

# Stakeholder perspective : Chemicals Industry



NVT Risk Assessment Section  
Autumn symposium:  
REACH revision & endocrine disruption:  
Are we up for the challenge?

10 October 2023  
NVWA, Utrecht

Dr. Nina Hallmark, on behalf of CEPIC

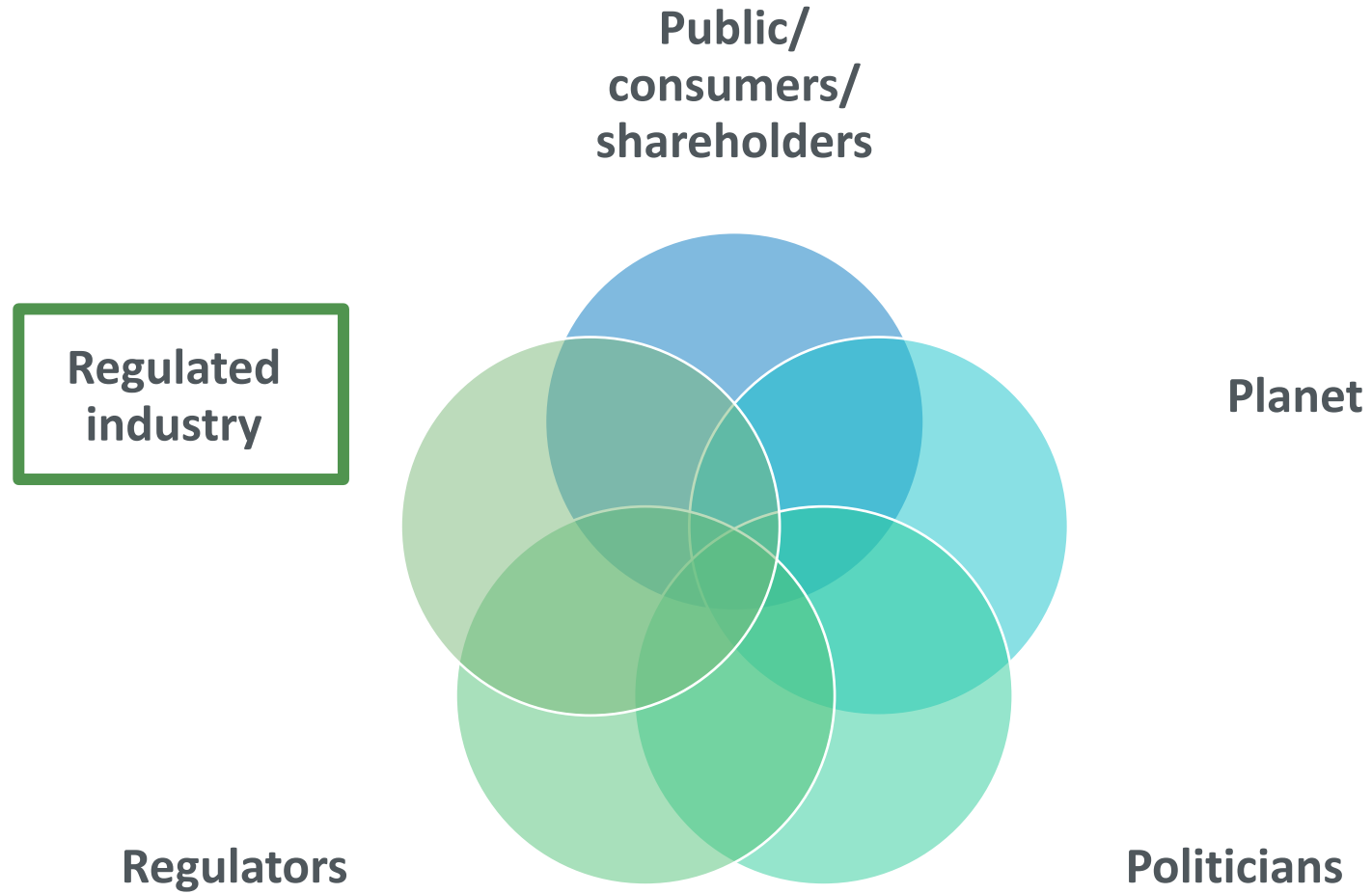


# Outline

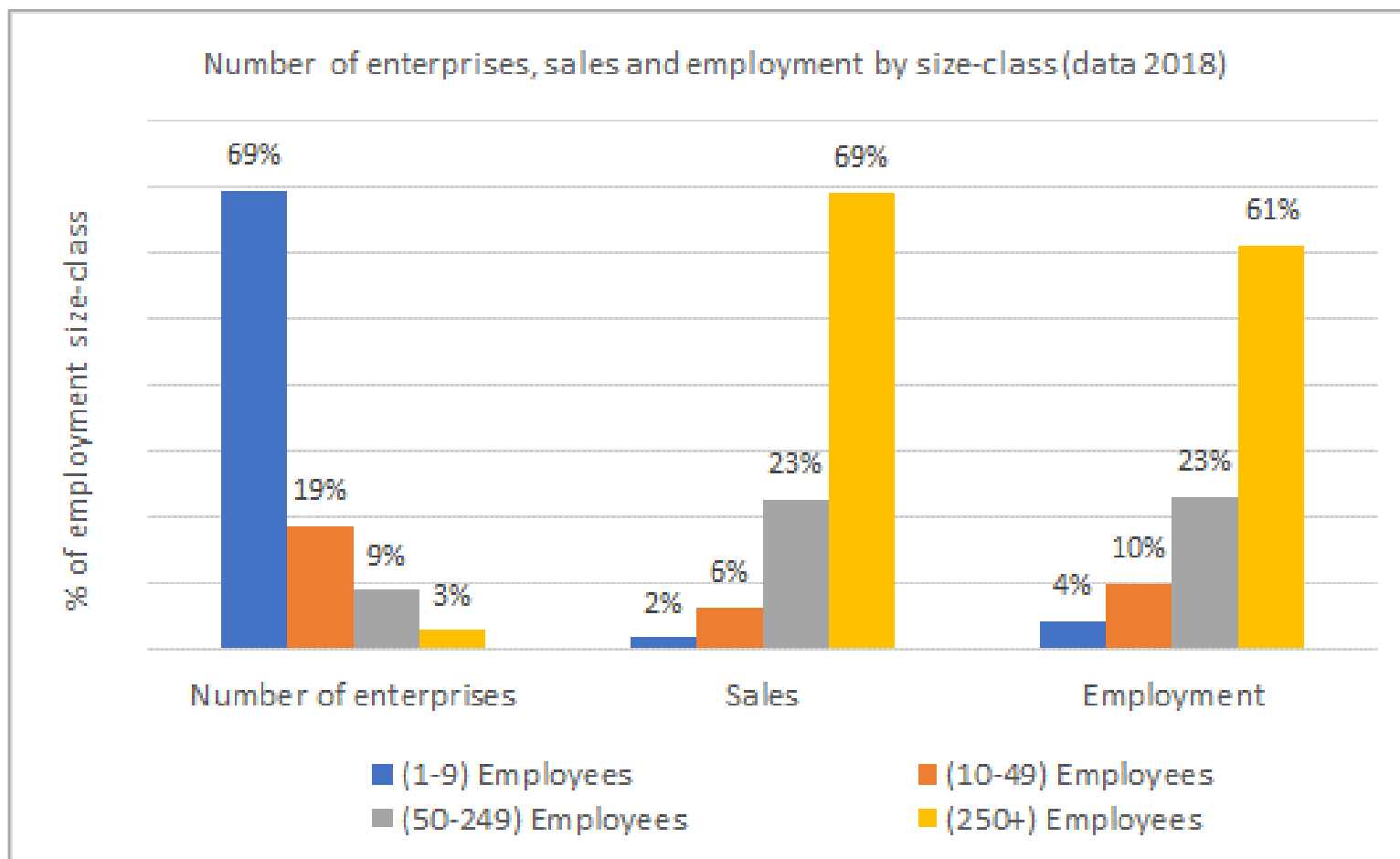
- Already covered today, based on agenda
  - REACH and CLP revision, ED, hazard vs risk - RIVM
  - Lessons learned in biocide and pesticide ED assessments – an authority perspective - CtgB
- View of regulated industry: CEFIC
  - Who / what is the regulated chemicals industry
  - Developing an EU legislative framework for ED regulation: focus on REACH
  - Other regulations and relevant supporting guidance
  - Food for thought: responsibility; protection goals; scientific scope, 3Rs, NAMs and AOPs
  - Future: Safer + sustainable by design
  - Summary



