ED: regulatory approaches plant protection products and biocides - experiences gathered so far

13.02.2024, Advanced Couse AK RegTox and 3R, 9th GPTS

Dr. Vera Ritz
Dept. Pesticides Safety
German Federal Institute for Risk Assessment

Agenda

- Current endocrine disruptor (ED) assessment under Biocides and Plant Protection Products Regulations (BPR, PPPR)
- Differences between both fields:
  - what is assessed?
  - involved committees, decision making
  - dealing with data gaps
- Potential impacts of the new CLP classes on BP and PPPR
- Developments regarding AOPs/NAMs for ED

Current ED Assessment under BPR and PPPR: Background

COMMISSION DELEGATED REGULATION (EU) 2017/2100

of 4 September 2017

setting out scientific criteria for the determination of endocrine-disrupting properties pursuant to Regulation (EU) No 528/2012 of the European Parliament and Council

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

ECHA EUROPEAN CHEMICALS AGENCY

GUIDANCE

efsa European Food Safety Authority

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)

According to the ED criteria a substance shall be considered to have ED properties if it meets all of the following criteria:

a) it shows an adverse effect […]
b) it has an endocrine mode of action, i.e. it alters the function(s) of the endocrine system;
c) the adverse effect is a consequence of the endocrine mode of action.

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Current ED Assessment under PPPR

EFSA (Active Substances Plant Protection Products):

Information from [ED Report 21-12-203]

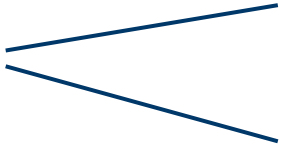
Outcome (preliminary) HH ED Assessment	No.
no ED	39
waiving of ED Assessment	30
not applicable	3
ED	17
ED (provisional)	1
additional information necessary/ no conclusion possible	26
total	**116**

Modality	No.
EAS	6
T	10
EAS + T	1

Current ED Assessment under BPR

ECHA (Active Substances Biocides)
information from Biocidal Products Committee opinions an active substance approval

Outcome	No.
no ED	19
waiving of ED assessment	16
not applicable	1
ED	4
no conclusion possible	7
total	**47**



Modality	No.
EAS	1
T	3

Differences between both fields – What is assessed?

Under PPPR:

- Assessment of active substances acc. to the ECHA/EFSA Guidance Document
- In principle, assessment of safeners and synergists acc. to the ECHA/EFSA Guidance Document
- Inclusion of co-formulants in Annex III of the PPPR if they are identified under REACH Art. 57 or BPR as ED;
  currently in Annex III (amended by Commission Regulation 2021/383):
  diisobutyl phthalate, *n*-butyl phthalate, (ethoxylated) nonyl-phenols, (ethoxylated) octyl-phenols

Differences between both fields – What is assessed?

Under BPR:

- Assessment of active substances acc. to the ECHA/EFSA Guidance Document
- Assessment of impurities
- Screening of co-formulants
- Risk assessment for residues and disinfection-by-products

Differences between both fields – What is assessed?

Under BPR:

- ED properties of impurities: exclusion criteria could be met (CA-March21-Doc.5.1- ED properties impurities_final.docx)
- ED properties of disinfection-by-products (defined as residues): products could possibly not be authorised for the general public (CA-March21-Doc.5.2 - ED properties DBPs_final.docx)
- e. g. chlorate and bromate can be both – different outcomes of the assessments depending on the definition?

Differences between both fields – What is assessed?

Assessment of co-formulants in biocidal products:

Step 1: Check if co-formulant is an active substance under BPR and PPPR and fulfills the ED criteria
Step 2: Check if co-formulant is on the SVHC list under REACH due to ED properties
Step 3: Check if co-formulant is a food/feedstuff material acc. to Reg. 178/2002
Step 4: Check the Activities Coordination Tool (ACT) on all REACH and CLP regulatory activities
Step 5: Check if harmonised or self-classification for potential ED properties
Step 6: Optional: check US databases, literature and/or structural similarities with ED substances

Substance name	CAS no.	ED relevant classification (MSDS)	active substance under BPR	active substance under PPPR	Food/Feed-Stuff	ECHA ED list	ECHA dissemination database	PACT list	CoRAP list	SVHC list	Literature

