Harmonizing approaches for mixture assessment

possibilities and pitfalls

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Harmonization of mixture risk assessment

Harmonization should ensure that the same conclusions on the presence or absence of risk are reached, independent of a particular regulatory framework

Harmonization

- Political and legal mandate
- Terminology
- Approaches for mixture toxicity assessment
- Approaches for single substance risk assessment
- Conclusions on presence / absence of risk

Approaches for mixture risk assessment

- Whole mixture testing
- Conclusions from similar mixtures
- Component-based approaches (Concentration Addition, Independent Action)

Sidestep: Mixture toxicity concepts

Dissimilarly acting substances: Independent Action

$$E_{Mix} = 1 - \prod_{i=1}^{n} (1 - E_i)$$

E_{Mix} = Effect of the mixture of *n* compounds

E_i = Effect of substance *i*, when applied singly

Similarly acting substances: Concentration Addition

$$ECx_{(Mix)} = \left(\sum_{i=1}^{n} \frac{p_i}{ECx_i} \right)^{-1}$$

c_i = Concentration of component *i* in the mixture (*i = 1...n*)

ECx_i = Concentration of substance *i* provoking a certain effect *x* when applied alone

$ECx_{(Mix)}$ = Predicted total concentration of the mixture, that provokes x% effect.

pi = relative fraction of component *i* in the mixture

Prospective Assessment per use category

Class	Regulation / Directive
Industrial Chemicals	Regulation 1907/2006 (REACH) Regulation 1272/2008 (CLP)
Pesticides	Regulation (EC) No 1107/2009, Regulation (EC) No 546/2011 Regulation (EC) No 396/2005 Commission Regulation (EU) 283/2013 Commission Regulation (EU) 284/2013
Biocides	Regulation (EU) No 528/2012
(Human) Pharmaceuticals	Directive 2001/83/EC

Retrospective Assessment per environmental compartment

Environmental Mixture Risk Assessment

	Legal Mandate?	Guideline(s)?
Industrial Chemicals	(✓)	(✓)
Pesticides	(✓)(✗)	✓
Biocides	✓	✓
Pharmaceuticals	✗	✗

Human Health Mixture Risk Assessment

	Legal Mandate?	Guideline(s)?
Industrial Chemicals	(✓)	✗
Pesticides	✓	✓
Biocides	✓	✓
Pharmaceuticals	✓	✓

