

BfR-Position on thresholds for adverse effects of substances with endocrine disrupting properties with respect to human health

The European Commission invited European regulatory agencies to deliver their positions on the existence of thresholds for Endocrine Disruptors (ED) in the context of Article 138(7) of Regulation (EC) No 1907/2006 (REACH).

With respect to human health hazard assessment, possible thresholds for EDs should be based on **adverse** effects, because an ED is defined as a substance causing adverse effects in an intact organism, or its progeny, or (sub)populations (WHO/IPCS, 2002).

The general paradigm is that toxic effects are based on threshold modes of action. This is due to the interaction with **multiple target** molecules (i.e. receptors, enzymes) in a signal transduction cascade, which have to be triggered to cause a toxic effect. Thus, this concept is basically applicable to endocrine effects which are determined by complex toxicokinetic, toxicodynamic and feedback regulation processes. An exception from this rule is given by i.e. DNA-reactive genotoxic substances causing irreversible changes in a **single target** molecule (DNA).

Recently, toxicological risk assessment of EDs is challenged by the possibility of non-monotonic dose-response relationships especially in the lower dose-range. Although toxic effects at low doses are in principle difficult to investigate, it has to be noted that non-monotonic dose responses would not be in disagreement with threshold modes of action. However, identification of threshold doses may become even more difficult.

Even though not all underlying mechanisms are fully understood up to now, in toxicological risk assessment of EDs two cases might be distinguished:

- (1) Substances for which the available toxicological information allows the derivation of a No Observed Adverse Effect Level (NOAEL) with sufficient confidence and there is no reliable data on adverse effects at dose levels below the NOAEL. Here, it is commonly accepted regulatory practice to establish safe exposure levels by use of uncertainty factors, e.g. toxicological reference values such as Acceptable Daily Intake (ADI) or Derived No-Effect Level (DNEL).
- (2) For some substances, indications for endocrine related effects may be observed in non-standard toxicity tests at dose levels below the NOAEL derived from standard toxicity tests. At present, there is no harmonized concept of how to integrate such low dose effects for regulatory decision. Hence, case by case decisions are needed, taking into account unique peculiarities and the higher degree of uncertainty in the assessment of such effects.

Expert judgement based on the current knowledge is generally required to assess the toxicological significance of the experimental observations. It should be considered that the arguments presented above may not be specific to substances affecting the endocrine system but to toxic substances in general.

In conclusion, following science based principles of toxicological risk assessment; **the assumption for EDs should be that a threshold of adversity exists.**