Endocrine Disruptors - Recent global regulatory developments and data requirements for endocrine disruptor testing and assessment

Martina Duft, Agnes Schimera, Anja Rämisch

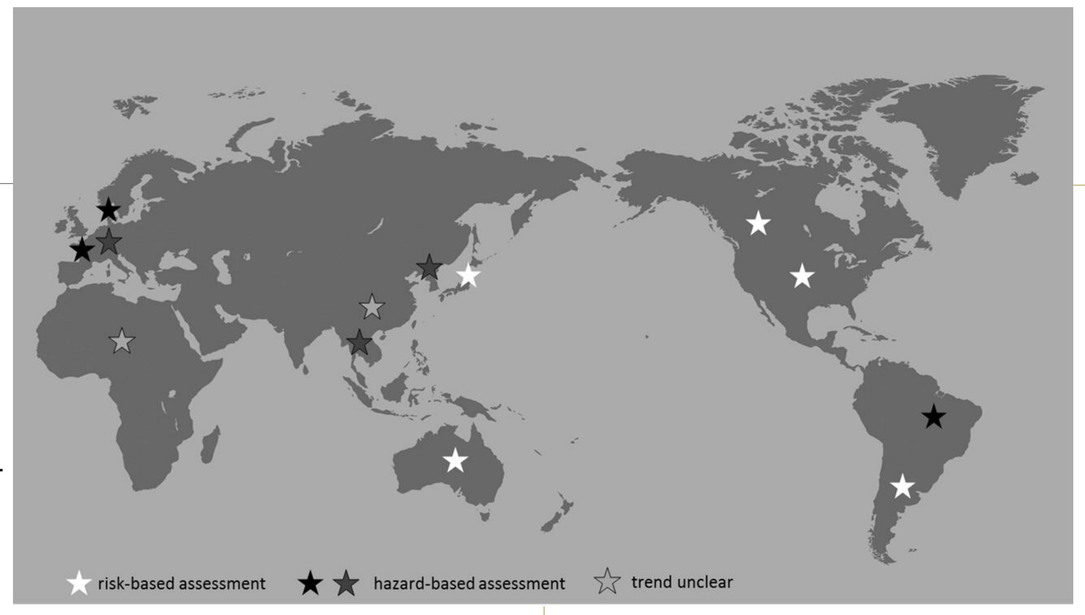
knoell worldwide registration

"*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*" (WHO, ICPS, 2002)

Introduction

Despite decades of scientific research as well as extensive discussions and work within regulatory panels, an intended consensus on the assessment of substances with an endocrine disrupting potential, so-called **endocrine disruptors**, has not yet been reached.
Various diverging proposals for an assessment of industrial chemicals, plant protections products or biocidal products to consider potential endocrine effects are available. This poster aims to give a global overview on present regulatory proposals, recent regulatory developments and data requirements for the **assessment of endocrine disrupting chemicals**.

EUROPE



European Commission (EC):

- Development of Community Strategy for EDCs: short-/medium-/long-term activities
- Priority list of substances for further evaluation
- 2014/15: **Roadmap and Public Consultation** *to define criteria for identifying EDCs (*plant protection and biocidal products regulation)
- 2016: Criteria to be announced before summer

Biocidal Products Regulation (528/2012), Plant Protection Products Regulation (1107/2009):

- **Non-approva**l of substances considered to have endocrine disrupting properties; interim criteria
- Exceptions: negligible exposure/risk, necessity of substance to combat serious pests

REACh (1907/2006):

- Eligible as substances of very high concern, SVHC (equivalent level of concern (Art. 57f) as for PBT, CMR substances) – **authorisation** required, socio-economic analysis

Cosmetics Regulation (1223/2009):

- Currently under review, EDCs not restricted

European Food Safety Authority (EFSA):

- 2013: Scientific Opinion on scientific criteria, available test methods and strategies, **risk assessment is supported**

Scientific Committee on Consumer Safety (SCCS):

- Dec 2014: Memorandum on Endocrine Disruptors
- Support EFSA opinion on scientific criteria

***Various member state proposals*:**

- DK (2011): strictly hazard assessment, cut-off criterion
- D/UK (2011), D (BfR 2015): severity/potency to be included into assessment
- F (2014): national strategy on ED, strictly hazard assessment, substitution

⟹ **mostly hazard-based assessment, limited risk elements**

USA

US EPA:

- **Endocrine Disruptor Screening Program (EDSP):** two-tiered testing strategy (estrogen, androgen and thyroid hormonal systems, and wildlife)