Prospective M-ERA of industrial chemicals under REACH

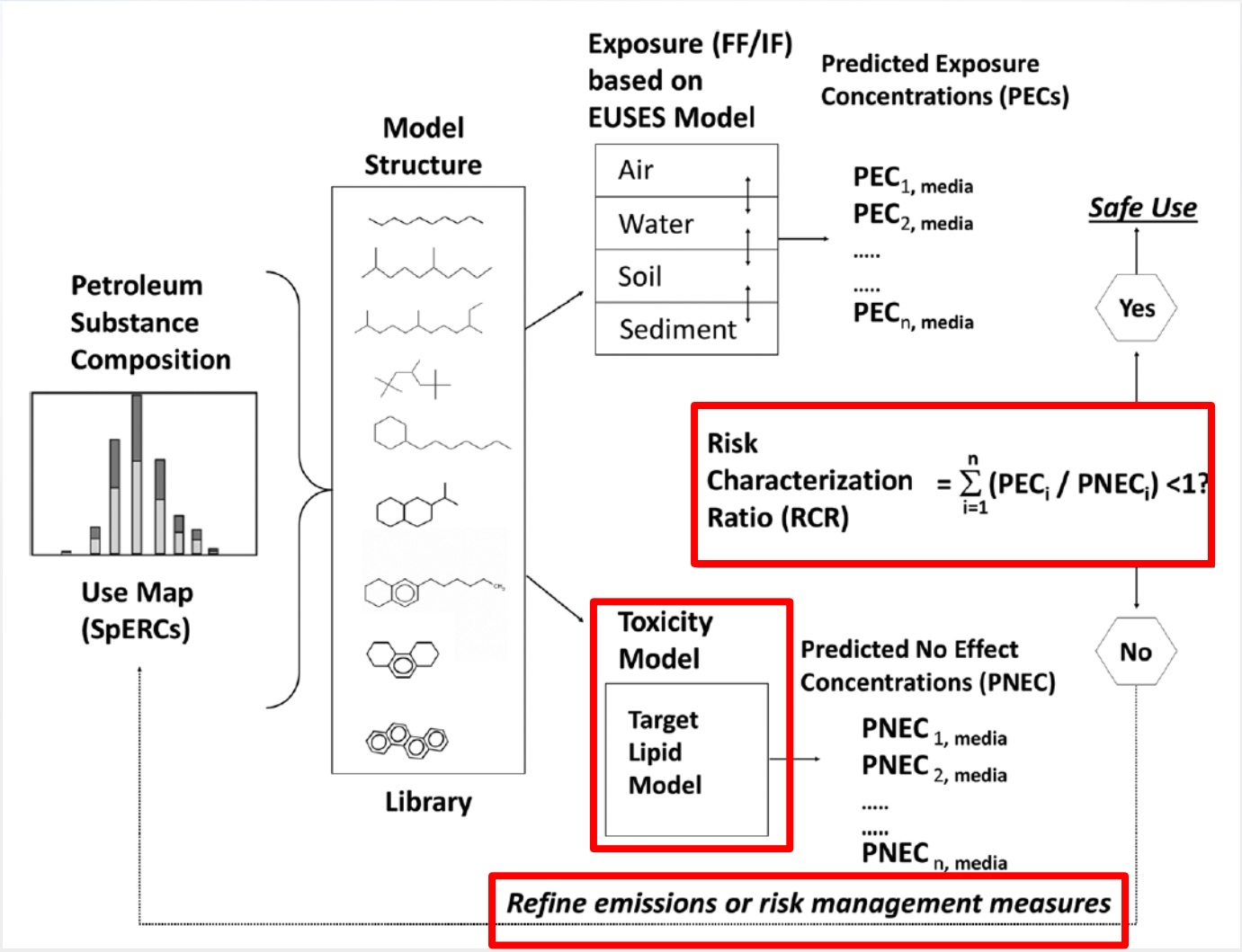
- REACH provides the mandate for assessing individual ***substances***.
- A substance can also be a “Multi-Constituent Substances” (MCS), or a “Substance of Unknown or Variable composition, Complex reaction products or Biological materials” (UVCB)

  ↳Whole mixture testing

Prospective M-ERA of industrial chemicals under REACH

- Substantial work on M-ERA of petroleum products (hydrocarbon-block method)
- Based on the summation of PEC/PNEC ratios of the representative hydrocarbon blocks (Petrorisk)
  - Simplification of a complex mixture
  - Application of CA

Prospective M-ERA of industrial chemicals under REACH



Redman et al., Int Env Ass Man, 2014

Prospective M-ERA of pesticides

Article 4(2) of Regulation 1107-2009

The residues of the plant protection products, consequent on application consistent with good plant protection practice and having regard to realistic conditions of use, shall meet the following requirements:

(a) they shall not have any harmful effects on human health, […], ***taking into account known cumulative and synergistic effects*** […]

(b) they shall not have any unacceptable effect on the environment.

Common Position (EC) No 25/2008

Article 4(2) of Regulation 1107-2009

b) … shall not have any unacceptable effect on the environment

For 1st and 2nd reading in the European Parliament, the Committee on the Environment, Public Health and Food Safety recommended to amend this environmental requirement also by

*…, **taking into account cumulative and synergistic effects and all relevant exposure routes to organisms in the environment**;*

<u>This initiative was unsuccessful.</u>

Despite the lack of a clear mandate for M-ERA of pesticides

- ❑ EFSA guidance for edge-of-field scenarios
- ❑ EFSA guidance for birds & mammals
- ❑ EFSA guidance for bees
- ❑ EFSA guidance for non-target terrestrial plants

<u>ALL</u> consider mixture effects in an environmental context

Prospective M-ERA of pesticides

Article 29(6) of Regulation 1107-2009

Following these principles, interaction between the active substance, safeners, synergists and co-formulants shall be taken into account in the evaluation of plant protection products.

