

Combination effects of chemicals – the importance of summing up risk quotients

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Mixture effects:

Too difficult

Not necessary

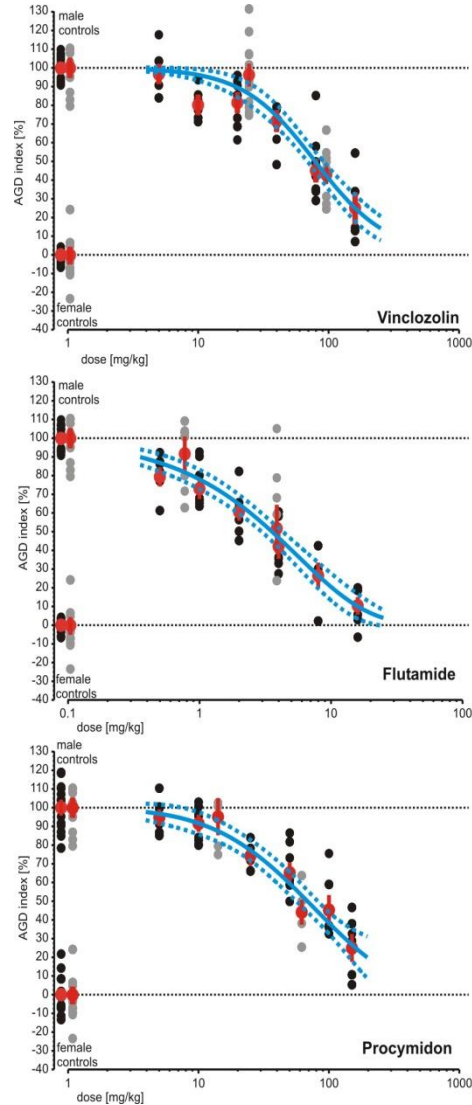
“Protection from mixture effects is achieved, as long as exposures stay below thresholds”

Astronomically large
numbers of combinations

Test everything?

