FEDERAL INSTITUTE FOR RISK ASSESSMENT

BfR

Risiken erkennen – Gesundheit schützen

ASSESSING ENDOCRINE DISRUPTING SUBSTANCES

Handling of risk assessment under different regulations

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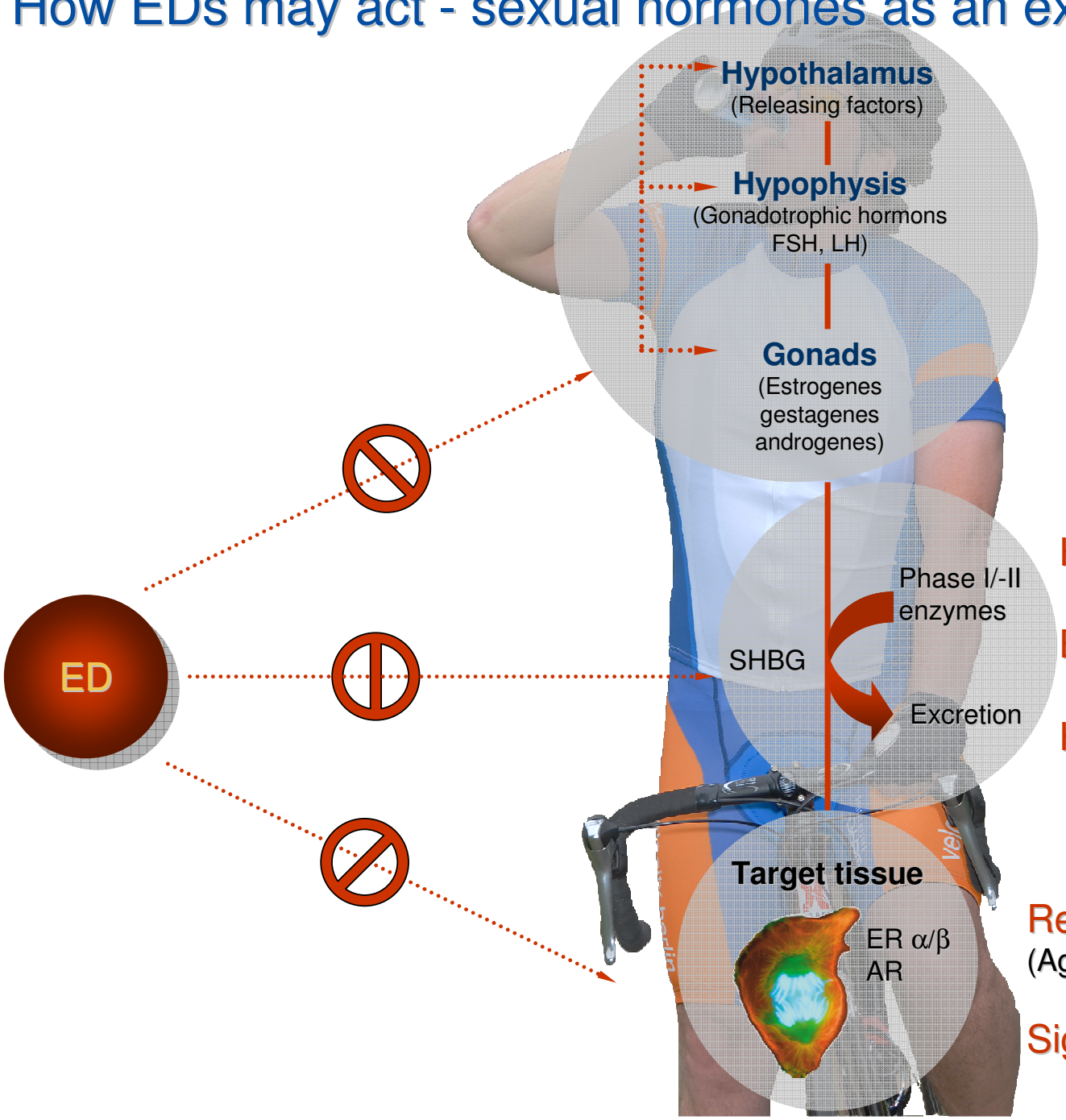
How EDs may act - sexual hormones as an example



Feed back mechanisms

Hormone biosynthesis

Binding to transport proteins

Hormone metabolism

Receptor binding
(Agonist/antagonist)

Signal transduction

What is an Endocrine Disruptor?

