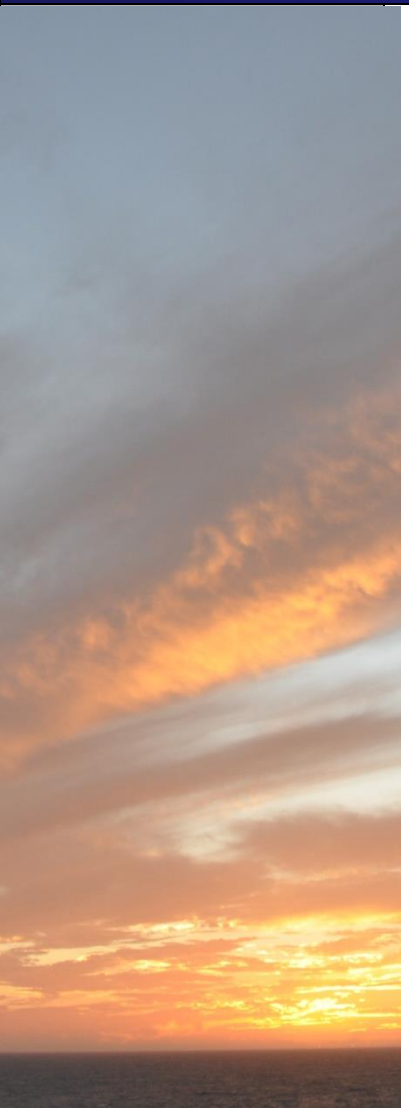
EFSA Scientific Colloquium



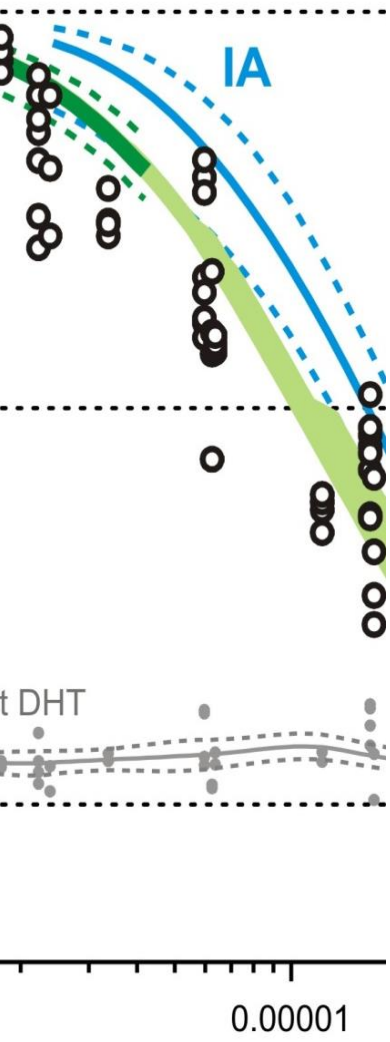
Harmonisation of human and ecological risk assessment of combined exposure to multiple chemicals