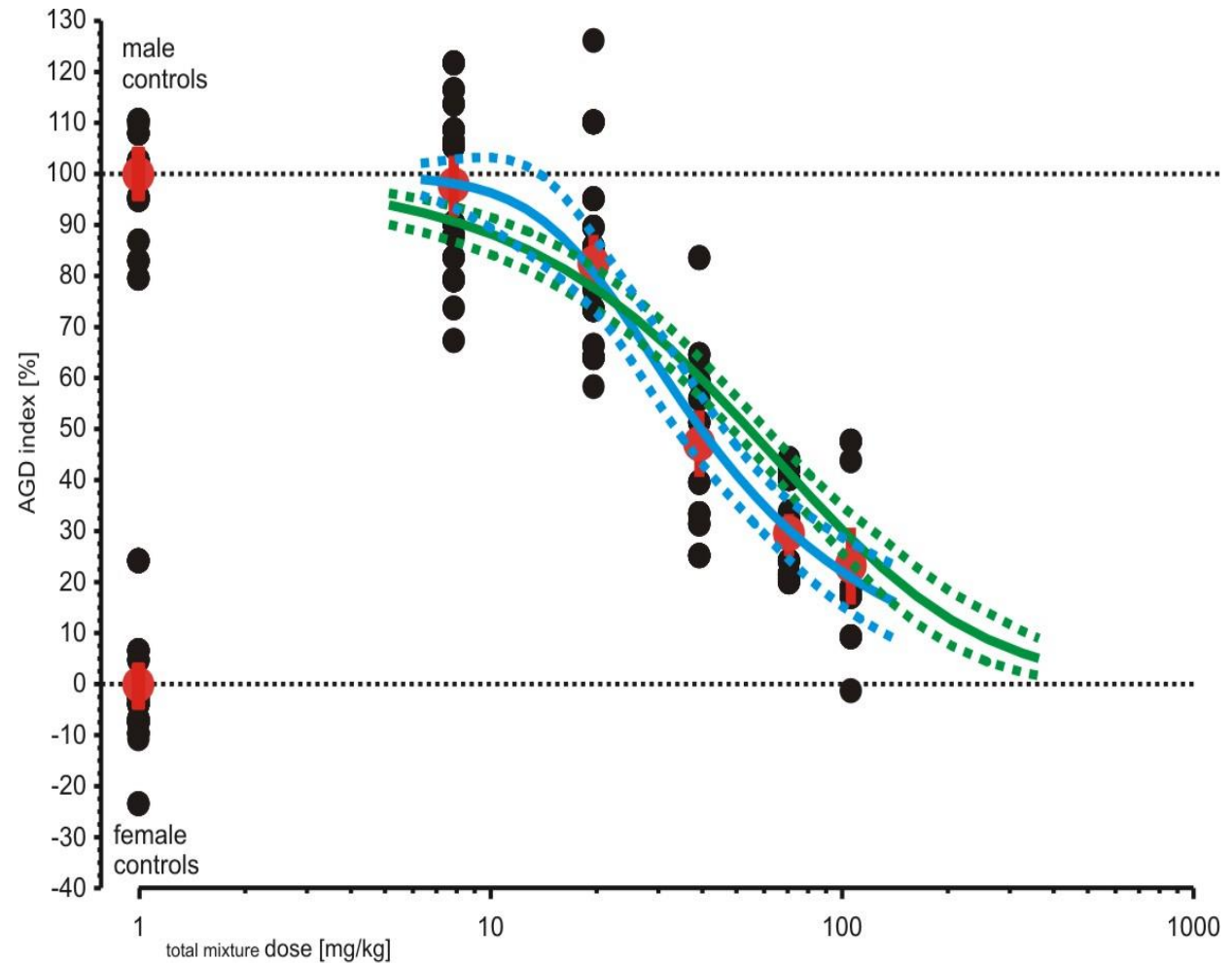
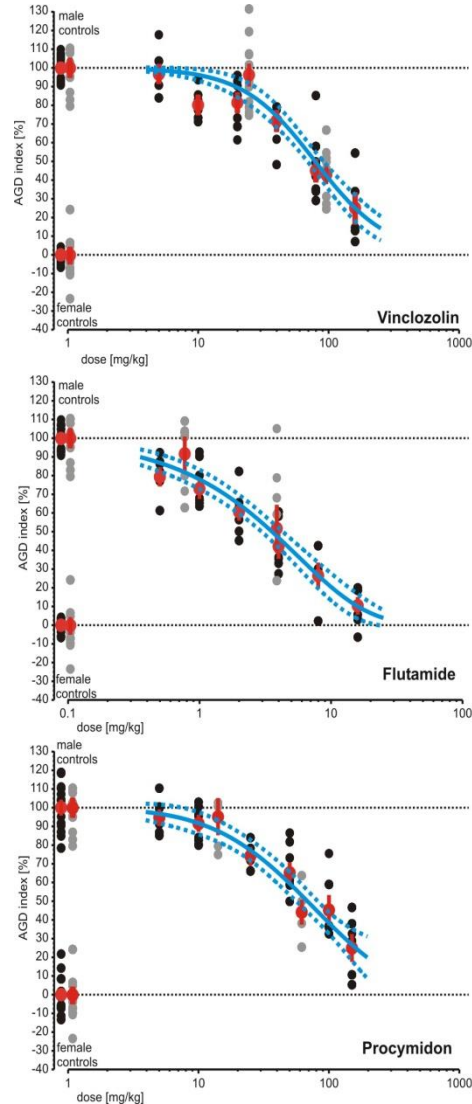
Predictive approaches

