Regulatory Toxicology and Pharmacology 70 (2014) 590–604

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

# Assessment of three approaches for regulatory decision making on pesticides with endocrine disrupting properties ☆

P. Marx-Stoelting *, L. Niemann, V. Ritz, B. Ulbrich, A. Gall, K.I. Hirsch-Ernst, R. Pfeil, R. Solecki

*Bundesinstitut für Risikobewertung (Federal Institute for Risk Assessment), Max-Dohrn-Str 8-10, 10589 Berlin, Germany*

ARTICLE INFO

*Article history:*
Received 7 April 2014
Available online 17 September 2014

*Keywords:*
Pesticides
Endocrine Disruption
Decision criteria

ABSTRACT

Recent EU legislation has introduced endocrine disrupting properties as a hazard-based "cut-off" criterion for the approval of active substances as pesticides and biocides. Currently, no specific science-based approach for the assessment of substances with endocrine disrupting properties has been agreed upon, although this new legislation provides interim criteria based on classification and labelling.

Different proposals for decision making on potential endocrine disrupting properties in human health risk assessment have been developed by the German Federal Institute for Risk Assessment (BfR) and other regulatory bodies. All these frameworks, although differing with regard to hazard characterisation, include a toxicological assessment of adversity of the effects, the evaluation of underlying modes/mechanisms of action in animals and considerations concerning the relevance of effects to humans.

Three options for regulatory decision making were tested upon 39 pesticides for their applicability and to analyze their potential impact on the regulatory status of active substances that are currently approved for use in Europe: Option 1, based purely on hazard identification (adversity, mode of action, and the plausibility that both are related); Option 2, based on hazard identification and additional elements of hazard characterisation (severity and potency); Option 3, based on the interim criteria laid down in the recent EU pesticides legislation. Additionally, the data analysed in this study were used to address the questions, which parts of the endocrine system were affected, which studies were the most sensitive and whether no observed adverse effect levels were observed for substance with ED properties.

The results of this exercise represent preliminary categorisations and must not be used as a basis for definitive regulatory decisions. They demonstrate that a combination of criteria for hazard identification with additional criteria of hazard characterisation allows prioritising and differentiating between substances with regard to their regulatory concern. It is proposed to integrate these elements into a decision matrix to be used within a weight of evidence approach for the toxicological categorisation of relevant endocrine disruptors and to consider all parts of the endocrine system for regulatory decision making on endocrine disruption.



## 1. Introduction

Recent EU legislation has introduced endocrine disrupting properties as one of a number of new hazard-based "cut-off" criteria for the approval of active substances in plant protection products (Reg. (EC) No 1107/2009; European Council, 2009). Accordingly, substances with endocrine disrupting properties that may cause adverse effects in humans may only be approved if exposure is negligible.

However, no specific science-based criteria for the assessment of substances with endocrine disrupting properties have been agreed upon so far. For pesticides, the EU Commission is required

*Abbreviations:* ANSES, Agence Nationale de Securite Sanitaire de l' Allimentation de l'environment et du travail (French National Agency for Food Safety); BfR, Bundesinstitut für Risikobewertung (German Federal Institute for Risk Assessment); CLP, Classification, Labelling and Packaging (of Chemicals); CRD, Chemicals Regulations Directorate; EC, European Commission; ECETOC, European Centre for Toxicology and Ecotoxicology; ED, Endocrine Disruptor; EFSA, European Food Safety Authority; EPA, Environmental Protection Agency; ESIS, European Substance Information System; GHS, Globally Harmonized System (of Classification and Labelling of Chemicals); HPA, Hypothalamic Pituitary Adrenal Axis; HPG, Hypothalamic Pituitary Gonadal Axis; HPT, Hypothalamic Pituitary Thyroid Axis; IPCS, International Programme on Chemicals Safety; MRL, Maximum Residue Level; REACH, Registration, Authorisation and Evaluation of Chemicals; Reg, Regulation; WHO, World Health Organisation.

☆ **Disclaimer**: This paper presents results of a research project of the Pesticides Safety Department of the BfR and does not necessarily represent the regulatory position of the institute.

* Corresponding author.
*E-mail address:* philip.marx-stoelting@bfr.bund.de (P. Marx-Stoelting).

http://dx.doi.org/10.1016/j.yrtph.2014.09.001
0273-2300/

to present a draft of measures concerning specific scientific criteria for the determination of endocrine disrupting properties in the near future. Pending adoption of specific scientific criteria, the new plant protection products regulation provides interim criteria for identification of some substances with endocrine disrupting properties for non-approval, based on classification and labelling: "*. . .substances that are or have to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as carcinogenic category 2 and toxic for reproduction category 2, shall be considered as having endocrine-disrupting properties. . . .substances such as those that are or have to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as toxic for reproduction category 2 and which have toxic effects on the endocrine organs, may be considered as having endocrine-disrupting properties*" (Reg. (EC) No 1107/2009; European Council, 2009). Similar provisions for a regulatory "cut-off", based on endocrine disrupting properties and including interim criteria for the determination of endocrine disrupting properties are also provided in the new EU biocides regulation 528/2012 (European Parliament and Council, 2012).

