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

Andreas Kortenkamp

Brunel University London

**Mixture effects:**

Too difficult

Not necessary

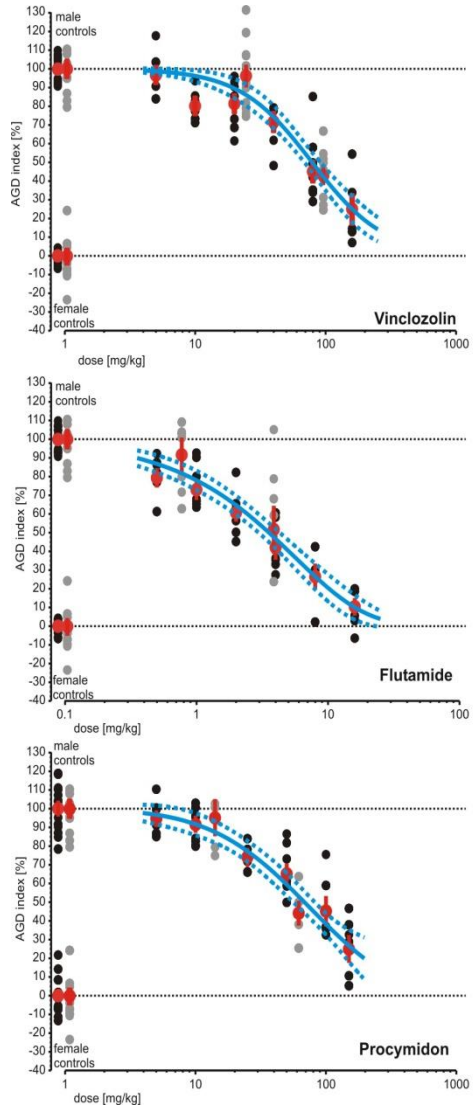
“Protection from mixture effects is achieved, as long as exposures stay below thresholds”

