Faglig vurdering af foreløbig SCCS vurdering for Propylparaben

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NOTAT: Faglig vurdering af foreløbig SCCS vurdering for Propylparaben

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 stofferne, 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.

Kommissionen har anmodet SCCS om at vurdere om Propylparaben er sikkert, når det anvendes som konserveringsmiddel i kosmetiske produkter op til en maksimal koncentration på 0,14% på baggrund af de bekymringer, der er forbundet med Propylparabens potentielle hormonforstyrrende egenskaber. Herudover skal SCCS vurdere den maksimale koncentration af propylparaben, der betragtes som sikker som konserveringsmiddel i kosmetiske produkter, samt om SCCS har yderligere videnskabelige bekymringer med hensyn til brugen af Propylparaben i kosmetiske produkter.

Besvarelse

DTU Food har evalueret farevurderingen, der danner baggrund for SCCS' risikovurdering af propylparaben. Denne besvarelse har tre dele: den konkrete fare- og risikovurdering af propylparaben, problematikken omkring tærskelværdi, samt problematikken omkring udsættelse for andre stoffer med samme virkningsmekanisme. Det skal bemærkes, at DTU ikke har haft adgang til alle relevante studierapporter.

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

- DTU Food er overordnet set enige i konklusioner vedrørende toksikokinetik og metabolisme, men har ikke vurderet eksponeringsberegninger foretaget af SCCS. Det noteres, at den tilladte grænse på 0.14% (som syre) gælder summen af butylparaben og propylparaben.

- DTU Food er ikke enig i farevurderingen foretaget af SCCS. DTU finder, at de præsenterede studier viser effekter, som kan anvendes til at fastsætte NOAEL/LOAEL for propylparaben. Dermed bør NOAEL på 1000 mg/kg bw/dag (højeste testede dosis i flere studier) revideres og justeres til et lavere niveau. DTU er dermed også uenig i den beregnede Margin of Safety (MoS) på >12.000.

- DTU Food mener, at de observerede effekter i dyr eksponeret under udviklingen støtter en mulig hormonforstyrrende effekt af propylparaben. Der er begrænsede data tilgængelige ved denne vurdering af propylparaben, men DTU har tidligere (2012) identificeret propylparaben som mistænkt hormonforstyrrende stof ifølge WHO kriterier og ud fra de dengang tilgængelige data.

- Det er ikke muligt at bevise eller modbevise tilstedeværelse af tærskel for hormonforstyrrende effekt af propylparaben, 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 (CEHOS 2019).

- For propylparaben vil en ekstra "mixture assessment faktor" 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.

Background: Hazard- and risk assessment of propylparaben by SCCS

SCCS describes that use of propylparaben is allowed in cosmetic products at up to 0.14% as acid and as the sum of propyl- and butylparaben. Propylparaben is not allowed as additive in foods in EU, but can be present in pharmaceutical products at concentrations that may correspond to up to 50-140 mg/day. From cosmetics, maximum use of propylparaben in all products lead to systemic exposure dose (SED) of 0.08 and 0.03 mg/kg bw/d in a worst-case and a realistic scenarios. Another exposure estimation on child exposure is cited with a reported exposure dose of 1 mg/kg bw/day in children (Gosens et al. 2014).

The toxicity evaluation considered NOAELs of 980 mg/kg bw/d for males and 1076 mg/kg bw/d for females based on a combined repeated dose toxicity and reproduction/developmental study in rats (Harlan et al. 2012) showing no effect at the top dose except for reduced body weight gain in males and increased plasma triglycerides. A more recent (2018) 90-day study in rats comprised 10 males and 10 females exposed to doses up to 1000 mg/kg bw/day showed no adverse effects or effects of toxicological relevance. SCCS found that old chronic toxicity studies in rats and dogs corroborate the NOAEL of 1000 mg/kg bw/d.

For fertility and reproductive toxicity SCCS refers to their previous opinions on studies on male juvenile rats. In addition, they present results of a study using infantile to adult exposure (Sivaraman et al. 2018) and an extended one-generation reproductive toxicity study in rats (Clariant GMBH 2019), and a prenatal developmental toxicity study. Based on the studies performed after the publication of previous Opinion (SCCS/1514/13), the SCCS still concludes that reproductive toxicity, neurotoxicity and immunotoxicity data (in rats) suggest a NOAEL of 1000 mg/kg/day.

Regarding potential endocrine disruption, SCCS notes that estrogenic effects have been observed with propylparaben, particularly clear estrogenic effect in vitro, weak androgen receptor antagonism in vitro, and increased uterine weights, uterine myometrial hypertrophy and altered steroidogenesis in vivo. It is however concluded that "*although the available data on propylparaben provide some indications for potential endocrine effects, the current level of evidence is not sufficient to conclusively regard it as an endocrine disrupting substance or to derive a specific endocrine-related toxicological point of departure for use in safety assessment*".

DTU FOOD's evaluation of SCCS report

DTU does not agree with the toxicity evaluation presented by SCCS, and it is noted that DTU did not evaluate the exposure assessment. Specifically, DTU does not agree with NOAEL determination in available studies and does not agree that propylparaben should not be considered an endocrine disrupting substance.

DTU did not have access to data from the reported toxicity studies (repeated dose, reproductive and developmental toxicity studies) except for a few publicly available publications, of which the study by

Sivaraman et al., 2018 is evaluated below. DTU does not agree with NOAEL determination in available studies, specifically due to toxicity observed in a study using exposure from PND 4 to 90 (Sivaraman et al. 2018) and an extended one-generation reproductive toxicity study in rats (Clariant GMBH 2019).

