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Science-based regulation of endocrine disrupting chemicals in Europe: which approach?

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**Identifying Chemicals That Disrupt Hormone Systems And Threaten Health:
The Right Approach Keeps Refinement Possible**

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Endocrine disruptors (EDs) are defined by the World Health Organization (WHO) as “exogenous compounds or mixtures that alter function(s) of the endocrine system and consequently cause adverse effects in an intact organism, or its progeny, or (sub)populations” (1). European laws on pesticides (Plant protection products regulation, PPPR) and biocide products regulation (BPR), enacted in 2009 and 2012, respectively, place restrictions on the use of active substances with severe forms of toxicity, including carcinogenicity, mutagenicity, reproductive toxicity and endocrine disruption. Chemicals with such properties will in future not receive authorization for placement on the market as active substances in pesticide or biocide products. Compared to earlier EU law, these legal provisions are innovative in two respects: for the first time, pesticides and biocides with endocrine disrupting properties are regulated; secondly, these severe toxicities are regulated solely on the basis of hazard identification, and not risk assessment, as previously. This requires that scientific criteria for the identification of endocrine disruptors (EDs) are developed, and the European Commission (EC) was obliged by law to publish such scientific criteria within the context of PPPR and BPR, by 2013.

47 Chemical industries have strongly lobbied against “hazard-based cut-off” criteria for EDs
48 and succeeded in convincing the EC to conduct an impact assessment before defining the
49 ED criteria (2). Inevitably, this has delayed the process to such an extent that Sweden and
50 other EU Member States brought a case against the EC. In December 2015, the European
51 Court of Justice judged that the EC acted unlawfully in failing to publish the criteria, and
52 that an impact assessment was not necessary for their development (3).

53
54 To this day (May 2016), the EC has not published the ED criteria and continues to justify
55 this delay with reference to a controversy within the scientific community (4). However,
56 we have recently shown that the “controversy” is not about the basics of ED science, but
57 is the result of a confusion of risk assessment and hazard identification (5). Very recently,
58 this confusion was resolved, and a consensus among the scientists engaged in the
59 previous disputes has emerged (6). We also demonstrated that EDs can be identified
60 using a scientific strategy analogous to that implemented for carcinogens by the
61 International Agency for Research on Cancer (IARC) (5). Accordingly, no one would
62 suggest making the definition of carcinogens dependent on an impact assessment study,
63 as should apply to EDs.

64
65 Whilst a great deal is known about how hormones affect health and disease, there
66 remains much to learn. Similarly, we know a great deal about how some manufactured
67 chemicals can cause adverse effects in humans, farm animals and wildlife by interfering
68 with hormones (7). Recent research demonstrates that EDs can produce epigenetic
69 modifications and transgenerational effects (8). This is honest science that must be
70 considered appropriately for its implications for human health today and for future
71 generations. Robust science at the leading edge allows us to discriminate among the
72 known, the possible and the unknown. Therefore, the decision taken by the EC should be
73 based on what we know now, and allow for incorporating new information as it becomes
74 available.

75 In its 2014 impact assessment, the EC has proposed a roadmap with four different options
76 for defining regulatory ED criteria (9). The first one does not provide defining criteria,
77 and is therefore not operable. Two options (labelled 2 and 3) both rely on WHO
78 definition of EDs; option 2 defines a single category of EDs, while option 3 further
79 identifies suspected endocrine disruptors and endocrine active substances (Fig. 1A). Such
80 categories based on level of evidence are consistent with those used in the EU for
81 carcinogens, mutagens and reprotoxicants, which are hazards of equivalent concern to
82 EDs. An assessment of the strength of the evidence has also been used in studies on the
83 cost of managing health consequences of EDs in the EU. With more than 99%
84 probability, this cost exceeds 160 billion Euros per year (10). Moreover, option 3
85 provides the necessary characteristics that will allow for incorporation of new data as it
86 becomes available which might trigger revised categorizations (Fig. 1A). The responders
87 to the public consultation initiated by the EC about ED identification criteria made no
88 mistake about it since the vast majority selected option 3 (11). The Endocrine Society, the
89 world's largest organization devoted to research on hormones and the clinical care of
90 endocrine disorders, also supports option 3.

The last option (option 4, Fig. 1B) uses a binary definition (ED or non-ED) and incorporates potency as a criterion. The idea of including potency was initiated by UK and German authorities. Mindful of the potential economic impact on industry of regulating substances with ED properties in a hazard-based system, the stated intention was to regulate only the “worst offenders” (12). Potency, however, is not mentioned in the accepted WHO definition (1) and has been deemed irrelevant to identify EDs (5). Potency is actually quite complex to apply as a criterion and scientifically indefensible because a single chemical may appear differently potent depending on the endpoint and the testing conditions (Fig. 1B). Potency is measured by a dose-response function; however, the variability of “response” and the corresponding likelihood of overlooking effects is what makes “potency” so complicated. Historically, diethylstilbestrol (DES) and thalidomide provide examples. These drugs were prescribed for pregnant women without any adverse effects being observed in these women. However, the children of treated women showed adverse effects – either at the time of birth, or several years later. In these cases, the prediction of negligible potency from some *in vivo* testing gave physicians the confidence to prescribe these drugs but was tragically missing developmental issues. In a recent position statement about EU regulation of EDs, the Endocrine Society also recommended to exclude potency from identification criteria (13). Similarly, the recent consensus statement from the scientists engaged in the previous disputes states that potency considerations have no place in the hazard identification process of ED properties (6).

