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Für Mensch und Umwelt

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Division IV Chemical Safety
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UBA comment on the revision of Article 60 (3) of the REACH legislation according to Article 138 (7)

Introduction:

According to Art 138(7) "the Commission shall carry out a review to assess whether or not, taking into account latest developments in scientific knowledge, to extend the scope of Article 60(3) to substances identified under Article 57 (f) as having endocrine disrupting properties. "

Art 60 (3) describes that for certain substances authorization "may only be granted if it is shown that socio-economic benefits outweigh the risk to human health or the environment arising from the use of the substance and if there are no suitable alternative substances or technologies." Currently Art 60 (3) is restricted to substances of very high concern according to Article 57 (a), (b), (c) or (f) for which it is not possible to determine a threshold, and to substances meeting the criteria in Art 57 (d) or (e). Thus it focuses on substances for which, with regard to human health no threshold can be derived (CMR substances) or substances for which, with regard to the environment , it is not possible to derive a predicted no effect concentration (PNEC) with sufficient certainty (PBT or vPvB substances). In this context it is important to understand, that with regard to PBT or vPvB substances, inclusion into Art 60 (3) is not based on the fact that there is no threshold for these substances (i.e. that a single molecule may already cause an effect). PBT and vPvB substances are included because, due to the combination of different intrinsic properties, it is not possible to derive a 'safe' concentration in the environment with sufficient reliability using traditional quantitative risk assessment methodologies (EC, 2007, ECHA 2008). Thus although a threshold may exist, it is currently not possible to determine where it may be.

In conclusion, with regard to Art 138 (7) and with regard to the environmental concern, the question arises whether or not it is possible to derive a 'safe' concentration in the environment for Endocrine Disruptors with sufficient reliability using traditional quantitative risk assessment methodologies.

The German Federal Environment Agency (UBA) funded a research project addressing this question focusing on the aspect whether uncertainties to derive such a safe concentration are higher for Endocrine disruptors compared to other substances with regard to the environment. (Duis et al, 2012).

Results of the project are summarized followed by an UBA conclusion with regard to Art 138 (7).

Summary of project results

Within the project, factors that may lead to an increased uncertainty of the assessment of environmental effects were identified, mainly on the basis of review publications and documents of international organisations (e.g. OECD). Specific examples for the identified factors were included. For these examples, the original literature was reviewed. The relevance of the identified factors, which might lead to an increased uncertainty of the environmental risk assessment (ERA) for EDCs, was evaluated.

The following factors were identified and further analysed:

- Availability and implementation of tests for assessing endocrine effects
- Possibility to extrapolate results for test species to other species in the environment
- Influence of sensitive time windows or delayed effects
- Influence of irreversibility of effects
- Importance of effects that might not be covered by traditional risk assessment methods (behavioural effects, other effect with uncertain relevance for the population, transgenerational / epigenic effects, immunotoxicological effects)
- Influence of potential unusual dose-concentration relationships (low dose effects, non-monotonic dose response curves)
- Mixture effects and exposure assessment

Results of the project are summarized in Table 1.

According to the project the following two key factors contribute most to an increased uncertainty of the environmental risk assessment of endocrine active substances as compared to baseline toxicants:

(1) the limited availability of test methods and

(2) the limited knowledge on the feasibility of cross-species extrapolation.

Both factors have highest relevance for aquatic invertebrates.

With regard to (1) the conclusion drawn was that for effects on the estrogen/androgen and thyroid axis of aquatic vertebrates the uncertainty is acceptable given that these effects are covered reasonably well by a tiered testing strategy. However, for other endocrine modes of action (e.g. effects on the corticosteroid system) in aquatic vertebrates resulting uncertainty of the environmental risk assessment is higher. Current test methods for fish are restricted to teleost fish, the most important fish taxa and thus it is not possible to assess whether an assessment based on teleosts is protective for these taxonomic groups. With regard to aquatic invertebrates only a few tests are available which do not cover endocrine specific endpoints. Further research is needed to systematically evaluate if test results obtained with these species are sufficiently protective for other invertebrate groups and consequently uncertainties for aquatic invertebrates are high.

