BfR concept for assessment of endocrine disrupting substances under different regulations

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Endocrine active substances are chemicals that can interact or interfere with normal hormonal activity in mammals or humans; when this leads to adverse effects these substances are called endocrine disruptors. Substances with endocrine disrupting properties have been addressed in several major pieces of EU legislation. In the European Union Plant Protection Products Regulation (EC) No 1107/2009 and the Biocide Product Regulation (EC) No 528/2012 any active substance, (also safener and synergists in Plant Protection Products) with endocrine disrupting properties that may cause adverse effects in humans cannot be approved for marketing and use unless the exposure of humans under realistic proposed conditions of use is negligible. Within the REACH Regulation (EC) No 1907/2006, identification of substances as endocrine disrupters in accordance with the criteria in Article 57(f) may lead to their inclusion in the list of substances of very high concern (SVHC) as possible candidates for authorisation. However, commonly accepted scientific criteria suitable to identify and characterize Endocrine Disruptors for regulatory purposes within these pieces of legislation have yet to be established. In the interest of predictability, efficiency and consistency, any future concept in this regard should ensure a high level of protection of human health based on a scientific weighting of available data, resulting in transparent legal decisions. The Federal Institute for Risk Assessment (BfR) has proposed a concept for the assessment of endocrine disruptors suitable for the main EU Regulations. This concept follows the principle of “one substance - one assessment”.

Option model considering substances under different regulations

The BfR concept described herein has been developed to assess substances with endocrine disrupting properties in relation to human health. It is designed to provide a common principle for the evaluation and approval/authorisation of Endocrine Disruptors (EDs) to ensure a harmonised approach within the major EU regulations. Following a science-based hazard analysis consisting of ***hazard identification*** and ***hazard characterization***, the BfR concept differentiates between EDs of higher and lower regulatory concern. This builds up the base for a subsequent clear decision for further regulatory measures in accordance with the individual legal provisions.

General considerations

The key element of the proposed concept is, in agreement with the current discussions on the EU level on identification of EDs, the general acceptance of the WHO/IPCS definition (WHO 2002):
“*An endocrine disruptor is an exogenous substance or mixture that alters functions of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations.”*

The definition implies essential requirements to be fulfilled for the identification of a substance as an EDs which are included as a central step in the decision tree. To be in agreement with the WHO/IPCS definition, it is essential to verify that: 1) the substance alters the function of the endocrine system; 2) this alteration causes an adverse health effect which 3) should occur in an intact organism, its progeny or (sub) populations.
There is agreement that these general criteria should be evaluated adopting a weight of evidence approach.

After hazard identification, several criteria of hazard characterization will have to be taken into account. First, an assessment whether the adverse effects observed in animals are relevant to humans (to be assumed by default) is considered necessary. After that, **specificity**, **severity**, **reversibility** and **consistency** of effects as well as **potency** (i.e. the dose level causing adverse effects) are to be considered.

In the final categorisation or prioritisation step, Endocrine Disruptors are differentiated into higher and lower regulatory concern. This differentiation facilitates a clear decision for the purpose of further regulatory measures in accordance with the individual legal provisions taking into account both hazard identification and elements of hazard characterization. Yet, for regulatory purposes, the assessment process has to substantiate whether an observed endocrine perturbation results in adverse effects, such as pathology or functional impairment. Therefore, in accordance with procedures established in other areas of regulatory assessment (e.g. for classification and labelling purposes according to Regulation (EC) No. 1272/2008), a decision matrix is used which takes into account:

- s**everity** of effect
- r**eversibility** of effect
- c**onsistency** of effect
- p**otency** (e.g. guidance values of CLP criteria for STOT-RE Category 1 classification)
- others (if applicable)

Details of the assessment procedure are described in detail elsewhere (Marx-Stoelting et al. 2011).

Special considerations for substances under different regulations with different data bases

The BfR is aware of the fact that the present concept of categorization works best in a data-rich situation (e. g. for pesticides, biocides, high production volume chemicals under REACH). For data-poor substances, for which it is difficult to judge whether or not they meet the WHO/IPCS definition (e.g. because no *in vivo* data are available), assignment of a substance to a category may be difficult or impossible. In these cases, a requirement for additional toxicological data might be considered depending on the level of evidence available for potential ED effects.