The current scientific consensus on the relevance of the WHO definition of EDs (1), the irrelevance of potency for the identification of EDs (5, 6) and the inapplicability of impact assessment studies to provide scientific definition of EDs (5, 13) all support our conclusion as scientists: science provides all necessary arguments towards implementation of relevant criteria to identify EDs. Such criteria are actually consistent with an option already formulated by the European Commission (option 3 of the EC roadmap). Public health urgently deserves science-based regulations.

Declaration of interests:

The authors have no conflicts of interest other than BD who is cofounder of the company WatchFrog.

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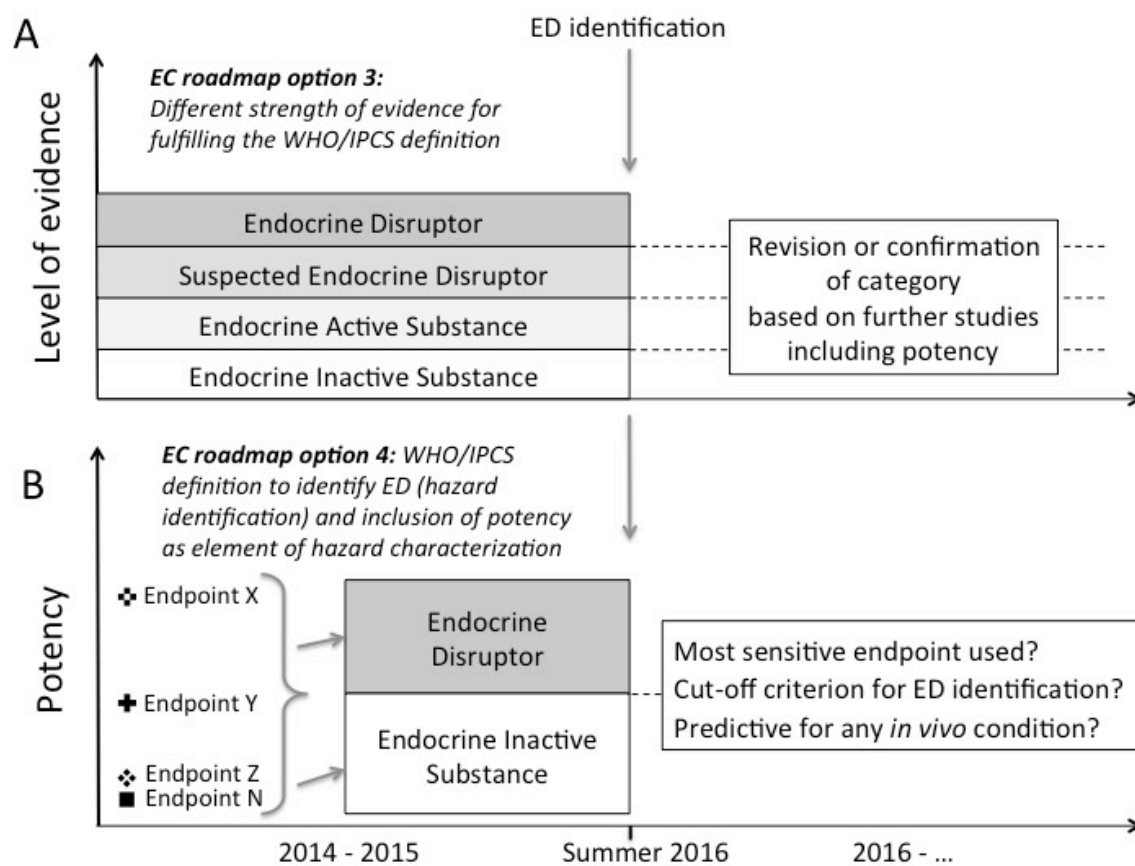


Figure 1. In a 2014 roadmap, the EC has proposed criteria for ED identification through four options, two of which being schematically represented in panel A (option 3) and panel B (option 4). By this summer 2016, EDs will be identified based on one option or the other. Option 3 identifies endocrine inactive substances and three ED categories based on the level of evidence. It allows for further revision using new scientific information. Option 4 uses potency as a criterion and identifies only one ED category. Its application implies further questions about selected endpoints, cut-off criteria and predictive value. In panel B, the 4 symbols arbitrarily denote different levels of potency of a given chemical depending on the studied endpoint.