Predicting mixture effects



Predicting mixture effects

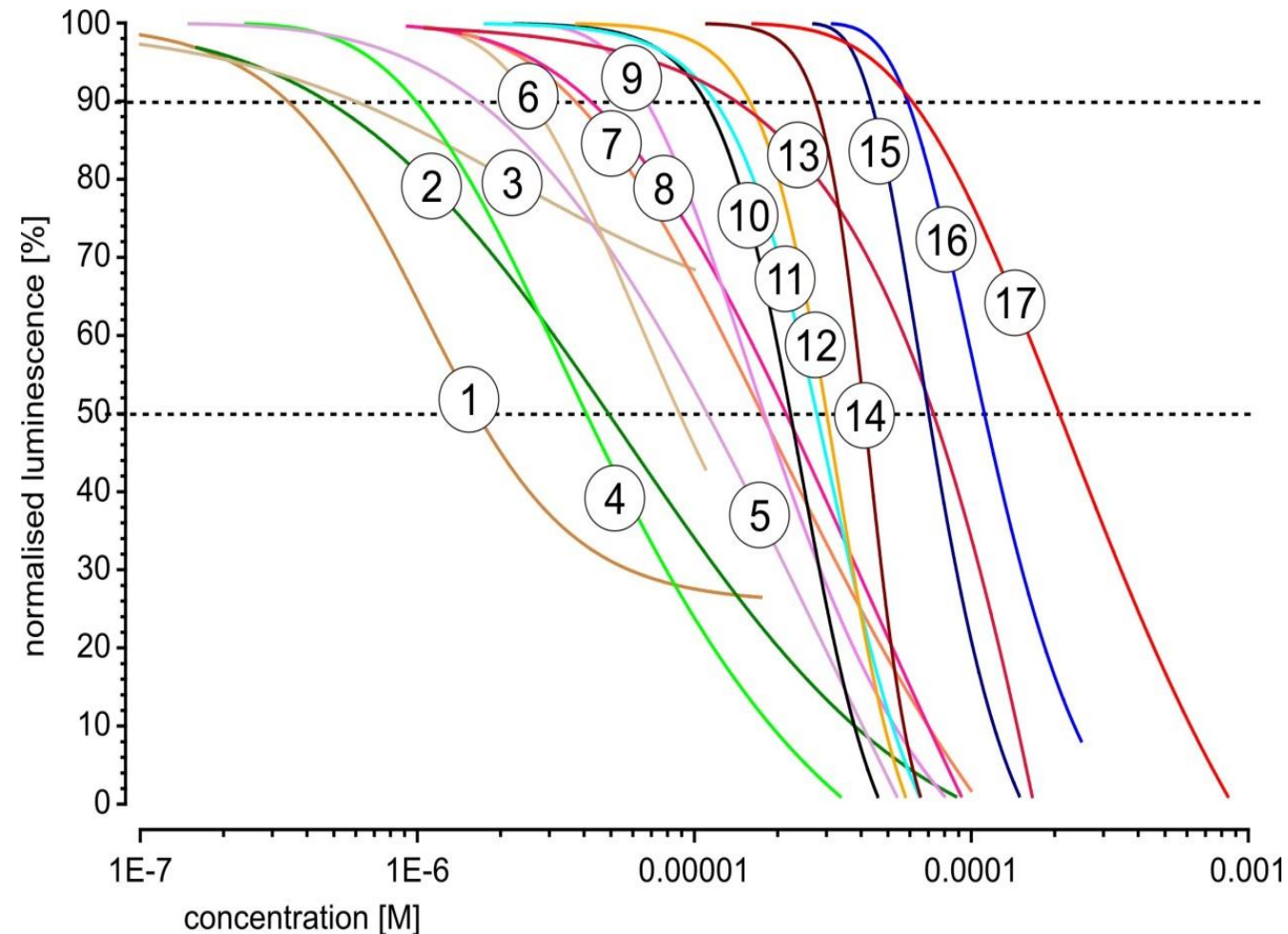
Hass *et al.* 2007 EHP **115** Suppl 1, 122