# Stakeholders in chemicals regulations



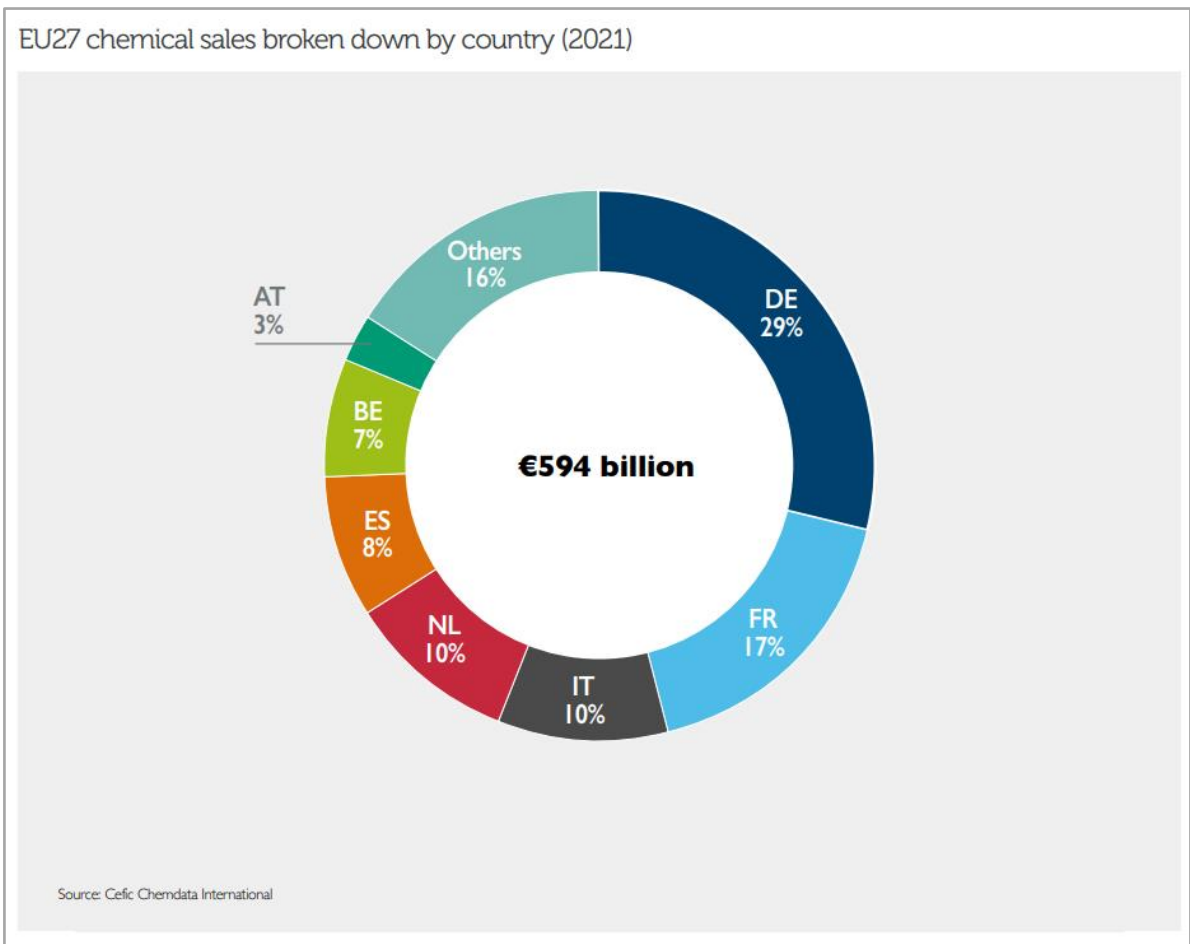
# Who, what, is the regulated chemicals industry?



