

Foundations of Mixture Toxicology and Their Regulatory Implications

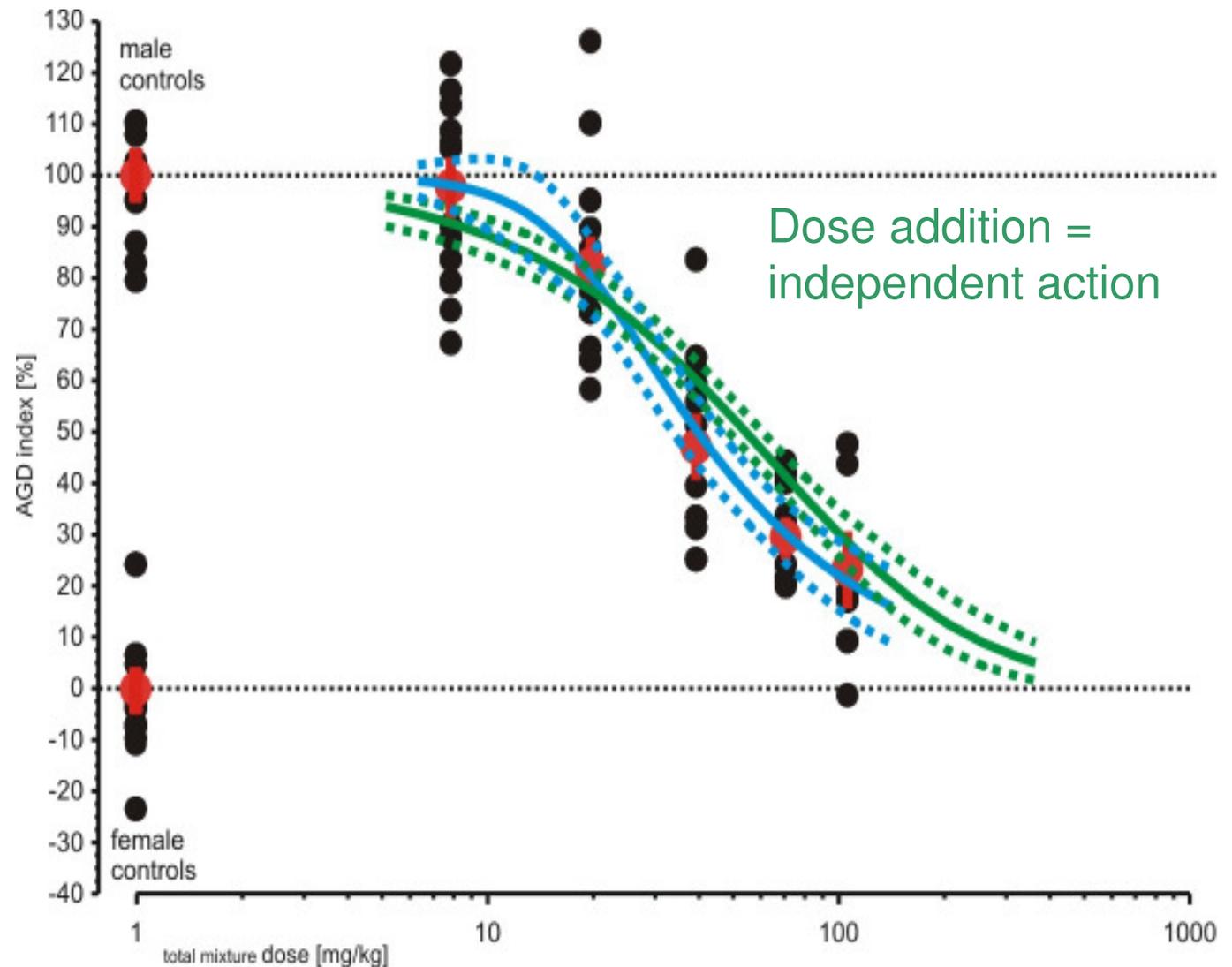
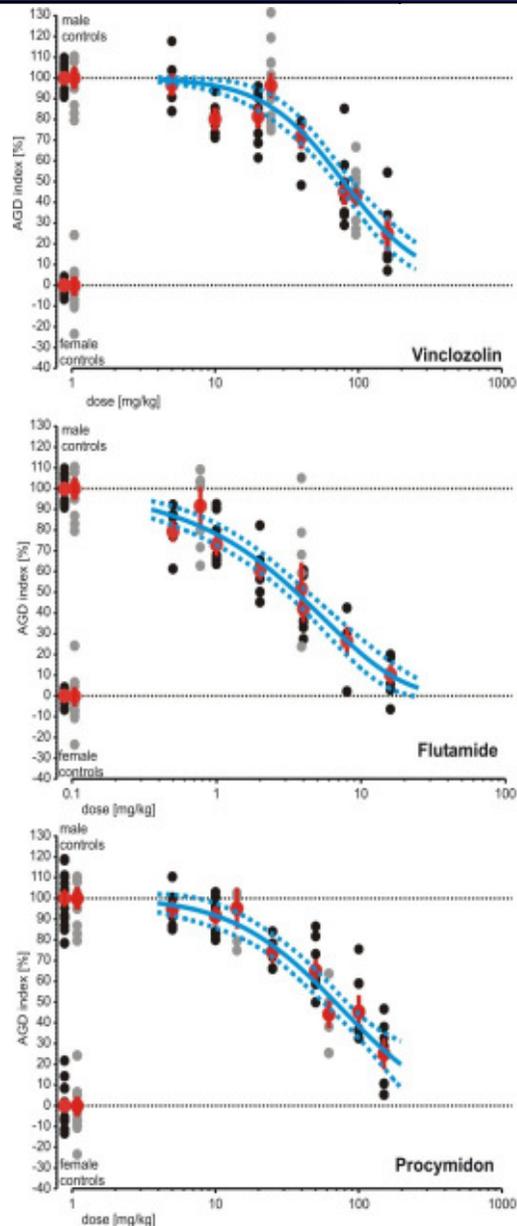
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19 March 2013

