FEDERAL INSTITUTE
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BfR
Bundesinstitut für Risikobewertung

Endocrine Disruptors - Outcome of an international expert meeting

Andreas Hensel

BfR - Expert Meeting to Reach Scientific Consensus on Endocrine Disruptors

Goals and objectives

An expert conference on endocrine disruptors organised by the Federal Institute for Risk Assessment (BfR) was held in Berlin on 11 and 12 April 2016. The meeting focussed on the following questions:

- How should endocrine disruptors be defined in the regulatory context of health assessment?
- What are the general principles of endocrinological effects from a toxicological, pharmacological and endocrinological perspective?
- Which sources of uncertainty influence the regulatory decision-making process?
- What adverse effects can already be documented using the existing investigation methods?
- Which scientific research activities should be initiated for the better identification of endocrine disruptors?

The aim of the scientific discourse was to discuss the issues amongst the participants and, where possible, to identify ways of resolving the differences of opinion that exist.

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Outcome

- 23 scientists from Europe, the USA, Japan and four observers of the EU Commission, the European Food Safety Authority (EFSA) and the European Chemicals Agency (ECHA) discussed the basic principles and open questions on the assessment of endocrine disruptors
- The international experts clarified open questions in criteria for endocrine disruptors and hazard identification of harmful endocrine substances
- Report and paper published at BfR and EFSA web site as well as accepted by EHP

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

http://www.bfr.bund.de/cm/349/scientific-principles-for-the-identification-of-endocrine-disrupting-chemicals-a-consensus-statement.pdf

ehp ENVIRONMENTAL HEALTH PERSPECTIVES

Brief communication

"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)

Solecki, Roland[1,*,+]; Kortenkamp, Andreas[2*]; Bergman, Åke[3]; Chahoud, Ibrahim[4]; Degen, Gisela H[5]; Dietrich, Daniel[6]; Greim, Helmut[7]; Håkansson, Helen[8]; Hass, Ulla[9]; Husoy, Trine[10]; Jacobs, Miriam[11]; Jobling, Susan[2]; Mantovani, Alberto[12]; Marx-Stoelting, Philip[1]; Piersma, Aldert[13]; Slama, Remy[14]; Stahlmann, Ralf[4]; van den Berg, Martin[15]; Zoeller, R. Thomas[16]; and Boobis, Alan R[17]

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Breakthrough in the scientific discussion of endocrine disruptors

- A **consensus** was reached on background, definition of an ED, related concepts, sources of uncertainty, scientific principles important for ED identification, and research needs.
- Relevance for assessment according to the principle “One Substance – One Toxicological Assessment”.
- Next steps: The consensus is offered as advice to the European Commission for the first step in their decision-making process to meet their legal obligations.
- Suggestion: EFSA and ECHA to initiate the discussion for a harmonised guidance for both biocides and plant protection products.

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Thank you for your attention

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Picture sources: BfR; UNEP

One Substance – One Toxicological Assessment?

Real world: - different regulations
- different data requirements
- different regulatory consequences

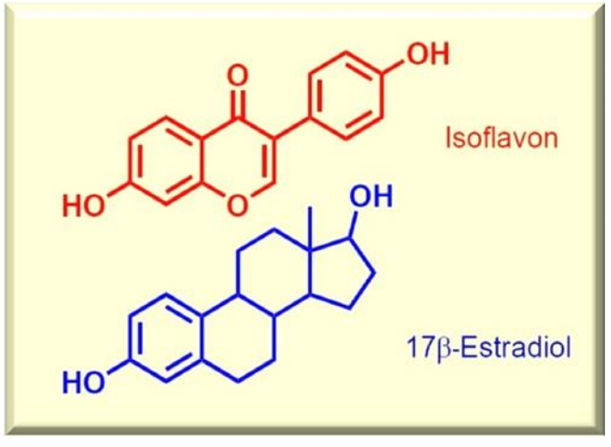
Plant Protection Products (EC1107/2009) / Biocides (EU 528/2012)	Pharmaceuticals	Food additives (EC 1333/2008)	REACH (EC 1907/2006)	Plastics with food contact (EU 10/2011)	Cosmetics (EC 1223/2009)	Food and others
Are data requested under the regulation sufficient for identification?						
✓	✓	✓	(✓) depending on production volume	(✓) depending on migration from material	(✓) depending on intended use	👎 usually no product specific tox data
What are the principle(s) of regulation?						
Approval procedure	Approval procedure	Approval (EU lists of approved additives: AII/III)	Registration, authorisation	Risk assessment + authorisation (EU list of authorised substances)	Risk assessment + inclusion in a list of restricted or allowed substances	Risk assessments General provisions
What are regulatory consequences for substances identified as endocrine disruptors?						
Ban			Authorisation required		Assessment if criteria approved	

