Faglig vurdering af foreløbig SCCS vurdering for octocrylene

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Publication date:
2021

Document Version
Publisher's PDF, also known as Version of record

/ MAAP

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Opgavebeskrivelse

Departementet for ministeriet for Fødevarer, Landbrug og Fiskeri ønsker DTU Fødevareinstituttets faglige vurdering, af den farevurdering som SCCS har foretaget (SCCS 2021), som baggrund for en risikovurdering. Desuden ønskes der en vurdering af, om der er en tærskelværdi for stofferne og om risikovurderingen af den grund burde være foretaget på et andet grundlag, samt en vurdering af 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 skulle være foretaget. Derudover ønskes en vurdering af, om der er taget højde for de kilder der er fra andre kosmetiske produkter og fra andre kilder eksempelvis andre forbrugerprodukter, lægemidler, indeklima, fødevare og miljø.
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 offentliggjort deres foreløbige vurdering af stoffet octocrylene, hvor sikkerheden ved brug i kosmetiske produkter er vurderet på baggrund af anmodning fra Kommissionen (SCCS 2021). Octocrylene er mistænkt for at være hormonforstyrrende og er på Kommissionens liste over hormonforstyrrende stoffer, der er prioriteret som gruppe A stof. Kommissionen har anmodet SCCS om at vurdere om octocrylene er sikkert, når det bruges som UV-filter i kosmetiske produkter i koncentration op til 10% (som syre), på baggrund af de bekymringer, der er forbundet med stoffets potentielle hormonforstyrrende egenskaber. Herudover er SCCS blevet bedt om at vurdere om der er en maksimal koncentration, der betragtes som sikker til brug af octocrylene som UV-filter i kosmetiske produkter samt om SCCS har yderligere videnskabelige bekymringer med hensyn til brugen af octocrylene i kosmetiske produkter.

Besvarelse

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

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

- SCCS finder, at NOAEL for octocrylene er på 153 mg bw/kg/dag. DTU FOOD vurderer, at det ikke er er den korrekte NOAEL værdi, da der ved denne dosis observeres histopatologiske forandringer i skjoldbruskkirtelen samt øget vægt af kirtlen.

- SCCS medtager ikke disse fund på skjoldbruskkirtlen i rotter, da de anser dem som adaptive og ikke 'adverse', og ikke relevante for mennesker.

- DTU FOOD vurderer, baseret på ECHA/EFSA's vejledning for identificering af hormonforstyrrende stoffer (ECHA/EFSA 2018, appendix A) at de fundne effekter på skjoldbruskkirtlen bør ses som 'adverse', samt at disse fund er relevante at inddrage ift. human farevurdering og bør føre til en nedsættelse af NOAEL værdien fra 153mg/kg til 55 mg/kg/dag. En sådan ændring vil påvirke alle de konklusioner SCCS drager omkring sikre koncentrationer af octocrylene i kosmetiske produkter.

- 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 octocrylene, 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 octocrylenes tilfælde betyder dette, at brugen ikke kan betragtes som sikker ved det højeste beskyttelsesniveau, idet den beregnede MoS (også med DTU-foreslået NOAEL) er mindre end 10.000.

- Mange stoffer i vores miljø kan påvirke thyreoidea-hormonsystemet. For octocrylene 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.

- Hvis der i risikovurderingen af octocrylene både tages højde for eksponering for andre stoffer med thyreoidea-hormonforstyrrende virkemåde ved at inkludere en MAF, samt inkluderes ekstra usikkerhedsfaktorer grundet octocrylenes hormonforstyrrende egenskaber, vil de beregnede MoS værdier være lavere end hvad der kan betragtes som sikre.