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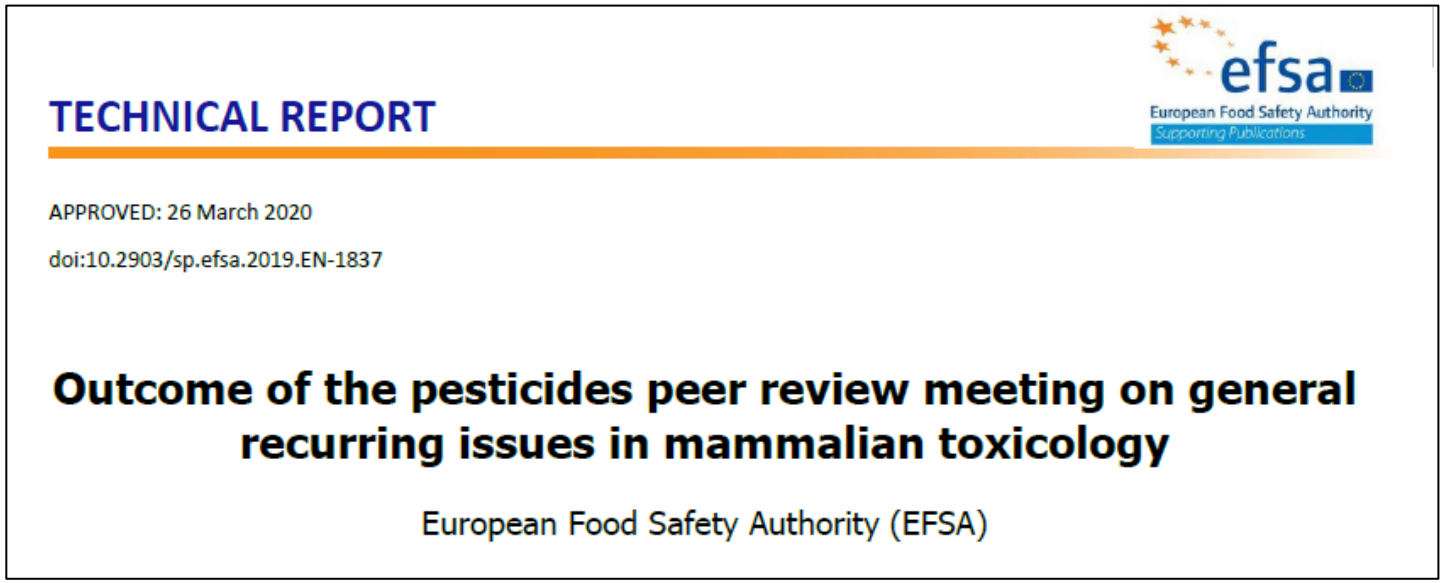
Experiences & lessons learned from the pesticides peer review



TECHNICAL REPORT

efsa European Food Safety Authority Supporting Publications

APPROVED: 26 March 2020

doi:10.2903/sp.efsa.2019.EN-1837

Outcome of the pesticides peer review meeting on general recurring issues in mammalian toxicology

European Food Safety Authority (EFSA)

Summary of dicussions of ED topics on:

- documentation of ToxCast data
- waiving ED assessments
- completeness of EAS dataset
- sufficiency of T dataset
- use of carcinogenicity studies
- hormone measurements
- uncertainty analysis
- assessment of thyroid disruption
- update of the Guidance Document

New CLP classes

31.3.2023 EN Official Journal of the European Union L 93/7

COMMISSION DELEGATED REGULATION (EU) 2023/707

of 19 December 2022

amending Regulation (EC) No 1272/2008 as regards hazard classes and criteria for the classification, labelling and packaging of substances and mixtures

(Text with EEA relevance)

New CLP classes

ED category 1 human health

Known or presumed endocrine disruptors for human health

Classification largely based on evidence from:

A) human data
B) animal data
C) non-animal data (equivalent predictive capacity)

Substance meets all the following criteria:

1) endocrine activity
2) an adverse effect in an intact organism or its offspring or future generations
3) a biologically plausible link between the endocrine activity and the adverse effect.

ED category 2 human health

Suspected endocrine disruptors for human health

Classification based on the following criteria:

a. Evidence of
   i. endocrine activity and
   ii. an adverse effect in an intact organism or its offspring or future generations
b. The evidence under a. is not sufficiently convincing for cat. 1.
c. There is evidence of a biologically plausible kink between the endocrine activity and the adverse effect.