Andreas Kortenkamp

Institute of Environment, Health and Societies, Brunel University London

11-12 September 2014, Edinburgh

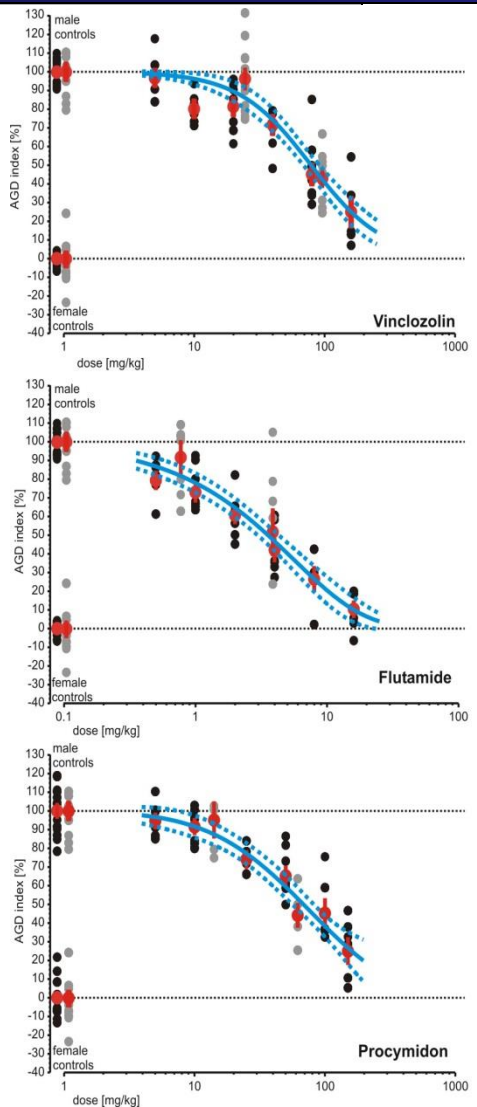
Mixture toxicology

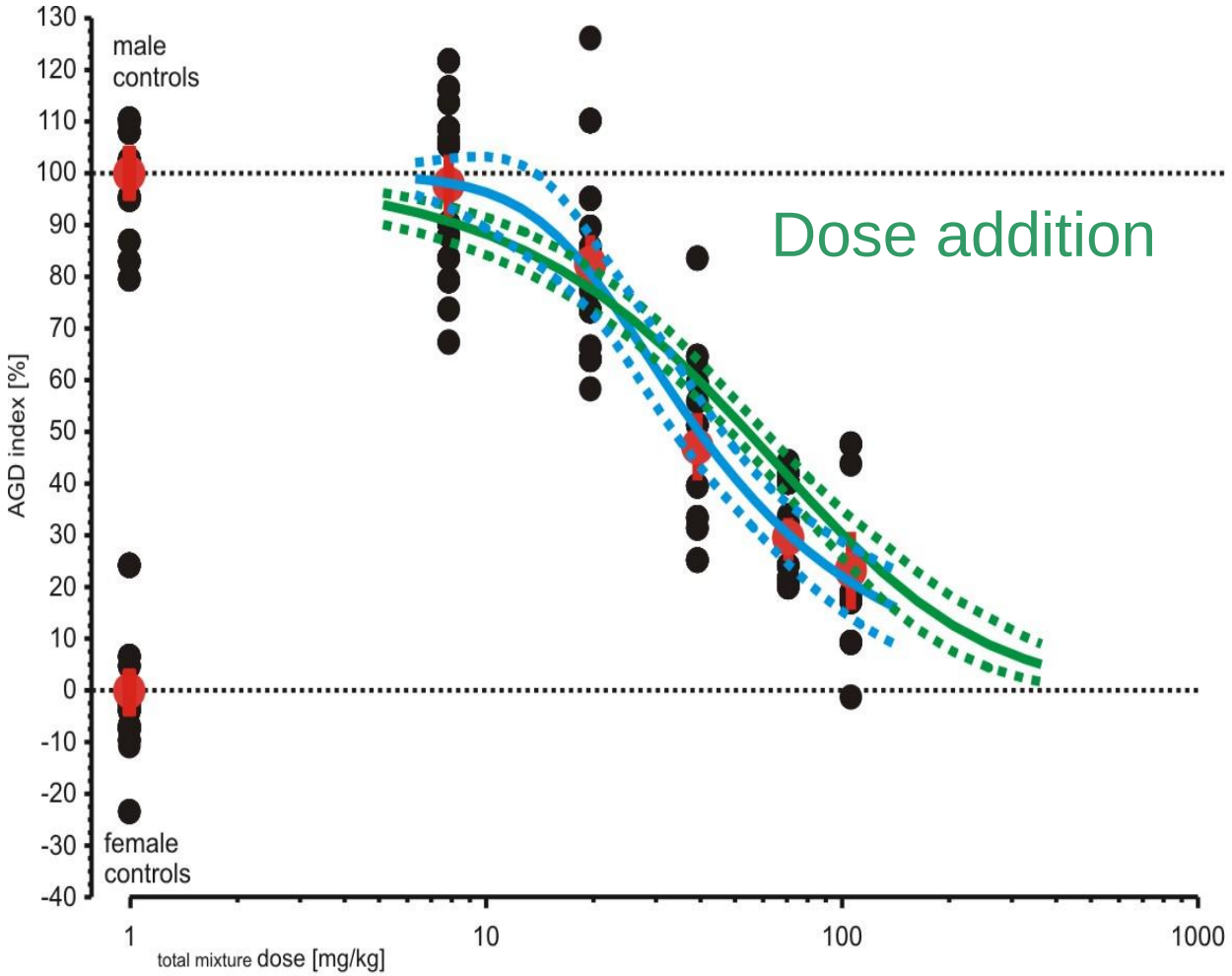


- Prediction of mixture effects when effects of components are known – applicable only if **all components produce effect of interest**
- Assumption: chemicals act without interfering with each other
- Effects can be predicted by using ***dose (concentration) addition*** or ***independent action***
- 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