Predictability: AR antagonist chemicals

17 components AR-Lux

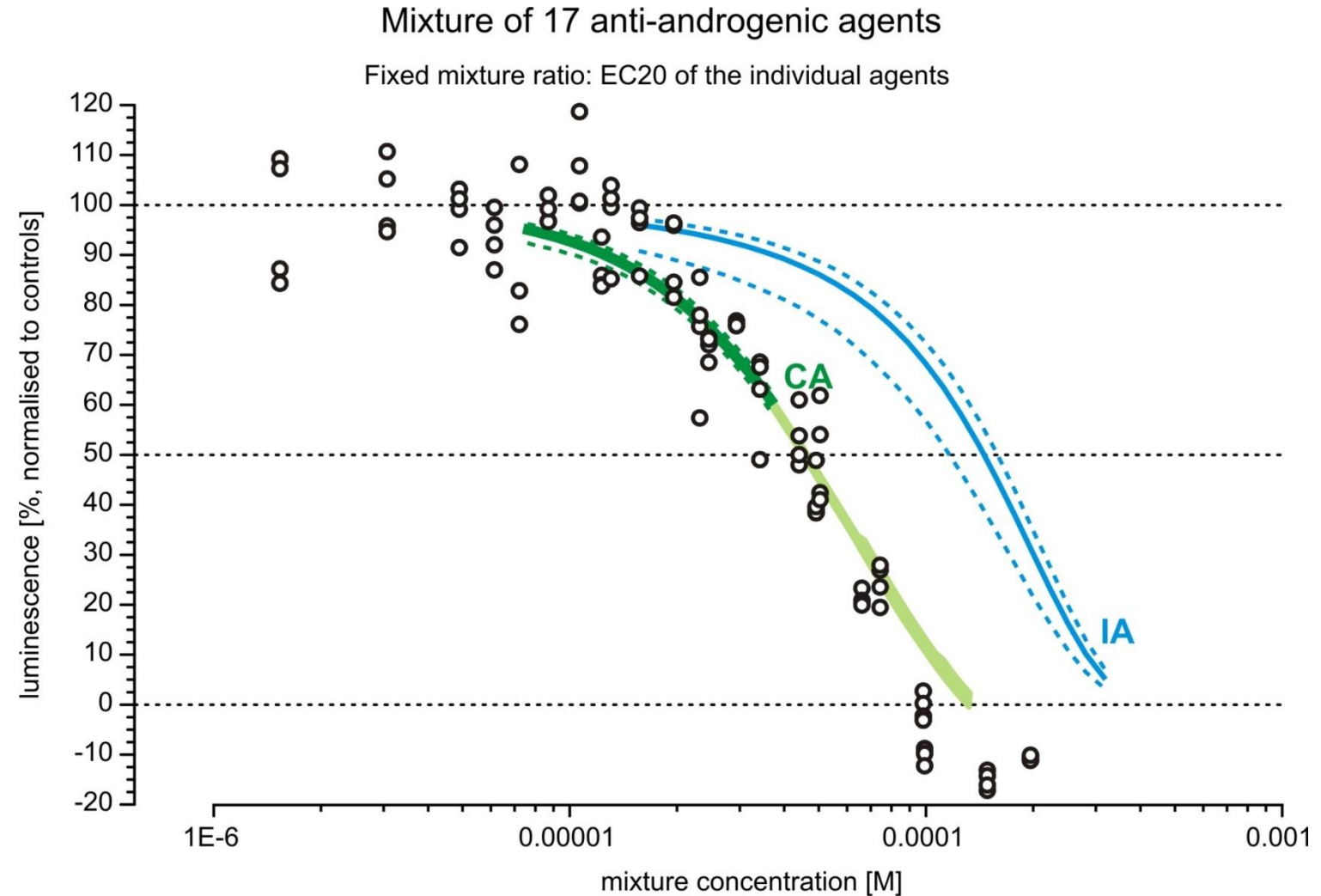
BDE100
benzophenone 2
benzo(α)pyrene
bisphenol A
HHCB
PCB138
BHA
AHTN
benzophenone 3
PFOS
3-BC
4-MBC
BHT
n-butyl paraben
n-propyl paraben
ethyl paraben
methyl paraben



