1. juli 2015
JUBO

Siloxan D5 og kriterier for hormonforstyrrende effekt.

Forbrugerrådet TÆNK spørger i forbindelse med ny opinion fra SCCS vedr D5, cyclopentasiloxane, om stoffet kan vurderes at være hormonforstyrrende eller mistænkt i forhold til "de danske kriterier" for hormonforstyrrende effekt, jf. en tidligere rapport (Hass et al., 2012).

Da vi ikke har adgang til data for stoffet, og da SCCS har lavet en udførlig datagennemgang, vil vurderingen her udelukkende tage udgangspunkt i konklusioner fra SCCS' opinion fra marts 2015 (SCCS 2015).

"De danske kriterier" for hormonforstyrrende stoffer kan anvendes til vurdering af et stof som "Endocrine disrupter", "Suspected endocrine disrupter" eller " Substances with indications of ED properties (indicated ED)" defineret som beskrevet her:

Category 1 - Endocrine disrupter
Substances are placed in category 1 when they are known to have produced ED adverse effects in humans or animal species living in the environment or when there is evidence from animal studies, possibly supplemented with other information, to provide a strong presumption that the substance has the capacity to cause ED effects in humans or animals living in the environment.
The animal studies shall provide clear evidence of ED effect in the absence of other toxic effects, or if occurring together with other toxic effects, the ED effects should be considered not to be a secondary non-specific consequence of other toxic effects. However, when there is e.g. mechanistic information that raises doubt about the relevance of the adverse effect for humans or the environment, category 2a may be more appropriate.
Substances can be allocated to this category based on:

- Adverse *in vivo* effects where an ED mode of action is highly plausible
- ED mode of action *in vivo* that is clearly linked to adverse *in vivo* effects (by e.g. read-across)

Category 2a - Suspected ED
Substances are placed in category 2a when there is some evidence from humans or experimental animals, and where the evidence is not sufficiently convincing to place the substance in category 1. If for example limitations in the study (or studies) make the quality of evidence less convincing, category 2a could be more appropriate. Such effects should be observed in the absence of other toxic effects, or if occurring together with other toxic effects, the ED effect should be considered not to be a secondary non-specific consequence of other toxic effects.
Substances can be allocated to this category based on:

- Adverse effects *in vivo* where an ED mode of action is suspected
- ED mode of action *in vivo* that is suspected to be linked to adverse effects *in vivo*
- ED mode of action *in vitro* combined with toxicokinetic *in vivo* data (and relevant non test information such as read across, chemical categorisation and QSAR predictions)

Category 2b – Substances with indications of ED properties (indicated ED)
Substances are placed in category 2b when there is *in vitro*/*in silico* evidence indicating potential for endocrine disruption in intact organisms. Evidence could also be observed effects *in vivo* that could be ED-mediated.

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Der kræves således viden om en adverse in vivo effect med "highly plausible" hormonforstyrrende (ED) mode of action, hvis et stof skal kategoriseres som "hormonforstyrrende", alternativt viden om en ED mode of action, der er "clearly linked" til en adverse in vivo effekt. Dette er ikke tilfældet for D5, som derfor ikke kan konkluderes at være "Endocrine disrupter", kategori 1. Derimod er der fundet adverse effekter in vivo med en mistænkt ED mode of action, hvilket fører til en vurdering af D5 som en "suspected ED", kategori 2a.

Disse adverse effekter samt en foreslået mulig ED mode of action er beskrevet i SCCS' opinion fra 2015 og opsummeres kort herunder.

I SCCS' opinion om siloxan D5 gennemgås en række studier af stoffet, og det konkluderes, at D5 ikke har effekt på en række reproduktionsparametre, men der ses øget forekomst af uterine tumorer (uterine endometrial adenocarcinomas) i langtidsstudier og der ses forstyrrelser af østrus cyklus hos aldrende rotter (SCCS 2015). Disse adverse effekter kan være relateret til en hormonforstyrrende mode of action. Der er udført yderligere studier for at undersøge mode of action, og det foreslås at: "*there are indications that D5 might act, as also suggested for D4, as a dopamine agonist and thereby affects prolactin secretion in the rat. However, the relevance of this mode of action in humans is unclear at present*" (SCCS 2015; s. 59).

