

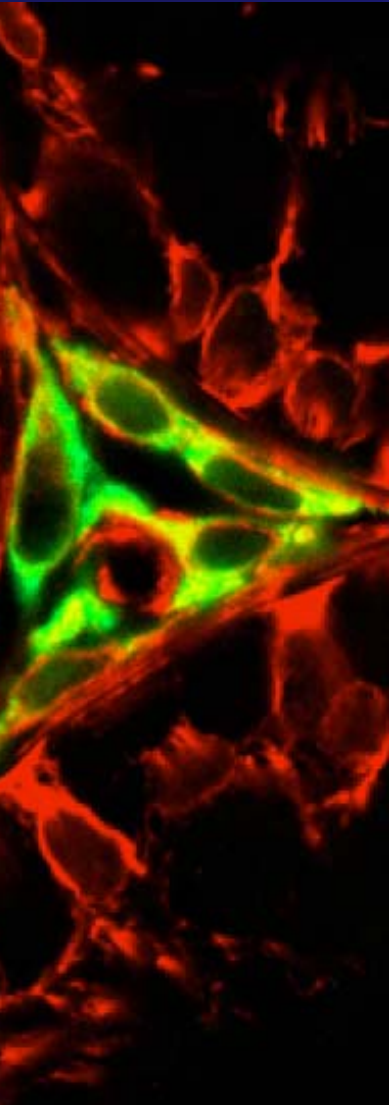
# BfR ED Forum

## **Exposure to endocrine disruptors at low doses – implications for testing and risk assessment**

Andreas Kortenkamp

*The School of Pharmacy, University of London*

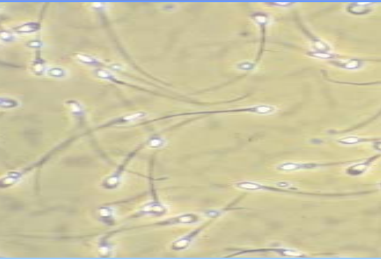
Berlin, 19-20 April 2010



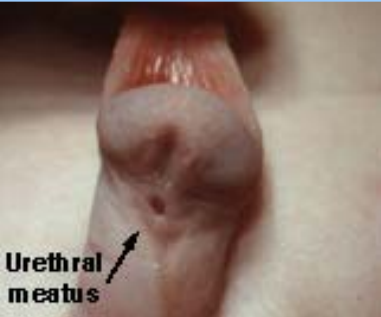
# Testicular dysgenesis syndrome



Cryptorchidism



Poor semen quality

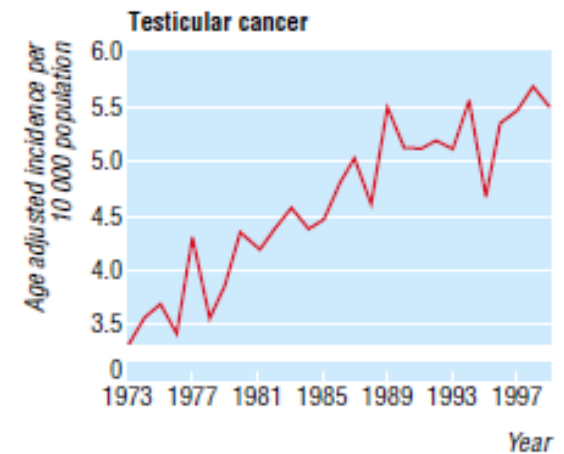
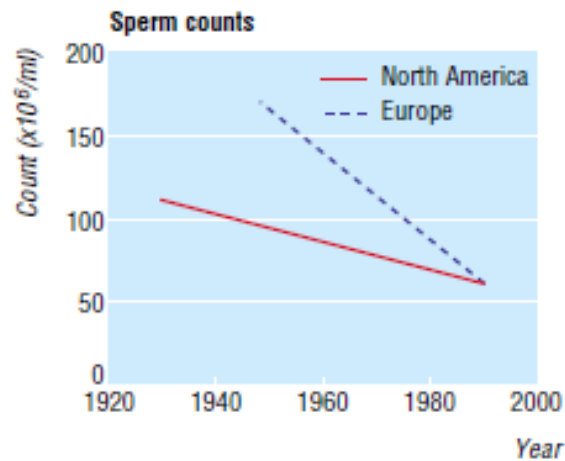
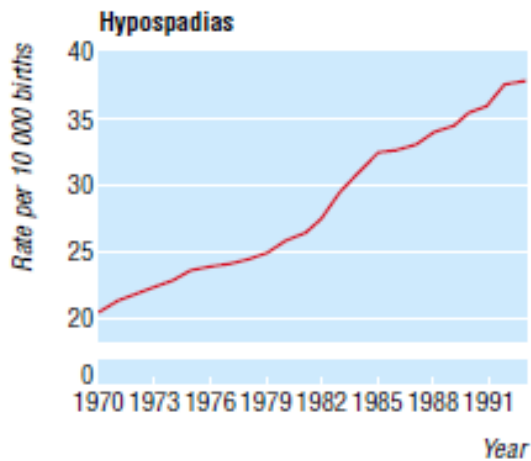


Hypospadias



Testis cancer

# Trends in reproductive health



Sharpe 2008

# The action of...



... the male sex hormone in the womb makes a man!

