Identification, assessment and management of “endocrine disruptors” in wildlife in the EU substance legislation—Discussion paper from the German Federal Environment Agency (UBA)

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HIGHLIGHTS

• Consistency in the identification, assessment and management of ED substances is needed.
• Scientifically robust weight-of-evidence approaches for regulatory decision making are needed.
• More debates on socioeconomic benefits in the context of decision making are needed.

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ABSTRACT

A discussion paper was developed by a panel of experts of the German Federal Environment Agency (UBA) contributing to the on-going debate on the identification, assessment and management of endocrine disruptors with a view to protect wildlife according to the EU substance legislation (plant protection products, biocides, industrial chemicals). Based on a critical synthesis of the state-of-the-art regarding regulatory requirements, testing methods, assessment schemes, decision-making criteria and risk management options, we advise an appropriate and consistent implementation of this important subject into existing chemicals legislation in Europe. Our proposal for a balanced risk management of endocrine disruptors essentially advocates transparent regulatory decision making based on a scientifically robust weight of evidence approach and an adequate risk management consistent across different legislations. With respect to the latter, a more explicit consideration of the principle of proportionality of regulatory decision making and socioeconomic benefits in the on-going debate is further encouraged.

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1. Introduction

In 1999, the European (EU) Commission approved the “Community Strategy for Endocrine Disruptors – a range of substances suspected of interfering with the hormone systems of humans and wildlife” (COM(1999)706), followed by several Commission documents reporting on the progress of implementation of this subject into legislation, with the most recent report published last year (SEC(2011)1001). As key objectives, the strategy claims to identify the problem, causes and consequences of endocrine disruption in both humans and wildlife, and to identify appropriate policy action. As most important long-term measure, the Commission envisaged to amend the EU legislative instruments covering substances as well as consumer, health and environmental protection. Legislative implementation has made considerable progress in the last years such that many pieces of EU chemicals legislation now contain specific provisions on this issue: Particularly, the regulations of industrial chemicals (REACH Regulation 1907/2006), plant protection products (PPP; Regulation 1107/2009) and biocidal products (forthcoming Regulation to replace Directive 98/8/EC) are taking specific account of endocrine disruptors (however, the exact wording used across the regulations is different). All regulations require these substances, once identified, to be subjected to rather strict regulatory action which encompasses hazard classification (i.e. from “fulfilling the exclusion criteria”, to “no low-risk active-substance” or even “candidate for substitution” under PPP and Biocide Regulation and “substance of very high concern” under REACH) and targeted risk management (i.e. hazard-based non-approval under PPP and Biocide Regulation and authorization procedure under REACH, either risk-based or on socioeconomic considerations). The current draft of the biocides regulation focuses on the regulation of endocrine disruptors that
may cause adverse effects in human or which are identified in accordance with Articles 57(f) and 59(1) of REACH.

UBA (Federal Environment Agency) as the German regulatory authority for environmental risk assessment in chemical substance legislations advocates the widely accepted WHO/IPCS (2002) definition of “Endocrine Disruptor” (ED) as one basis for a consistent implementation under different substance legislations. According to this definition an ED is: “An exogenous substance or mixture that alters the function(s) of the endocrine system and consequently causes adverse health effects in an intact organism or its progeny or (sub)populations”. However, regulatory decision making on ED has to consider different protection goals regarding human health and wildlife. Human health risk assessment and management aims to protect individuals from any harmful effects, whereas in general in environmental risk assessment and management, effects on non-target wildlife species might be considered acceptable as the result of an (implicit or explicit) risk–benefit analysis, provided that the long-term stability of populations is not at risk. In order to make the new ED-related regulatory requirements applicable in future decision making, important issues to be discussed are:

- The availability of internationally agreed ED specific testing methods and assessment strategies, respectively, according to the state-of-the-art in science and for all relevant groups of organisms. Differences in (standard) data requirements between the substances legislation have to be taken into account in this respect, too.
- Implementation of specific scientific criteria suitable for regulatory decision-making on whether or not a substance having endocrine disrupting properties should be subject to regulatory measures. A respective proposal (at least with regard to human health) has to be put forward by the EU commission by 14. December 2013 according to Regulation 1107/2009.
- Agreement on how to adequately decide on substances that have been intentionally designed to act on target organisms via endocrine disruption (most pharmaceuticals, several pesticidal and biocidal active substances) with respect to their effects on non-target wildlife species.

In view of this challenges, UBA strongly supports the strategy as laid out in the most recent Commission report (SEC(2011)1001): “In order to respond to the regulatory requirements (…), the Commission intends to develop a systematic approach for the identification and assessment of endocrine disruptors which can be applied across the different pieces of legislation. The detailed application of a general framework will necessarily need to be adapted to the specific requirements of each piece of legislation. However, the general concept should be consistent and should ensure that endocrine disruptors are dealt with in a consistent and coordinated manner.”