Tier 1: identification and classification of potential EDCs by in-vitro and in-vivo assays; Series 890 - EDSP Test Guidelines
Tier 2: concentration-response relationships in animal models; TGs partly under development

- **initial list of chemicals to be screened** in 2009; second list in 2010, final in 2014

Future objectives according to **Comprehensive Management Plan** for 2014-2019:

- **List 1 chemicals**: Data review of all Tier 1 assays results together with scientifically relevant data → decision on Tier 2 testing and test orders by US EPA (results from Tier 2 data reviews will directly support **risk assessments** for registration review and new registration actions). *2015: Tier 1 screening results for 52 chemicals published.*
- Further priorization of **List 2 chemicals** and decisions on exemption of some chemicals from Tier 1 testing.
- Promotion of computational toxicology and exposure methods, e.g. ToxCast™, for the development of a more efficient and robust screening program. Application of these methods for a **draft third list of chemicals (List 3**) envisaged in 2016.

US Food and Drug Administration (FDA):

- Development of an **Estrogenic Activity Database** for evaluation of estrogenic activity of chemicals.
- 2013: draft guidance for evaluation of endocrine disruption potential of drugs, evaluation of potential EDCs using standard batteries of nonclinical tests and assessment of potential effects.

⟹ **risk-based assessment**

EU-US cooperation on EDCs, 2014

OECD

- *OECD Conceptual Framework*: tool box for testing and assessment of EDCs on 5 levels
- Promotion of further method development and validation via the *OECD TGs program*
- *OECD Guidance Document No. 150* for evaluating chemicals for endocrine disruption

ASIA

EDSP TG develop-ment

China

Draft of agro-industrial standard "*Evaluation methods for pesticide endocrine disruptors*", review by the Ministry of Agriculture (MoA) late 2014 (not effective or published yet)

- Including two tiers and seven toxicological study types
- Aiming to evaluate probable endocrine disrupting properties of pesticides

Thailand

No specific legislation or regulatory program concerning EDCs, however the *Hazardous Substance Act B.E. 2535* (1992) may be used for dealing with EDCs. Chemicals are classified into type 1, 2, 3 or 4 based on toxicological data, dangerous properties, international obligations and necessity. For type 4 compounds, production, import, export and possession is prohibited. Hazardous substances are compiled in the Notification List B.E. 2556 (2013, 2015).

South Korea

Since 2001: Collaboration Korea-Japan. 1999: Mid-long term research plan for suspected endocrine disruptors. 2007-2011: 5-year research plan, review of results, safety management of EDCs. 2013: K-REACh: authorisation, restriction for EDCs.

Japan

The Japanese Ministry of Environment (MoE) promotes

- Basic research on the mechanisms of endocrine disruption
- Environmental monitoring (wildlife observation, exposure levels)
- Development of test methods, hazard and risk assessment, risk management, information sharing and risk communication

Several projects were launched:

- SPEED '98: literature research on endocrine disrupting effects on wildlife, determination of chemicals to be tested (VTG assay, *Medaka* fish assays)
- ExTEND 2005: various chemicals tested for endocrine effects on *Medaka* fish
- ExTEND 2010: further actions on EDCs, and establishment of assessment methods and environmental risk assessment.
- Collaboration with US regarding test guideline development (EDSP)

⟹ **risk-based assessment**

Conclusion

As scientific criteria for the evaluation of endocrine disrupting properties of a substance are still not available yet, assessment is mostly conducted on a case-by-case basis at the moment. For companies intending or supporting global registrations for their substances, this results in substantial uncertainty regarding data requirements or testing and assessment strategies.

→ **"Weight of evidence" evaluation and expert assessments** tailored for respective regulatory programs are required for evaluation of endocrine disrupting properties of the substances.
→ Envisaged or requested studies should be carefully set up to meet global requirements and to avoid redundant testing.
→ Results obtained by studies prepared for one regulatory program will need to be dealt with in any other regulatory program.

References

www.oecd.org/env/ehs/testing/oecdworkrelatedtoendocrinedisrupters
www.env.go.jp/ed
http://www.fda.gov/ScienceResearch/BioinformaticsTools
www.jetro.go.jp/thailand www.epa.gov/endo/

Acknowledgements

Many thanks to our colleagues from Dr. Knoell Consult Thai Co. Ltd. and Dr. Knoell Consult Shanghai Co. Ltd. for their support.

Dr. Knoell Consult GmbH | Dynamostr. 19 | D-68165 Mannheim | Germany | Tel. +49 621 718858 - 282 | Fax. -100 | mduft@knoell.com | **www.knoell.com**