Assessment and prediction (1)

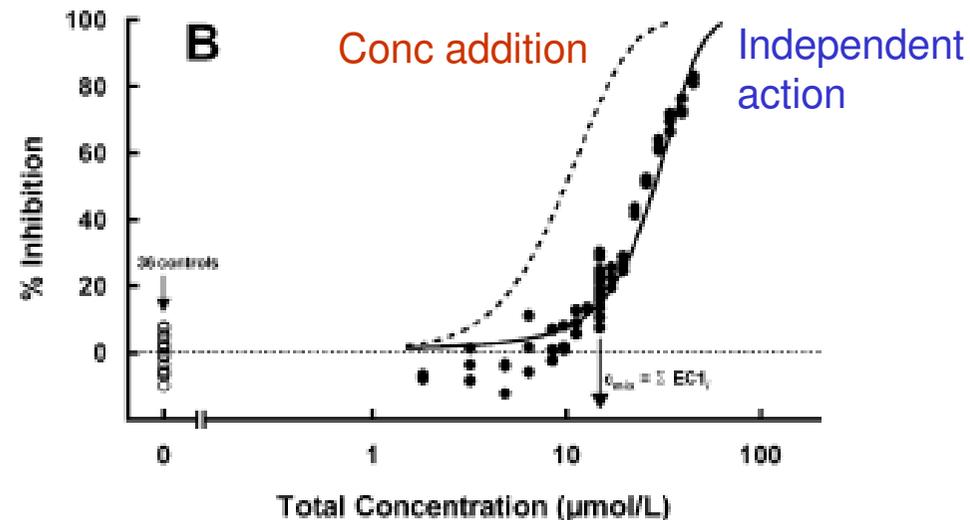
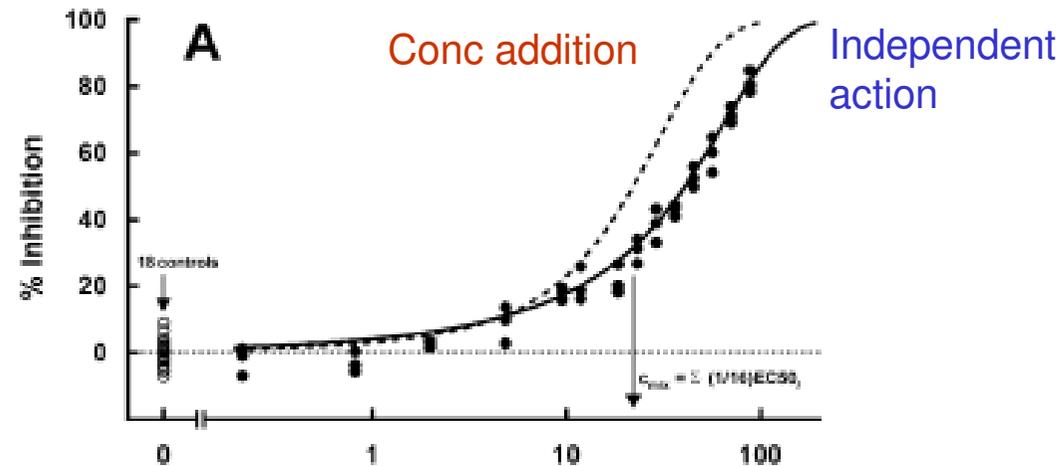
Hass *et al.* 2007 EHP 115 Suppl 1, 122