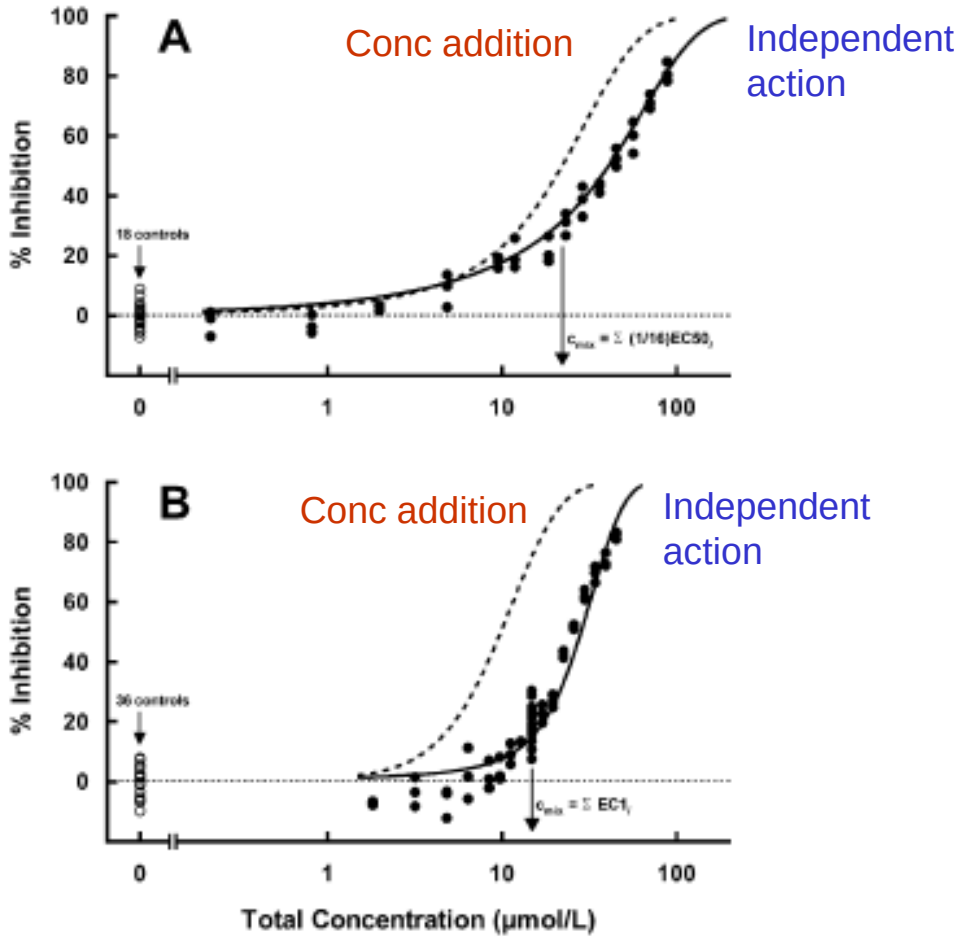




Algal toxicity of 16 dissimilarly acting toxicants

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."*

Guidance Document No: 27 Technical Guidance For Deriving Environmental Quality Standards, p 117

Grouping in human toxicology

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

…but more recently:

Move 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
- US National Acad of Sciences (2008): Similar structures too narrow - **common adverse outcomes**

