Response to EU Public consultation ED criteria regarding implementation of PPPR and BPR

Introduction

The roadmap defines 4 different options for the establishment of criteria for determining endocrine disrupting properties. In the consultation, for each option the question is raised whether the respondent has conducted or is aware of any assessment of substances that would be identified as an endocrine disruptor according to that option. For practical reasons it is nearly impossible to fill in the questionnaire. There are currently no harmonized criteria for endocrine disruptors and therefore no active substance has been assessed according to the different options, with the exception of option 1 which proposes the interim criteria as they are currently used. To be able to fully answer the question it would have to be determined for each of the approved active substances on the basis of their assessment reports (DARs/CARs) if the substance would be defined as an endocrine disruptor under the different options. Considering the workload and financial consequences we are not able to perform such an assessment.

Moreover, the public consultation also asks for each option about the socio-economic impact if the identified substances were regulated without further risk assessment. We are not able to answer these questions since socio-economic impact is not part of the assessment framework of active substances.

2.1.4 Considering Option 1: no policy change, interim criteria continue to apply

is option is undesirable in view of the existing public awareness for endocrine disruption, requiring concrete dedicated action, and the clear need to generate a formal framework for the regulation of endocrine disrupters. The current situation, in which different criteria are used within the various regulatory frameworks for the assessment of endocrine disruption, is undesirable. In particular, it seems odd that a specific substance may be considered to be an endocrine disruptor for instance under the BPR but not under the PPPR. Moreover, the situation may appear that this same substance may also be used i.e. as a veterinary drug or under REACH. It seems logical therefore to strive to harmonization of the criteria for approval of substances within the different frameworks.

2.2.4 Considering Option 2: WHO/IPCS definition (hazard identification)

We are of the opinion that the WHO/IPCS definition contains all the essential elements required to designate a compound as an endocrine disrupter. The strength of this definition lies in the fact that this definition is purely hazard based and that it asks for causality between the endocrine mechanism affected and the adverse health effect observed. It should be stressed that this link between the mechanism and the adverse effect in the definition is of high importance.

However, we also recognize that this definition meets with practical difficulties. In practical terms, it is impossible in most cases to unequivocally prove a causal relationship between hormonal changes and adverse health effects in an experimental study. One of the reasons for this is that the current regulatory (animal) study guidelines were designed for the assessment of adversity. These studies were not designed to reveal mechanism of action, let alone any possible causal relationships between mechanism and adverse effect. Simply speaking: changes in hormone levels accompanying adverse health effects are not proof of causality per se, as hormonal imbalance may be secondary to the adverse effect observed.

We therefore propose that the WHO/IPCS definition is applied case by case by using expert judgment weighing all available evidence, considering whether the adverse effect observed is most likely to be endocrine mediated. Cases of high plausibility of causality should lead to designation of a compound as an endocrine disrupter. The application of the concept of plausibility is in line with earlier statements by JRC (2013)[1] and EFSA (EFSA Journal 2013;11(3):3132).

With regard to weight of evidence, EFSA noted that "a limitation of the current suite of test methods available for the identification of EDs is the lack of a single study involving exposure through the complete life cycle of a mammal, from conception to old age or a single study involving developmental exposure with follow-up into old age". EFSA further mentioned that "several recent review reports concluded that current mammalian tests do not cover certain endpoints that might be induced by exposure during foetal or pubertal development but emerge later in life like certain cancers (breast, prostate, testis, ovarian and endometrial) and effects on reproductive senescence". Given the limited capability of current animal studies to prove cause and effect of endocrine disruption, we also advocate an in depth study into possibilities to enhance current test guidelines with additional adverse outcome parameters that can be endocrine mediated. The extent to which the addition of these endocrine parameters could shed light on cause and effect should be considered. In addition, the inclusion of in vitro screening studies in regulatory frameworks to detect potential endocrine disruptors at an early stage is highly recommended.

2.3.4 Considering Option 3: WHO/IPCS definition plus 'suspected' and 'endocrine active' substance categories

From the regulatory perspective, we consider it useful to define a single category of 'potential endocrine disrupters', which can be used to trigger further dedicated testing on a case by case basis. This will allow prioritization of further dedicated work on specific (groups of) substances, and will reduce animal use and costs. We are not in favor of using the term 'suspected', given the legal flavor of that term, related to classification and labelling.
Moreover, we are not in favor of the construction of additional sub groups because this will most likely lead to more confusion rather than clarity and does not provide added value for the regulatory process.

