

# 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.

In 2016, the [Danish EPA requested that the Danish Centre reclassify 17 of the substances which they had previously labeled as “confirmed EDCs”](#) this time using only the WHO/IPCS definition of an EDC and ignoring the proposed Danish EPA criteria. This resulted in only 10 of the 17 being classified as EDCs. In the judgment of the Centre various limitations in the data for the remaining seven would make it difficult to achieve international agreement that they are EDCs.\

In 2016, [the Danish EPA also asked the Danish Centre to identify an updated list of substances which meet the WHO/IPCS definition of an EDC from several thousands of substances of “suspected EDCs” included on various lists that have been compiled by authorities](#) (i.e., the European Chemicals Agency and the Priority List of Chemicals from the European Commission) as well as by NGOs (ChemSec’s SIN list, TEDX, the Trade Union Priority List, and the 2012 WHO/UNEP State of the Science report). After several rounds of prioritization of substances, they selected 13 for more thorough evaluation of the evidence and concluded that 9 fulfill the WHO/IPCS definition of an EDC.

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

The initial 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.

The pool of chemicals included in the 2016 update was much larger and numbered in the thousands, as the Danish EPA asked the Danish Centre to work from several lists of “suspected EDCs” that had been compiled by authorities and NGOs.

### **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.

For the 2016 update, the Danish EPA asked the Danish Centre to abandon the liberal EDC classification criteria they had employed in the initial effort in favor of using the WHO/IPCS definition of an EDC. The consequence of this was that only 10 of the 17 substances the Danish Centre had originally classified as confirmed EDCs were so classified, with the remaining 7 no longer classified as such. Of the several thousand substances the Danish Centre evaluated most recently, only 9 were judged to fulfill the WHO/IPCS definition of an EDC.

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

For their initial classification effort the Danish Centre used the Danish EPA’s proposed criteria which 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.

For the 2016 update, the Danish Centre used only the WHO/IPCS definition rather than the proposed Danish EPA criteria. The fact that only 10 of the 17 substances originally classified as “confirmed EDCs” were found to meet the WHO/IPCS definition provides prima facie evidence that the proposed Danish EPA criteria were indeed quite liberal.

### **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 original two studies conducted by the Danish Centre, as well as the 2016 update, has a Ph.D. and is a professor of reproductive toxicology at the Technical University of Denmark. She is also a past president of the European Teratology Society. Her co-authors from the National Food Institute differed between the original two studies and the update, but all are similarly reproductive toxicologists with doctorates.

Other collaborators on the original two studies included senior researchers from the Department of Growth and Reproduction, Copenhagen University Hospital. All of them 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. Note, that none of these Hospital researchers were included in the 2016 update. Additional collaborators on both the original studies and the 2016 update include faculty from the Institute of Biology, University of Southern Denmark. All of them have doctorates and conduct ecotoxicology research with specialization on endocrine effects. None of the authors have training or experience in epidemiology.

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## **Do the authors of the list engage other stakeholders?**

No. The two original reports and the 2016 update were prepared by the listed authors and there is description of any external peer-review, although immediately under the title of the update report the following curious statements are made “*Final report, December 21th, 2017 (Some mainly editorial chances were made in September 2018)*”.

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

Although for the original two studies and the 2016 update, the authors started with lists of “suspected EDCs” which had been compiled by other organizations, they conducted their own search and evaluation of the scientific literature independent of those organizations.

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

Possibly. It is unclear whether the Danish EPA plans to regularly request updates on an ongoing basis.

## **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.
- Although the original two studies used the liberal Danish EPA EDC criteria, it appears from the update they have now abandoned those criteria in favor of the more widely accepted WHO/IPCS definition.
- For the 2016 update, the authors started with a very large list (several thousands of substances) of what they described as “suspected EDCs”.
- The authors appear to have rigorously searched the literature to identify and evaluate relevant studies.

## **What are the weaknesses of the list?**

- The process for prioritizing chemicals for evaluation, which whittled the several thousand chemicals down first to 180, then 52, and ultimately 13 for full evaluation, while well-described, employed much expert judgment and it is unclear how reproducible it is.
- The authors were often restricted to evaluating only published studies and thus ignored many relevant studies and test results that have been submitted to regulatory agencies.
- The authors bemoaned the lack of available data, but again confined themselves to only the published literature rather than the more extensive data available from regulatory authorities.
- The research team lacked epidemiological expertise; however, this may not have been a large problem because many of the chemicals lacked epidemiological evidence.
- 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.
- No independent peer review process was described.
- It is not clear that the Danish Centre would ever find sufficient evidence to conclude a substance is NOT likely to be 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 may deny themselves access to some valuable chemicals that actually do not pose an unacceptable risk in many potential uses.