Source: Source: Eurostat Economical indicator for structural business statistics [INDIC\_SB], Industry by employment size class (NACE Rev. 2, B-E) [SBS\_SC\_IND\_R2\_\_custom\_4043982]

# Did you know ...

## Two thirds of EU27 chemical sales are generated in four Member States



# The voice of the chemical industry in Europe

## CEFIC: the European Chemical Industry Council, founded in 1972

- Chemicals are everywhere, and are present in more than 90% of manufactured goods, excluding pharmaceuticals.
- Most chemicals have intrinsic hazardous properties (e.g. irritant), but only some may cause harm to human health and the environment, **depending on the uses.**
- To ensure safe use, it is important that the **well established concept of scientific risk assessment is maintained.**
- **A key principle is that there cannot be a compromise on chemical safety, for humans and the environment. And compliance with existing regulations is a must.**
- Members: 650 members and affiliates, representing chemicals value chain
- Mission: serve its members by generating and aggregating scientific knowledge that fosters the purpose of the Association in critical areas, offer services and expertise to its members in regulatory, scientific and technical matters, engage, advocate and represent the industry in order to create the right support and policy frameworks in Europe and beyond, add value as a collective compared to individual companies' activities.
- A key contributor to international matters: active member of the International Council of Chemical Associations (ICCA), Cefic seeks to strengthen existing cooperation with global organisations such as UNEP and the OECD to improve chemicals management worldwide.



Cefic is registered in the EU Transparency Register under n° 64879142323-90.

# REACH : Regulation (EC) No 1907/2006 – Article 57 (f)

30.12.2006

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L 396/141

(b) uses in food contact materials within the scope of Regulation (EC) No 1935/2004.

6. Paragraphs 1 and 2 shall not apply to the use of substances when they are present in preparations:

- (a) for substances referred to in Article 57(d), (e) and (f), below a concentration limit of 0,1 % weight by weight (w/w);
- (b) for all other substances, below the lowest of the concentration limits specified in Directive 1999/45/EC or in Annex I to Directive 67/548/EEC which result in the classification of the preparation as dangerous.

## *Article 57*

### *Substances to be included in Annex XIV*

The following substances may be included in Annex XIV in accordance with the procedure laid down in Article 58:

- (a) substances meeting the criteria for classification as carcinogenic category 1 or 2 in accordance with Directive 67/548/EEC;
- (b) substances meeting the criteria for classification as mutagenic category 1 or 2 in accordance with Directive 67/548/EEC;

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- (c) substances meeting the criteria for classification as toxic for reproduction category 1 or 2 in accordance with Directive 67/548/EEC;
- (d) substances which are persistent, bioaccumulative and toxic in accordance with the criteria set out in Annex XIII of this Regulation;
- (e) substances which are very persistent and very bioaccumulative in accordance with the criteria set out in Annex XIII of this Regulation;
- (f) substances - such as those having endocrine disrupting properties or those having persistent, bioaccumulative and toxic properties or very persistent and very bioaccumulative properties, which do not fulfil the criteria of points (d) or (e) - for which there is scientific evidence of probable serious effects to human health or the environment which give rise to an equivalent level of concern to those of other substances listed in points (a) to (e) and which are identified on a case-by-case basis in accordance with the procedure set out in Article 59.



# REACH : Regulation (EC) No 1907/2006 – Article 138 (7)

L 396/230

EN

Official Journal of the European Union

30.12.2006

## Article 138

### Review

1. By 1 June 2019, the Commission shall carry out a review to assess whether or not to extend the application of the obligation to perform a chemical safety assessment and to document it in a chemical safety report to substances not covered by this obligation because they are not subject to registration or subject to registration but manufactured or imported in quantities of less than 10 tonnes per year. However, for substances meeting the criteria for classification as carcinogenic, mutagenic or toxic for reproduction, category 1 or 2, in accordance with Directive 67/548/EEC, the review shall be carried out by 1 June 2014. When carrying out the review the Commission shall take into account all relevant factors, including:
  - (a) the costs for manufacturers and importers of drawing up the chemical safety reports;
  - (b) the distribution of costs between actors in the supply chain and the downstream user;
  - (c) the benefits for human health and the environment.

