Mixture toxicity

Background, concepts, applicability

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Outline

- What's important about mixtures?
- How can we work with it?
- How do we handle the problem?

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Mixtures?

- ECHA >100000 substances in C&L database
- Flame retardants, preservatives, pesticides, disinfectants, biocides, pharmaceuticals, cosmetics..
- Simultaneous exposure to several substances

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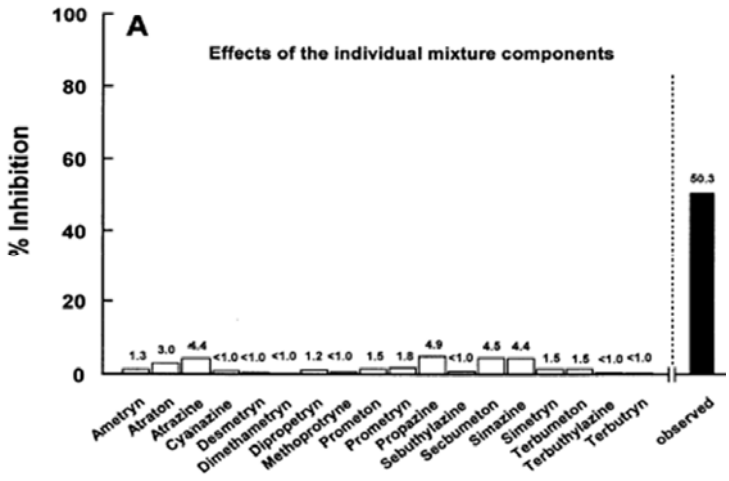
Traditional risk assessment is not good enough

- Effect of mixture > effect of most potent chemical



Faust et al 2001

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How can we work with it?

- Test mixtures. (Infinite combinations)
  - Doable for small fraction of all possible combinations
- Predict effect of mixtures
  - Effects can be modelled with acceptable precision

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Predicting effect of mixtures

- Requires data
  - Detailed information on composition of mixture
  - Toxicity of the single substances
- Models predict effect
  - Assume that substances do not interact

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Concentration or Dose Addition, CA

- Concept:
  - Chemicals in mixture act as diluters of each other and only differ in relative potency
- Corresponds to substances with similar structure and mechanism of action

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CA

- Addition of concentrations
- Any concentration (even below NOEC/NOAEL) adds to effect of mixture

$$\frac{c_{mix}}{ECx_{mix}} = \sum_{i=1}^{n} \frac{c_i}{ECx_i}$$

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Independent Action or Response Addition, IA

- Concept:
  - Joint probability of statistically independent events
- Interpreted as the chemicals having dissimilar mechanisms of action

$$E_{mix} = \prod_{i=1}^{n} \left[E(c_i) \right]$$

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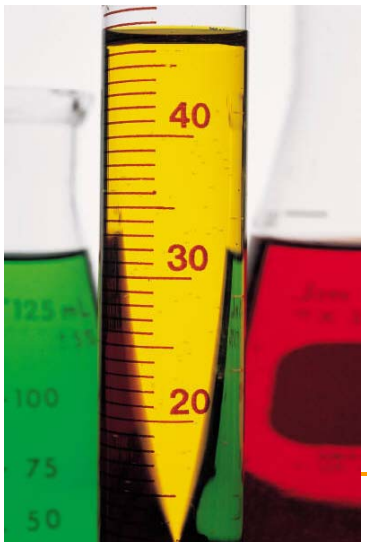
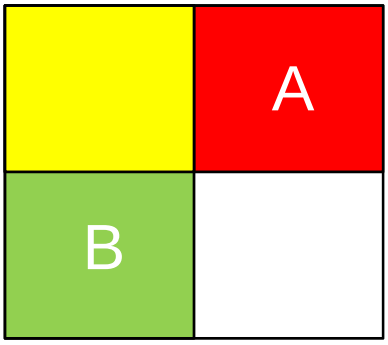
IA





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IA

- Summation of effects
- Only concentrations above NOEC/NOAEL are considered to contribute to mixture effect
- Is NOEC/NOAEL truly zero effect?

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Substances at or below NOAEL lead to significant effect in mixture

Reference	Mixture components	Species / Endpoint	Individual concentrations	Joint effect
Hermens et al. 1985 Ecotoxicol Environ Saf 9: 3211-326	33 aquatic pollutants from 3 groups with probably different modes of action	Fish / Acute mortality	4% of EC50 (assumed to be below NOEC)	50%
Payne et al. 2001 Environ Health Perspect 109: 391-397	4 organo-chlorine pesticides exerting effects on cell proliferation in different ways	MCF-7 cell proliferation	25-100% of NOEC	Significant proliferative effect
Walter et al. 2002 Ecotoxicology 11: 299-310	11 aquatic priority pollutants selected for structural diversity by chemometric analysis	Algae / Reproduction	NOEC	64%
Faust et al. 2003 Aquatic Toxicol 63: 43-63	16 toxicants known to interact with completely different molecular target sites in algae	Algae / Reproduction	6.6-66% of NOEC	18%

Applicability

CA	IA
• Relatively low data demands	• High data demands
• Slight over-predictions of toxicity	• May underestimate toxicity
• Pragmatic first choice	• Refined risk assessments in certain cases

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Adaptation

- EFSA 2006
- State of the art report on Mixture Toxicity - 2009
- Conclusions of the European Council – 2009
- WHO/IPCS Framework 2011
- Nordic Council of Ministers 2012
- Anticipated: EU Commission 2012
- Implementation in EU Chemical legislation. PPP, Biocides, Reach etc.

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Summary

- What's important about mixtures?
  - Chemical risk assessment must consider mixtures to not underestimate risk
- How can we work with it?
  - Mixture effects can be predicted by using simple models
- How do we handle the problem?
  - Implement mixture toxicity into chemicals legislation

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