Using Science to Set Regulatory Criteria Identifying Endocrine Disrupting Chemicals in the European Union

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29 June 2016

Conflict of interest statement

- I have no competing financial interest to declare

- This talks reflects my opinion and is not the official position of Inserm or University Grenoble-Alpes

Abbreviations

- CMR substances: Carcinogenic, Mutagenic, toxic for Reproduction
- ED: Endocrine Disruptor
- EC: The European Commission
- EU: The European Union

Aim of the talk

- To discuss the options proposed in the European Commission's 2014 roadmap as possible criteria defining EDs in Europe
- To briefly discuss the proposal made by the European Commission on this matter on June 15th 2016.

Outline

- Endocrine Disruptors (EDs): what are we talking about?
- EDs in the legislation of the European Union
- The EU Pesticides regulation
- 4 options considered by the EU (2014)
- The European Commission's proposal of June 15, 2016

1. Introduction

Endocrine Disruptors: some milestones

- 1960s Identification of the effect of persistent organic pollutants (POPs) on wildlife
  E.g., DDT effects on egg shells thinning
- 1971: In utero exposure to DES shown to induce vaginal adenocarcinoma in humans
- 1978: TBT-containing antifouling paints shown to induce imposex in marine gastropods
- 1993: First scientific publication mentioning “Endocrine Disruptors” (Colborn et al., *EHP*)
- 1995 Raleigh workshop on EDs (sponsored by US-EPA)
- 1996 Weybridge (UK) ED workshop, co-organized by the EC
- 2001: Stockholm international convention on POPs
- 2002, 2012: WHO/IPCS state of the science reports on EDs. Kortenkamp et al state of the art (EU) report (2011)

EDs in the broader context of health/environmental hazards

Carcinogens

Adverse effect

Mutagens

Mode of action

Reprotoxicants

Adverse effect

EDs

Adverse effect

x Mode of action

...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.

Explosives, inflammable substances

Physical or chemical properties

Persistent compounds

(WHO/IPCS, 2002)

2. Regulation of EDs in the European Union

Where do EDs appear in the EU regulation?

The EU is probably the first large economy which has regulated EDs.

- 1999: EU strategy on EDs
- 2000: Water framework directive
- 2006: REACH (European Regulation on Registration, Evaluation, Authorization and Restriction of Chemicals)
- 2009: Cosmetics regulation
- 2009: Plant Protection Products Regulation (PPPR)
- 2012: Biocidal Products Regulation (BPR)

The 2009 pesticides regulation ("PPPR")

An active substance, safener or synergist shall only be approved, if,
on the basis of [relevant tests literature review],
it is not or has not to be classified (...) as Carcinogen category 1A or 1B,
as Mutagen category 1A or 1B
as toxic for Reproduction category 1A or 1B
it is not considered to have endocrine disrupting properties that may cause adverse effect in humans,
unless the exposure

of humans to that active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use,

is negligible,

that is, the product is used in closed systems or in other conditions excluding contact with humans

and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.

Annex II, Articles 3.6.2 to 3.6.5

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Annex II, Articles 3.6.2 to 3.6.5

The Parliament's request to the Commission…

By 14 December 2013, the Commission shall present to the Standing Committee on the Food Chain and Animal Health a draft of the measures concerning specific scientific criteria for the determination of endocrine disrupting properties to be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 79(4).