# Astronomically large numbers of combinations

# Test everything?

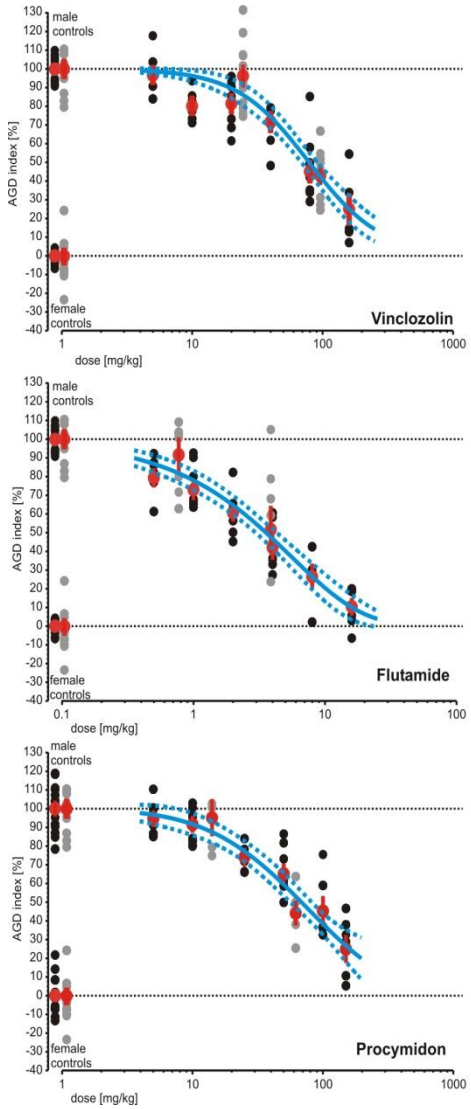
# Predictive approaches

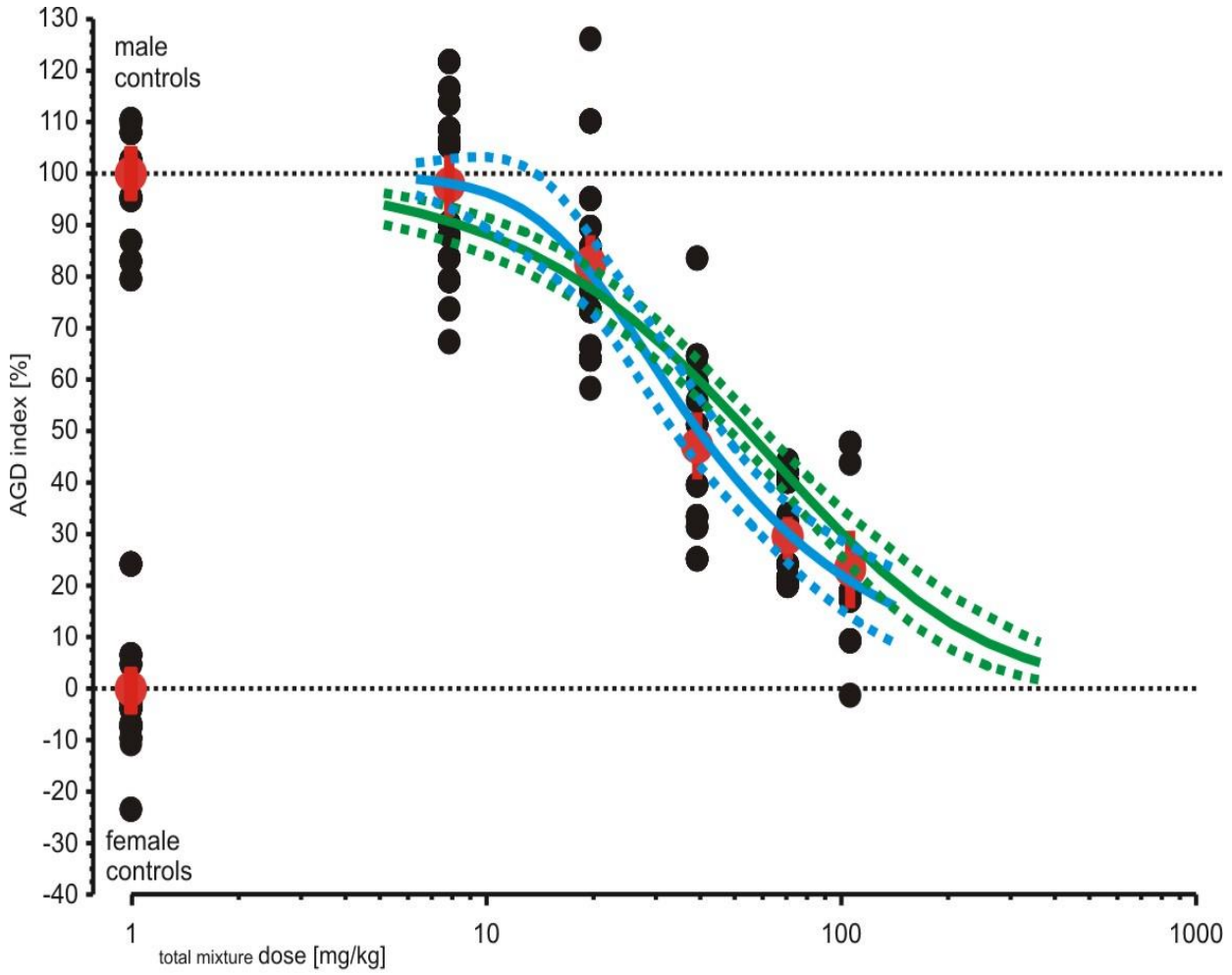
# Predicting mixture effects