On the basis of these reviews, the Commission may, if appropriate, present legislative proposals to extend this obligation.

L 396/232

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5. The Commission shall carry out a review of Annex XIII by 1 December 2008, to assess the adequacy of the criteria for identifying substances which are persistent, bioaccumulative and toxic or very persistent and very bioaccumulative, with a view to proposing an amendment to it, if appropriate, in accordance with the procedure referred to in Article 133(4).
6. By 1 June 2012 the Commission shall carry out a review to assess whether or not to amend the scope of this Regulation to avoid overlaps with other relevant Community provisions. On the basis of that review, the Commission may, if appropriate, present a legislative proposal.
7. By 1 June 2013 the Commission shall carry out a review to assess whether or not, taking into account latest developments in scientific knowledge, to extend the scope of Article 60(3) to substances identified under Article 57(f) as having endocrine disrupting properties. On the basis of that review the Commission may, if appropriate, present legislative proposals.

- **Re: legislative proposals, where are we today vs. 2013 goal?**



# Developing an EU legislative framework for ED regulation

- 1999: Strategy on EDs by European Commission
- Since then, EDs in **chemical products are regulated in the EU through a number of legal instruments** e.g.,:
  - REACH (Regulation on the Registration, Evaluation and Assessment of Chemicals ((EC) No 1907/2006)
  - CPR Cosmetics Products Regulation ((EC) No 1223/2009).
- 2013: Revisions to EU legislation on chemicals took this strategy into account e.g., the 7th Environment Action Programme (EAP), which **provides for the harmonisation of hazard-based criteria for the identification of EDs.**
  - PPP Plant Protection Product Regulation ((EC) No 1107/2009 and Commission Regulation (EU) 2018/605)
  - BPR Biocidal Product Regulation ((EU) No 528/2012, and Commission Delegated Regulation (EU) 2017/2100)
- 2018: Scientific Criteria for the identification of substances with endocrine disrupting properties in pesticides (PPP) and biocides (BPR) were published along with a Guidance document developed by the EFSA, ECHA with JRC
- 2018: Communication adopted by the Commission, confirming its commitment to protecting citizens and the environment from hazardous chemicals and delivers on the commitment ... to identify endocrine disruptors in the areas of pesticides and biocides. It ... follows up from the 7th Environment Action Programme.
- 2023: CLP new hazard classes for ED = HH in Category 1 and Category 2 (Endocrine disruption for human health) and ED ENV in Category 1 and Category 2 (Endocrine disruption for the environment)
- **Are these 2018 criteria and guidance potentially applicable under other EU legislations / regulations? Scientifically, legislatively?**



