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Integrated Environmental Assessment of Endocrine Disruption Effects in the New EU REACH System

Hans-Christian Stolzenberg[1], Barbara Werschkun[2]

[1] Ecotoxicological Assessment of Substances
Federal Environment Agency (UBA), Dessau, Germany

[2] Federal Institute for Risk Assement (BfR), Berlin, Germany

Outline

- Relevant aspects of new REACH regulation
- REACH Implementation Project RIP 3.3-2
- Guidance for integrated environmental assessment of endocrine active substances
  - Information requirements and information sources
  - Evaluation of information
  - Conclusions on endocrine activity
  - Integrated assessment of potential endocrine activity

Relevant REACH aspects

- **R**egistration
  (30,000 substances > 1 tonne/year)
- **E**valuation
  (5,000 substances > 100 tonnes/year + substances of concern)
- **A**uthorisation
  (1,400-2,000 substances of very high concern)
- **CH**emicals

- Authorisation

  ➔ *Substances of very high concern:*
  CMR, PBT, vPvB
  + substances of equivalent concern (e.g. having endocrine disrupting properties)

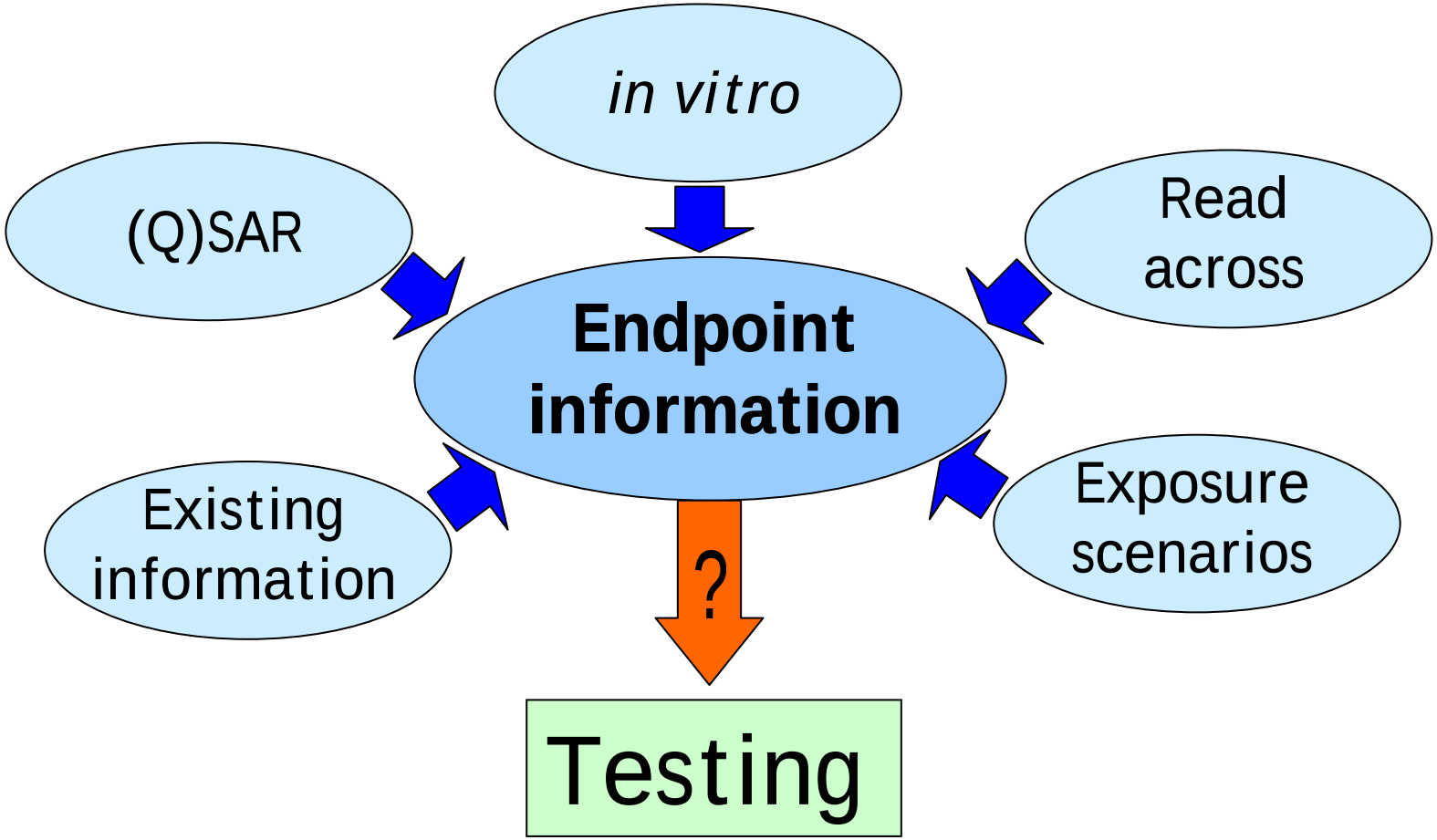
  - Authorisation limited to specified uses
  - Adequate control of risk, socio-economic analysis, assessment of alternatives