One Substance – One Toxicological Assessment?

Critical considerations:

- For some substances with a broad data package (e.g. pesticides) the strictest regulatory consequences (ban) are proposed while for other groups of substances with fewer data (and a higher level of uncertainty) less strict consequences may have to be applied
- For hazard based regulations exposure may not have to be considered
- It may be difficult to come to similar toxicological assessments for the same substance under different regulations (as illustrated by a few examples)

One Substance – One Toxicological Assessment?
Example 1 – isoflavones in food and feed



Isoflavones (e.g. formonenetin)

Sheeps on meadows with red clover

Isoflavones (e.g. genistein, daidzein)

Extracts, novel food etc.

- High amounts of certain isoflavones
- No clarified safety for a longterm intake with high isoflavone dose

„Clover Disease“

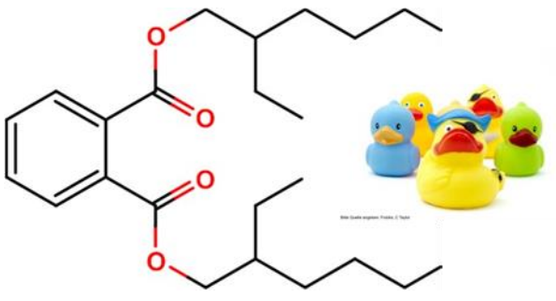
- disturbance of fertility (reversible/irreversible)
- early aborts
- enlargement of uterus/udder

One Substance – One Toxicological Assessment? Example 1 – isoflavones in food and feed

For each of the several isoflavones, the aim one substance one toxicological assessment is difficult to achieve because:

- Different strength of evidence for ED effects by different isoflavones
- Classical toxicology (e. g. definition of NOAEL values) and hazard-based risk assessment do not fit for the risk evaluation of food supplements
- So far **no regulatory options** for endocrine active substances in food supplements (Regulation (EC) No 178/2002, Article 14 „**Food must be safe**“)

One Substance – One Toxicological Assessment? Example 2 – DEHP



Di(2-ethylhexyl)phthalate

DEHP as food contact material

Specific migration limit:
1,5 mg/kg food
Restrictions: plasticiser in repeated use materials and articles containing non fatty food.

Critical effect on the male reproductive system: NOAEL = 5 mg/kg body weight per day
TDI (EFSA, 2005) = 0.05 mg/kg body weight per day

DEHP as REACH chemical

Mode of action: inhibition of testosterone production

DEHP – Not yet identified as human health ED under REACH

One Substance – One Toxicological Assessment? Example 2 – DEHP

For DEHP, the aim one substance one toxicological assessment is difficult to achieve because:

- DEHP is regulated under different pieces of legislation
  - E.g. as food contact material and industrial chemical under REACH
  - Different regulations contain different regulatory consequences for potential ED
- Without harmonized criteria applicable to all regulations the same substance may be regulated differently

One Substance – One Toxicological Assessment?
Example 3 – Copper compounds

Copper compounds as REACH chemical

SVHC candidate?

Copper compounds as pesticide

Ban ?