Endocrine active substances (EAS)

⇨ effects on the endocrine system

Endocrine disruptors (EDs)

⇨ effects on the endocrine system
⇨ induce adverse health effects

Definition of „Endocrine Disruptors“

WHO/IPCS 2002 definition

An Endocrine Disruptor is

- an exogenous substance or mixture
- that alters function(s) of the endocrine system
- and consequently causes adverse health effects
- in an intact organism, or its progeny, or (sub) populations.

in vitro or in vivo methods

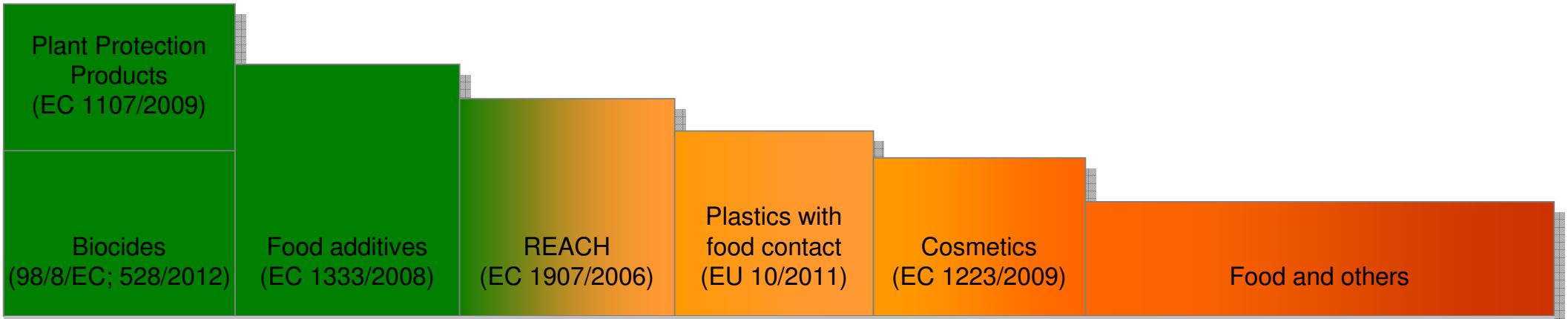
in vivo methods

Definition of “adversity” (WHO/IPCS 2004)

“A change

- in morphology, physiology, growth, reproduction, development or lifespan of an organism
- which results in impairment of functional capacity
- or impairment of capacity to compensate for additional stress or increased susceptibility to the harmful effects of other environmental influences.”

…One substance – one toxicological assessment!



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 toxicological data from manufacturers for the authorities available