"these principles" = Common principles (Commission Regulation 546/2011)

Prospective H-ERA of pesticides

Driven by Regulation 396/2005 (Maximum Residue Levels)

- EFSA Opinion from 2008 on suitable methodologies
- EFSA Opinion from 2009, triazole test-case
- EFSA Opinion from 2013, on the relevance of dissimilar modes of action

Grouping of mixture components

- No final guideline available, several EFSA opinions, OECD Guidance Document (July 2014)
- Discussed for M-HRA of pesticides
- Different aims, different needs, different efficiency
  - to select between CA and IA, to provide decision criteria whether a M-HRA is needed in the first place (→ presentation by A. Kortenkamp)
  - Read-across, QSAR modeling
  - to facilitate exposure and fate modeling (→ REACH and petroleum products)

Prospective M-ERA of human pharmaceuticals

- Legal basis for ERA is article 8(3) of Directive 2001/83/EC
- Details in EMA guideline EMEA/CHMP/SWP/4447/00 corr 1
- Based on a classical tiered approach

Regulatory M-ERA of human pharmaceutials

- Mixtures not considered in the final EMA guidelines
- Draft from 2005 for human pharmaceuticals states that "*Existing information on synergistic effects in the environment should be included in the risk assessment.*"
- The passage that was dropped in the final guideline

Prospective M-ERA of human pharmaceuticals

- Tier 0, the “Action Limit” is based solely on an exposure estimation and hazard considerations:
- If the PEC(aquatic) is < 0.01 µg/L, no ERA is deemed necessary.
- Unless endocrine activity or PBT

- **Conceptually similar to the TTC**
- **Not usable in a mixture context, unless adapted**

Selected issues: Tier 0 assessment

Identification of "relevant" compounds in order to simplify the mixture

- Hazard based (e.g. "substances of concern", "synergists)
- Concentration based (CLP)
- Risk based, i.e. substances present at sufficiently high individual RQs (10% of the total sum of Toxic Units is suggested for the M-ERA of pesticides)

Selected Issues : Deviations from CA, Synergism, Antagonism

Industrial Chemicals: No decision rules provided

Pesticides: Synergism/antagonism indicated by a deviation from CA by a factor exceeding 5

Biocides: Synergism/antagonism indicated by a deviation from CA by a factor exceeding 5

Determining such factors implies that experimental data for the mixture and all relevant components are at hand

Selected Issues : Deviations from CA, Synergism, Antagonism

Guideline for M-ERA of Biocides provides a set of guiding questions

- Compounds in the product specifically to synergise the active ingredient?
- Annex 3 with known cases of synergists
- Do compounds enhance uptake of others?
- Structural alerts present?
- Etc

Summary & Conclusions

- Harmonization of Mixture Risk Assessment (M-ERA, M-HRA) is an ongoing process
- Largely achieved on the scientific level (CA as the first tier)
- Legal mandate is missing or unclear (to me at least) for
  - M-ERA for pharmaceuticals
  - M-ERA for pesticides
- Agreed guidelines, accepted by the regulatory authorities, are missing for
  - industrial chemicals
  - human pharmaceuticals

Summary & Conclusions

Harmonization is lacking in the following aspects:

1) Identifying deviations from CA and/or IA

2) EU-wide, overarching compilation of known cases of synergistic interactions

3) Grouping: when, why, how?

4) Tier 0: common criteria for inclusion of a compound in mixture risk assessment

5) EU-wide, overarching compilation of single substance tox and ecotox data

THE main challenge

Integration and harmonization between prospective and retrospective risk assessments

THE main challenge: retrospective assessment

Compartment	Regulation / Directive
Freshwater	Directive 2000/60/EC (WFD) Directive 2008/105/EC (EQS)
Marine waters	Directive 2008/56/EC (MSFD)
Soil	None
Public health	None (??) (Maximum residue levels for mixtures of pesticides)

THE main challenge

Prospective (Emission based):

In the context of an application for market approval

Retrospective (Immission based)

In the context of the Water Framework Directive or the Marine Strategy Framework Directive

THE main challenge

Legal mandate

Ecosystem perspective: the environmental compartment should have “good ecological status”

Scientific approaches

- Interlinked assessment of chemical and biological status
- Quality standards for individual compounds
- Inadequate, see e.g. Carvalho et. al, Tox Sci 2014

THE main challenge

Specific issues

- Which mixtures occur under which conditions in which waters?
- Means for simplification ? Prioritization?
- How to act on it?
- How to amend the current regulatory system?

THE main challenge

Integration and harmonization between prospective and retrospective risk assessments

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