# Predicting mixture effects

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



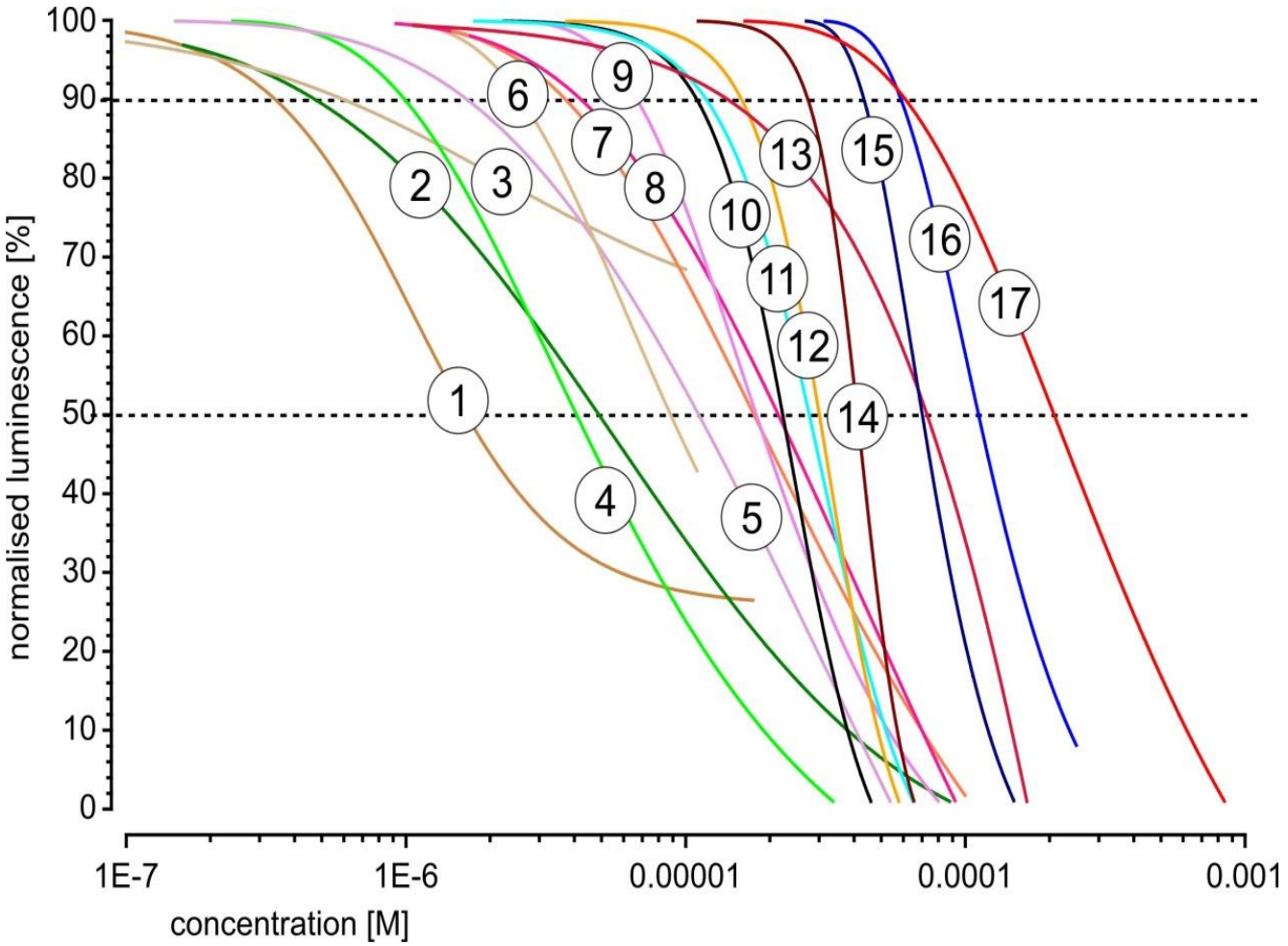



# Predictability: AR antagonist chemicals

**17 components**

AR-Lux

