Title: “Scientific principles for the identification of endocrine disrupting chemicals – a consensus statement”

Outcome of an international expert meeting organized by the German Federal Institute for Risk Assessment (BfR)

Introduction

Endocrine disruption is a form of chemical toxicity, in which hormone actions are perturbed to such an extent that adverse effects result. One consequence of this can be impairment of the role of hormones in programming development. Endocrine disruption was identified from morphological and reproductive changes observed in a number of aquatic and terrestrial species such as molluscs, crustaceans, fish, reptiles, birds and mammals in various parts of the world, as well as in laboratory animals. There are a variety of natural and anthropogenic chemicals that can produce such harmful effects on the body's endocrine (hormone) system, so-called endocrine disruptors (EDs).

In the light of concern about potential negative human health and environmental impacts caused by EDs, the EU adopted a Strategy on Endocrine Disruptors in 1999 and introduced specific legislative obligations, which include the aim of protecting human health and the environment from exposures to EDs.

In the summer of 2013, when an initial draft of criteria for the identification of EDs was discussed within the European Commission, a controversy developed among scientists about the scientific principles that should guide the assessment of EDs. This dispute has complicated the decision-making process in the European Commission regarding the ways in which EDs should be assessed. In the aftermath of a European Commission conference on EDs held in Brussels, 1 June 2015, a group of scientists involved in these debates began to explore whether it might be possible to overcome the apparently differing views and develop a common understanding.

These efforts resulted in a meeting that took place in Berlin on 11-12 April 2016, hosted by the German Federal Institute for Risk Assessment (BfR). Twenty-three international scientists convened and discussed basic principles and open questions on the assessment of endocrine disruptors. Dame Anne Glover, the Scientific Advisor of former European Commission President Jose Manuel Barroso, kindly agreed to act as the moderator of the discussions. The expert meeting focused on the following open questions:

- How should endocrine disruptors be identified in the regulatory context of health assessment? What are the general principles of endocrine effects from a toxicological, pharmacological and endocrinological perspective?

- Which sources of uncertainty influence the regulatory decision-making process? Is it possible to determine toxicological limit values for endocrine disruptors? What role is played by so-called “low-dose effects” with regard to hazard identification?
- What are the sources of scientific certainty that influences regulatory decision-making? Is it possible that what we know can be employed more effectively to make these decisions?
- What are the scientific foundations of regulatory decision-making? What adverse effects can already be documented with confidence using the existing investigation methods?
- Which scientific research needs should be initiated for the better identification of endocrine disruptors?

The regulatory background

The meeting considered a number of EU regulations that require information leading to data on the endocrine disrupting potential of substances. However, the data requirements vary strongly among the regulations so that the “One Substance – One toxicological Assessment” concept cannot be met (see Figure 1 for a presentation of the data requirements and principles of regulation in different EU regulations).

For substances with substantial data requirements (e.g. pesticides), the strictest regulatory consequences are proposed while for other groups of substances with fewer data requirements (and a higher level of uncertainty), the consequences may be less significant. Using the examples of isoflavones, di(2-ethylhexyl)phthalate (DEHP), and copper compounds, it was briefly discussed whether the same substance may be regulated differently without harmonized criteria applicable to all regulations.

In order to implement regulatory actions for EDs, a number of initiatives have been taken in the past years at EU level, aimed at reaching agreement about scientific principles. that could be used as input to European Commission work on the development of criteria for the identification of EDs. However, the implementation of the established legislation has been hampered by what appeared as a scientific disagreement among endocrinologists and toxicologists, which arose during the process of developing ED criteria.