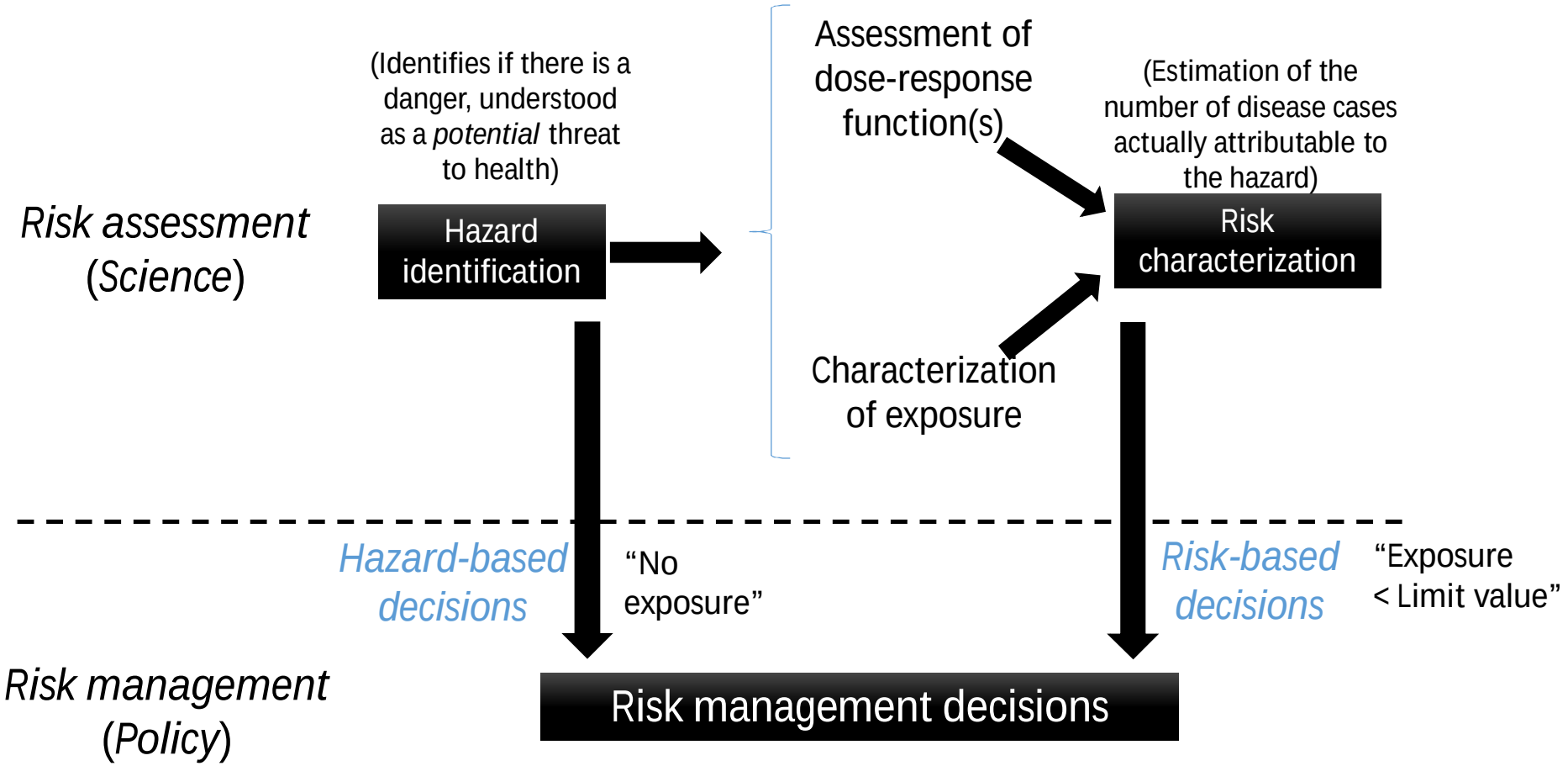
Meanwhile, interim criteria shall be applied:

Pending the adoption of these criteria, substances that are or have to be classified, (…) as carcinogenic category 2 *and* toxic for reproduction category 2*, shall be considered to have endocrine disrupting properties.