Algal toxicity of 16 dissimilarly acting toxicants

Faust *et al.* (2003) *Aquat Toxicol* 63, 43

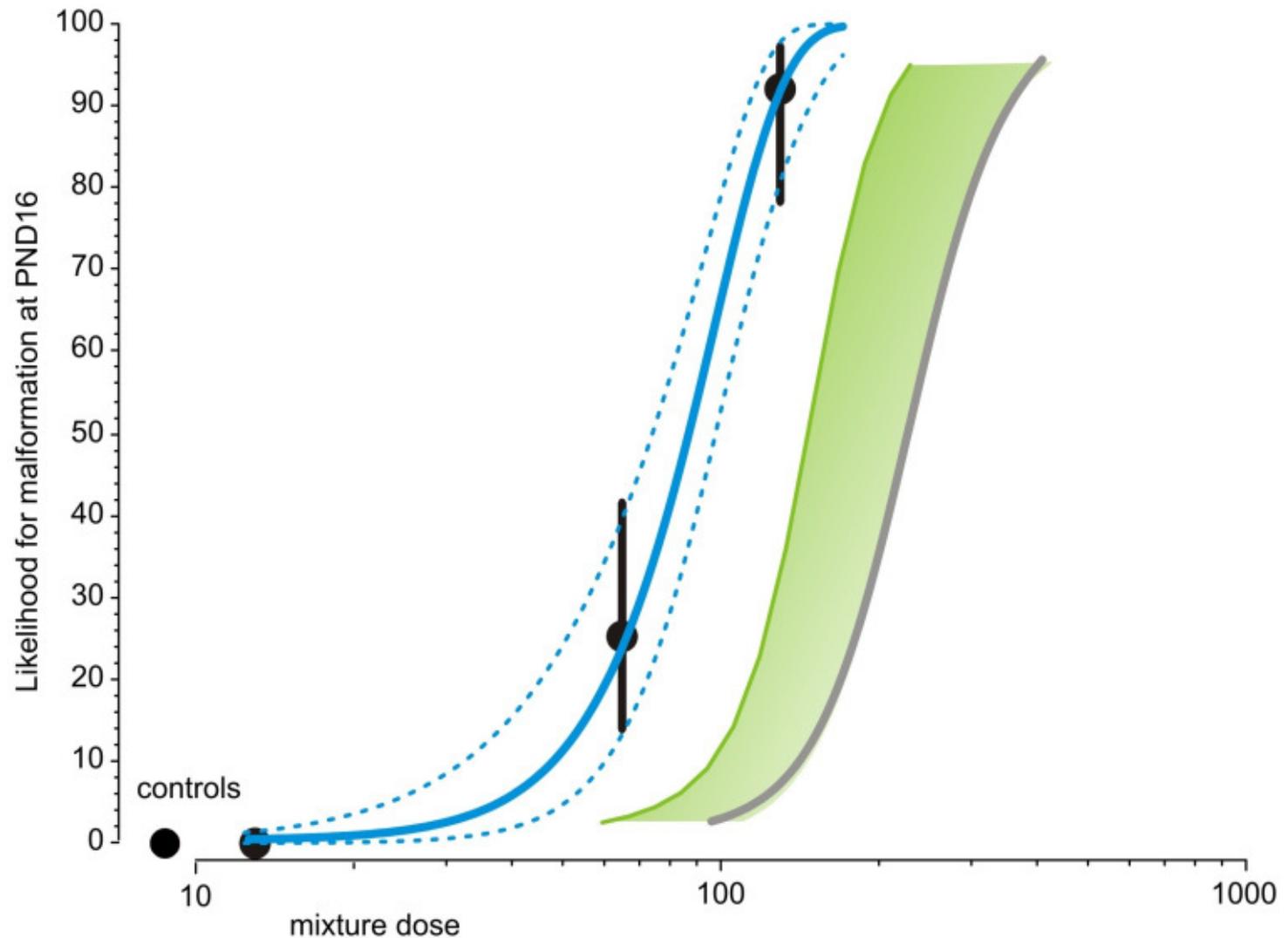
Aclonifen
8-Azaguanine
Azaserine
CCCP
Chloramphenicol
DTMAC
Fenfuram
Kresoxim-methyl
Metalaxyl
Metazachlor
Metsulfuron-methyl
Nalidixic acid
Norflurazon
Paraquat
Terbutylazim
Triadimenol