Background: Hazard- and risk assessment of Octocrylene by SCCS

The SCCS concludes the following (answers to questions *in italic*):

1. In light of the data provided and taking under consideration the concerns related to potential endocrine disrupting properties of Octocrylene, does the SCCS consider Octocrylene safe when used as a UV-filter in cosmetic products up to a maximum concentration of 10% (as acid)?
On the basis of safety assessment, and considering the concerns related to potential endocrine disrupting properties of Octocrylene (CAS No 6197-30-4), the SCCS considers that it is safe at concentrations of up to 10% when used individually or together as a UV-filter in cosmetic products, i.e. in sunscreen cream/lotion, sunscreen pump spray, face cream, hand cream and lipstick. Also, the use of sunscreen propellant spray is considered safe at concentrations of up to 10% when used individually but not safe when used together with face cream, hand cream, and lipstick.

2. Alternatively, what is according to the SCCS the maximum concentration considered safe for use of Octocrylene as a UV-filter in cosmetic products? *The use of Octocrylene in sunscreen propellant spray is considered safe when its concentration does not exceed 9% when used together with face cream, hand cream and lipstick containing 10% Octocrylene*.

3. Does the SCCS have any further scientific concerns with regard to the use of Octocrylene in cosmetic products? *The SCCS considers that, whilst there are indications from some in vivo studies to suggest that Octocrylene 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. Contact sensitisation to Octocrylene has been reported, however, taking into consideration the widespread use of Octocrylene in cosmetic products, the number of reported cases of allergic contact dermatitis appears to be negligible. It should be noted that occurrence of photoallergy to Octocrylene is strongly related to a previous photoallergy to topical ketoprofen. Exposure to Octocrylene from other products than those in this Opinion has not been considered.*

DTU FOOD's evaluation of the SCCS risk assessment

In their report, the SCCS has evaluated which concentrations of Octocrylene can be regarded as safe, both for separate product types and for aggregated exposure (SCCS 2021). For their MoS calculations the SCCS has identified a NOAEL of 153 mg/kg bw/day.
DTU FOOD has reviewed the available toxicity data for Octocrylene and does not agree to the NOAEL identified by the SCCS. This changes the conclusions that can be reached regarding the MoS calculations. It is noted that DTU FOOD has not evaluated the exposure assessment performed by the SCCS.

DTU FOOD finds that the toxicity data clearly shows that Octocrylene is a thyroid hormone system disrupting chemical. Below is a summary of the studies showing thyroid hormone system disrupting effects.

In a recently performed repeated dose oral toxicity study (BASF SE 2019), Octocrylene was provided via feed for 14 or 28 days, to Wistar rats (n=5/sex) at dose levels of 0, 1000ppm (63-72 mg/kg),

3000ppm (188-215 mg/kg) and 10.000ppm (630-720 mg/kg). In the high dose group (~670 mg/kg bw/day), adverse exposure-related effects were seen on the thyroid hormone system after both 14 and 28 days. About half of the animals showed hypertrophy/ hyperplasia of the follicular cells and altered colloid. Also TSH concentrations were significantly increased, when measured on days 14, 21 and 29, whereas no significant changes occurred for T3 and T4.
In the same study, a mechanistic investigation showed an induction of liver enzymes (PROD, BROD, T4-specific UDP-glucuronosyltransferase) accelerating the thyroid hormone clearance in both sexes. As a result, a compensating positive feedback mechanism was installed, leading to higher TSH levels and hypertrophy/hyperplasia of follicular thyroid gland cells.
In the mid dose group (~200 mg/kg bw/day) the clinical and pathological examinations showed no significant treatment–related adverse effects on the thyroid gland, whereas the mechanistic investigations revealed effects similar to the ones observed in the high dose animals, including increased PROD- ,BROD- and T4-specific UDP-glucuronosyltransferase-activities. These results indicate that at the dose level of 3000 ppm, Octocrylene also affected the thyroid hormone system of the rats, but not enough to result in observable adverse effects after 14 and 28 days of exposure.

