

Endocrine disruptors Human Toxicology

Costanza Rovida – *ecopa*

costanza.rovida@chimici.it

The primary aim of *ecopa* is to promote "the three Rs"
(Replacement, Reduction and Refinement)
in the use of animals in research, testing, education and training in Europe.
ecopa strives for consensus between all four stakeholders in attempting to
achieve its goals:

1. Government and regulatory authorities
2. Academia
3. Industry
4. Animal protection and welfare organisations

ecopa supports the establishment of
National Consensus Platforms which
promote the three Rs and include
representatives of all four stakeholders
in their governing body.

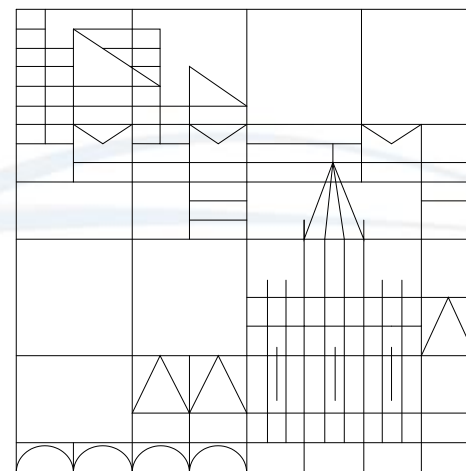




JOHNS HOPKINS
UNIVERSITY



JOHNS HOPKINS
BLOOMBERG
SCHOOL of PUBLIC HEALTH



University
Konstanz

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Costanza Rovida
costanza.rovida@chimici.it

REGULATION (EC) No 1107/2009 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 21 October 2009

concerning the placing of plant protection products on the market and repealing Council Directives
79/117/EEC and 91/414/EEC

Article 23

Approval criteria for basic substances

1. ...
2. (b) **does not have an inherent capacity to cause endocrine disrupting**, neurotoxic or immunotoxic effects; ...

ANNEX II

Procedure and criteria for the approval of active substances, safeners and synergists pursuant to Chapter II

3.6.5 An active substance, safener or synergist shall only be approved if, on the basis of the assessment of Community or internationally agreed test guidelines or other available data and information, including a review of the scientific literature, reviewed by the Authority, **it is not considered to have endocrine disrupting properties that may cause adverse effect in humans** ...

(same for the environment)

OECD Series on Testing and Assessment



**Revised Guidance
Document 150 on Standardised
Test Guidelines for Evaluating
Chemicals for Endocrine
Disruption**



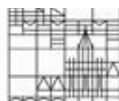
Level 1: Existing data and non-test information

Level 2: *In vitro* assays providing data about selected endocrine mechanism(s)/pathway(s)

Level 3: *In vivo* assays providing data about selected endocrine mechanism(s)/pathway(s)

Level 4: *In vivo* assays providing data on adverse effects on endocrine-relevant endpoints

Level 5: *In vivo* assays providing more comprehensive data on adverse effects on endocrine-relevant endpoints over more extensive parts of the life cycle of the organism



ADOPTED (ECHA): 5 June 2018

ADOPTED (EFSA): 5 June 2018

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

3.3.1.3. Human relevance

“According to the scientific criteria for determining ED properties applicable to the BP and PPP Regulations, ‘A substance shall be considered as having endocrine-disrupting properties that may cause adverse effect in humans [. . .] unless there is evidence demonstrating that the adverse effects identified are not relevant to humans’.

Note that the assessment of human relevance does not refer to adversity as such, but rather to the question as to whether an effect elicited by a substance in a test animal could also be elicited in a human being.

Therefore, to disprove human relevance it is necessary to demonstrate differences in the mechanisms of action of the substance in human and in test animals by having recourse to the MoAs.

Therefore, human relevance is addressed in the context of MoA analysis (Section 3.5.4.4).”

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3.3.1.3. Human relevance

“According to the scientific criteria for determining ED properties applicable to the BP and PPP Regulations, ‘A substance shall be considered as having endocrine-disrupting properties that may cause adverse effects in humans [. . .] unless there is evidence demonstrating that the identified effects are not relevant to humans’.

Note that the assessment of human relevance is not about the question of whether a substance in a test animal is an endocrine disruptor, but rather to the question of whether the effects identified in the test animal are relevant to humans.

Therefore, to disprove human relevance, it is necessary to demonstrate differences in the mechanisms of action of a substance in human and in test animals by having recourse to the MoAs.

Therefore, human relevance is addressed in the context of MoA analysis (Section 3.5.4.4).”

What about the opposite?

3S – Systematic, Systemic, and Systems Biology and Toxicology

*Lena Smirnova¹, Nicole Kleinstreuer², Raffaella Corvi³, Andre Levchenko⁴, Suzanne C. Fitzpatrick⁵
and Thomas Hartung^{1,6}*

Validity status of reprotox testing

- 1) Not robust (about 25% equivocal studies), [Bailey et al., 2005]**
- 2) 74 industrial chemicals tested in New Chemical Database: 34 showed effects on offspring, but only 2 chemicals have been classified as developmental toxic [Bremer & Hartung, 2004]**
- 3) 55% of positives in screening studies not in multi-generation studies [Bremer & Hartung, 2004]**
- 4) Group size limits statistical power [Hotchkiss 2008]**
- 5) 61% inter-species correlation [Hurrt 2003, Bailey 2005]**

Moreover

- a) Lack of objectivity of in vivo tests**
- b) Tests at high concentration**

Extended One Generation Reproductive Toxicity Study (EOGRTS) - OECD TG 443

Time per substance: 1.5-2 years

Cost per substance: 600,000€

EU capability: ~22 CROs

EU capacity for full study: ~ 50 per Year

efsa
European Food Safety Authority

Register of Questions

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How many existing EOGRTS? 0

How many years to test all? : 50

<http://registerofquestions.efsa.europa.eu/roqFrontend/ListOfQuestionsNoLogin?1>

https://echa.europa.eu/documents/10162/13630/echa_sr26_eogrts_en.pdf

Possible Solution: screening with OECD Levels 1 +2

QSAR – RASAR Approach &

VALIDATED in vitro methods:

OECD TG 493	In Vitro Assays to Detect Chemicals with ER Binding Affinity
OECD TG 455	In Vitro Assays to Detect Estrogen Receptor Agonists and Antagonists
OECD TG 456	H295R Steroidogenesis Assay
OECD TG 458	Detection of Androgenic Agonist and Antagonist Activity of Chemicals

(Thyroid Function assays under evaluation)

Total Costs per substance: ~ 30,000 €

Total time per substance: 3 months