Testis atrophy observed in one study where copper was injected at high dose levels

Mode of action: unclear

Copper is also an essential metal and can be found in food

One Substance – One Toxicological Assessment? Example 3 – Copper compounds

For copper, the aim one substance one toxicological assessment is difficult to achieve because:

- Copper would be regulated under different pieces of legislation
  - E.g. as pesticide and industrial chemical under REACH
  - Different regulations contain different regulatory consequences for potential ED
- Without harmonized criteria applicable to all regulations the same substance may be regulated differently

One Substance – One Toxicological Assessment! Lessons learned from the examples

- Without scientific criteria for the identification and characterisation of endocrine disruptors in all fields of risk assessment of chemical and natural substances the goal one substance – one toxicological assessment is not achievable

- To come to such criteria several underlying controversies (e.g. on thresholds, non-monotonic-dose response curves) have to be solved

- Aim of the workshop is to look for potential compromises in these controversial issues

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Goals and objectives

Several open questions should be answered:

- Do EDC have a threshold?
- Is the level of uncertainty different from other substances?
- How can we identify EDC in a scientific and transparent way?

There is a need for scientific advise to politics. Without scientific advise the decision on criteria might be driven by political issues alone.

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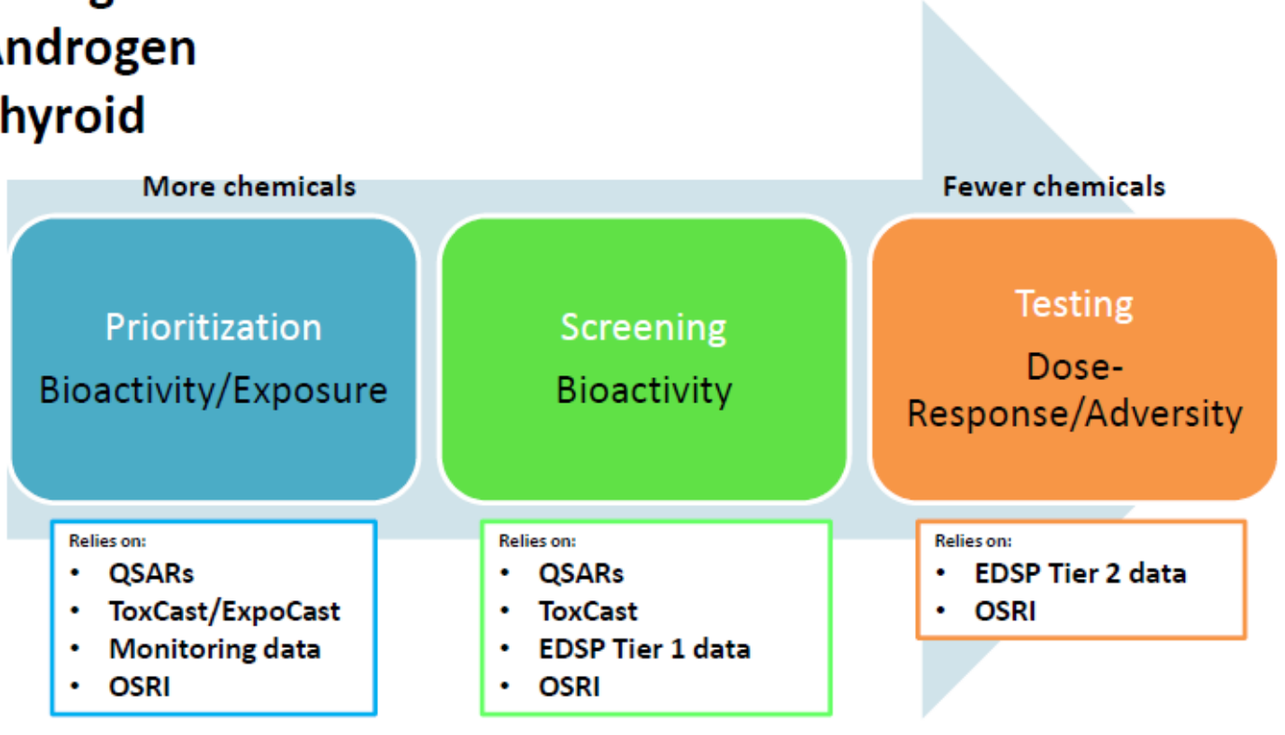
Goals and objectives

- Striving to reach a consensus with all participants.
- The intended outcome was to refine the circulated draft text such that all participants can lend their names to it.
- Identifying areas of agreement, together with topics where complete agreement cannot be reached.
- Distributing the results of this meeting decision makers in the European Commission.
- The risk managers should assess whether any potentially remaining aspects of disagreement are actually policy relevant.