Option 1: EDs under Plant Protection Product Regulation (EC) No 1107/2009 and the Biocide Product Regulation (EC) No 528/2012

Substances categorized as ED 1 are subject to hazard-based cut-off and their approval is in principle not possible. Substances categorized as ED 2 are subject to standard risk assessment. Their approval is only possible if safe use of the relevant (active) substance in plant protection or biocide products could be demonstrated in accordance with the principles of the specific regulations named above.

Option 2: EDs under REACH Regulation (EC) No 1907/2006

Substances categorized as ED 1 are considered to cause probable serious effects to human health which give rise to an equivalent level of concern to substances meeting the criteria for classification as carcinogenic, mutagenic or toxic for reproduction category 1A or 1B (CMR 1A or 1B substances) in accordance with article 57 (f) and thus are candidates for inclusion in annex XIV of Regulation (EC) No 1907/2006. For substances categorized as ED 2 it is

suggested to proceed with standard risk assessment. For substances showing inconclusive evidence for ED due to limitations in the data package, further data may be requested in accordance with article 46.

Option 3: EDs under Regulation (EC) No 1333/2008 (food additives approved for use in foods, food additives, food enzymes and food flavourings)

Substances categorized as ED 1 will not be included into either Annex I (food additives approved for use in foods and conditions of use) nor Annex II (food additives approved for use in food additives, food enzymes and food flavourings, and their conditions of use) respectively.

Option 4: EDs under Regulation (EC) No 10/2011 (Plastic materials with food contact)

Substances for use in plastic materials and articles intended to come into contact with foodstuffs undergo a risk assessment and authorization prior to addition into the Union list of authorised monomers, other starting substances, macromolecules obtained from microbial fermentation, additives and polymer production aids). Only substances included in this Annex I may be intentionally used in the manufacture of plastic layers in plastic materials and articles. As a general principle, the greater the exposure through migration, the more toxicological information will be required. However, endocrine effects (although not directly addressed) could in most cases only be uncovered from the data set for substances with migration above 5 mg/kg. Due to a limited data set (mainly focusing on genotoxicity), effects on the endocrine system of substances with low migration (less than 0.05 mg/kg) are generally not addressed. Here, suitable *in-vitro* studies addressing endocrine effects (e.g. Level 1 and 2 assays of the OECD Conceptual Framework) should be mandatory for substances with low migration. For substances showing inconclusive evidence for ED due to limitations in the data package, further data may be requested from the applicant(s).

Option 5: EDs under Regulation (EC) No 1223/2009 (Cosmetics)

Safety evaluation of cosmetic ingredients is carried out by the SCCS using toxicological data, quantitative structure activity relationship calculations, clinical studies, epidemiological studies and accidents. After risk assessment, substances may be added to lists of prohibited substances (Annex II), substances with restrictions (Annex III) or allowed substances (Annexes IV, V, VI). However, with the implementation of Directive 1223/2009, the placing on the market of cosmetic products shall be prohibited where, in order to meet the requirements of this Regulation, the final formulation ingredients or combinations of ingredients has been the *subject of animal testing*. This applies if animal testing is based on a method other than an alternative method that has been validated and adopted at Community level with due regard to the development of validation within the OECD. Since data on adverse toxicological effects potentially related to ED in intact organisms from acceptable *in-vivo* studies are essential for hazard assessment, prioritisation is impossible. However, clarification of suspected ED related hazard would require animal testing.

Literature

[1] Marx-Stoelting,P., Pfeil,R., Solecki,R., Ulbrich,B., Grote,K., Ritz,V., Banasiak,U., Heinrich-Hirsch,B., Moeller,T., Chahoud,I., Hirsch-Ernst,K.I. (2011). Assessment strategies and decision criteria for pesticides with endocrine disrupting properties relevant to humans. *Reprod. Toxicol* **31**: ***574-584***.

[2] WHO (2002). Global assessment of the *state-of-the-science* of endocrine disruptors. *International Programme on Chemical Safety*.