Predictability: AR antagonist chemicals

17
components
AR-Lux

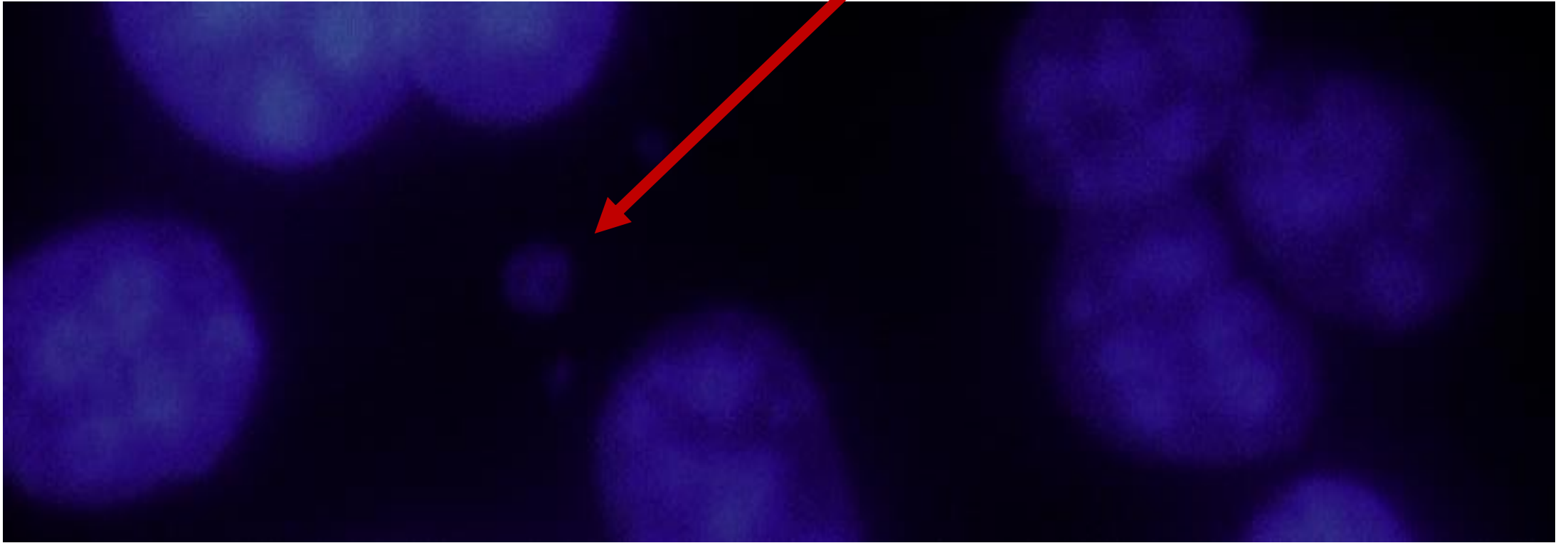
Ermiler *et al.* 2011
Tox. Appl.
Pharmacol. 257,
189-197