EDSP Prioritization, Screening & Testing

Pathways:

Estrogen
Androgen
Thyroid



Prioritization and Screening for bioactivity
Testing for dose-response and adverse effects

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U.S. EPA Endocrine Disruptor Screening Program

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Office of Chemical Safety and Pollution Prevention
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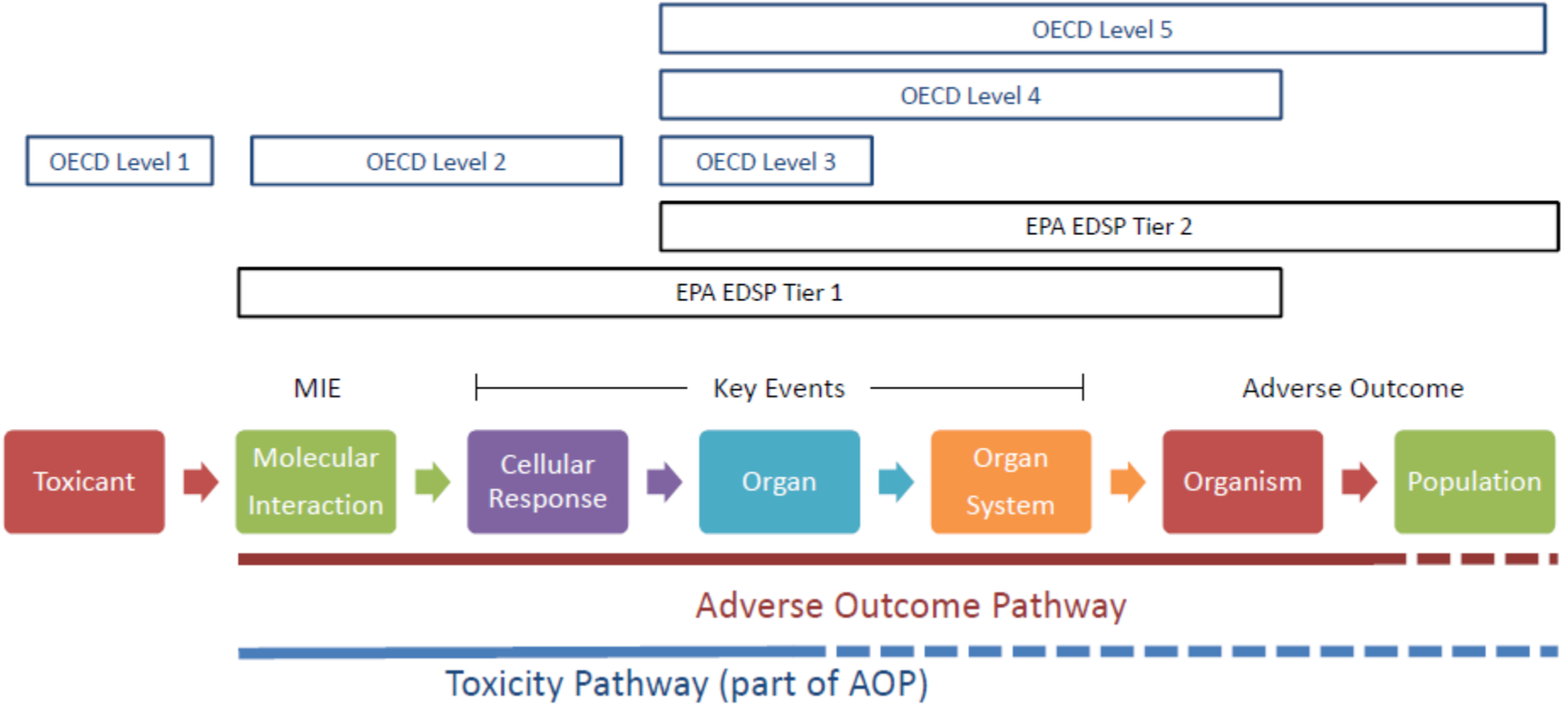
April 11th 2016
Expert Meeting to Reach Scientific Consensus on Endocrine Disruptors
Berlin, Germany

EDSP Screening and Testing



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Our Doubt about Inverted U-shape Dose-response

- ✓ Most studies reporting inverted U-shape dose-responses used small numbers of outbred animals carrying genetic polymorphism(s). ⟶ Genetic variation(s) might be the cause of such phenomenon.
- ✓ Most studies reporting inverted U-shape dose-responses used phytoestrogen-rich diets. ⟶ Can we exclude the interference by phytoestrogens?
- ✓ Most studies reporting inverted U-shape dose-responses did not elucidate the basic mechanism(s) of such phenomenon.