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

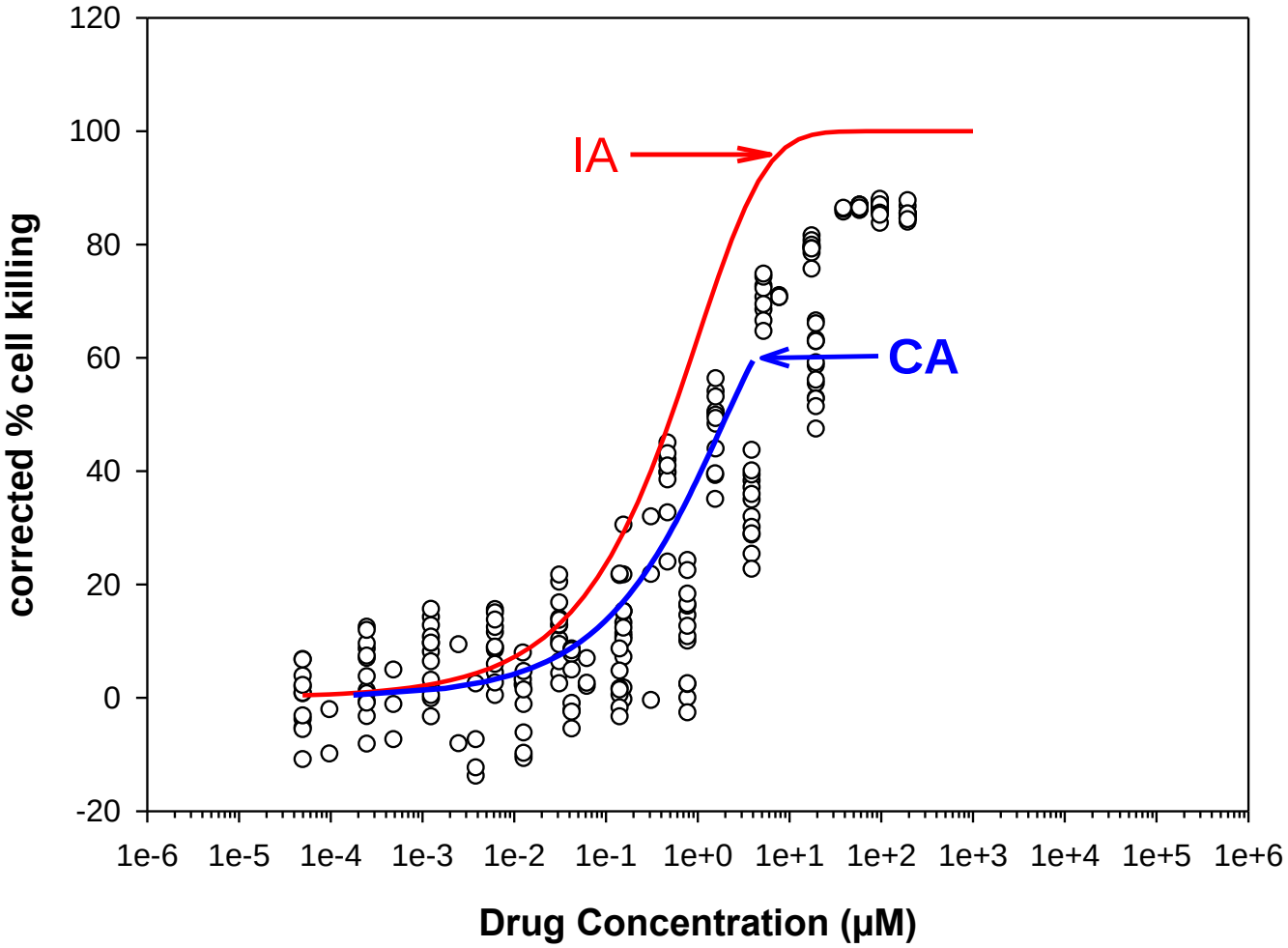
Doxorubicin

5 FU

Vincristine

Cis-Pt

Cyclophosphamide



Mixtures of aneugens and clastogens - micronuclei

Ermler *et al.* (2014) Arch Tox 88, 799

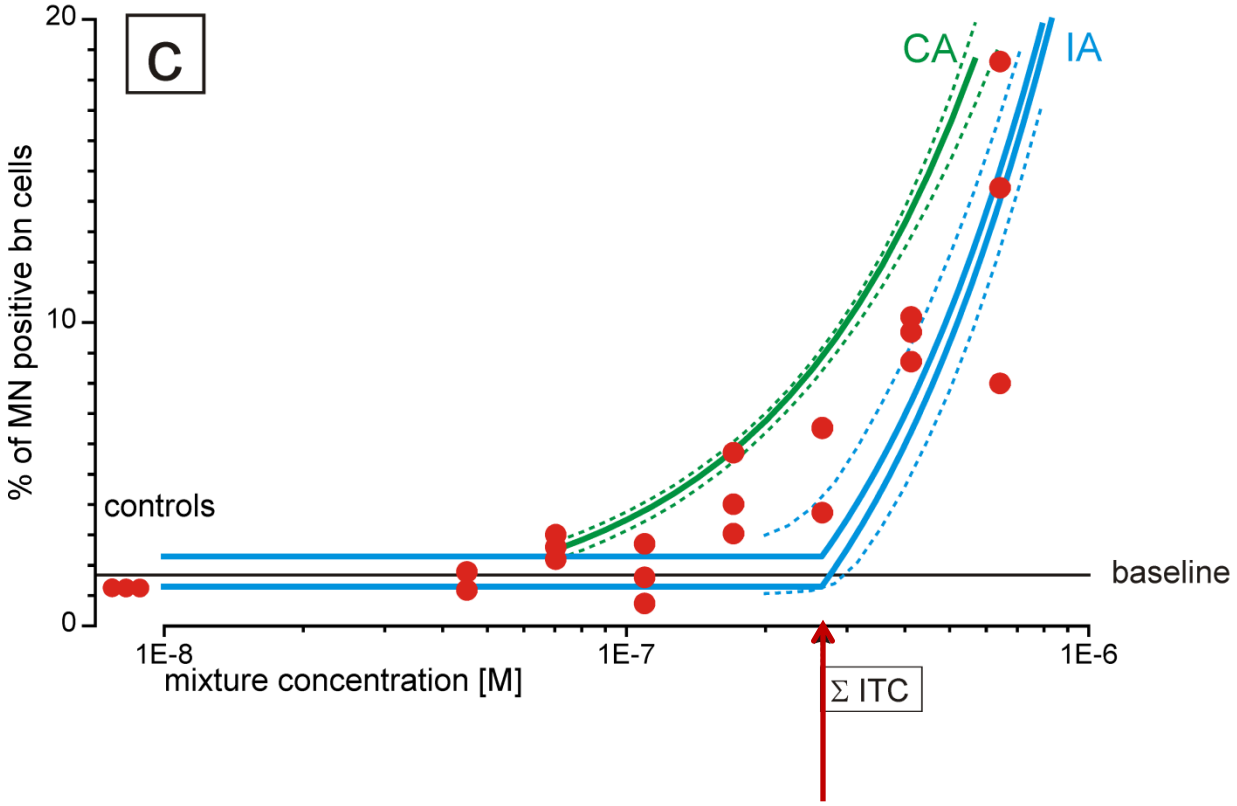
Flubendazole

Doxorubicin

Etoposide

Melphalan

Mitomycin C



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."*

SCHER, SCENIHR, SCCS (2011)
http://ec.europa.eu/health/scientific_committees/environmental_risks/docs/scher_o_155.pdf

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