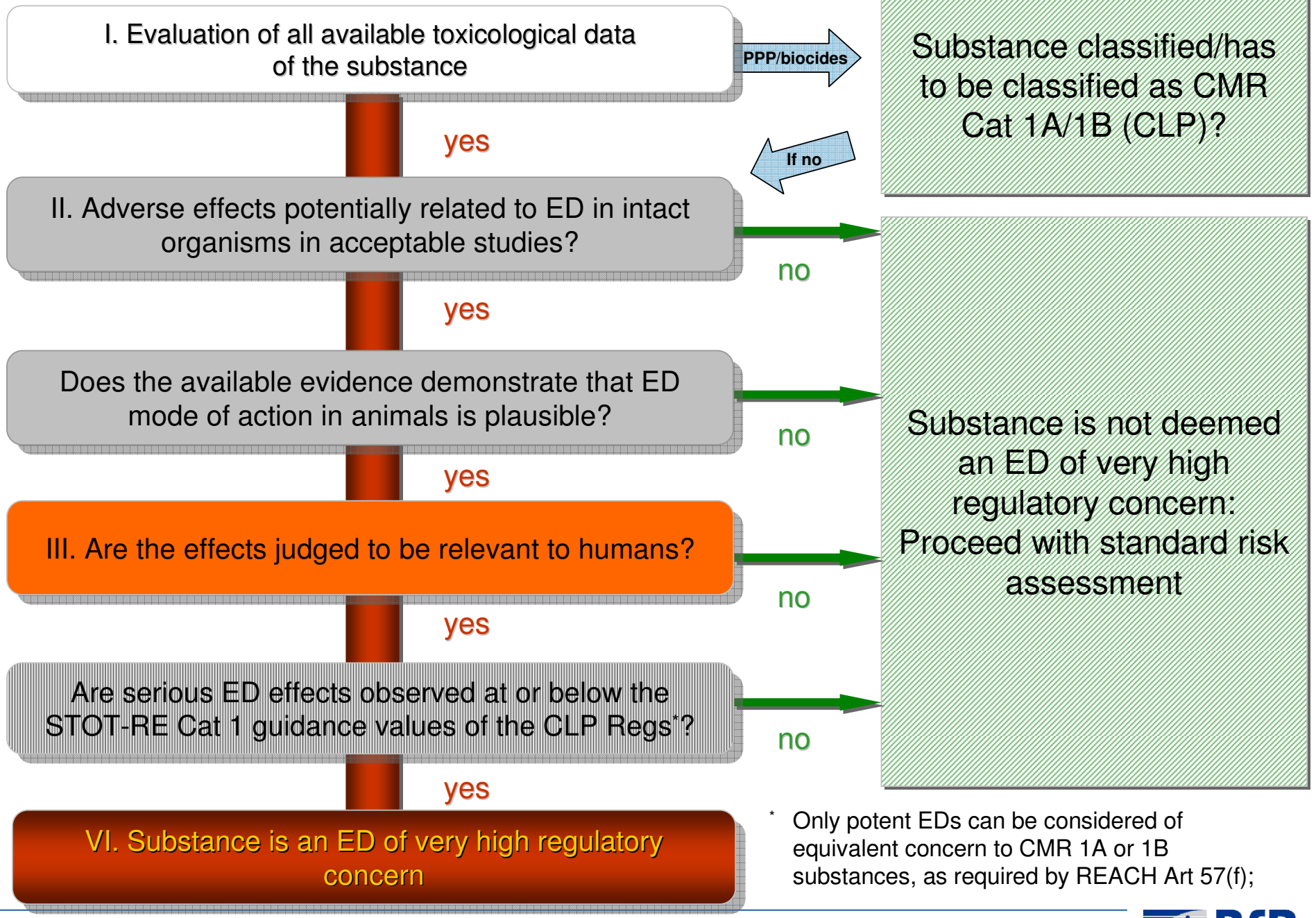
What are the principle(s) of regulation?

Approval procedure	Approval (EU lists of approved additives: AII/III)	Registration, Authorization	Risk assessment + authorization (EU list of authorized substances)	Risk assessment + addition to lists of • prohibited substances (AII) • substances with restrictions (AIII) • allowed substances (AIV, V, VI)	Risk assessments General provisions

Avoiding disparities in the assessment of toxicological properties between the different regulations

→ Predictability, efficiency, consistency

Identification of human health related ed properties (joint BfR-CRD proposal 2011)



* Only potent EDs can be considered of equivalent concern to CMR 1A or 1B substances, as required by REACH Art 57(f);

Decision tree to assess human health related ED properties

I. Data evaluation

Existing Data & non-test information

- Physical & chemical properties
- available toxicological data (standardized or non-standardized tests)
- Read across, QSAR, other *in silico* predictions, ADME modelling

II. Identification of EDCs

Weight-of-evidence process

- Are the adverse toxicological effects potentially related to ED in intact organisms in acceptable *in-vivo* studies (e.g. OECD CF Level 4/5)?
- The available data provide convincing evidence or demonstrate an ED mode of action?
- Are the effects judged to be relevant to humans?