Where there is evidence demonstrating that the adverse effects are not relevant to humans, the substance shall not be considered an endocrine disruptor for human health.

Timelines for the implementation of new hazard classes

https://echa.europa.eu/de/new-hazard-classes-2023

Potential impacts on PPP & BP assessment: thresholds for classification

Generic concentration limits of components of a mixture classified as endocrine disruptor for human health that trigger classification of the mixture

Component classified as:	Generic conc. limits triggering classification of a mixture as	
	Cat. 1 endocrine disruptor for human health	Cat. 2 endocrine disruptor for human health
Cat. 1 endocrine disruptor for human health	≥ 0.1 %	
Cat. 2 endocrine disruptor for human health		≥ 1 %

Note: The concentration limits in this Table apply to solids and liquids (w/w units) as well as gases (v/v units).

Note 1: If a Category 2 endocrine disruptor for the environment is present in the mixture as an ingredient at a concentration ≥ 0,1 % a SDS shall be available for the mixture upon request.

Potential impacts on PPP & BP assessment: Templates

Updated combined CLH/biocide CAR template includes sections for the new hazard classes:
https://www.echa.europa.eu/web/guest/support/guidance-on-reach-and-clp-implementation/formats/formats-for-the-authorities

No update yet for the combined template for DAR/RAR/CLH reports:
https://food.ec.europa.eu/system/files/2019-03/pesticides_ppp_app-proc_guide_doss_12592-2012.pdf

Potential impacts on PPP & BP assessment: Committees

Responsible for **harmonised classification and labelling** (in future including ED):

ECHA

- Risk Assessment Committee (RAC)
- Advisory group: Endocrine Disruptors Expert Group (EDEG)

Responsible for **active substance peer review under BPR:**

ECHA

- Biocidal Products Committee Working Groups (BPC WG)
- Advisory group: EDEG at ECHA

Responsible for **active substance peer review under PPPR:**

EFSA

- Pesticides Peer-Review Expert Meeting
- Advisory group: Endocrine Disruptors Working Group (ED WG)

Potential impacts on PPP & BP assessment: Guidance Documents

- Preparation of an CLP guidance update by ECHA in cooperation with EFSA to include ED guidance
- Publication is planned mid 2024
- Until then, the EFSA/ECHA Guidance Document can be used https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2018.5311
- For Category 1 the criteria are very similar to those under BPR and PPPR

Potential impacts on BP assessment: Review program

Communication of the European Commission:

- The practice to await the outcome of the RAC opinion on this matter is stopped.
- The ECHA BPC is entitled by the BPR to evaluate biocidal active substances and set up its own conclusions as regards to CMR properties and related exclusion criteria.
- Making progress on the review programme is considered a priority over awaiting the RAC opinion. Both regulations (BPR and CLP Regulation) have different purposes.