* Or "as toxic for reproduction category 2 and which have toxic effects on the endocrine organs"

(European Parliament, PPPR, Annex II, art. 3.6.5, 2009)

The PPPR follows a hazard-based logic for pesticides containing CMR or endocrine-disrupting substances



3. The 4 options outlined in the EC roadmap (2014)

- Option 1: No definition

  The PPPR interim criteria will apply

  i.e., EDs are defined as substances which simultaneously are suspected carcinogens (category 2) *and* toxic for reproduction category 2

- Option 2: "WHO/IPCS" definition of EDs

  Only one category.

  Endocrine disruptors are identified as *substances which are known or presumed to have caused endocrine-mediated adverse effects in humans or population-relevant endocrine-mediated adverse effects in animal species living in the environment …*

- Option 3: WHO/IPCS definition of EDs (as in option 2) +2 other categories based on the strength of evidence for fulfilling WHO definition

  Category I: Endocrine Disruptors

  Category II: Suspected endocrine disruptors

  Category III: Endocrine active substances

- Option 4: WHO/IPCS definition to identify endocrine disruptors and inclusion of potency as element of hazard characterization (hazard identification and characterization).

4. Comments on the 4 options from the 2014 roadmap from a scientific perspective

- Option 1: No definition

  The PPPR interim criteria will apply

  i.e., EDs are defined as substances which are simultaneously suspected carcinogens (category 2) *and* toxic for reproduction category 2

  Comment:

  No reference to an alteration of the endocrine system

  Endocrine disruptors can have adverse effects other than those on cancer occurrence and reproduction

  Option 1 is therefore not scientifically relevant

- Option 1: No definition

  The PPPR interim criteria will apply

  i.e., EDs are defined as substances which are simultaneously suspected carcinogens (category 2) *and* toxic for reproduction category 2

- Option 2: WHO/IPCS definition of EDs

  Only one category.

  Endocrine disruptors are identified as *substances which are known or presumed to have caused endocrine-mediated adverse effects in humans or population- relevant endocrine-mediated adverse effects in animal species living in the environment …*

Comment:

WHO/IPCS definition of EDs is widely accepted, including by European scientific authorities

"*Known or presumed*" endocrine-mediated adverse effects would require an equivalent level of proof than for pesticides containing carcinogenic, mutagenic substances or substances toxic for reproduction (1A or 1B)

Follows the logic of "equivalent concern" between EDs and CMR substances.

- Option 3: WHO/IPCS definition of EDs (as in option 2) +2 other categories based on the strength of evidence for fulfilling WHO definition
  - Category I: Endocrine Disruptors
  - Category II: Suspected endocrine disruptors
  - Category III: Endocrine active substances

Comment:

Category I: Known or presumed EDs

Category II: Substances for which the level of evidence is weaker

Category III: Substances for which there is only evidence regarding the mode of action

No expectable difference with option 2 in terms of substances receiving authorization, hence no expected difference in terms of public health and environmental impacts.

Practical advantages: greater readability of the level of scientific evidence; similarity with the logic used for CMRs

- Option 4: WHO/IPCS definition to identify endocrine disruptors and inclusion of potency as element of hazard characterization (hazard identification and characterization).

Comment:

The way potency would be combined to the WHO definition is not specified.

Potency is not defined.

Potency is a scientifically ill-defined concept (Neubig, *Pharmacol Rev*, 2003; Slama, *EHP*, in press).

The relevant related concept is the dose-response function.

Considering dose-response functions without considering exposure is not relevant from a risk assessment perspective…

…but going back to a risk assessment perspective would be contrary to the logic of the Pesticides (2009) regulation.

In summary

- Option 1 — Not relevant scientifically
- Option 2 — Relevant scientifically
- Option 3 — Relevant scientifically; Efficiently conveys the level of evidence. Similarity with the categories used for CMRs
- Option 4 — Not relevant scientifically if “potency” is not replaced by a clearly defined concept. Contrary to the hazard-based regulatory logic of the law.