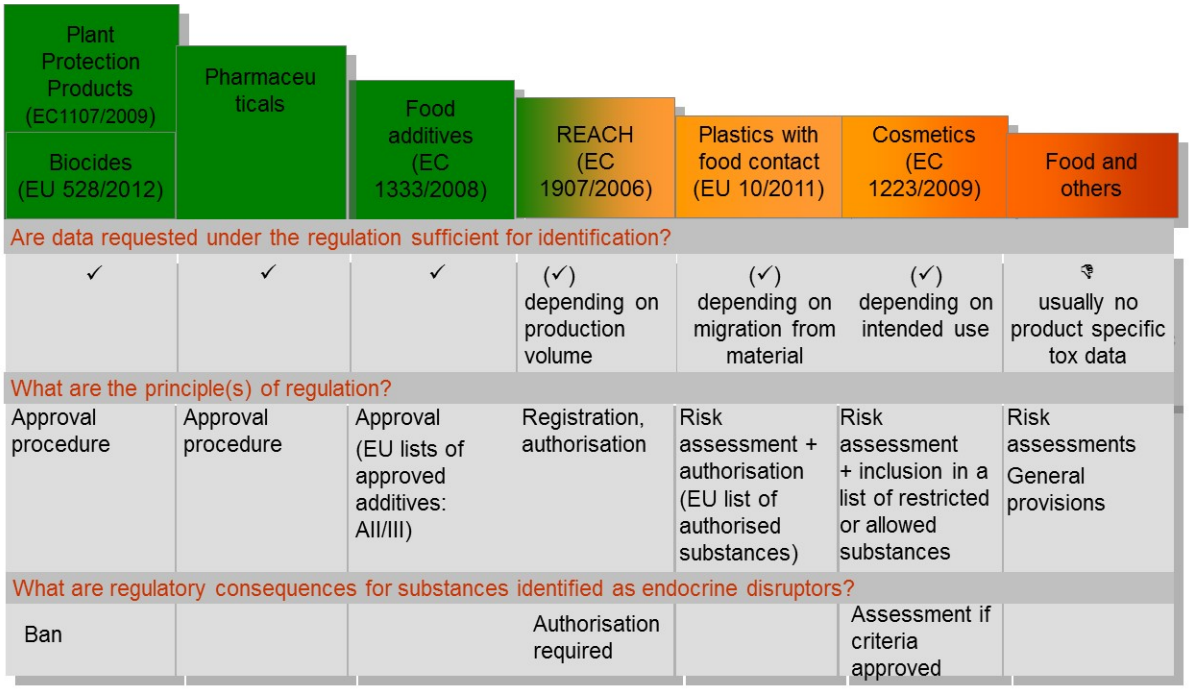

Figure 1: *Overview of data requirements and principles of regulation in EU legislation addressing endocrine disruptors (Source: Andreas Hensel, BfR, Expert meeting 11 April 2016).*

It was recognized that without scientific criteria for the identification and characterisation of endocrine disruptors in all fields of risk assessment of natural and anthropogenic chemicals, the goal of "One Substance – One Assessment" is not achievable.

It was emphasised that the outcome of the expert meeting was urgently needed to provide a consensus statement on the state of the science for ED identification, that could input to the European Commission's mandate to develop and implement criteria for ED identification as required by EU law, and that this had been reinforced by the recent ruling of the European Court of Justice (T-521/14). The court ruled that the European Commission (EC) failed to fulfil its obligations under the Biocidal Products Regulation No 528/2012 to adopt the delegated acts concerning the specification of scientific criteria for the determination of endocrine-disrupting properties by 13 December 2013 (Judgment in Case T-521/14).

Non-European procedures for assessment of EDs

David Dix (US EPA) and Hiroaki Aoyama (IET, Japan) presented information about procedures for the assessment of EDs in other jurisdictions, the USA and Japan. The United States Environmental Protection Agency (US EPA) established the Endocrine Disruptor Screening Program (EDSP) as one of the outcomes of the Food Quality Protection Act and Drinking Water Act. The EDSP is a two-tiered process consisting of a screening phase (Tier

1), which evaluates for potential bioactivities and endocrine modes of action of chemicals, and a testing phase (Tier 2), which, for those chemicals testing positive for bioactivity, evaluates their potential endocrine-related adverse effects. EDSP Tier 1 is comparable to the OECD Levels 1-3 activities, and Tier 2 is comparable to OECD Levels 4-5. Currently, the EDSP is focused on validating and screening assays in the estrogen, androgen and thyroid pathways as well as steroidogenesis. A recent achievement of the EDSP is the completion of the first screening of 52 chemicals (Federal Register published June 19, 2015; FRL-9928-69). Currently, the EDSP is continuing with data generation and analysis from the first screening and is pursuing validation of the employed test methods according to the OECD Guideline 34 using known reference chemicals. However, data generation using these methods takes some time, and currently the EPA is developing and assessing alternative high throughput approaches, using ToxCast and Tox21 methods. Some of these approaches are showing promise. The US EPA believes that the results generated, together with additional information on toxicokinetics and exposure, can be of use for the EU and to the research field of endocrine disruption.

In Japan, assessment of endocrine disruption is currently conducted by the Food Safety Committee of Japan (FSCJ). Japan also accepts the WHO/IPCS definition (2002) of an endocrine disruptor and believes that acceptable daily intake (ADI) values based on no-observed-adverse-effect-levels (NOAELs) can be obtained from existing toxicological studies and when necessary, mode of action data obtained from additional mechanistic studies. When it comes to non-monotonic dose response relationships (NMDR), it is believed that such phenomena may be a consequence of factors such as intra-strain genetic heterogeneity and variations in dietary phytoestrogen content. They therefore need to be carefully reconfirmed using genetically homogeneous inbred rodent strains and a phytoestrogen-free diet.

Developing the consensus

During the scientific meeting, issues defined in advance together with the participants, via a draft document, were discussed. The intention was to achieve a high-level constructive, scientifically acceptable outcome that could be agreed by all participants. During the meeting the draft text circulated in advance was refined such that it could be supported by all of the experts and could be distributed to decision makers in the European Commission, identifying areas of agreement, together with areas where complete agreement could not be reached. This would provide risk managers with the necessary information to determine whether any remaining areas of disagreement are actually policy-relevant or policy-critical. In the following sections, the text agreed by all experts is presented.

The statement has been submitted to the journal Archives of Toxicology for publication.