in view the evidence on endocrine disrupting properties of resorcinol, the SCCS assessment shows that resorcinol is safe when used as an oxidative hair dye in products intended for hair and eyelashes up to 1.25 % and up to 0.5 % in hair lotions and shampoos.*

2. Alternatively, what is according to the SCCS, the maximum concentration considered safe for use of Resorcinol as an oxidative hair dye in products intended for hair and eyelashes and for hair lotions and shampoos? *This is not answered by SCCS – probably because they conclude that the use of resorcinol evaluated in the previous question, is safe*

3. Does the SCCS have any further scientific concerns with regard to the use of Resorcinol in cosmetic products? *Resorcinol is a moderate skin sensitiser based on data from animal studies. Clinical studies show that the frequency of contact sensitisation in humans is low*.

DTU FOOD's evaluation of the SCCS risk assessment

The SCCS was asked to consider whether Resorcinol is viewed as safe when used as an oxidative hair dye in products intended for hair and eyelashes up to 1.25 % and up to 0.5 % in hair lotions and shampoo, in view of its possible endocrine disrupting properties. The SCCS concluded that based on their assessment resorcinol is safe when used in the above mentioned concentrations.

It is noted that DTU FOOD did not evaluate the exposure assessment. DTU FOOD finds that the SCCS has evaluated all relevant studies related to the endocrine disrupting properties of resorcinol, and applaud that they have also included conclusions from the CEHOS (2012) report, as well as the conclusions from the ECHA substance evaluation (ECHA 2017) and the French proposal for identification of resorcinol as a substance of very high concern (SVHC) (ECHA 2020a). They also included the information that SVHC proposal was discussed at an ECHA Member State Committee (MSC) meeting in June 2020, and that it here it was acknowledged by all member states that there is scientific evidence that resorcinol is an endocrine disruptor, as defined by the World Health Organization. However the MSC did not unanimously support the proposal to identify resorcinol as an SVHC (ECHA 2020b).
The SCCS report concurs with the CEHOS (2012) and ECHA (2020a) conclusions that resorcinol exerts anti-thyroid effects. However, the SCCS report specifies that while a clear level of exposure needed for such an effect cannot be derived from the available studies in humans, most of these studies point to a relatively high level of exposure. This indicates that the SCC finds that these effect may not occur at human relevant exposure levels.

When focusing on the animal studies investigating thyroid disrupting effects of resorcinol, a rat 2-generation study (USR 2005), with exposure through drinking water, has been chosen as the key study. In this study a large number of thyroid related endpoints in both parental animals and offspring were assessed at different ages, and the SCCS identified the highest tested dose (3000 g/L, corresponding to 173 mg/kg bw/day) as the NOAEL. Some statistically significant changes of thyroid function were reported at this dose, but based on the SCCS's evaluation their biological relevance was considered implausible, they were viewed as not test article-related or not considered adverse.
DTU FOOD does not agree with this conclusion, and finds that because of the significant effects on some thyroid endpoints observed at the highest dose of 173 mg/kg/day, this dose should be identified as the LOAEL, whereas the NOAEL should be the dose of 1000 g/L, corresponding to approximately 80 mg/kg bw/day.

In order do a proper risk assessment, the SCCS evaluated not only studies investigating thyroid disrupting properties of resorcinol, but also reviewed other toxicity results. Based on this evaluation they ended up deciding on a NOAEL of 80 mg/kg/day, for use in the Margin of Safety (MoS) calculation. This NOAEL was based on maternal effects in a prenatal developmental toxicity study and adverse effect seen at higher doses in a 13-week toxicity study (SCCS 2020). By comparing the NOAEL of 80 mg/kg bw/day with a calculated human exposure from the cosmetic products in question, the SCCS reached a MoS of 4000.
From a traditional toxicological point of view (MOS>100 = safe exposure), the use of resorcinol in the selected products and concentrations would be viewed as not posing a risk. DTU Food however finds that there are several additional factors that need to be taken into account in this risk assessment, as discussed below.

First of all, there seems to be quite a large difference in the severity of the effects observed between human and experimental data, as well as differences in the effects seen between different animal studies. Comparing the severity of effects between rodents and humans, a higher sensitivity of humans or certain humans cannot be excluded. The discrepancies between different experimental results seems to be dependent on the route of administration, and possibly also vehicle. These differences can lead to potential differences in toxicokinetics and internal exposures. It has thus been shown that oral exposures lead to very fast metabolism of resorcinol in rats, whereas this may not be the case with other exposure routes (dermal, inhalation or subcutaneous), but the differences have not yet been fully characterized. Hence, large uncertainties remain on the level of systemic exposure to resorcinol that induces effects on the thyroid and on the level of systemic exposure to resorcinol after different routes of exposure. Since dermal exposure is the main exposure route in humans, the comparison of a NOAEL from an oral study in rats, with a human exposure dose derived from dermal could introduce some additional uncertainty in the MoS calculation. DTU FOOD however acknowledges that no well performed and well reported rodent studies with dermal/subcutaneous or inhalation exposure were available.

Considerations on potential lack of threshold for endocrine disrupting chemicals

As described above, the SCCS calculated a margin of safety (MoS) of 4000, based on the NOAEL of 80 mg/kg bw/day the. In performing this risk assessment the SCCS used a threshold approach. This has historically been the normal procedure for assessing the risk of chemicals that were not identified as genotoxic carcinogen. 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 chemical (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. These recommendations included 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 occurring during critical developmental windows.
For resorcinol the issue of including additional uncertainty factors could be relevant. The two-generation study which, both by ECHA (2017) and the SCCS was regarded as the key study for the investigation of thyroid disrupting effects, includes measurement of a number of thyroid related endpoints at several different life stages. It could therefore be argued that inclusion of an additional ED assessment factor would not be needed in this specific case. There could however in the future be performed new studies using other dosing regiments (e.g. dermal exposure or inhalation), other test species, lower iodine concentrations in the feed, or even other yet unidentified endpoints for thyroid hormone disruption which could turn out to be more sensitive towards the endocrine disrupting properties of resorcinol, than the presently obtained knowledge. Therefore addition of an ED assessment factor could also be applicable in this case.

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* (European Parliament, 2019). The issue of toxicological threshold is mentioned in the Commission Staff working document on the *fitness check* on Endocrine disrupters (Oct. 2020). 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 2020b).

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). In relation to interpretation of MoS calculation, for substances where ED specific additional assessment factors of 10-100 are proposed, the lowest acceptable MoS value would be 1000 to 10.000

For resorcinol it is not possible to prove or disprove the existence of a toxicological threshold. It is possible that the available data on resorcinol are sufficient to identify this substance as an ED. However, if no safe threshold exists for the effects of resorcinol on the thyroid hormone system, it could be argued that linear extrapolation to 10^{-5} incidence would be the best way to protect human health. This would lead to the conclusion that exposure is not considered safe at the highest level of protection, i.e. a requirement of a MoS of >10.000.

Mixture risk assessment

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 (EC2020a).

The MAF was discussed at a workshop in October 2020[1] 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 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)

[1] 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

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 resorcinol the use of an additional factor of 10 would lead to a conclusion that the MoS would be reduced 10-fold from 4000 to 400.
In cases where the use of a MAF of 10 is considered relevant, the cut-off for the lowest acceptable MoS would be increased from the default of 100 to a value of 1000. In the case of resorcinol, the MoS of 4000 would still be considered safe even if taking into account co-exposure to substances with similar effects.

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