DTU notes that the study on exposure from PND 4 to 90 to propylparaben (Sivaraman et al. 2018) showed effects supporting an endocrine disrupting mode of action and consequent adverse effects. Specifically, the following findings were seen according to the publication:

- Significantly earlier vaginal opening was seen in female rats at the high dose of 1000 mg/kg bw/day administered from PND 4 to 90 (n=10 for examination at PND 90, n=25 for pubertal onset and estrous cyclicity). At this age, no difference in body weight was present between groups. The authors consider this due to unusually late pubertal onset in some controls. However, this response corresponds well with the known estrogenic mode of action of propylparaben seen in vitro and in some uterotrophic studies. Due to the earlier vaginal opening, the body weight at vaginal opening was also significantly reduced.
- Relative uterus weights were significantly increased at the end of dosing (PND 90) and a trend to increased absolute uterus weights was also noted, but may be related to more females being in proestrous or estrous (and thus having dilated uteri).
- In males, body weight at preputial separation was significantly higher, and a non-significant trend to later preputial separation was noted.
- No data on sperm count or quality were presented. No effects were seen on male fertility index, estrous cyclicity or weights of reproductive organs (ovaries, uterus testes, epididymides, prostate and seminal vesicles).

DTU finds that the possible earlier vaginal opening is a sign of endocrine disruption and note that the lack of investigation of sperm parameters is a major limitation of the study by Sivaraman et al. 2018.

DTU does not agree on the conclusion by SCCS that the extended one-generation reproductive toxicity (EOGRTS, OECD TG 443) study in rats (Clariant GMBH 2019) supports a NOAEL for reproductive endpoints to be 1000 mg/kg bw/day. DTU finds that the NOAEL should be lower due to the findings mentioned below. It should be noted, that the study report was not available to DTU at the time of evaluation (December 2020). This study included doses of 0, 100, 300 and 1000 mg/kg bw/day (n=20 in F1 and n=10 for some sub-cohort endpoints). Specifically, adverse effects are seen together with indications of endocrine activity:

- Statistically significant decrease of individual pup weight is considered an adverse finding relevant for NOAEL determination. This finding is considered robust, as it is seen at high dose in several cohorts of F1 offspring at birth and at several ages up to weaning PND 21. These findings warrant further examination of the study report, which was not available to DTU at the time.
- Changes in anogenital distance (AGD) and anogenital index was reported and warrants further examination of the study report.
- No effect on sperm count was reported, but indications of decreased sperm motility and increased number of abnormal sperm warrant further evaluation of the study report. Decrease of sperm motility and increase of abnormal sperm has also been seen in some studies on perinatal exposure to butylparaben

Collectively, DTU considers the adverse effects seen in these studies useful for NOAEL/LOAEL determination, and thus a revision of the NOAEL of 1000 mg/kg bw/day applied by SCCS for risk assessment. For the propylparaben risk assessment, the SCCS selected a NOAEL of 1000 mg/kg/day. By comparing with calculated human exposure from the selected cosmetic products in question, they

calculated a margin of safety (MoS) of 12.000 or more. DTU therefore disagrees with the selected NOAEL and thus the calculated MoS.

Further, these adverse effects in developmentally exposed animals support a possible endocrine disrupting effect of propylparaben. As all study data are not available, DTU cannot evaluate whether the available data are sufficient to consider propylparaben an endocrine disrupter according to definitions by European Commission (for pesticides and biocides). In a previous evaluation (2012) DTU identified propylparaben as a suspected endocrine disrupter according to WHO criteria and the available data at the time.

Considerations on presence or absence of threshold for effects of endocrine disrupting chemicals

As mentioned, the SCCS used a threshold approach and the selected NOAEL of 1000 mg/kg/day. By comparing with calculated human exposure from the selected cosmetic products in question, they calculated a margin of safety (MoS) of 12.000 or more. In addition to disagreement on the NOAEL selection, DTU points out that the issue of possible absence of a threshold for effects of endocrine disrupting chemicals should be considered.

The SCCS considered a traditional uncertainty factor of >100 as an indicator of safe use of the evaluated products. There are however a number of recent scientific papers and regulatory reports suggesting that we should start risk-assessing endocrine disrupting chemicals differently than other chemicals (CEHOS 2019, Demeneix 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 propylparaben, DTU proposes that the issue of including additional uncertainty factors should be addressed by SCCS for studies where effects were not seen with exposure in critical developmental studies. The EOGRTS evaluated does include exposure during critical developmental windows. DTU also notes a general lack of sensitive endpoints with regards to e.g. female reproductive toxicity and mammary development in the existing OECD guidelines, including EOGRTS.

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 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 specific 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 propylparaben, it is not possible to prove or disprove the existence of a toxicological threshold. It is possible that the available data on propylparaben (possibly in a read-across approach using information on butylparaben) are sufficient to identify this substance as an ED. However, if no safe threshold exists for the effects of propylparaben 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

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 20201 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) 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.

Specifically, for propylparaben the use of an extra mixture assessment factor of e.g. 10 could be employed to increase consumer protections due to additional risk from substances with similar effects or mode of action. An extra factor would imply that MoS need to be >1000 to be considered safe, as opposed to the default value of 100.

References:

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