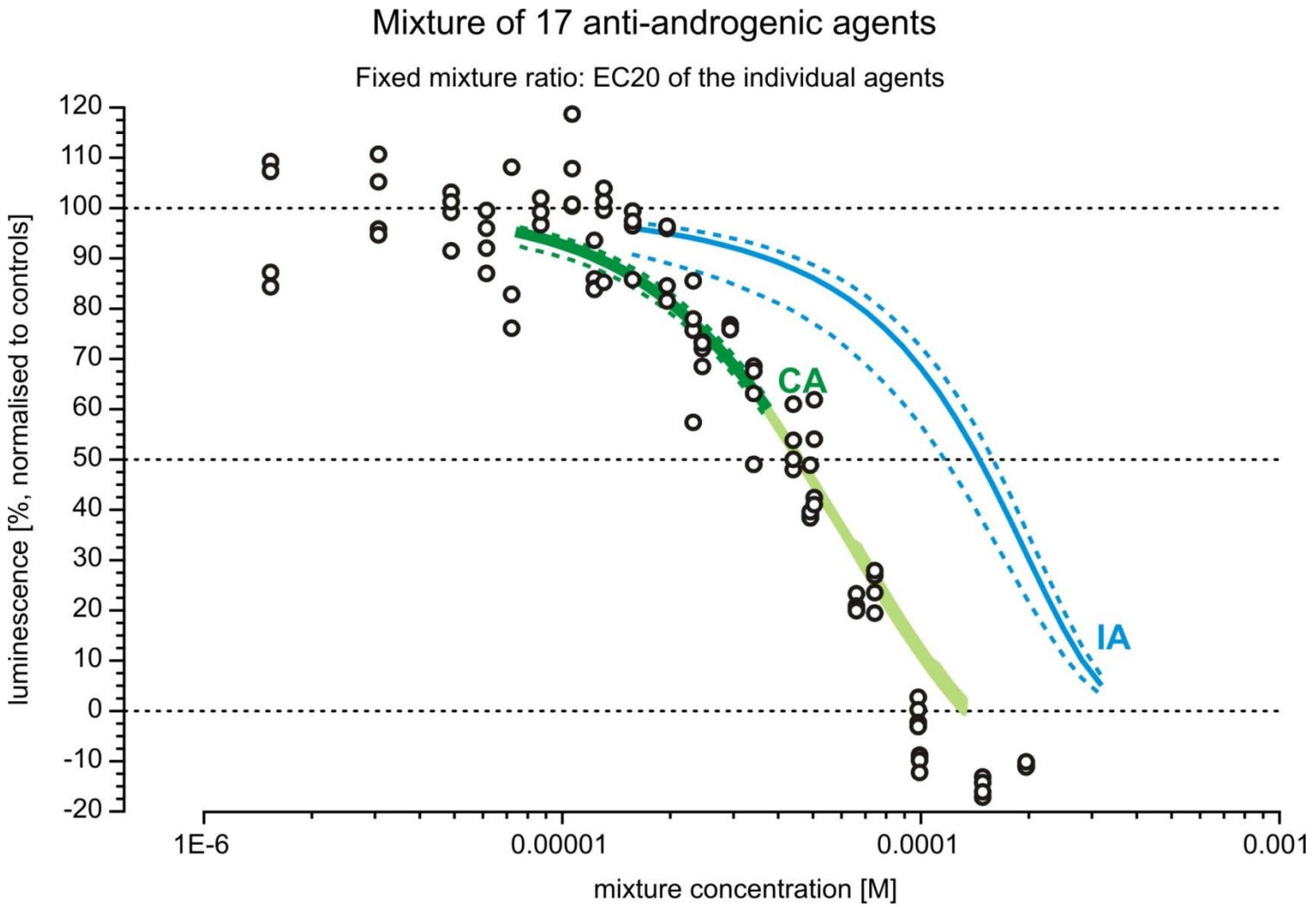
BDE100
benzophenone 2
benzo(α)pyrene
bisphenol A
HHCB
PCB138
BHA
AHTN
benzophenone 3
PFOS
3-BC
4-MBC
BHT
*n*-butyl paraben
*n*-propyl paraben
ethyl paraben
methyl paraben