SCCS beskriver side 48-49, at en nedsat prolactin sekretion mistænkes for at medføre en forstyrrelse af østrus cyklus samt medføre uterine tumorer. Den præcise virkemåde er ikke afklaret, og det er ikke afklaret om denne mode of action er relevant for mennesker. Det bemærkes dog, at "*Although the applicant states that this mode of action is not relevant in humans, due to the lack of a thorough mode of action in rodents and also in human for this type of tumours, the SCCS cannot exclude that these effects could be relevant in humans*" (SCCS 2015 side 49).

SCCS' kommentarer omkring mulige virkemåder er samlet her (SCCS 2015 side 48-49):

SCCS comments
There is evidence that D5 influences prolactin concentrations, although the effects are not consistent from *in vivo* to *in vitro* studies. Therefore the precise mechanism of action for alteration of pituary control of the oestrous cycle by D5 is not fully understood.
There are no data showing that D5 treatment **alters LH** in the rat in a similar manner as D4.
Studies have investigated the effects of D5 on the **oestrus cyclicity** in the ageing F344 rat. In a 90-day study in the ageing female rats exposed by inhalation to 160 ppm D5 six hours/day, 5 days/week, a significant increase in days in proestrus/oestrus was seen. In addition there was an increase in the combined incidence and severity of focal glandular hyperplasia (Ref 118).
In a 14-month mechanistic study, female F344 rats were exposed to D5 (160 ppm) by inhalation to 160 ppm D5 6 hours/day, 5 days/week, from 11 months of age to 25 months of age. The expected effect of decreased prolactin levels on oestrous cyclicity in normally cycling rats is an increase in the frequency of days in oestrogenic state. This effect was observed in the D5-exposed rats, in which the percent of days spent in an oestrogenic state was increased by an average of 44% during the first 45-day interval and 78% during the second 45-day interval. When compared to control animals the results of this study suggest an advancement of ageing in the D5-exposed reproductive tracts (Ref 119).
If the uterine adenocarcinomas are a spontaneous event that typically increases in frequency after 25 months of age, then this shift towards earlier senescence would be consistent with earlier appearance of spontaneous lesions.

SCCS comments on mode of action for uterine effects

Despite many mechanistic studies, the mechanism of action for uterine effects of D5 is still not understood. It is recognised that D5 may possibly act as a dopamine agonist, thus contributing to the observed tumorigenic effects in female rats. Although the applicant states that this mode of action is not relevant in humans, due to the lack of a thorough mode of action in rodents and also in human for this type of tumours, the SCCS cannot exclude that these effects could be relevant in humans. However, the limited negative genotoxicity results suggest that the tumours observed in the chronic toxicity/carcinogenicity study could be due to threshold effects.

Foruden effekter på østrus cyklus og forekomst af uterine tumorer ses en øget anogenital afstand hos hanrotter i et 2-generations forsøg, men SCCS konkluderer, at der ikke er set anti-østrogen eller androgen effekt af D5, som kan relateres til dette fund, og at der ikke er set effekter på kønsmodning, hvorfor der ikke lægges videre vægt på ændringen i anogenital afstand.

Konklusion:
Baseret på SCCS' opinion om D5 samt "de danske kriterier for hormonforstyrrende stoffer" vurderes det, at D5, cyclopentasiloxane, pt kan kategoriseres som "suspected endocrine disrupter" ("mistænkt hormonforstyrrende stof"). Der er fundet adverse effekter in vivo (uterine tumorer i langtidsstudie i rotter og ændret østruscyklus hos ældre rotter) med en mistænkt ED mode of action (nedsat prolaktin sekretion), hvilket fører til en vurdering af D5 som en "suspected ED", kategori 2a.

Referencer:
Hass et al., 2012 (Evaluation of 22 SIN List 2.0 substances according to the Danish proposal on criteria for endocrine disrupters, Danish Centre on Endocrine Disrupters. Report for Danish Environmental Protection Agency):
http://eng.mst.dk/media/mst/67169/SIN%20report%20and%20Annex.pdf

SCCS 2015 (Scientific Committee on Consumer Safety, Opinion on decamethylcyclopentasiloxane (cyclopentasiloxane, D5) in cosmetic products):
http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_174.pdf

Danish EPA, 2011: Establishment of Criteria for Endocrine Disruptors and Options for Regulation, 17 May 2011.
http://eng.mst.dk/media/mst/Attachments/DKEDcriteria110517_finalcorr1.pdf

Med venlig hilsen

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