This discussion paper was developed as a contribution to the ongoing debate on the identification, assessment and management of ED substances with a view to protect wildlife according to the EU substance legislation.

2. ED in wildlife: assessment and management

With regard to wildlife, assessment and management of EDs needs to consider the following aspects:

- First of all, it should be highlighted that in fact, population-relevant endocrine mediated effects by man-made chemicals occur in wildlife, indicating a need for a more thorough consideration of endocrine disruption in regulatory assessment and management.
- Standard environmental risk assessment (ERA) relies on the extrapolation from relevant endpoints determined in a rather narrow spectrum of test organisms to no-effect-thresholds in all potentially exposed wildlife species. Thus it is essential that laboratory methods testing species, life stages or other biological systems (e.g. cultured cells) on endocrine disrupting mechanisms or effects are adequately representing all relevant ecological and phylogenetical groups and are sufficiently sensitive for a protective risk assessment.
- Management of EDs needs to consider that adverse effects on non-target wildlife species by certain substances intentionally designed to act on target organisms via endocrine disruption (most human and veterinary pharmaceuticals, several pesticidal and biocidal active substances) might occur. Hence, for these substances, other benefits (e.g. socio-economic reasons) also need to be considered.

2.1. Assessment of endocrine disruptors

Lessons learned from known EDs (e.g. TBT) reveal that these substances may affect a variety of taxa such as insects, mollusks or crustaceans which are often not or only partly covered by standard data requirements (WHO/IPCS, 2002). Endocrine mediated adverse effects in vertebrates (e.g. fish, mammals, birds) and invertebrate taxa are typically observable in the longer term and hence observation of full life cycles is needed to ensure that the most sensitive life stages and endpoints are adequately covered in the effect assessment. It has to be emphasized that even short exposure during critical development stages might be sufficient to initiate endocrine mediated effects with these becoming observable only later in lifetime.

By comparing the effects expected for EDs with the endpoints that may be assessed in the available OECD standard test systems, it becomes obvious that adequate test systems capable to sensitively detect endocrine mediated effects for wildlife are hardly available. Corresponding test systems are currently under development for some taxonomic groups (fish, mollusks and frog) in the OECD test guidelines program. However, for other major groups of organisms known to be sensitive toward EDs, specific (respectively sensitive) test systems are missing yet (e.g. birds, reptiles). Although non-standard data are available, these are typically more difficult to interpret in regulatory decision making. Thus it appears challenging to close the large gap of scientific knowledge about ED related effects in wildlife taxa with a view to ensure a high level of protection by means of adequate test methods.

2.2. Proposal for a balanced risk management of endocrine disruptors

In principle, risk-based management approaches are applicable also for EDs, provided (i) adequate testing results are available and (ii) sufficient knowledge about uncertainties of the risk assessment in question allows deriving adequate assessment factors to conclude on realistic and safe effect thresholds in the environment (PNEC). Especially, the lack of testing methods covering certain taxa and endpoints and specific challenges to quantify additional uncertainties for individual ED assessments, justify adapting a more precaution-oriented, i.e. hazard-based, risk-management approach. Additionally, in view of the potential serious effects of endocrine disruptors to wildlife, the political demand of a more precautionary oriented decision making as laid down in the new legislations is recognized. However, even in this hazard-based risk-management approach, clear scientific criteria, testing results, and further scientific information are necessary for identifying those substances to be subjected to hazard-based decision-making. Additionally, some regulatory frameworks may require considering...
further political and socioeconomic issues. Transparent presentation and communication of the different reasoning lines contributing to final decision-making appears of particular importance.

A differentiated decision-making and risk management has to consider the fact that some substances may have endocrine disrupting properties (e.g. showing in vitro estrogen receptor binding activity) but either no adverse relevant effects as a result are observable or the endocrine mediated effects are negligible compared to other effects observed. Regarding certain intentionally designed endocrine disrupting substances, the risk management should trade off their adverse effects on non-target species against the benefits of their use, taking into account the environmental impact of alternatives. This applies particularly to many of the human and veterinary pharmaceuticals, several pesticidal and biocidal active substances.

Taking these aspects into account, the following interpretation of the current legal texts proposing hazard-based management approaches for substances having endocrine disrupting properties (REACH, Pesticides, Biocides) is suggested by the German Federal Environment Agency (UBA). It is suggested to differentiate between three groups of “substances having endocrine disrupting properties”.