With regard to (2) the conclusion is that, while for fish cross-species extrapolation is feasible with some restrictions, this does not hold true for invertebrates. For invertebrates, extrapolation between species is far more complex than for fish. This is due to the much

higher diversity and heterogeneity of invertebrates and to the often fragmentary knowledge on endocrine effects and the underlying processes in invertebrate species. Consequently uncertainty for invertebrates is high. For fish some aspects need further consideration such as the finding that fish species exhibiting a high metabolic capacity (which are usually tested in long-term tests) may not be protective for species with slower metabolism such as rainbow trouts. In addition, potential risks to seasonally spawning fish species (e.g. brown trout) may be underestimated when the PNEC is derived based on effects on standard test species.

The following two factors also increase the uncertainty of the ERA of EDCs: Given that aquatic organisms are very likely to be exposed to complex mixtures of substances with endocrine activity, potential additive effects of EDCs are relevant. Worst case exposure situations coinciding with sensitive periods in the development of seasonally reproducing organisms may be an additional relevant factor.

Table 1: Relevance and specificity of the factors that may contribute to an increased the uncertainty of the environmental risk assessment for substances with an endocrine mode of action (Duis et al, 2012).

Factor that may contribute to increased uncertainty		Relevance for environmental risk assessment	Specificity to EDCs	Feasibility to address this factor and to reduce the uncertainty that is causes
Limited availability and implementation of test methods	Fish	Low [1] / Medium [2]	Yes	High (but partly longer-term) [2]: further test development and standardisation / validation, implementation of tests
	Invertebrates	High	Yes	High (but partly longer-term) [4]: further test development, implementation of tests
Limited knowledge on feasibility of extrapolation between species	Fish	Low – medium	No	Medium – high (but longer-term): systematic evaluation, further studies
	Invertebrates	High	No	Medium (longer-term): systematic evaluation, further studies
Sensitive time windows for exposure, delayed effects	Fish	Low [1]	Yes	Not required: tiered testing framework with appropriate tests available [1]
	Invertebrates	Medium	Yes	Life-cycle testing in invertebrates
Irreversibility of effects		Low	No	Not required
Behavioural effects	Fish reproductive behaviour	Low [1]	Yes	Not required
	Other behavioural effects	(?) [5]	No	(Further investigations required)
Low-dose effects with non-monotonic dose-response relationship		Low	Yes	Not required
Effects with uncertain population relevance (secondary sexual characteristics in fish)		Low	Yes	High: triggering of further testing
Transgenerational / epigenetic effects		(?) [5]	No	(Further investigations required)
'Atypical' effects: immunotoxicity		(?) [5]	No	(Further investigations required)
Effects on the gene pool		(?) [5]	No	(Further investigations required)
Mixture effects		Medium – high	No	Medium to high (but partly longer-term)
Exposure assessment		Low – medium	No	High: worst case exposure estimates

(1) For estrogen receptor mediated effects, androgen receptor mediated effects and interference with steroidogenesis. (2) For other endocrine mechanisms of action. (3) Due to the lack of diagnostic endpoints in invertebrates. (4) For life-cycle tests without or with few specific diagnostic endpoints. (5) Further research is required to evaluate the relevance of these factors.

As summarized in Table 1 some of the uncertainties are specific to Endocrine Disruptors. Other uncertainties are considered not to be specific for Endocrine Disruptors. For example uncertainties in extrapolating from a few test species to other wildlife species applies to environmental risk assessment in general. However, several publications show that for substances with specific modes of action such as Endocrine Disruptors uncertainties are higher compared to substances with no specific mode of actions (baseline toxicants). This is due to a higher toxicity and higher variation in toxicity between species. Thus the project concludes that the uncertainties associated with the extrapolation from a few test species to other wildlife species are very likely to be higher for Endocrine Disruptors than for substances with a narcotic mode of action but may be high for other specific modes of action, too. Similar holds true to endpoints not covered in traditional risk assessment methods such as behavioral effects.