# CEFIC-LRI has supported scientific research into ED for decades

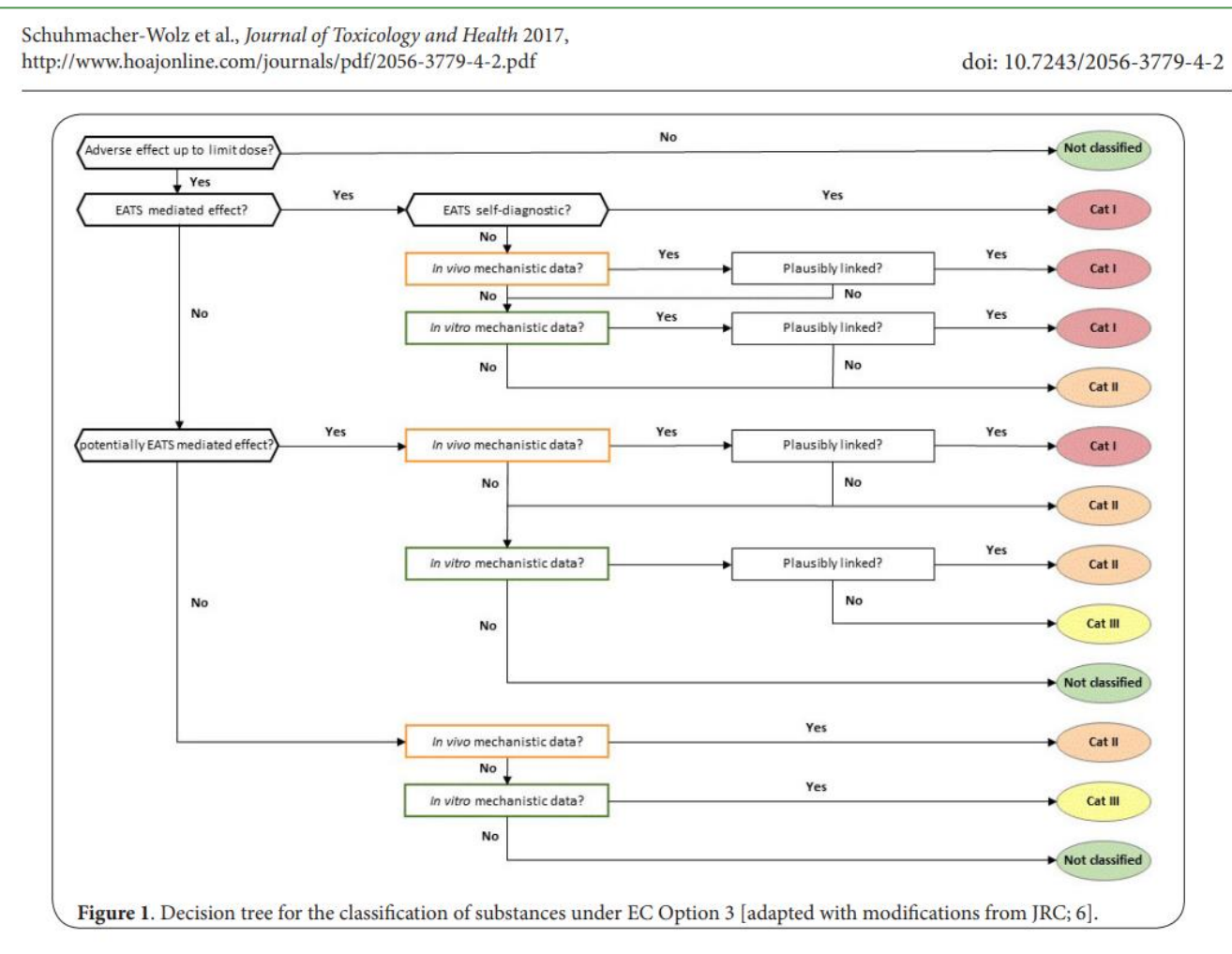
## The Long-range Research Initiative (LRI) started in 1996

- The mission of the LRI is to advance the scientific assessment of the safety of chemicals and to improve our understanding of the potential health and environmental risks and the LRI Programme has funded more than 250 research projects through its [grants](#) and [Innovative Science Award](#).
- And, because industry cannot act alone, every effort is made to build relationships with research programmes, government agencies, academics and non-governmental organizations to support the development of effective regulation for the sound management of chemicals.
- You might know/ recognise some of these names or topics:
  - 2002: 4<sup>th</sup> LRI Workshop - Andreas Kortenkamp, (London School of Pharmacy) described a cluster of new EU research projects on endocrine disruption
  - 2010 LRI-EMSG55: Comparison of natural and synthetic endocrine active compounds – Assessment of potential combinatory effects
  - 2013 LRI-EMSG57: Endocrine disruptors and obesity, diabetes and heart disease: State of the science and biological plausibility
  - 2013 LRI-EMSG58: Quality assessment of the epidemiological evidence of adverse effects to humans of endocrine active substances in the environment
  - 2013: 15<sup>th</sup> LRI workshop - Richard Sharpe, University of Edinburgh, presented on BPA ‘Keeping your eye on the goal: avoiding conflicts, agendas, emotions and presumptions’
  - 2015 LRI-ECO35: Assessment of potential endocrine activity in fish – elucidation of the role of liver toxicity in the vitellogenin response
  - 2020 LRI-EMSG60: Incidence trends of selected endocrine-related diseases and conditions in europe and north america, and the contribution of changes in human reproduction
  - 2020 LRI-EMSG59: Developing a quantitative aop for liver-mediated thyroid modulation after prenatal exposure to a xenobiotic compound in the rat