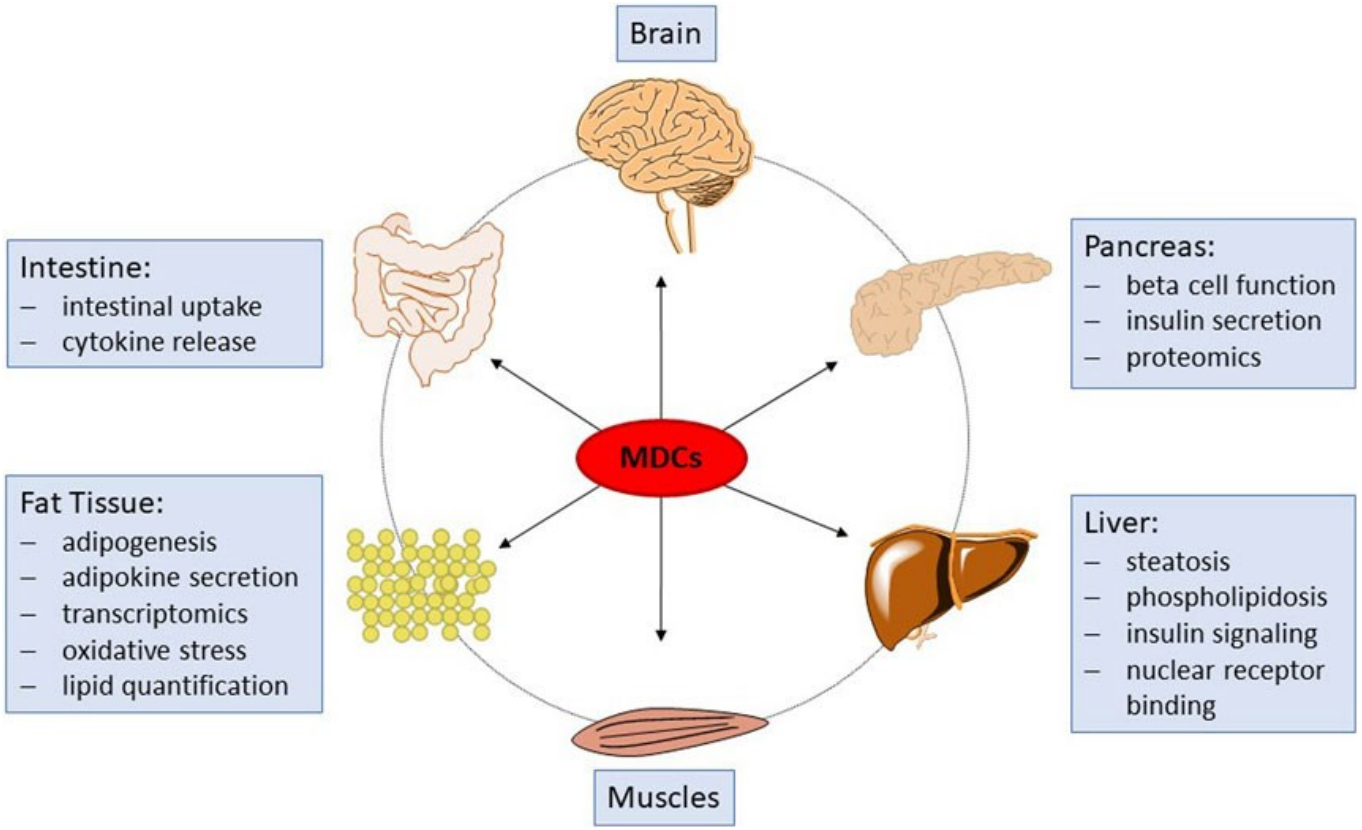
Developments regarding non-EATS modalities/risk assessment of EDs

Currently no guidance is available.

However,

- biocidal active substances with non-EATS modalities were considered to have ED properties, e.g. cholecalciferol, medetomidine,
- even substances with essential physiological functions in the organism used as biocidal active substances were considered to have ED properties, e.g. cholecalciferol, iodine, a bromide-containing active,
- justification for derogations from the exclusion criteria in at least one case: “negligible exposure” compared to background.
- But no risk assessment was accepted by a majority of MS.

Developments regarding AOPs/NAMs for ED: Metabolic Disruption



- Stable reporter cell lines to determine the potency and efficacy of chemicals on human nuclear receptors
- Analysis of MDC effects on lipid metabolism in human liver cells
- Disruption of pancreatic beta cell function by MDCs
- Measures for obesogenic effects of MDCs
- Zebrafish-based assays to detect metabolism -disrupting chemicals

Braeunig, A. et al., 2023. Development of new approach methods for the identification and characterization of endocrine metabolic disruptors—a PARC project https://doi.org/10.3389/ftox.2023.1212509

German Federal Institute for Risk Assessment

Dr. Vera Ritz
T +49 30 18412-26200
Vera.Ritz@bfr.bund.de

German Federal Institute for Risk Assessment
bfr.bund.de/en

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- soundcloud.com/risikobewertung

Abbreviations

ACT	Activities Coordination Tool
BP	Biocidal Product
BPR	Biocidal Products Regulation (Regulation (EU) No 528/2012)
CA	Competent Authority
Cat.	Category
CLP	Classification, Labelling & Packaging
DBP	Disinfection-by-product
EAS	estrogen, androgen, steroidogenesis
ECHA	European Chemicals Agency
ED	Endocrine Disruptor
EFSA	European Food Safety Authority
EU	European Union
No	Number
OECD	Organisation for Economic Co-operation and Development
PPP	Plant Protection Product
PPPR	Plant Protection Products Regulation (Regulation (EC) No 1107/2009)
REACH	REACH Regulation
T	thyroid
TG	Test Guideline
ToxCast	Toxicity ForeCaster