$$\frac{\text{Intake}_1}{\text{Tolerable Daily Intake}_1} + \frac{\text{Intake}_2}{\text{Tolerable Daily Intake}_2} < 1$$

If every component is present at **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

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%

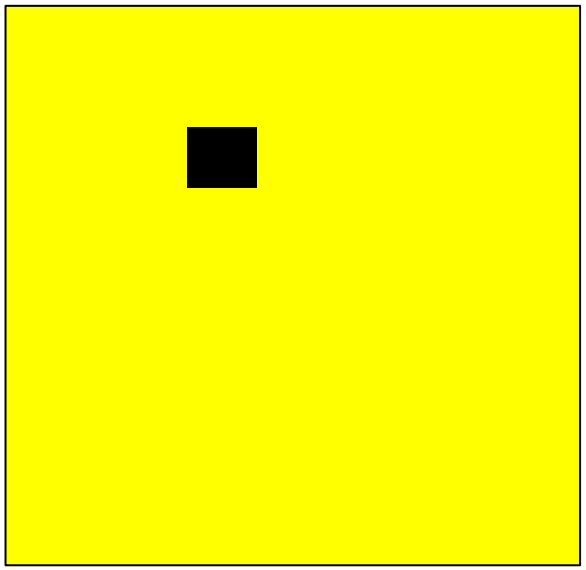
“NOAEL not a zero effect level”

SCHER, SCENIHR, SCCS (2011)
http://ec.europa.eu/health/scientific_committees/environmental_risks/docs/scher_o_155.pdf

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.

Harmonisation III: Terminology

Confusing and misleading terminology – a nightmare for risk communication:

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

Thank you