Review of Danish EPA List of EDCs

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For many years, Denmark has been very active on the endocrine issue. In 2011 the Danish EPA proposed a set of criteria for the EU Commission to use to identify EDCs. Quoting from the criteria:

"Substances are placed in category 1 (Confirmed ED) when they are known to have caused ED mediated 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 adverse ED effects in humans or animals living in the environment. The animal studies shall provide clear evidence of ED effects in the absence of other toxic effects, or if occurring together with other toxic effects, the ED effects should not be considered 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 effect for humans or the environment, category 2a (Suspected ED) may be more appropriate.

"Substances can be allocated to category 1 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 effects in vivo (by e.g. read-across)

"Substances are placed in category 2a (Suspected ED) when there is some evidence for ED effects 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 category 2a 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 categorization and (Q)SAR predictions).

"Substances are placed in Category 2b (Indicated ED) when there is some in vitro/in silico evidence indicating a potential for endocrine disruption in intact organisms. The evidence could also be observed effects in vivo where there is general but not specific evidence relating those to ED (i.e. that may, or may not, be ED-mediated)."

In 2012, at the request of the Danish EPA, the Danish Centre for Endocrine Disruption conducted a study whereby they applied their proposed criteria to evidence available on 22 substances on the ChemSec SIN List 2.0. These substances had been identified by ChemSec as Substances of Very High Concern (SVHC) according to the criteria in REACH, solely due to their endocrine disrupting properties. Furthermore, all 22 substances were also evaluated according to the Joint British-German Position Paper: Regulatory Definition of an Endocrine Disrupter in relation to Potential Threat to Human Health which takes potency into account using cut-off criteria. The conclusion of the study was that 15 of the 22 substances were classified as confirmed endocrine disruptors according to the Danish criteria proposal; 6 were classified as suspected endocrine disruptors; and 1 was not categorized due to lack of relevant data. Using the joint German-UK proposal, only 4 substances were classified as endocrine disruptors of very high regulatory concern.

The Danish Centre also conducted a similar study on four additional substances that have in common anti-fungal properties: tebuconazole, triclosan, methylparaben and ethylparaben. No rationale was provided for the choice of these substances. They reported that two of the substances were classified as confirmed endocrine disruptors using the Danish criteria and two were classified as suspected endocrine disruptors. Using the joint German-UK proposal which takes potency into consideration resulted in none of the four being classified as EDCs of very high regulatory concern.

What is the pool of chemicals considered for potential listing as EDCs?

The Danish EDC classification effort was highly restricted to a select group of substances. This included 22 substances that ChemSec had identified in their SIN List 2.0 as Substances of Very High Concern (SVHC) according to the criteria in REACH, solely due to their endocrine disrupting properties. It also included another four substances (tebuconazole, triclosan, methylparaben and ethylparaben) chosen for unknown reasons.

How many chemicals are listed as EDCs?

The Danish Centre's two studies identified 17 substances as confirmed EDCs and 8 substances as suspected EDCs using the proposed Danish criteria. Only 4 substances were identified as EDCs of very high regulatory concern using the joint German-UK proposal which takes potency into consideration.

Do the authors use the WHO/IPCS definition of an EDC?

Yes, although the proposed Danish criteria could be considered to be somewhat lax, particularly as they were applied in the two studies referenced above, thereby leading to an over-classification of substances as EDCs. For instance, merely the suspicion of an endocrine mode of action could be responsible for an adverse effect would be sufficient to classify a substance as a suspected EDC. A single, un-replicated in vitro or in silico study could be sufficient to classify a substance as an indicated EDC.

Is the list homogeneous or does it classify different categories of EDCs?

The Danish EPA proposes three categories of EDCs: Confirmed, Suspected and Indicated. Notably, the Danish criteria do not allow a chemical to be identified as not an EDC, which is problematic.

What scientific expertise do the authors have?

Ulla Haas, the lead author of the two studies conducted by the Danish Centre has a Ph.D. and is a professor of reproductive toxicology at the Technical University of Denmark. She is also the president of the European Teratology Society. Her co-authors from the National Food Institute are similarly reproductive toxicologists with doctorates.

Other collaborators include senior researchers from the Department of Growth and Reproduction, Copenhagen University Hospital. All three have doctoral or medical degrees, including Niels Skakkabeak, who has published extensively alleging lowered sperm counts among Danish men which he attributes to EDC exposures. Finally, additional collaborators include faculty from the Institute of Biology, University of Southern Denmark. All three of them have doctorates and conduct ecotoxicology research with specialization on endocrine effects.

None of the authors have training or experience in epidemiology.

Do the authors of the list engage other stakeholders?

No. These two reports were prepared as one time efforts by the listed authors and there is no evidence of further collaboration or of any external peer-review.

Is the list based on primary research or do they rely on other lists?

Although the authors drew the list of 22 substances from the SIN list, they conducted their own search and evaluation of the scientific literature independent of ChemSec.

Is the list updated on a regular basis with new information?

No. The two studies represent one time efforts. It is unclear whether they plan to conduct any additional work to apply the proposed Danish criteria.

Is there a process to appeal the listing of a chemical?

No.

What are the strengths of the list?

- The list is easily accessed and searched.
- The criteria for listing a chemical are fairly transparent.
- The criteria have the appearance of scientific rigor; however, their application may have been somewhat lax.
- They employed the WHO/IPCS definition of an EDC, however, the criteria used to classify substances as EDCs are somewhat lax.

What are the weaknesses of the list?

- The pool of chemicals evaluated was really quite small (N = 26).
- The research team lacked epidemiological expertise; however, this may not have been a large problem because many of the chemicals lacked epidemiological evidence.
- A relatively low threshold for listing a chemical resulting in too many chemicals that truly are not EDCs being listed as potential EDCs
- It is not apparent that the authors applied a weight of the evidence evaluation of a body of literature on a chemical and a cursory review of

specific chemicals suggests they may have placed undue weight on single studies with un-replicated findings
- Once a chemical is listed, no amount of new contradictory data appears sufficient to get it unlisted.
- There was no independent peer review done of the two studies.
- The fact that their criteria identified such a high proportion of chemicals to be EDCs, especially compared to the U.K.-German criteria, suggests the Danish criteria are too lax.
- The Danish criteria do not allow a chemical to be identified as not an EDC, which is problematic.

What are the implications of the list for the Value Chain?

If downstream users rely on the Danish EPA list they will deny themselves access to some valuable chemicals that actually do not possess endocrine disrupting properties.