The additional category of 'potential endocrine disrupter' proposed here still needs careful definition, which could be developed by elaborating the requirements currently listed for the proposed 'suspected' category . A substance should only be designated to this 'potential endocrine disrupter' category in case of a concern based on relevant data indicating that further information on endocrine activity and possibly related adversity of the substance is desirable, but where the existing data is not sufficient to designate the substance as an 'endocrine disrupter'. In addition, criteria should be formulated for allowing removal of substances from this category when additional data provides justification for such action. Again, case by case assessment based on weight of evidence and expert judgment will be needed to designate a compound as potential endocrine disruptor.

2.4.4 Considering Option 4: WHO/IPCS definition plus potency consideration

The consideration of potency is highly inappropriate in the context of defining an endocrine disruptor, given that the designation of 'endocrine disrupter' is, and should be purely hazard based.

[1] Key scientific issues relevant to the identification and characterisation of endocrine disrupting substances - Report of the Endocrine Disrupters Expert Advisory Group. Report JRC79981, Ispra Italy.

Potency is, and should be, taken into account in the risk assessment process, where it serves an important role to determine the risk of an endocrine disruptor given the exposures at hand. The process of risk assessment takes hazard, potency and exposure into consideration to make sure that a substance is regulated in an appropriate manner. It thereby prevents that a substance is regulated on basis of the fact that it exerts an effect only at high dose levels. Therefore, risk management of endocrine disrupters should be based on risk assessment and not on hazard assessment only.

Another reason why regulatory potency cutoffs shouldn't be used in hazard assessment for endocrine disrupters (such as applied e.g. for substances in classification & labelling for acute toxicity) is that the set of available test data and the quality of this set of test data vary strongly between endocrine disruptors. At this moment, the situation is such that relatively old data that were obtained using tests that covered only a small number of ED-parameters will most often indicate a lower potency than the newer, more sensitive tests that have been updated to cover more and more sensitive ED related parameters. Using potency to set cut-offs in the definition for EDs assumes that current testing protocols have sufficient statistical power to detect all hormonal and adverse changes.
This implies that old substances, tested a long time ago will be favoured over "new" substances simply because the new substances were tested using more sensitive test methods and therefore show higher potency. Furthermore, in view of animal welfare and cost there is a tendency to use less animals in shorter duration studies, and to include not all relevant and sensitive parameters, which reduces the power and with that the observed potency. We advocate initiating an international discussion about the adequacy of the current regulatory testing paradigm and its underlying animal study protocols, with a view to modernization based on state-of-the-art scientific and statistical knowledge.

4.1 Conclusion

In summary, we support the application of the WHO/IPCS definition as the criterion for designating a substance as an endocrine disrupter. This definition is based on the observation of an adverse health effect in an intact animal that is causally related to an endocrine mechanism being perturbed. We stress that current regulatory toxicity testing methods have not been designed to assess mechanistic cause and effect, and therefore, weight of evidence should inform about plausibility. In case of high plausibility, a compound can be designated as endocrine disrupter.
We also support the option to define a substance as 'potential endocrine disrupter' in case of limited but adequate evidence, as a regulatory means to require further study to assess whether or not the substance should be considered an endocrine disrupter. We are not in favor of more than these two categories, as this would not provide added value for the regulatory process.

We do not support the application of potency cutoffs in the criteria of endocrine disrupters, given the fact that this is included in the risk assessment and given the variability in study designs.

In general terms, the issue of endocrine disruption has shown that the study designs of current regulatory test methods, globally harmonized in OECD test guidelines, are less than optimal for assessing mechanistic cause and effect relationships. Designs could be enhanced for endocrine parameters and endocrine mediated adverse outcomes. Moreover, study design, critical window of exposure, power and statistical analytical tools require attention for innovation. In a wider context, this issue supports the development and regulatory implementation of animal-free alternative methods that can inform about mechanism of action, and their grouping informed by predefined adverse outcome pathways (including the definition of findings representative of adverse outcomes) in an integrated approach to testing and assessment.