III. Categorization/priorization

Decision matrix

- guidance values STOT (Repeated Dose) Category 1 (CLP)
- severity of effect
- reversibility of effect
- others if applicable

ED effect suspected

Request for further toxicity testing

ED 1

No approval
no authorization
no placing on the market

ED 2

Standard Risk Assessment

- e.g. regulation according to the most sensitive toxicological endpoint

Regulatory consequence(s)*

*	Biocides	(EU) No 528/2012
	Plant Protection Products	(EC) No 1107/2009
	Chemicals	(EC) No 1907/2006
	Cosmetic ingredients	(EC) No 1223/2009
	Food additives	(EC) No 1333/2008
	Plastic with food contact	(EC) No 10/2011
	Food	(EC) No 178/2002

ED classes with relevance to regulation*

Decision matrix	ED 1	ED 2
Guidance values for specific target organ toxicity after repeated exposure (STOT Repeated Dose Category 1, CLP)	below STOT 1 values	exceeded
Severity of effect(s)	severe	significant effects
Reversibility of effect(s)	(i)rreversible	reversible
Other aspects	(if applicable)	(if applicable)

* ED Categorization: implies direct regulatory consequence (e.g. no approval)

* ED Priorization: implies no direct regulatory consequence (e.g. SVHC identification acc. Article 57f/REACH)

* based on WHO/IPCS definition (2002)

Substances in plastic materials with food contact*

* EU No 10/2011 (Plastic materials and articles intended to come into contacts with food)
EFSA (2008) Note for Guidance (Food Contact Materials)

A. Migration < 0.05 mg/kg of food:

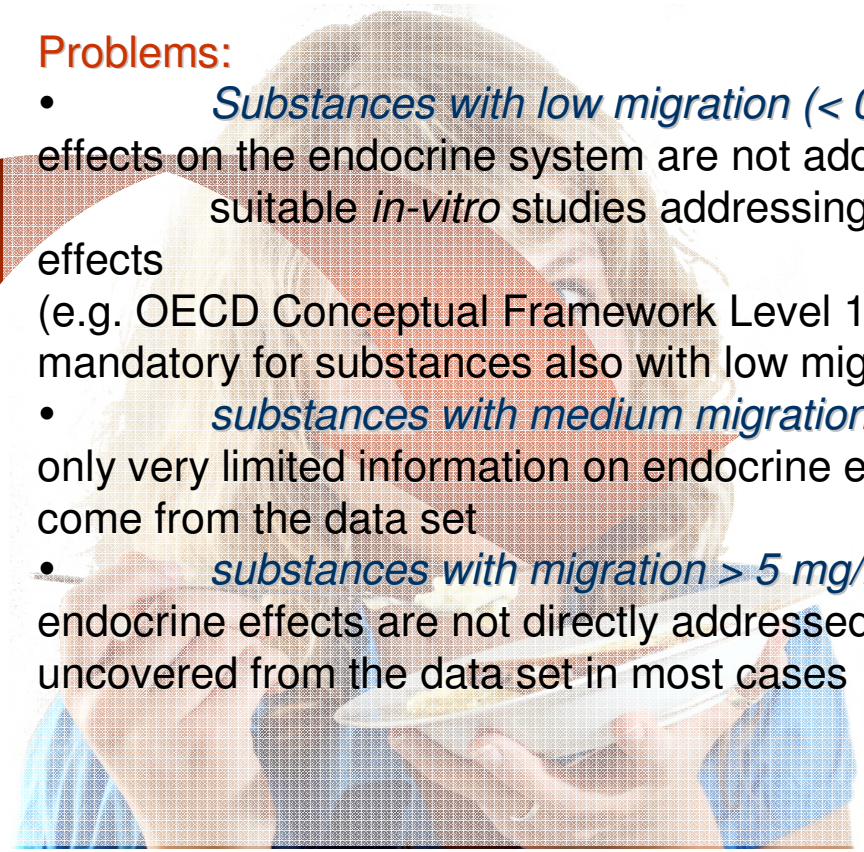
- Quantification of migration
- Genotoxicity assays:
  * bacterial assay (Ames test)
  * mammalian gene mutation assay
  * chromosome aberration assay