# Predictability: AR antagonist chemicals

**17 components**
AR-Lux

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

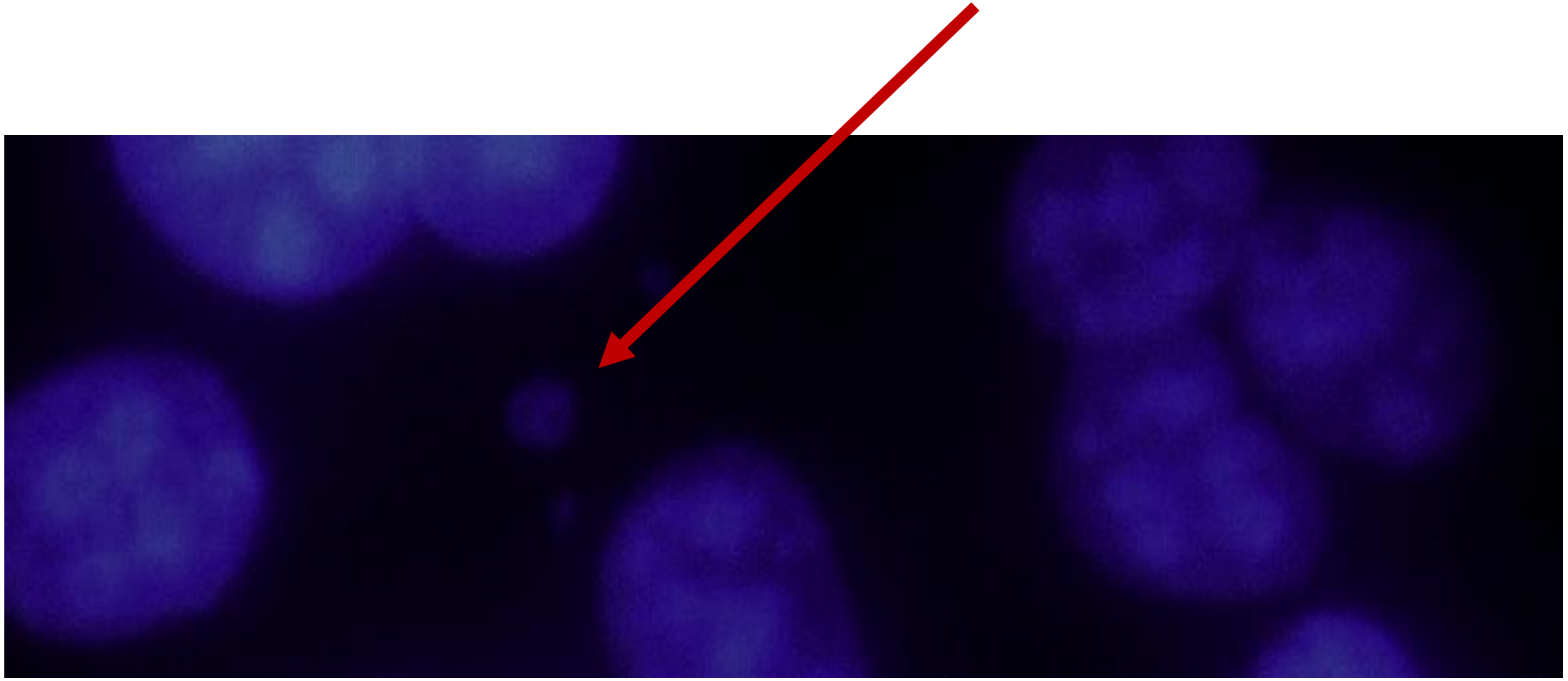


# Low dose mixtures: theory expectations

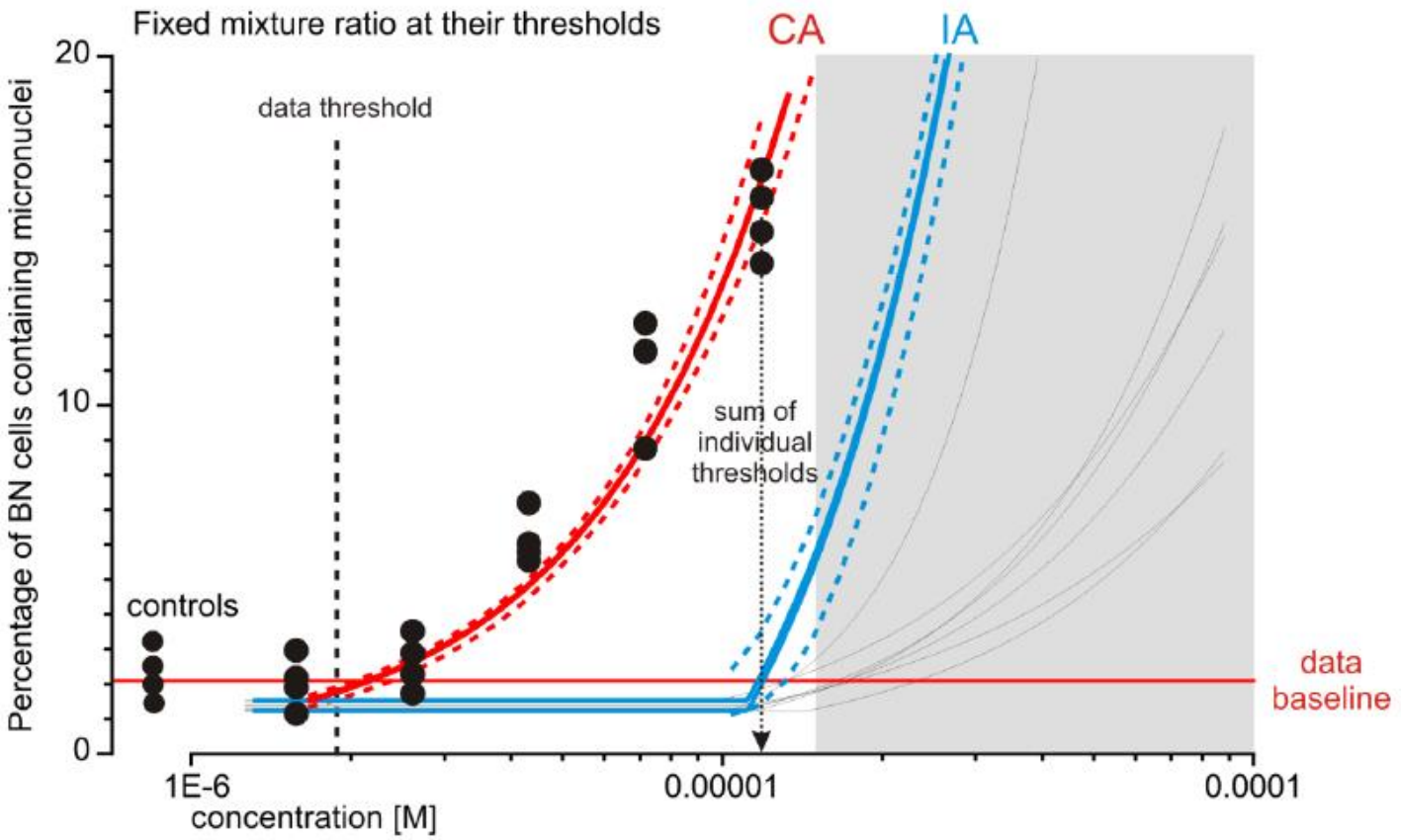
- **Dose addition**:
- Mixture effects expected if **sufficient numbers** of chemicals are combined, even at doses **below zero effect levels**

- **Independent action**:
- Mixture effects **not expected** if all chemicals stay **below zero effect levels**