A Japanese View on Assessment of Endocrine Disrupting Chemicals

Hiroaki Aoyama, Ph.D.
Executive Director, Toxicology Division
Institute of Environmental Toxicology

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Our Proposal and Conclusions

- ✓ An endocrine disruption is one of the typical modes of action of toxicity, through which adverse health effects are induced.
- ✓ NMDR (or inverted U-shape dose response) should be carefully reconfirmed by using an inbred strain of rats or mice without any genetic variations and artificially synthesized phytoestrogen-free diet, if a common toxicology study revealed such phenomenon.
- ✓ We think we will be able to set ADI based on the results of a series of common toxicology studies and additional mechanistic studies for examining the mode of action.

A Japanese View on Assessment of Endocrine Disrupting Chemicals

Hiroaki Aoyama, Ph.D.
Executive Director, Toxicology Division
Institute of Environmental Toxicology

BfR - Expert Meeting to Reach Scientific Consensus on Endocrine Disruptors

First Results

Scientific principles for the identification of endocrine disrupting chemicals – a consensus statement

Background

1. Key pieces of EU chemicals regulation, including the Plant Protection Product Regulation (EU No 1107/2009), the Biocidal Product Regulation (EU No 528/2012), the Water Framework Directive (2000/60/EC), REACH (EU No 1907/2006) and the Cosmetics Regulation (2009/1223/EC) include the aim of protecting human health and the environment from exposures to endocrine disruptors.

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First Results

Definition of endocrine disruptors and related concepts

10. We acknowledge the WHO definition of an endocrine disruptor as follows: "An ED is an exogenous substance or mixture that alters the function(s) of the endocrine system and consequently causes adverse effects in an intact organism, or its progeny, or (sub)populations."

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First Results

Scientific foundations of regulatory decision-making

19. The various relevant pieces of EU chemicals regulation require both hazard and risk assessment approaches for decision making to be applied in different ways. Some regulations stipulate mainly hazard-based criteria for regulation (e.g. EU No 1107/2009, EU No 528/2012).
20. The determination of a compound as an endocrine disruptor is a hazard identification procedure. Established principles governing disruption of the programming function of hormones mean that hazard identifications for endocrine disruption have to take account of the timing of exposure during development and the irreversibility of adverse effects.

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First Results

21. We recognise that certain adverse outcomes appearing to be arising from endocrine disruption can also occur through non-endocrine modes of action. Moreover, adverse effects or modes of action compatible with endocrine disrupting characteristics but demonstrated to be non-specific effects secondary to another toxic effect should not be considered relevant for identification of endocrine disruption. The identification of a chemical as an endocrine disrupter therefore has to rely on weight-of-evidence evaluations of both adversity and mode of action together. We agree that endocrine activity on its own should not trigger a chemical's identification as an endocrine disruptor.
22. We agree that a chemical's potency to induce an adverse effect is an important factor for consideration during the characterisation of the hazards of endocrine disruptors. However, potency is not applicable for identification of a compound as an endocrine disruptor. There

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First Results

24.

This document has focused on the identification of endocrine disruptors. However, the assessment of the corresponding risks on human health and wildlife would further require consideration of dose-response relationships, including potency, exposure assessment and risk characterisation, including susceptible sub-populations, severity and reversibility of effects. This emphasizes the one chemical – one assessment philosophy which has implications for data generation of both regulated and unregulated chemicals.