- Registration
  - ➔ *Ecotoxicological standard information requirements:*
    - Annex VII (>1t/a): *Daphnia* acute, algal growth
    - Annex VIII (>10t/a): + fish acute (“consider long-term”)
    - Annex IX (>100t/a): + *Daphnia* repro, fish long-term, i.e. OECD 210, 212, 215
    - Annex X (>1000t/a): + long-term testing terrestrial and sediment organisms, birds
- ➔ *No specific identification of endocrine activity!*

- REACH Implementation Projects
  RIPs develop guidance and IT-tools for the Agency, industry and the authorities
  http://ecb.jrc.it/reach/rip/

- RIP 3.3-2: guidance for industry how to fulfill the information requirements on intrinsic properties of substances

ITS Integrated Testing Strategies



- Specific Guidance Endpoint Aquatic Toxicity
  - **Appendix 5** – Assessment of available information on endocrine and other related effects
  - **Section 1** - Information requirements: -/-
  - **Section 2** - Information and its sources:
    non-testing data (Q)SAR, read across, chemical categories
    testing data *in vitro / in vivo* screening assays, confirmatory tests with vertebrates (fish, frog, …) and invertebrates

➔ *reference to OECD toolbox, EDTA special activity*

- Environmentally relevant ED-specific information currently available in REACH?
  - Specific test data on endocrine effects in fish, e.g. from scientific papers ➔ *very few substances*
  - Specific *in vitro* data on endocrine modes of action, e.g. from scientific papers ➔ *very few substances*
  - Information on chemical structure indicating potential endocrine activity ➔ *all substances*
  - Test data from mammalian toxicity studies indicating potential endocrine activity ➔ *many substances*

REACH information requirements: Toxicity

Testmethod	*Life stage, duration*	*Endpoints*	*Indication for ED*
Annex VIII / IX: short-term toxicity (rodents)			
OECD 407/408	adult, 28/90 days	clinical state biochemistry organs, histology	sexual organs (weight, histology)
Annex IX: Reproductive toxicity (rodents)			
OECD 414	implantation until birth	prenatal development	[developmental failures]
OECD 416	two generations	menstrual cycle, spermatology, reproduction, development, sexual organs	
Annex X: Carcinogenicity / long-term toxicity (in rodents)			
OECD 452	adult, up to 2 years	clinical state biochemistry organs, histology	sexual organs (weight, histology)

- Specific Guidance Endpoint Aquatic Toxicity
  - **Appendix 5** – Assessment of available information on endocrine and other related effects

… continued (1)

  - **Section 3** – Evaluation of information:
    Assist the registrant in judging and ranking the adequacy (reliability + relevance) of information.
    Structure as in section 2 along non-testing, *in vitro*, *in vivo* screening and testing methods/data

- Specific Guidance Endpoint Aquatic Toxicity
  - **Appendix 5** – Assessment of available information on endocrine and other related effects

... continued (2)

  - **Section 4** – Conclusion on endocrine activity: *Give guidance if and how information relating to endocrine activity and resulting adverse effects should be considered for regulatory conclusions.* Structure along regulatory endpoints: C+L, PBT assessment, Chemical Safety Assessment, Art. 57f

- Specific Guidance Endpoint Aquatic Toxicity
  - **Appendix 5** – Assessment of available information on endocrine and other related effects

... continued (3)

  - **Section 5** – Integrated assessment of potential endocrine activity:
    Integrate previous sections about how to gather and evaluate existing information and how to relate this to REACH purposes + requirements.
    1) Preliminary indication, 2) Indication,
    3) Characterisation of long-term adverse effects

Integrated assessment of potential endocrine activity

Standard information:

- Chemical structure
- Toxicity in rodents

= may **indicate** potential endocrine action

→ *propose substance evaluation, generate additional data, if necessary*

Non-standard information:

- *in vitro* assays
- Biomarker

= **confirm** endocrine mode of action

→ *propose substance evaluation, generate additional data, if necessary*

- Sexual development
- Reproductive success

= **characterise** long-term adverse effects

→ *regulatory consequences*

Summary

- Ecotoxicological REACH standard information requirements are not sufficient to identify substances of very high concern, such as endocrine active substances
- Integrated assessment of endocrine disruption effects uses:
  - Standard and non-standard information
  - Testing and non-testing information, *in vitro* and *in vivo* screening data, confirmatory *in vivo* test data
  - Judging and ranking of data reliability and relevance
  - Preliminary indication, indication and characterisation of long-term adverse effects for conclusions on regulatory decisions: C+L, PBT and chemical safety assessment, authorisation procedure according to REACH Art. 57f

Take Home Message

- First guidance to assess endocrine active substances to be used in European regulatory schemes
- Case-specific flexibility, testing tools development is work in progress
  ➔ requires careful learning by doing

Thank you!

Like discussion or clarification?

➔ *mailto:hans-christian.stolzenberg@uba.de*