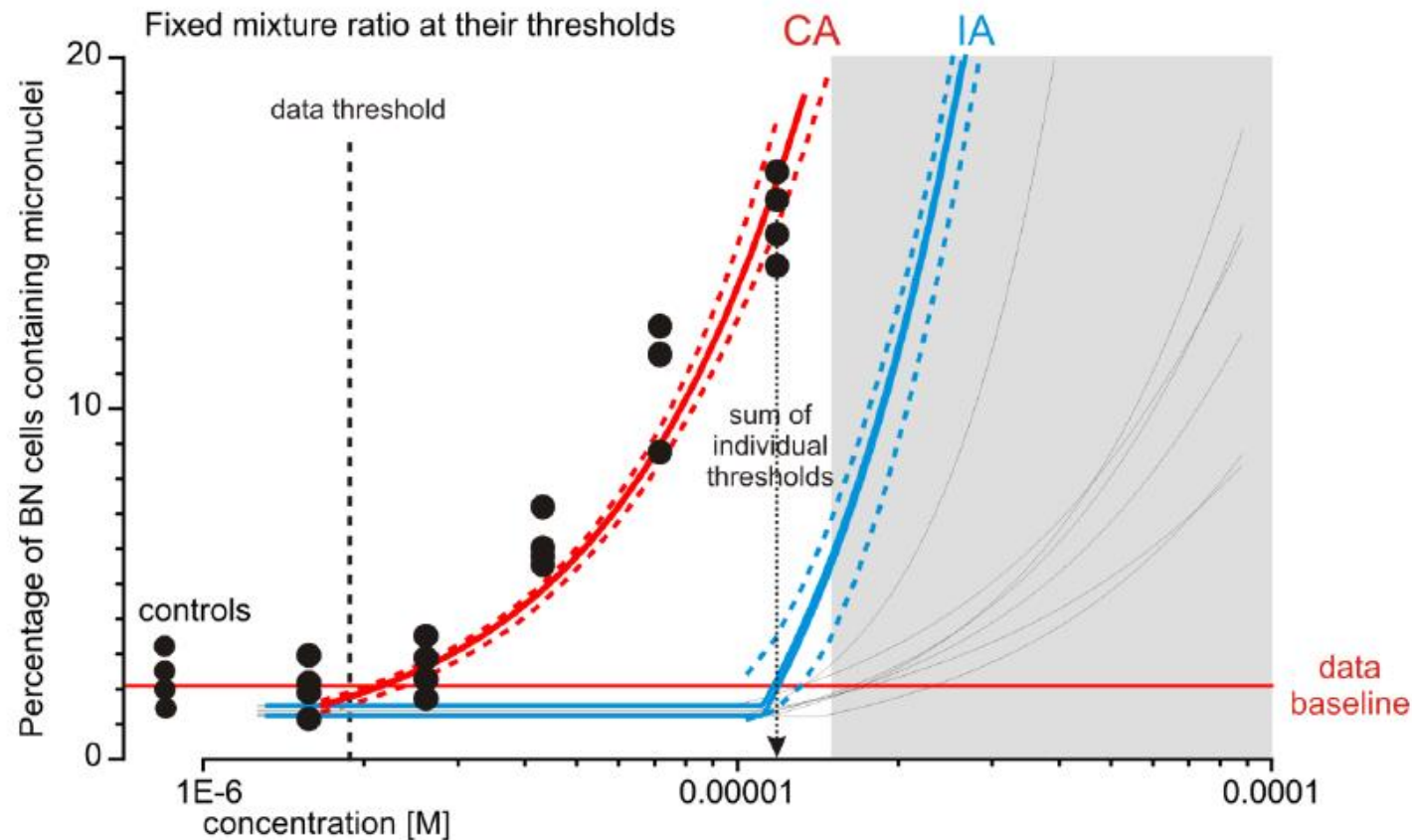
Low dose mixtures: theory expectations

- **Dose addition:**
 - Mixture effects expected if **sufficient numbers** of chemicals are combined, even at doses **below zero effect levels**
- **Independent action:**
 - Mixture effects **not expected** if all chemicals stay **below zero effect levels**

Micronuclei



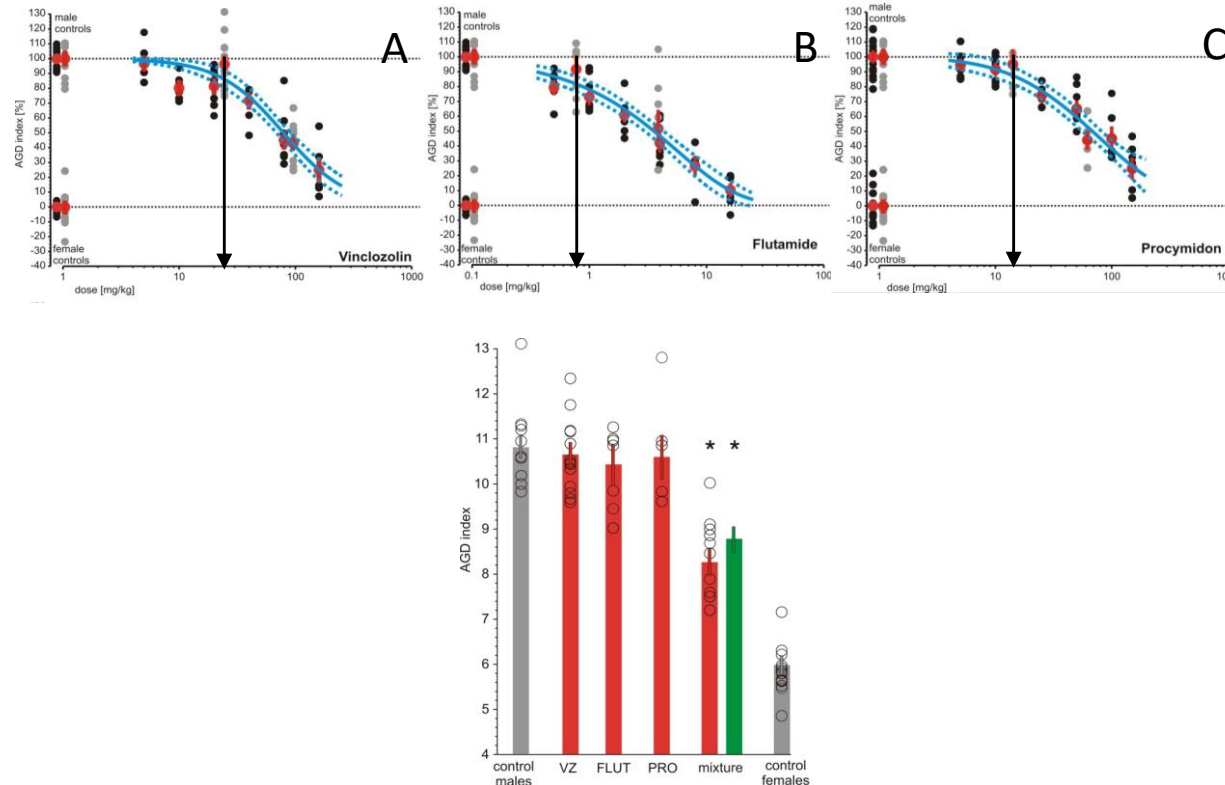
Benzimidazole low dose mixture: micronuclei