Prediction of mixture effects?

Synergism
with genital
malformations

Christiansen *et al.*
2009, EHP **117**,
1839



Is a consideration of mixture effects necessary from a scientific viewpoint?

- Chemicals risk assessment normally ignores mixture effects
- Exposure: to several chemicals simultaneously

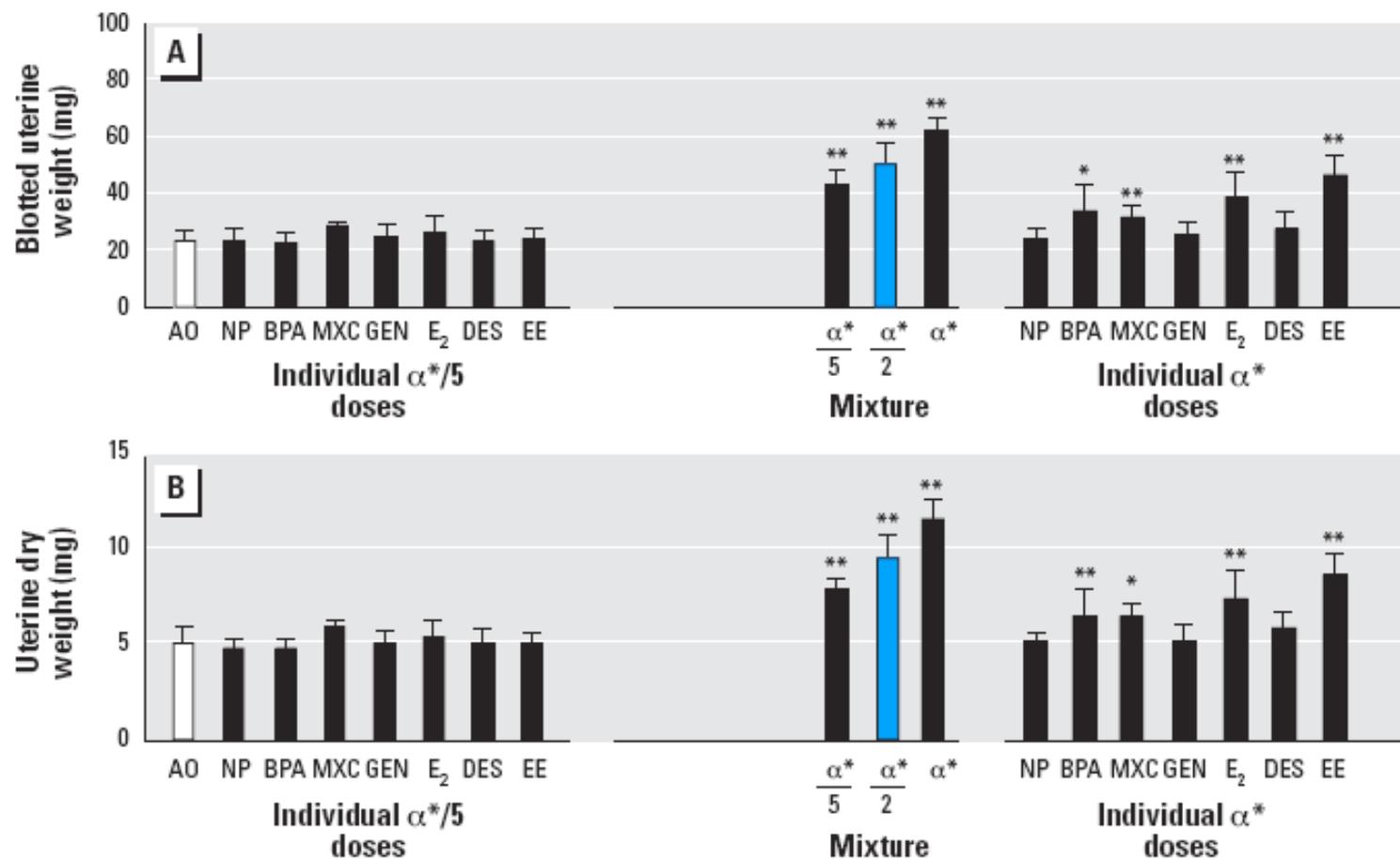
Is a consideration of mixture effects necessary from a scientific viewpoint?