5. The European Commission's proposal of June 15, 2016

On 15 June 2016, the European Commission published

- An impact assessment study (summary + full report)
- A draft regulation setting criteria for EDs in the context of the 2009 *pesticides* regulation
- A draft regulation setting criteria for EDs in the context of the 2012 *biocides* regulation

Main content of the EC's proposal regarding the pesticides regulation (1)

1) The EC proposes to modify the annex II of the pesticides (PPPR) law, so that the exclusion clause authorizing pesticides containing EDs whose *exposure* is negligible would be replaced by a clause authorizing pesticides containing EDs for which *risk* is negligible.

Comment:

- This would imply to conduct a risk assessment before deciding if a pesticide with endocrine-disrupting properties can be authorized
- If risk is deemed negligible, the substance would be authorized even if exposure is not negligible
- This would imply to abandon two key principles of the 2009 law
  - Hazard-based management of pesticides with endocrine-disrupting properties
  - Equivalent handling of EDs and CMR substances

Main content of the EC's proposal regarding the pesticides regulation (2)

2) Identification of EDs: The EC proposes not to consider potency in the identification of EDs (former option 4).

Comment:

This actually does not mean that potency (dose response functions) would really be abandoned, as risk evaluation (which considers dose-response function) is planned to be applied after the step of hazard identification

3) The EC proposes to identify substances with endocrine disrupting properties relevant for human health as those known to cause an adverse effect relevant for human health, which have an endocrine mode of action and for which the adverse effect is a consequence of this mode of action

4) A similar definition is proposed for substances with endocrine disrupting properties relevant for non-target organisms [i.e. fauna not targeted by pesticides]

Comment:

Note the change of wording from "known or suspected to cause an adverse effect…" (former option 2) to "known to cause an adverse effect..."

This would be equivalent to considering only 1A (and not 1B) CMRs

This is not the WHO/IPCS definition (which does not restrict EDs to those relevant for human health)

Instead of suggesting one definition, the EC suggests to split the WHO definition in 2 (*Homo sapiens*/non sapiens)

A definition of Endocrine-disrupting properties specific to non-target organisms?

...An active substance, safener or synergist shall be identified as having endocrine disrupting properties with respect to non-target organisms if it is a substance that meets all of the following criteria:

(1) it is known to cause an adverse effect for non-target organisms, 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, considered relevant at the population level;

(2) it has an endocrine mode of action;

(3) the adverse effect relevant for the non-target organism at the population level is a consequence of the endocrine mode of action.

Comment:

Note here that the definition is restricted to adverse effects « considered relevant at the population level »