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First Results

Research needs

25. More effective regulation could be achieved by closing certain knowledge gaps. We recommend that these knowledge gaps should be identified through a systematic gap analysis. Notwithstanding such an analysis, we recognize that future research needs include the following main areas:
    a. Exposure assessment of substances with ED properties,
    b. Experimental research to clarify ED modes- and mechanisms-of-action, to produce an improved understanding of the molecular events underlying adverse outcomes and to better understand whether irreversible effects of developmental programming are induced in a threshold-dependent manner or not, and
    c. Test method and biomarker development, including validation, to ensure more sensitive and robust identification of EDCs.

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First Results

Research needs

27. Resolution of the issues of non-monotonic dose-response relationships and threshold-mediated action requires systematic efforts of understanding the mechanism underlying adverse effects of endocrine disruptors.
28. The existence of dose-thresholds for endocrine disruptors continues to be debated. We recognize that it may be difficult to distinguish a true threshold from an apparent threshold which merely arises from the limits of detection of the experimental system. Thus, the question of dose-thresholds for endocrine disruptors cannot be resolved through empirical studies, but has to rely on mechanistic investigations and increased knowledge on the functions and programming of the endocrine system during specific windows of sensitivity.

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The BfR publishes workshop report based on the expert meeting on endocrine disruptors

BfR communication No. 11/2016, 4 May 2016

On the occasion of an expert meeting organised by the Federal Institute for Risk Assessment (BfR) held in Berlin on 11 and 12 April 2016, a consensus was reached on the identification of endocrine disruptors. The BfR has now published the workshop report from the conference. It contains, among other things, the consensus paper agreed by all participants. The report is published at
http://www.bfr.bund.de/cm/349/scientific-principles-for-the-identification-of-endocrine-disrupting-chemicals-a-consensus-statement.pdf

The presentations given at the meeting as well as a preliminary conclusion from the conference are available as videos on the website of the BfR:
http://www.bfr.bund.de/en/international_expert_meeting_on_endocrine_disruptors-197246.html

The consensus paper will be published in a scientific journal soon.

"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)

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Background: Endocrine disruption is a specific form of toxicity, where natural and/or anthropogenic chemicals, known as "endocrine disruptors" (EDs), trigger adverse health effects by disrupting the endogenous hormone system. There is need to harmonize guidance on the regulation of EDs, but this has been hampered by what appeared as a lack of consensus among scientists.

Objectives: This publication provides summary information about a consensus reached by a group of world-leading scientists that can serve as the basis for the development of ED criteria in relevant EU legislation.

Methods: Twenty-three international scientists from different disciplines discussed principles and open questions on ED identification as outlined in a draft consensus paper at an expert meeting hosted by the German Federal Institute for Risk Assessment (BfR) in Berlin, Germany on 11-12 April 2016.