For most of the uncertainties discussed, it is in principle feasible to reduce them. However, this may require further test development, systematic evaluations, further investigations and additional tests to be included in the traditional risk assessment. In most cases this implies that uncertainties can be reduced in the long-term only.

In conclusion, the study is suggesting that with respect to wildlife assessing a safe concentration for the environment is connected with higher uncertainties than for other substances and that it may require long-term actions to reduce these uncertainties.

<u>UBA conclusion with regard to Art 138 (7) and the environment</u>

With regard to the environment, the assessment of endocrine disruptors is influenced by the fact that the endocrine system, especially the hypothalymic-pituitary-gonadal axis which involves sex- steroids such as estradiol and testosterone is widely conserved in vertebrates. Several reviews show that these vertebrate type sex-steroids are also involved in reproduction in a range of invertebrate taxa including jellyfish, crustaceans, mollusks and echinodermata like sea urchins (see Duis et al, 2012 and Kortenkamp et al, 2011 for details). Thus it is very likely that once released to the environment, such substances will cause effects in a variety of species including very different taxonomic groups.

Based on the analysis by Duis et al (2012) it seems to be possible to derive a 'safe' concentration in the environment with sufficient reliability for sex steroids in gonochorist, frequently spawning teleost fishes with high metabolic acitivity using current test methods available. However, the analysis also indicates that this might not be true for all teleost fish species and that especially for seasonal spawners with low metabolic activity effects might be underestimated. With regard to invertebrates the analysis clearly shows that it is not possible to derive a 'safe' concentration as it is currently unknown whether or not results obtained with the test methods available or under development are sufficient protective for other invertebrate groups. Results observed for some groups such as sea urchins indicate that they may not be protective enough. Although similar uncertainties might hold true for substances with other specific modes of action, they are higher than for substances with non-specific narcotic modes of action which account for at least 60% of all chemicals under the scope of REACH.

As indicated by Duis et al (2012) it might be possible to overcome these shortcomings on the long-term. However, this would require intensive research and probably would increase the testing requirements significantly.

Based on this analysis UBA draws the conclusion that for Endocrine Disruptors identified as SVHC according to Art 57 (f) due to their concern for the environment, it is currently not possible to predict a no effect concentration for the environment with sufficient certainty, and, hence, no risk quotient should be derived with regard to the environment. Thus, similar to PBT and vPvB substances, Endocrine Disruptors identified as SVHC according to Art 57 (f) due to an environmental concern should only be authorized, if it is shown that socio-economic benefits outweigh the risk arising from the use of the substance and if there are no suitable alternative substances or technologies. In conclusion the scope of Art 60 (3) should be extended to substances identified under Article 57 (f) as having endocrine disrupting properties causing serious effects for the environment. This conclusion is based on the following considerations:

- Due to the conservation of the endocrine system in various taxonomic groups during evolution it is very likely that once released to the environment, Endocrine Disruptors may cause adverse effects in a variety of species including very different taxa.
- Due to the differences in the endocrine response and the high variety of taxa involved, it is currently impossible to identify which species are sufficiently representatives for wildlife with regard to endocrine effects.
- Currently available test methods are very limited and especially with regard to invertebrates do not cover sensitive taxa and life stages.

Although it might be possible to overcome these shortcomings in future this is considered to be a long term activity and, based on the already available indications of harmful effects in the environment, it seems not to be adequate to await this progress.

References:

Duis et al, (2012): “Substances of very high concern under EACH – an evaluation of uncertainties in the environmental risk assessment of endocrine active substances”. Project report.

Kortenkamp A., et al, (2011), "State of The Art Assessment of Endocrine Disrupters, Final Report", Project Contract Number 070307/2009/550687/SER/D3, 23.12.2011. Page 27 http://ec.europa.eu/environment/endocrine/documents/4_SOTA%20EDC%20Final%20Report%20V3%206%20Feb%2012.pdf