Assessment and regulation of substances with potential endocrine disrupting properties is associated with a number of challenges. The endocrine system is extremely complex and is involved in virtually all functions of the vertebrate organism (WHO/IPCS, 2002; WHO/UNEP, 2013). Consequently, any effect observed in a toxicity study might theoretically be linked to an alteration of function of the endocrine system. Since administration of high doses of test chemicals in pre-approval animal studies is mandatory according to internationally harmonised test guidelines and data requirements under regulatory frameworks, the majority of active substances in plant protection or biocidal products have been found to show at least some significant toxicity. Currently, the mechanism or mode of action leading to a toxic effect is often not clear and judgement whether it is endocrine mediated or not is difficult.

A related challenge is that the process of endocrine disruption does not correspond to a single endpoint per se. Endocrine disruption includes a variety of different mechanisms of toxicity that may affect different individual endpoints. Moreover, even though in the past decade several assays have been developed and validated to detect substance-induced effects caused by interference with the hypothalamic-pituitary-gonadal (HPG) axis, there are many other components of the endocrine system, for which at present no or only insufficiently validated specific mechanistic assays are available. In fact, if endocrine disruption is discussed in the public, the focus is very often on substances potentially affecting fertility and reproduction via interaction with steroid hormone systems such as the estrogen or androgen systems. Sometimes additionally effects on the thyroid hormone system are discussed whereas other parts of the endocrine system like the adrenal gland or the pancreas are seldomly taken into consideration.

Although substances with endocrine disrupting properties have been addressed in different sections of EU chemicals regulation (e.g. plant protection products regulation, biocides regulation, REACH), current data requirements and options for management decisions differ significantly between regulations. While data requirements under the recent EU pesticides regulation cover an extensive set of toxicity studies in at least four animal species, the scope of the data package for chemicals under REACH (Regulation EC No. 1907/2006) depends on the production volume and may not be as comprehensive as for pesticides (Beronius et al., 2009). Furthermore, the downstream regulatory consequences for substances with endocrine disrupting properties currently appear to differ between regulations. Active substances, safeners or synergists with endocrine disrupting properties to be used in plant protection are not to be authorised even if risk assessment demonstrates that there is no risk associated because of very limited exposure. This "cut-off" is to be applied "unless the exposure of humans to that active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, when the product is used in closed systems or in other conditions excluding contact with humans and where its residues in food and feed do not exceed the default value set in accordance with point (b) of Article 18(1) of Regulation (EC) No 396/2005" (European Council, 2009). By contrast, chemicals under REACH (Reg. (EC) No 1907/2006) that have endocrine disrupting properties for which there is scientific evidence of probable serious effects to human health may be nominated for a candidate list in accordance with Article 57f. That means that these substances should become subject to an authorisation procedure and may not be placed on the market unless they have been authorised (European Council, 2006).

Although conclusions on endocrine disruptors in a regulatory context are required under the European regulations on plant protection products and also on biocides (European Parliament and Council, 2012) the lack of agreed criteria makes implementation of these pieces of legislation difficult. For toxicological hazards like carcinogenicity, reproductive toxicity or specific target organ toxicity, criteria for categorisation have already been established and internationally agreed upon in the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) which was implemented into European legislation by Regulation (EC) No 1272/2008 (CLP regulation) (European Council, 2008). However, the CLP regulation does not define a specific hazard class of endocrine disruptors. In this context it has been argued that endocrine disruption is based on a variety of mechanisms of action that may lead to adverse health outcomes like cancer, reproductive disease or specific target organ toxicity, but does not represent in itself a single endpoint that would require classification or labelling (ECETOC, 2009). Furthermore, any substance that causes cancer or effects on reproduction and development like reduced fertility or malformations by an endocrine mode of action would be expected to be classified accordingly. However, consideration of specific toxicity on endocrine-related target organs also seems to be important in assessment of endocrine disruptors. If the regulatory "cut-off" was based alone on current classification for carcinogenicity (C) and/or reproductive toxicity (R), a substance with specific toxic effects on the adrenals or the pancreas might not be banned as an endocrine disruptor, in contrast to a substance known or presumed to cause reproductive toxicity by an endocrine-related mechanism in humans.

Recently, different sets of criteria have been discussed, addressing the challenges mentioned above (Bars et al., 2011; Marx-Stoelting et al., 2011). Governmental agencies such as the Danish EPA (Danish Ministry of the Environment, 2011), French ANSES (ANSES, 2012), British CRD/German BfR (BfR and CRD, 2011) and non-governmental organisations like ECETOC (2009) or Chemtrust (2011) have made proposals available on their websites. A number of these proposals have been summarised in a EU report (Kortenkamp et al., 2012). Scientific issues on the identification and characterisation of endocrine disruptors have also been discussed by expert panels at the European level and results of these discussions have been summarised in recent reports (EFSA Scientific Committee, 2013; Endocrine Disrupters Expert Advisory Group, 2013). While most of these approaches have some principles in common regarding hazard identification, they also show differences especially when it comes to proposals for decision making concerning the regulatory "cut-off". Most proposals are based on the WHO/IPCS definition for endocrine disruptor as "*. . .an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations*" (WHO/IPCS, 2002), and as such concentrate on adverse effects caused by a substance, taking into account the mode or mechanism of action which has to be related to endocrine disruption. In addition, most