Current practice justified if:

- Only one chemical is toxic, all others “inert”
- Joint effect of mixture not larger than effect of most toxic component

Comparing mixture effects with those of components

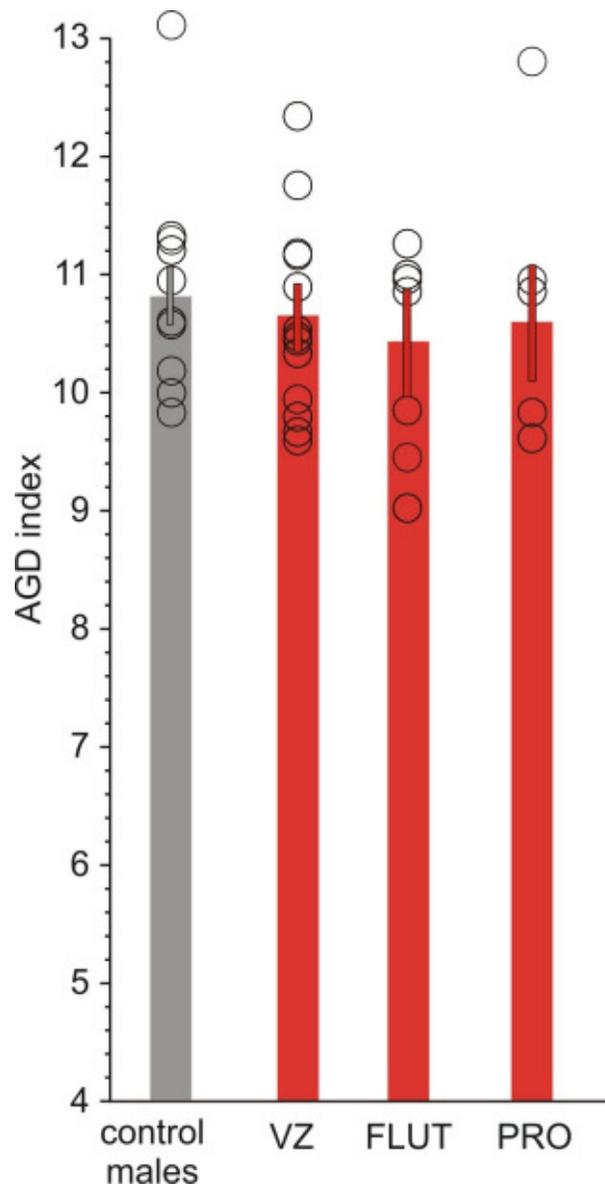
Tinwell and Ashby (2004)
EHP 112, 575



Comparing mixture effects with those of components

Similarly acting chemicals: Something from “nothing”

Hass *et al.* 2007, EHP 115 (Suppl 1), 122



Is there sufficient protection at exposures not exceeding ADI's or PNEC's?

- **Scientific consensus:** mixtures of similarly acting compounds require special consideration
- **Dose addition:** Every component contributes, even at doses below thresholds



When is a mixture “safe”?

The case of dose addition


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

Mixture effect equal (no) effect at TDI if every component is present at **TDI / n**

How many mixture components are we dealing with?

Independent action – the traditional view

- Mixtures pose no health concern as long as each component stays below NOAELS (Feron et al. 1995, COT 2002)
- "As a matter of **fact**, presently available data on exposure to mixtures of chemicals at doses well below the NOAELS of the individual constituents indicate that such exposure is of no health concern" (Carpy et al. 2000, *European Crop Protection Association*).