2.2.1. Endocrine disruptors subject to hazard-based measures

Although the legal text does not exactly match the WHO definition of an endocrine disruptor (i.e. the causal link between the endocrine mode of action and adverse effects is not stressed) it is understood that the essentially similar legal text in REACH, Pesticides legislation and draft Biocide legislation aims at specifically regulating substances with endocrine disrupting properties due to their potential special harm to wildlife and the environment. Thus it seems to be feasible that only those endocrine disrupting substances that cause adverse effects should be regulated by a hazard-based approach. If a substance is a relevant endocrine disruptor and the endocrine mode of action is not intended for fulfilling a certain purpose, e.g. of a pesticide, a hazard-based approach is considered adequate, since such an approach would encourage substitution of substances with such an undesired mode of action. Those substances would be subject to non-approval under the pesticides and also under the draft biocides legislation if they are identified in accordance with Articles 57(f) and 59(1) of REACH and should be considered as substances of very high concern under REACH.

Further guidance has to be developed on the weight of evidence that is needed to conclude that adverse effects observed are endocrine mediated, especially with regard to organism groups other than fish and mammals. Such guidance should take into account that current tests procedures make it difficult to definitively prove a causal linkage, what is why a weight of evidence approach is needed in regulatory decision making. It would be beneficial, if respective guidance would be developed under the OECD umbrella in the near future.

2.2.2. Substances having endocrine disrupting properties not subject to hazard-based measures

Some substances may have endocrine disrupting properties e.g. in in vitro tests but no subsequent adverse effects are observed in vivo (i.e. the WHO ED definition is not fulfilled). For these substances it can be assumed that they do not result in specific, endocrine mediated harm to wildlife. As for these chemicals a risk-based assessment and management seems to be possible with sufficient certainty, they should not be managed by a hazard-based approach. The same may hold true for substances which do evoke endocrine mediated adverse effects but these effects are considered not relevant with respect to the overall (eco)toxicological profile of the substance (e.g. endocrine mediated effects were observed under clearly unrealistic exposure conditions resulting in rather non-specific “systemic” toxicity or if non-endocrine mediated effects are predominating).

In order to properly differentiate – on a case-by-case basis – these substances from those that should undergo hazard-based management, further guidance and criteria need to be developed (e.g. on the level of confidence that is needed to ensure that the endocrine mediated effect is not relevant with respect to the overall (eco)toxicity profile). A careful analysis is needed to ensure that the available tests data are appropriate to sensitively detect endocrine mediated effects.

2.2.3. Endocrine disruptors exempted from hazard-based measures

It is suggested that pesticidal and biocidal active substances that were intentionally designed to specifically act on target organisms from the group of invertebrates or plants by endocrine disrupting properties (e.g. insect growth regulators, pheromones, plant growth stimulators) should be exempted from the hazard-based approach due to their benefits in fulfilling a certain purpose. Rigorous interpretation of the new endocrine cut-off criterion would result in non-approval of plant protection and also biocidal products containing such active substances if they are identified in accordance with Articles 57(f) and 59(1) of REACH. It should be acknowledged that the on-going use of existing and the future development of selectively endocrine acting pesticides and biocides is justifiable: While a risk for phylogenetically closely related non-target organisms (from the group of invertebrates or plants) due to the endocrine disrupting properties is to be expected and has to be assessed and managed properly, these active substances typically show a rather low toxic potential for vertebrates (including humans). However, case-by-case decision-making, based on comparative environmental hazard and risk profiles (i.e. comparison with alternative active substances) and comprehensive and transparent risk–benefit analysis is considered mandatory for this group of active substances. International agreement and explicit guidance on how to conduct both types of analyses is needed; important issues to be discussed in this respect are the requirements regarding a sufficient indicator endocrine action (best case: only few target species affected) and an acceptable persistence-limitation of the active substance in the environment. Thereby, an approach consistent to endocrine active substances in human and veterinary pharmaceuticals would be followed; also for the latter the socioeconomic benefits of use are compared (however, typically not explicitly) to the well-described (e.g. ethinylestradiol in contraceptive pills) or supposed (from mode of action and potency considerations) environmental hazards and risks.

3. Concluding remarks

This paper is reflecting the state-of-the-discussion of UBA experts involved in the identification, assessment and management of ED substances according to the EU substance legislation, mainly for plant protection products, biocides and industrial chemicals. It is to be understood as a contribution to the on-going debate on the appropriate and consistent implementation of this important subject into existing legislation in Europe. Essentially, the proposal presented advocates a differentiated regulatory decision making based on a scientifically robust weight of evidence approach and an adequate risk management consistent across different legislations. With respect to the latter, a more explicit consideration of the principle of proportionality of regulatory decision making and socioeconomic benefits in the on-going debate is encouraged. Clearly, the proposal presented is preliminary
such that any feedback is acknowledged and continued cooperation with interested member states, regulatory bodies and other stakeholders in the near future is highly welcomed.

Conflict of interest statement

The authors have no conflict of interest.

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