# Proactive contribution to regulatory guidance development

- Historical approach has focused on EATS modalities
- Decision Tree based methodology based on the criteria
- Starts with Adverse Effects
- Questions
  - What happens if (non-endocrine) toxicity occurs below the limit dose
  - Can the same be applied for non-EATS modalities



## ED assessment as a harmonised process, across EU, with 3 outcomes \*

1. Gather available **scientific data**, evaluate it for reliability and relevance against **established criteria**
2. **Assemble, assess** and **integrate relevant information** into lines of evidence, for Endocrine activity and separately for Endocrine adversity
3. Analyse whether the relevant parameters been sufficiently investigated?
  - If no, discuss whether further data generation is possible, as **conclusion not currently possible**
    - Data availability varies e.g., pesticides (*in vivo* data required) vs. cosmetics (no new *in vivo* data)
  - If yes, determine whether there is a plausible link between the observed activity and adversity
    - If no (i.e., no adversity and/ or no activity), ED criteria are not met. Stop.
    - If yes (i.e., adversity and related activity) determine if human or ecotox population relevance is observed
      - If not relevant, ED **criteria are not met**. Stop.
      - If relevant, ED **criteria are met**. Stop.
4. Under CLP, no data should be generated for the purposes of classification and labelling → No classification can be based on assumptions due to missing data (absence of evidence)



\* See draft approach developed with and published via ECETOC (2017) <https://www.ecetoc.org/wp-content/uploads/2021/10/ECETOC-TR-130-7SI-ED.pdf>

# Data requirements for PPP per **283/2013**, then criteria per 2018/605

COMMISSION REGULATION (EU) No **283/2013** of 1 March 2013 setting out the data requirements for active substances, in accordance with Regulation (EC) No **1107/2009** of the European Parliament and of the Council concerning the placing of plant protection products on the market

- **17 lines of text**
- SECTION 5 Toxicological and metabolism studies
  - 5.8. Other toxicological studies (p. 32)
- SECTION 8 Ecotoxicological studies
  - 8.1. Effects on birds and other terrestrial vertebrates (p. 56)
  - 8.2. Effects on aquatic organisms (p. 58)

## 5.8.3. *Endocrine disrupting properties*

If there is evidence that the active substance may have endocrine disrupting properties, additional information or specific studies shall be required:

- to elucidate the mode/mechanism of action,
- to provide sufficient evidence for relevant adverse effects.

Studies required shall be designed on an individual basis and taking into account Union or internationally agreed guidelines, in the light of the particular parameters to be investigated and the objectives to be achieved.

## 8.1.5. *Endocrine disrupting properties*

Consideration shall be given to whether the active substance is a potential endocrine disruptor according to Union or internationally agreed guidelines. This may be done in consulting the mammalian toxicology section (see Section 5). In addition, other available information on toxicity profile and mode of action shall be taken into account. If as a result of this assessment, the active substance is identified as a potential endocrine disruptor, the type and conditions of the study to be performed shall be discussed with the national competent authorities.

## 8.2.3. *Endocrine disrupting properties*

Consideration shall be given to whether the active substance is a potential endocrine disruptor in aquatic non-target organisms according to Union or internationally agreed guidelines. In addition, other available information on toxicity profile and mode of action shall be taken into account. If as a result of this assessment, the active substance is identified as a potential endocrine disruptor, the type and conditions of the studies to be performed shall be discussed with the national competent authorities.