In a repeated dose toxicity study with 90-day exposure (BASF AG 1993), adverse effects on the thyroid hormone system were observed in male and female Wistar rats (n=10/sex). Octocrylene was administered at doses of 750, 2250, 4500 and 15000 ppm in the diet, corresponding to approx. 58, 175, 340, 1085 mg/kg bw/day. A treatment-related hypertrophy of the follicular epithelium of the thyroid gland was observed in the two high-dose groups (340 and 1085 mg/kg bw/day). An increase in the incidence of hypertrophic cells in the pituitary gland (thyroidectomy cells) was also seen, suggesting interference in the homeostatic feedback mechanism. Taken together, the observed effects on thyroid and pituitary gland were considered to have occurred as a secondary consequence of hepatic enzyme induction. Based upon the above-mentioned findings, the NOAEL under the conditions of this study was set at 175 mg/kg bw/day.

Two newly performed reproductive toxicity studies further confirm that Octocrylene has thyroid hormone system disrupting properties, and one of them shows that adverse thyroid effects can occur at even lower doses that shown in the repeated dose toxicity studies.

A dose-range-finding study (Triskelion B.V. (2018)), was performed in Wistar rats (n=12/sex/dose) prior to performance of an extended one-generation reproductive toxicity study (EOGRTS). Males were exposed for 42 days (premating, mating and post-mating) and females for approximately 13 weeks (premating, mating, gestation and lactation until weaning) to oral doses of 0, 5000 ppm (279-399 mg/kg/day) or 15000 ppm (812-1271 mg/kg). Higher thyroid weights were observed in males and females of both treatment groups. The low- and high-dose animals showed activated appearance of the thyroid gland (18/24 low-dose animals and 21/24 high-dose animals) in comparison with the controls. It was characterized by loss of colloid from the follicles, hypertrophy and hyperplasia of follicular epithelial cells.

Also the EOGRTS (OECD 443) (Triskelion B.V. (2019)), the study on which the SCCS based it's NOAEL value, showed clear evidence of thyroid disruption. In this study, using 28 rat/sex/dose, parental animals were exposed during premating, mating, gestation, lactation and the feed exposure continued in the F1 offspring after weaning in Cohorts 1A, 1B , 2A and 2B. The tested doses were 750 ppm (55-58 mg/kg), 2100ppm (153-163 mg/kg) and 7000 ppm (534-550 mg/kg bw).

In the high dose group, a 25-30% increase in thyroid weights was observed in male and female animals of the parental generation (F0) as well as in the adult offspring (Cohort 1A). At this dose, terminal body weights were decreased by ~5 to 10% and the relative liver weights were increased by ~20-30%. The decreased terminal body weights were by the SCCS considered to be adverse, whereas the increased liver and thyroid weights were considered to be adaptive.
Octocrylene exposure also caused activated appearance of the thyroid gland. This histopathological effect was seen in **high dose parental animals (F0) and offspring (Cohort 1A)** but also in the **F0-generation animals from the mid-dose group**. The changes were characterized by loss of colloid from the follicles and hypertrophy and hyperplasia of follicular epithelial cells. These findings were by the SCCS considered to be related to treatment but to be adaptive changes in rats, rather than adverse.
In accordance with the findings from previous studies, no significant effects were observed on T4 levels in any of the dose groups at any examined age. Also, no statistically significant effects were observed on TSH concentrations in animals of the F0-generation or in adult animals of Cohort 1A in any dose group. Since the animals in the high dose group had clearly increased thyroid gland weights and altered histopathology, an increase in TSH levels would be expected. It may be speculated that the lack of statistically significant effects on TSH levels could reflect low sensitivity of the used TSH assay.

Based on finding of decreased parental and offspring body weights, a lower number of implantation sites and lower number of pups delivered at the highest exposure dose (534 mg/kg bw/day) the NOAEL in the EOGRTS for parental systemic toxicity, reproductive performance, and offspring development was set at 2100 ppm (153 mg/kg bw/day). This NOAEL was used by the SCCS as the point of departure in their safety evaluation. Thus, the statistically significant increases in thyroid gland weight and increased incidence of activated appearance of the gland, seen at the mid dose (153 mg/kg/day) was not seen as an adverse effect and not included in the setting of the LOAEL/NOAEL.