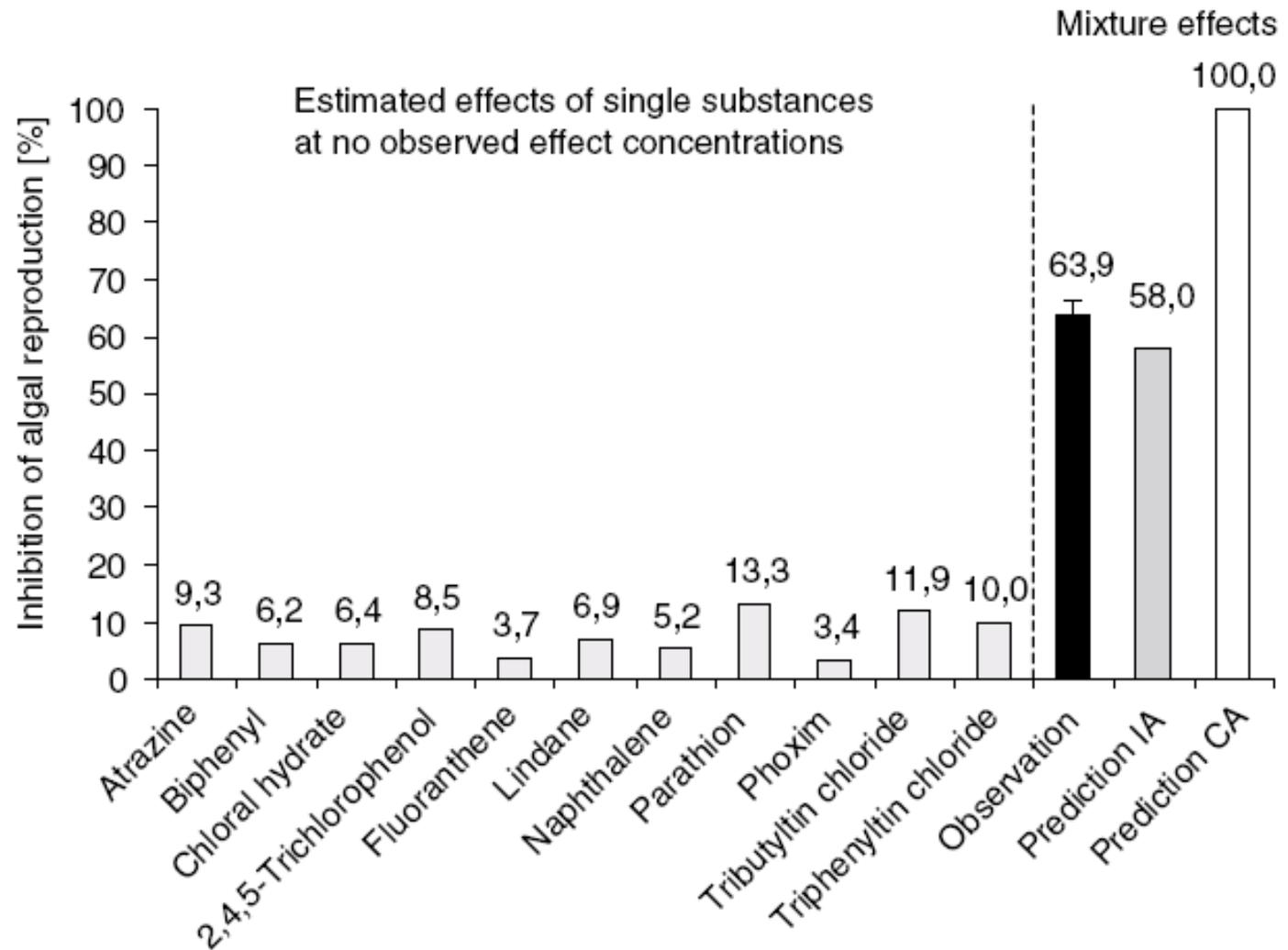
Independent action – the traditional view (contd.)

- **VKM (2009)** “When combined exposure to plant protection products with simple dissimilar action ... are below their respective effect *threshold levels (NOAELs, BMDs)*, it is assumed that combined action of all plant protection products *will be zero* (see section 2.1).”
- **VKM (2009)** “For substances exhibiting dissimilar modes of action ..., adverse effects from multiple exposures are *not expected* when the exposures to the individual components of the mixture are below their respective *ADIs/TDIs*.”
- **COT (2002)** “Thus, where exposure is to multiple pesticides or other chemicals at doses less than the *NOAEL*, adverse reactions to such exposure is *unlikely*.”