B. Migration 0.05 – 5 mg/kg of food:

in addition to (A)
- 90d toxicity study (oral)
- investigation of bioaccumulation

C. Migration 5-60 mg/kg food:

in addition to (B):
- Toxicokinetics and metabolism
- Chronic toxicity and carcinogenicity
- Developmental toxicity
- Reproductive toxicity



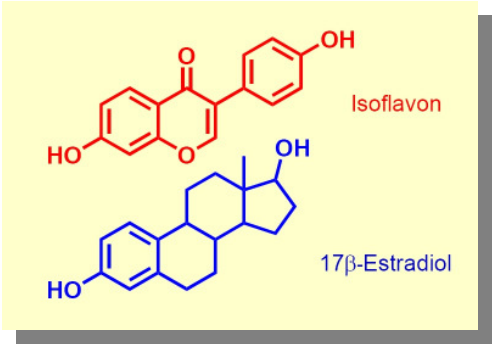
Problems:

- *Substances with low migration (< 0.05 mg/kg)*: effects on the endocrine system are not addressed suitable *in-vitro* studies addressing endocrine effects (e.g. OECD Conceptual Framework Level 1/2) should be mandatory for substances also with low migration!
- *substances with medium migration (< 5 mg/kg)*: only very limited information on endocrine effects might come from the data set
- *substances with migration > 5 mg/kg*: endocrine effects are not directly addressed but could be uncovered from the data set in most cases

Substances in food

Examples:

isoflavones (e.g. genistein and daidzein), botanical extracts etc.



- Food supplements contain often high amounts of certain nutrients/compounds

  intake often not achievable via „normal“ food items

- Usually a lot of toxicological data available for single ingredients

  But often only limited toxicological data available for single products (necessary for case-by-case decisions)

- Very limited safety evaluations in human studies

- So far no risk assessment concept or regulatory options for endocrine active substances in food supplements (Regulation (EC) No 178/2002, Article 14 „Food must be safe“)

Core messages

1. In the interest of predictability and efficiency, the purpose of this concept is to ensure a consistent high level of protection of human health under different regulations based on a scientific weighting of available data.

2. The decision tree combines a flexible scientific weight of evidence process and a conclusion based on a decision matrix including established toxicological guidance values (STOT RE Category 1 of CLP) which ensures
   - comprehensive decisions
   - assures predictability of legal decisions (e.g. in authorization procedures)

3. The concept was originally designed for substances where a complete set of toxicological data is available.

   Yet, it provides a common principle for the evaluation and authorisation of ED substances to ensure a harmonised approach e.g. for

• Biocides	under Regulation (EC) No 528/2012
• Plant Protection Products	under Regulation (EC) No 1107/2009
• Chemicals	under Regulation (EC) No 1907/2006 (REACH)
• Cosmetic ingredients	under Regulation (EC) No 1223/2009
• Food additives	under Regulation (EC) No 1333/2008
• Plastic with food contact	under Regulation (EC) No 10/2011
• Food	under Regulation (EC) No 178/2002

BUNDESINSTITUT FÜR RISIKOBEWERTUNG

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THANK YOU FOR YOUR ATTENTION

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