Clear combination effects at
sub-threshold doses

= Dose addition expectation

Anti-androgens in a rat developmental toxicity model



Hass U, Scholze M, Christiansen S, Dalgaard M, Vinggaard AM, Axelstad M, Metzdorff SB, Kortenkamp A: **Combined exposure to anti-androgens exacerbates disruption of sexual differentiation in the rat.** *Environ Health Perspect* 2007, 115(Suppl 1):122-128.

Application to risk assessment practice

Hazard Index

$$\frac{\text{Intake}_1}{\text{Reference dose}_1} + \frac{\text{Intake}_2}{\text{Reference dose}_2} < 1$$

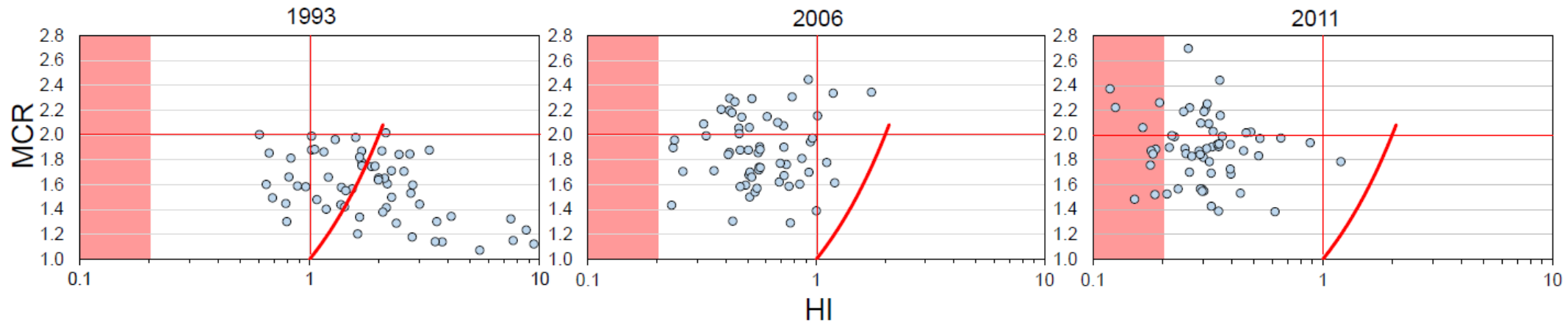
- **Assumptions**

- Dose addition as a good approximation
- No synergisms

- **Interpretation**

- Exceedance of combined acceptable **exposures**
- NOT estimation of effect size!

Phthalate mixture risk assessment



Based on German Environment Specimen Bank
27 years of biomonitoring

Apel, Kortenkamp et al.
(2020) Env International

Conclusions and perspectives

- Toxicity **underestimated** by ignoring mixtures
- Single chemical reference doses **not protective**
- **Summing up of risk quotients** practicable

Acknowledgements

- Olwenn Martin, Richard M Evans, Michael Faust, Martin Scholze
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- CONTAMED
- Norwegian EPA



Thank you!