# Micronuclei



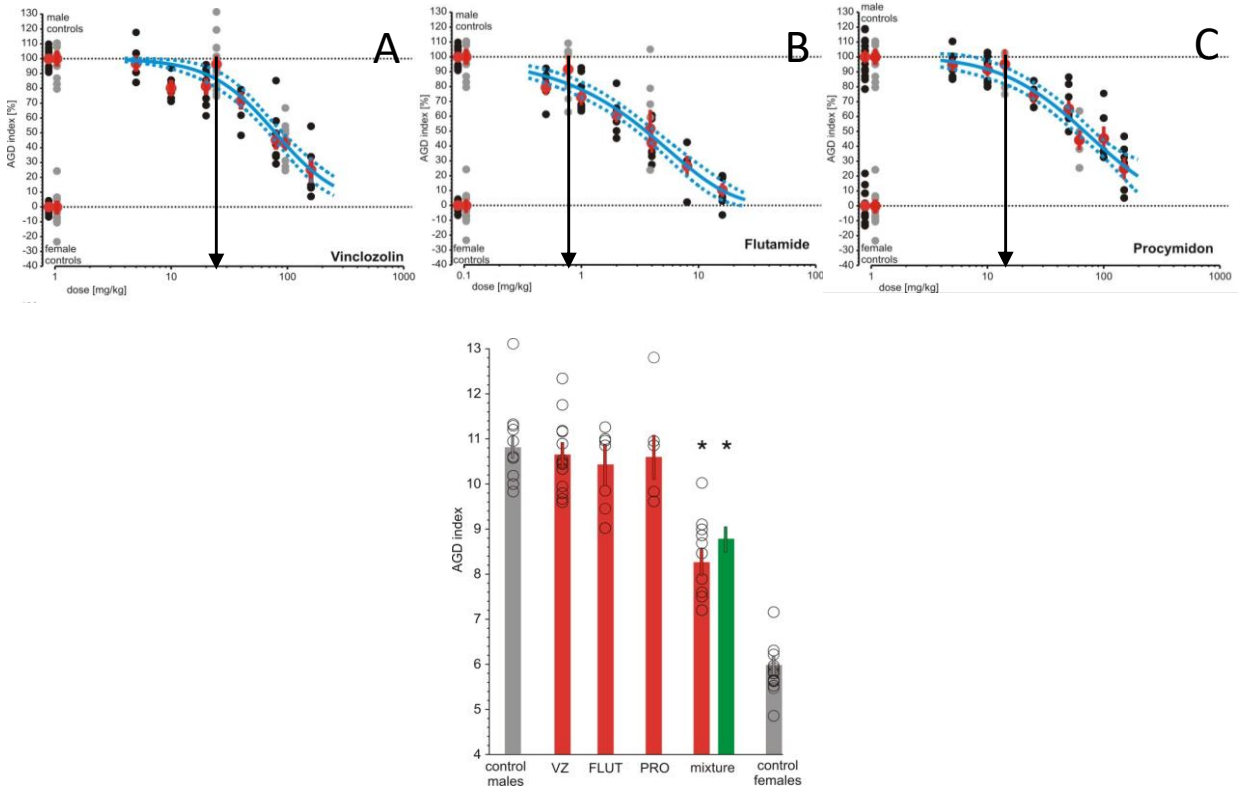
# **Benzimidazole low dose mixture**: micronuclei




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

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

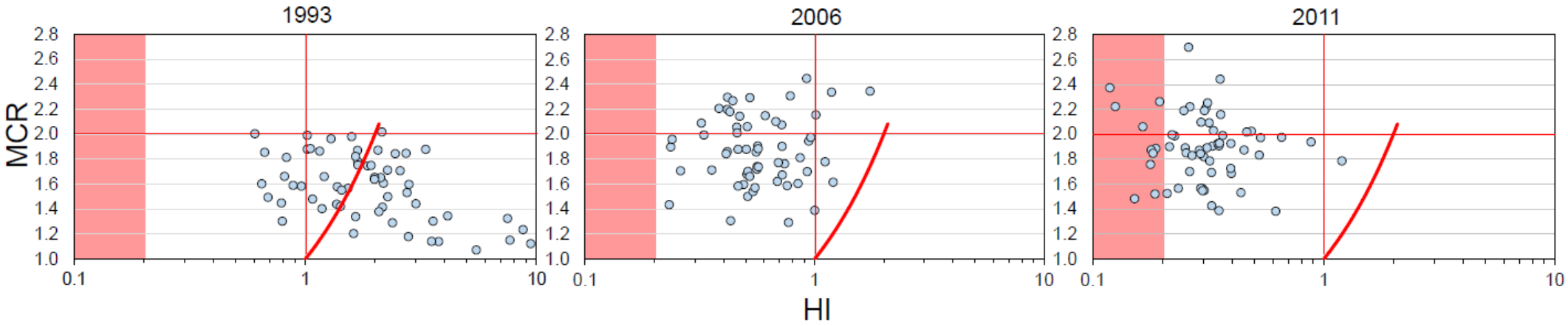
- **Assumptions**

- 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

- OAK Foundation
- CONTAMED
- Norwegian EPA


# Thank you!