In the Octocrylene report the SCCS states that humans, unlike rodents, possess a T4 binding protein that greatly reduces susceptibility to plasma T4 depletion and thyroid stimulation, caused by increased liver-related thyroid hormone clearance, and that the effects seen in rats therefore cannot be directly extrapolated to humans.

Contrary to this statement, the ECHA/EFSA guidance for identification of endocrine disrupting chemicals (ECHA/EFSA 2018, appendix A) proposes a very different approach when evaluating the relevance of thyroid data from rodent studies. The guidance proposes that the following assumptions should be applied when interpreting data [related to thyroid disruption] from experimental animals:
1) Substances inducing histopathological changes (i.e. follicular cell hypertrophy and/or hyperplasia and/or neoplasia) in the thyroid, with or without changes in the circulating levels of THs, would pose a hazard for human thyroid hormone insufficiency in adults as well as pre- and post-natal neurological development of offspring.
2) Substances that alter the circulating levels of T3 and/or T4 without histopathological findings would still present a potential concern for neurodevelopment.
3) In the absence of substance-specific data which provide proof of the contrary, humans and rodents are considered to be equally sensitive to thyroid-disruption (including cases where liver enzyme induction is responsible for increased TH clearance).

Hence, the ECHA/EFSA guidance specifically states that in cases where a thyroid hormone disrupting effects is caused by liver enzyme induction (as is very likely the case with Octocrylene) significant effects on the thyroid gland weight and histology and TSH levels should not be dismissed as irrelevant to humans, but the effects should instead be viewed as equally sensitive in rats and humans and as potential hazards for human thyroid hormone insufficient and developmental neurotoxicity.

DTU Food finds that by following the recommendations set out in the ECHA/EFA guidance the NOAEL of the EOGRTS should have been set at 55 mg/kg bw/day, rather than at 153 mg/kg bw/day.

For their MoS calculations the SCCS used information that oral bioavailability of Octocrylene is 50%, and based on this provided an adjusted NOAEL of 76.5 mg/kg bw/day.
In order to derive a MoS of 100 for aggregated exposure for lipstick, face cream, hand cream and sunscreen as a propellant spray, the total systemic exposure dose (SED) should be maximally 0.765 mg/kg bw/day. Linear extrapolation of the SED for 10% Octocrylene shows that this can be achieved by reducing the Octocrylene concentration from 10% to 9% in the propellant spray. This changes the MoS for aggregated exposure (to lipstick, face cream, hand crème and sunscreen propellant spray) from 92 to 101.

Had the ECHA/EFSA guidance been followed regarding consideration of thyroid effects as being adverse and human relevant, a NOAEL of 55 mg/kg bw/day would have been set on the bases of the results from the EOGRTS study. Then the adjusted NOAEL would have been 27,5 mg/kg bw/day. Such a drastic change would alter all of the MoS calculations, as well as the conclusions as to the safety of Octocrylene, for both individual and aggregate exposures. A reduction of the NOAEL by a factor 2.8 will thus lead to a reduction of MoS values by a factor 2.8. For several of the presented exposure scenarios, the resulting MoS values would then be below 100 and not be considered safe.

DTU Food further finds that there are several additional factors that need to be taken into account in this risk assessment, as discussed below.

Considerations on potential lack of threshold for endocrine disrupting chemicals

In performing their 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.

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 Octocrylene it is not possible to prove or disprove the existence of a toxicological threshold. It is possible that the available data on Octocrylene are sufficient to identify this substance as an ED. However, if no safe threshold exists for the effects of Octocrylene 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

[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

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.
The use of an additional factor of 10 would lead to a conclusion that the MoS (for single and aggregate expose) would be reduced 10-fold .
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.

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