Harmonisation of human and ecological risk assessment of combined exposure to multiple chemicals

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Mixture toxicology

- Prediction of mixture effects when effects of components are known – applicable only if all components produce effect of interest
- Assumption: chemicals act without interfering with each other
- Effects can be predicted by using dose (concentration) addition or independent action
- Concepts have been allied with modes of action: dose addition – similar action; independent action – dissimilar action
Three androgen receptor antagonists
Hass et al. 2007 EHP 115 Suppl 1, 122

Dose addition
Algal toxicity of 16 dissimilarly acting toxicants
Faust et al. (2003) Aquat Toxicol 63, 43

Aclonifen
8-Azaguanine
Azaserine
CCCP
Chloramphenicol
DTMAC
Fenfuram
Kresoxim-methyl
Metalaxyl
Metazachlor
Metsulfuron-methyl
Nalidixic acid
Norflurazon
Paraquat
Terbutylazim
Triadimenol
Topics with divergent approaches in human and ecotoxicology

- Criteria for creating cumulative assessment groups (grouping)
- Combination effects at levels assumed to be safe for individual chemicals
- “Filtering devices” to keep the number of chemicals manageable
Approaches to grouping

• **What** chemicals should be grouped for mixture risk assessment?

• **How** should grouping be done (criteria)?

• Is grouping according to **similar mechanisms** (similar action) viable?
Grouping in ecotoxicology

In the past, emphasis on **common adverse outcomes**, less so on mechanisms

…but more recently:

“EQSs may be defined for **grouped substances that exert a similar mode of action** and may be expressed according to the concept of Toxic Equivalent [TEQ] concentrations in environmental samples.”

Grouping in human toxicology

Traditionally, emphasis on **similar modes of action**, in relation to quite specific effects

...but more recently:

*Mvov towards common adverse outcomes*

EFSA Scientific Opinion 2013, EFSA Journal (2013); 11(12) 3472
Softening stance in human toxicology

• US EPA: Common mechanisms – similar chemical structures

Similar or dissimilar action?

- Are hypotheses about modes of action a reliable basis for declaring “similar action”?

- If similar action is thought unsuitable, does dissimilar action apply?
Mixtures of anticancer drugs

Phul et al. (in prep)
Etoposide
Melphalan
Doxorubicin
5 FU
Vincristine
Cis-Pt
Cyclophosphamide
Mixtures of aneugens and clastogens - micronuclei

Ermel et al. (2014) Arch Tox 88, 799

Flubendazole
Doxorubicin
Etoposide
Melphalan
Mitomycin C

![Graph showing the effect of mixture concentration on the percentage of MN positive bin cells]
What is “dissimilarity”?

• Clear **definitions not available**
• Dissimilarity is **not** the simple negation of “similarity”
• Clear reference cases for **validity of independent action** with mammalian toxicity endpoints **not available**
• Number of chemicals **exceeds** the number of available dissimilar modes of action
Harmonisation I: Abandon dichotomous approaches based on similarity / dissimilarity

- EFSA 2013: Apply dose addition also for dissimilarly acting pesticides
- This is credible, because:

  There is no example in the literature where IA provides more conservative predictions than DA that are also correct.

  A practicable assessment concept based on IA is not available.

  The distinctions in terms of MOA normally used to decide on application of DA or IA are problematic and hard to use in practice.

  The prediction differences between IA and DA are small and of little relevance in risk assessment practice.
Mixture effects at levels below regulatory values

“The question therefore … [is] if exposures to mixtures well below … [NOEL or NOEC], … at the level assumed to be safe for each component (TDI, DNEL, PNEC or equivalent) may produce adverse effects. The answer to this question is different for human health and ecological assessments.”


**Human toxicology:** TDI expected to produce zero effects – no combination effects if all substances have *dissimilar modes of action*

**Ecotoxicology:** PNECs associated with small population level effects may still protect populations when single chemicals are considered. But with several chemicals mixture effects will be higher, even with dissimilarly acting chemicals.
Differences in protection goals

**Human toxicology:** individual

ADI / TDI assumed to be zero effect  
Dissimilar action assumed  
No combination effect expected

**Ecotoxicology:** populations (can survive a degree of loss)

PNECs often > zero effect  
Even with dissimilar action combination effects expected
When is a mixture “safe”?  
The case of dose addition

\[
\frac{\text{Intake}_1}{\text{T tolerable Daily Intake}_1} + \frac{\text{Intake}_2}{\text{T tolerable Daily Intake}_2} < 1
\]

If every component is present at \(\text{TDI} / n\) the mixture effect is equal to an effect associated with TDI (the assumption: Effect = 0)

**How many mixture components are we dealing with?**

**How many are present at TDI / n?**
When is a mixture “safe”? The case of independent action

\[ E_{1,2,...n} = 1 - [(1-e_1)(1-e_2)...(1-e_n)] \]

100 agents with zero effect: joint effect = 0
100 agents with 1% effect: joint effect = 63%
100 agents with 0.1% effect: joint effect = 9.5%

“NOAEL not a zero effect level”

SCHER, SCENIHR, SCCS (2011)
Harmonisation II: Adopt ecotox stance on low doses also for human toxicology

Human toxicology position on mixture effects at ADI / TDI only correct if:

- ADI / TDI = zero effect
- Conditions of dissimilar action fulfilled

No example exists for the applicability of independent action in human toxicology.
Confusing and misleading terminology – a nightmare for risk communication:

- PNEC associated with effects
- NOAEL associated with effects
- DNEL?
- ADI / TDI
Thank you