6. In summary

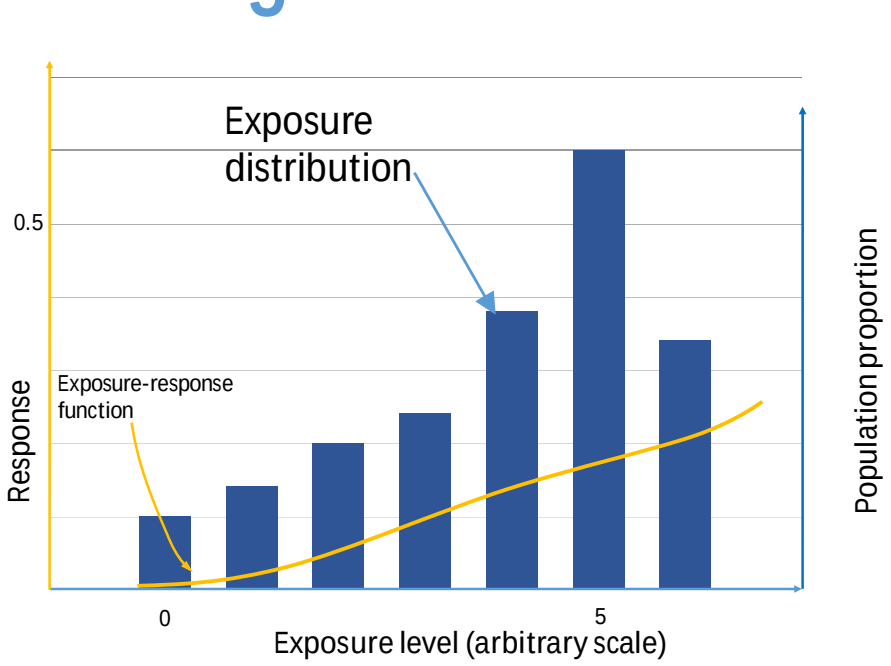
Summary

- The European 2009 pesticides regulation decided to ban pesticides recognized as EDs or CMRs for which exposure is not negligible
- The European 2009 pesticides regulation required the EC to present draft measures regarding the identification of substances with endocrine disrupting properties
- The EC draft (15 June 2016) replies to this question but also proposes to abandon the hazard-based logic to regulate EDs in pesticides
- In practice, this would result in neutralizing the law paragraph relative to EDs and to lower the guard against EDs
- The EC draft proposes to handle differently EDs and CMRs and distinguishes EDs relevant to human health and those relevant to other species
- It does not propose to distinguish *known (1A)*, *presumed (1B)*, and suspected (II) EDs (as conveniently done for CMRs)
- As presented in its impact assessment study (not discussed here), the EC seems to consider that the level of public health concern related to EDs is not equivalent to that induced by CMRs
- The draft measures would entail continuing exposure of the population to pesticides with endocrine-disrupting properties known to cause adverse health effects in humans

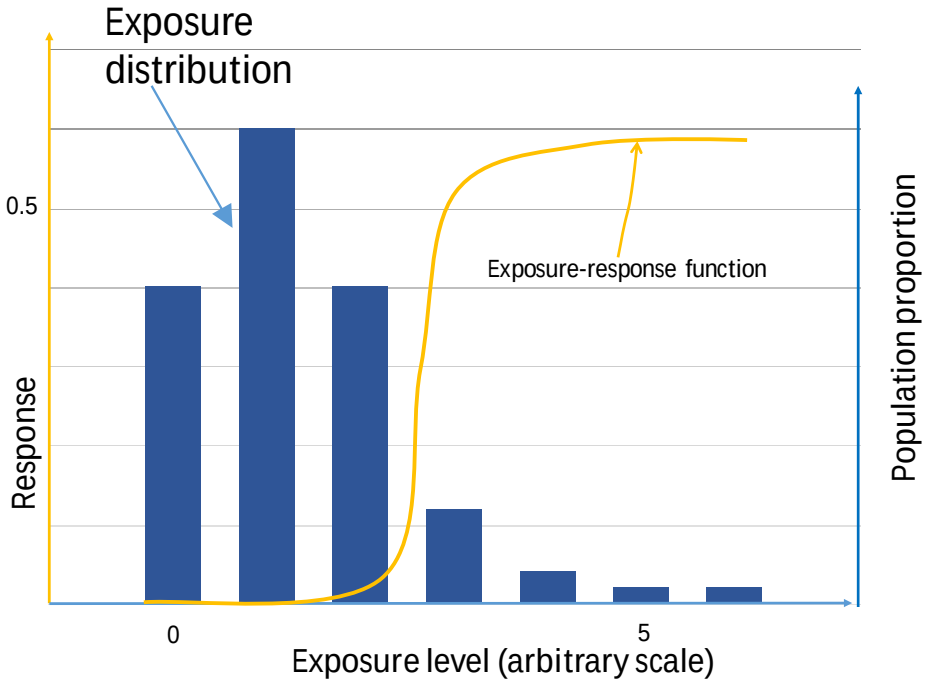
Thank you for your attention

Additional slide

The dose-response function("Potency") alone is not enough to estimate risk



Shallow dose-response function (and low potency) with a large proportion of highly exposed subjects, hence entailing a possibly high risk.



Steep dose-response function (and high potency) with a low proportion of highly exposed subjects, hence entailing a possibly similar or lower risk.

(Slama et al., *EHP*, in press)