Combination effects of **dissimilarly** acting chemicals at conc < NOAEL

Mixture of dissimilar algal toxicants
Walter *et al.* (2002)
Ecotoxicol **11**, 299

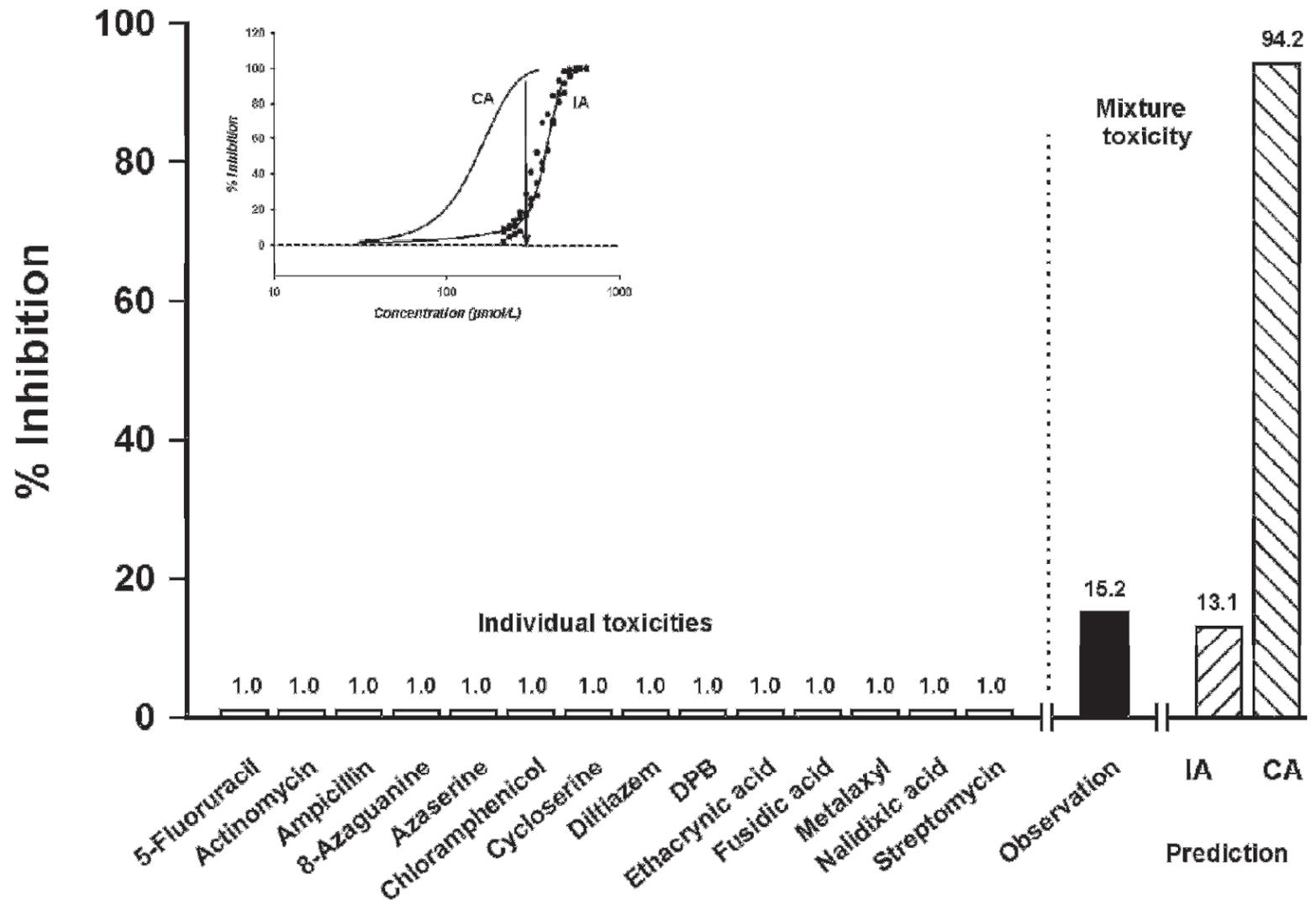


Combination effects of **dissimilarly** acting chemicals at conc < NOAEL

Mixture of dissimilarly acting bacterial toxicants and pharmaceuticals

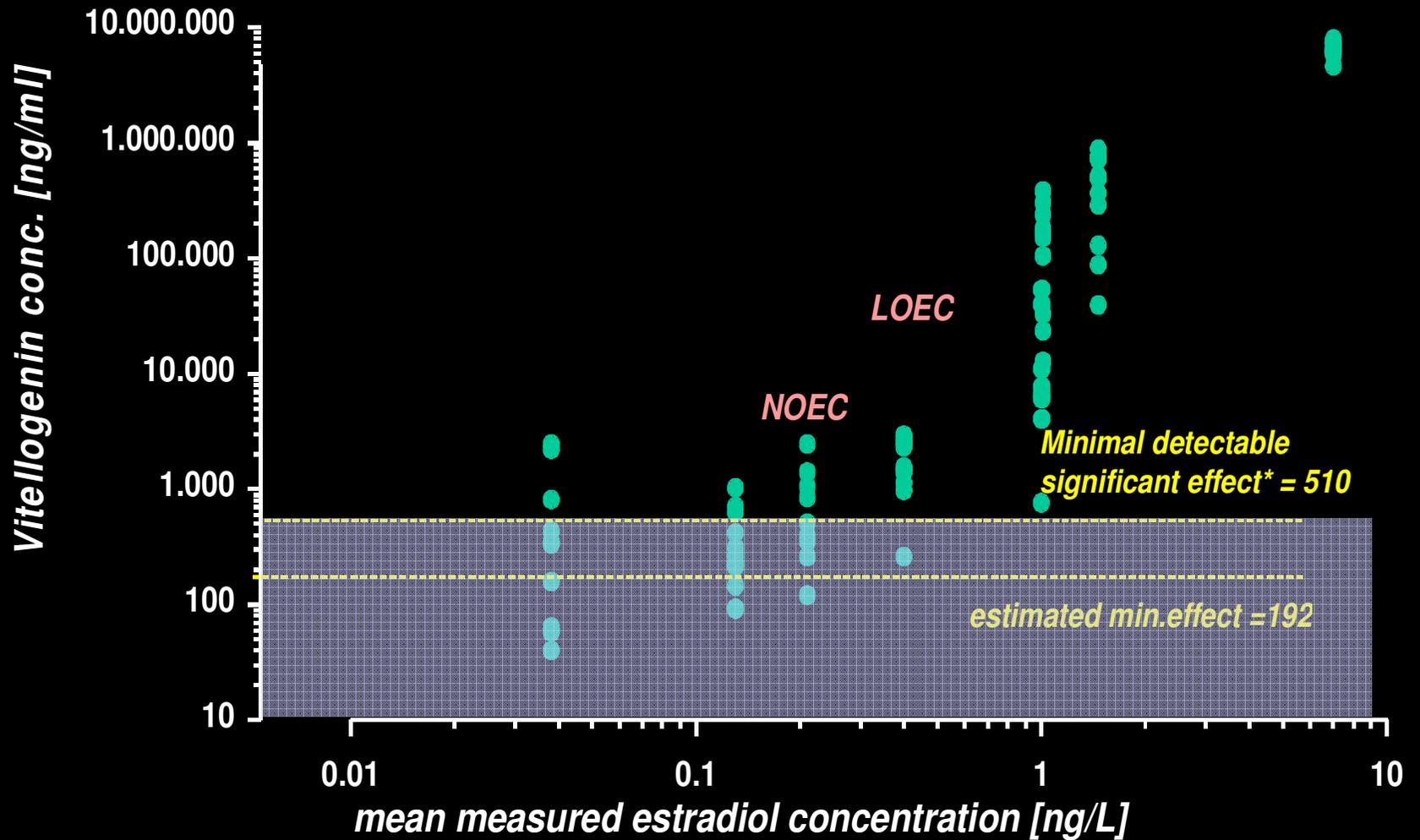
Backhaus, Sumpter and Blanck (2008)

In Kümmerer (Ed.)
Pharmaceuticals in the Environment, 3rd revised ed., pp. 257-276, Springer, Berlin, Heidelberg



What is a NOAEL?

Vitellogenin induction in fish



*Dunnett test, one-sided, alpha=5%, beta=10%

NOAEL

“A grey zone where effects can neither be confirmed nor ruled out with certainty”

M. Faust



When is a mixture “safe”?

The case of independent action

Independent
action

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

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%

Pertinent issues

- ADI (TDI, PNEC) - zero effect levels?
- How many chemicals act together?
- Which chemicals should be considered / grouped together?

Combined exposures - a topic for risk assessment!



Thank you