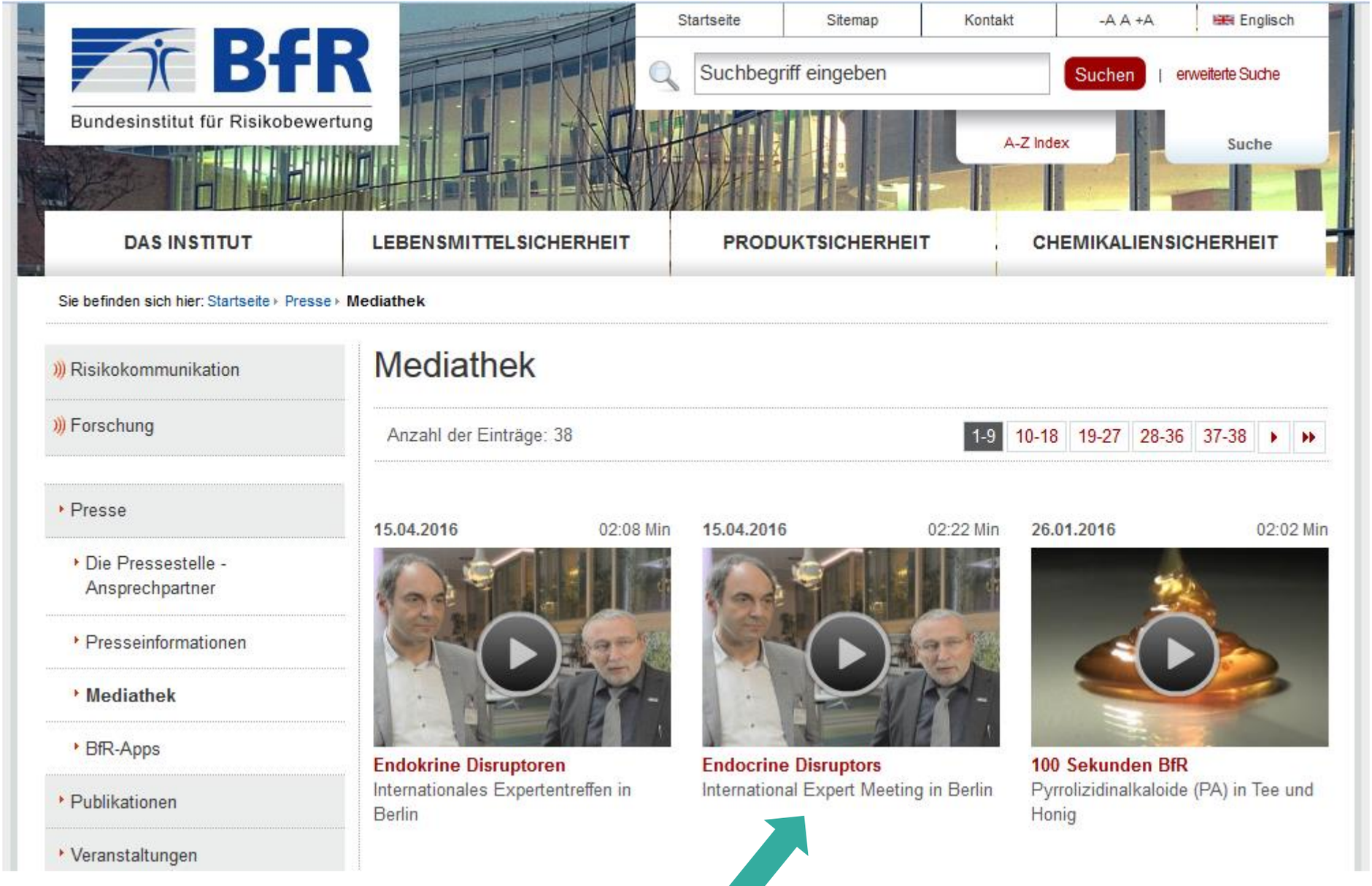
Discussion: Participants reached a consensus regarding scientific principles for the identification of EDs. The paper discusses the consensus reached on background, definition of an ED and related concepts, sources of uncertainty, scientific principles important for ED identification, and research needs. It highlights the difficulty in retrospectively reconstructing ED exposure, insufficient range of validated test systems for EDs, and some issues impacting on the evaluation of the risk from EDs, such as non-monotonic dose-response and thresholds, modes of action, and exposure assessment.

Conclusions: This report provides the consensus statement on EDs agreed among all participating scientists. The meeting facilitated a productive debate and reduced a number of differences in views. It is expected that the consensus reached will serve as an important basis for the development of regulatory ED criteria. Further details about the expert meeting can be found at

Endocrine disruptors: scientific discussion on the basic principles for the assessment of substances that influence the hormonal system

BfR Communication no. 007/2016 of 12 April 2016

On the initiative of a group of scientists, a meeting of experts has taken place on 11 and 12 April 2016 on the topic of substances that harm the hormonal system. The meeting was organised by the Federal Institute for Risk Assessment (BfR) with the aim of constructively promoting scientific discourse in this area. The precondition for determining whether the use of a specific product might result in a health risk to the consumer is the existence of a well-founded scientific assessment of the endocrine disruptors that may be present in the product in question. There are currently differing opinions among scientists who work in this area of research with regard to the basic principles used for the assessment of substances that are harmful to the hormonal system. Substances that are foreign to the body can be designated as "endocrine disruptors" if they harm the health of an organism by altering the function of the hormonal system. Such substances can occur naturally in plants, be administered in medications or contained in chemical substances and products such as plant protection products, biocides, food additives or cosmetics. The findings of the meeting will be published on the BfR website and additionally in a scientific journal.



Meeting video available