# Data requirements for PPP per 283/2013, then criteria per 2018/605

COMMISSION REGULATION (EU) 2018/605 of 19 April 2018 amending Annex II to Regulation (EC) No 1107/2009 by setting out scientific criteria for the determination of endocrine disrupting properties

- 4 pages, including scientific criteria and ...

... additional 135-page guidance document, with appendices including data capture templates (.xls)

20.4.2018	Official Journal of the European Union	L 101/35
ANNEX		
Annex II to Regulation (EC) No 1107/2009 is amended as follows:		
(1) in point 3.4.5 the following paragraphs are added after the fourth paragraph:		
From 20 October 2018, an active substance, safener or synergist shall be considered as having endocrine disrupting properties that may cause adverse effect in humans if, based on points (1) to (4) of the sixth paragraph, it is a substance that meets all of the following criteria, unless there is evidence demonstrating that the adverse effects identified are not relevant to humans:		
(1) it shows an adverse effect in an intact organism or its progeny, which is a change in the morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences;		
(2) it has an endocrine mode of action, i.e. it alters the function(s) of the endocrine system;		
(3) the adverse effect is a consequence of the endocrine mode of action.		
The identification of an active substance, safener or synergist as having endocrine disrupting properties that may cause adverse effect in humans in accordance with the fifth paragraph shall be based on all of the following points:		
(1) all available relevant scientific data (in vivo studies or adequately validated alternative test systems predictive of adverse effects in humans or animals as well as in vitro, in vivo, or, if applicable, in silico studies informing about endocrine modes of action):		
(a) scientific data generated in accordance with internationally agreed study protocols, in particular those listed in the Commission Communications in the framework of setting out the data requirements for active substances and plant protection products, in accordance with this Regulation;		
(b) other scientific data selected applying a systematic review methodology, in particular following guidance on literature data which is listed in the Commission Communications in the framework of setting out the data requirements for active substances and plant protection products, in accordance with this Regulation;		
(2) an assessment of the available relevant scientific data based on a weight of evidence approach in order to establish whether the criteria set out in the fifth paragraph are fulfilled; in applying the weight of evidence determination, the assessment of the scientific evidence shall, in particular, consider all of the following factors:		
(a) both positive and negative results;		
(b) the relevance of the study designs, for the assessment of adverse effects and of the endocrine mode of action;		
(c) the quality and consistency of the data, considering the pattern and coherence of the results within and between studies of a similar design and across different species;		
(d) the route of exposure, toxicokinetic and metabolism studies;		
(e) the concept of the limit dose, and international guidelines on maximum recommended doses and for assessing confounding effects of excessive toxicity;		
(3) using a weight of evidence approach, the link between the adverse effect(s) and the endocrine mode of action shall be established based on biological plausibility, which shall be determined in the light of current scientific knowledge and under consideration of internationally agreed guidelines;		
(4) adverse effects that are non-specific secondary consequences of other toxic effects shall not be considered for the identification of the substance as endocrine disruptor.		



GUIDANCE



ADOPTED (ECHA): 5 June 2018

ADOPTED (EFSA): 5 June 2018

doi: 10.2903/j.efsa.2018.5311

## Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009

European Chemical Agency (ECHA) and European Food Safety Authority (EFSA) with the technical support of the Joint Research Centre (JRC)

Niklas Andersson, Maria Arena, Domenica Auteri, Stefania Barmaz, Elise Grignard, Aude Kienzler, Peter Lepper, Alfonso Maria Lostia, Sharon Munn, Juan Manuel Parra Morte, Francesca Pellizzato, Jose Tarazona, Andrea Terron and Sander Van der Linden

### Abstract

This Guidance describes how to perform hazard identification for endocrine-disrupting properties by following the scientific criteria which are outlined in Commission Delegated Regulation (EU) 2017/2100 and Commission Regulation (EU) 2018/605 for biocidal products and plant protection products, respectively.

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**Keywords:** biocidal product, plant protection product, endocrine disruptor, guidance, hazard identification

**Requestor:** European Commission

**Question numbers:** EFSA-Q-2016-00825, ECHA-18-G-01-EN

<https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32018R0605&from=EN>

<https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5311>