# Certain chemicals...

...disrupt hormone action in foetal life by

- blocking the receptor
- suppressing sex hormone synthesis



**Demasculinisation**

# Estimating low effect doses

- Doses of a test chemical associated with low effects
- No-observed-adverse-effect-level

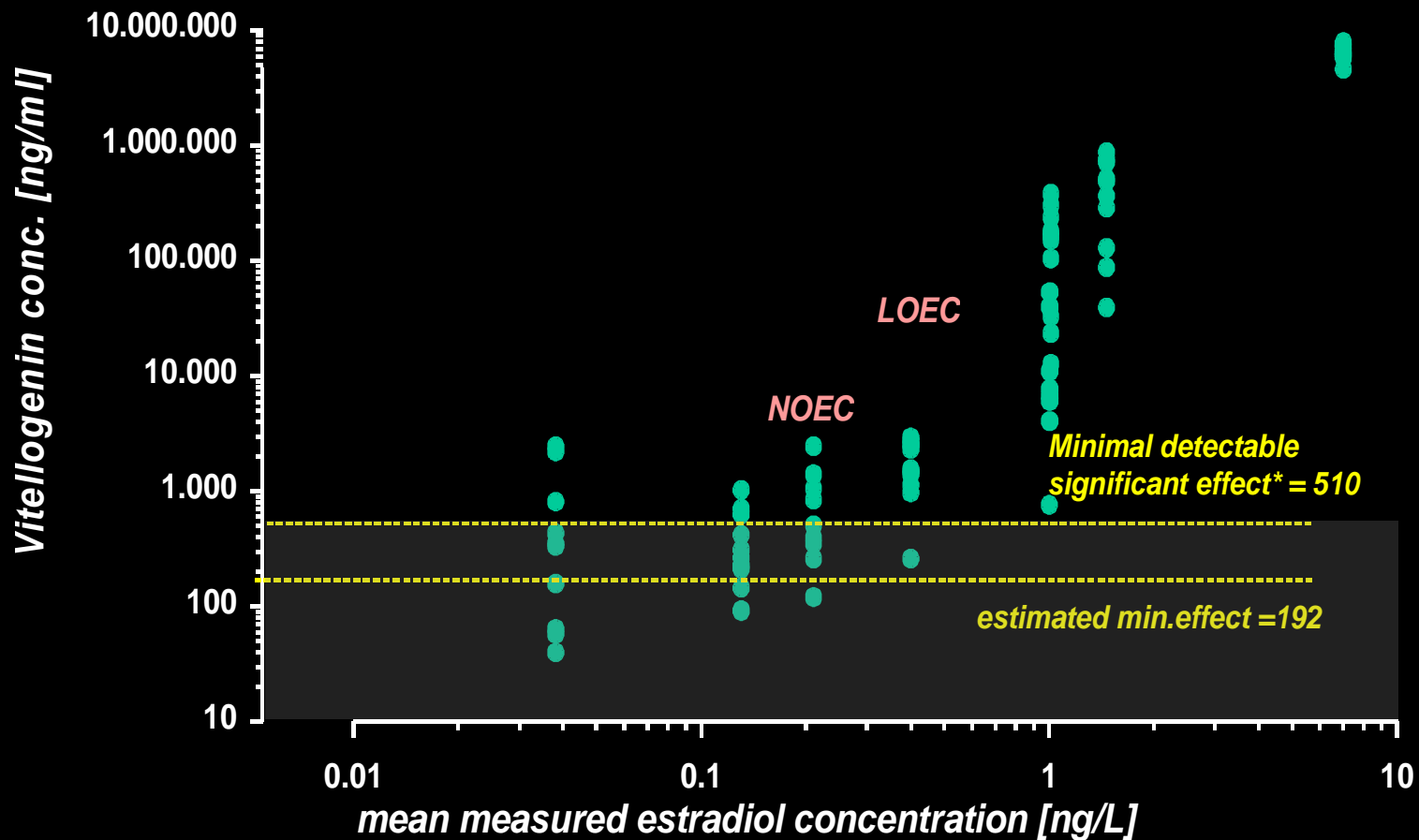
# Minimum significant effects

Estradiol

Vitellogenin  
induction

Thorpe *et al.*  
2001, EST 35,  
2476

Data analysis:  
Martin Scholze



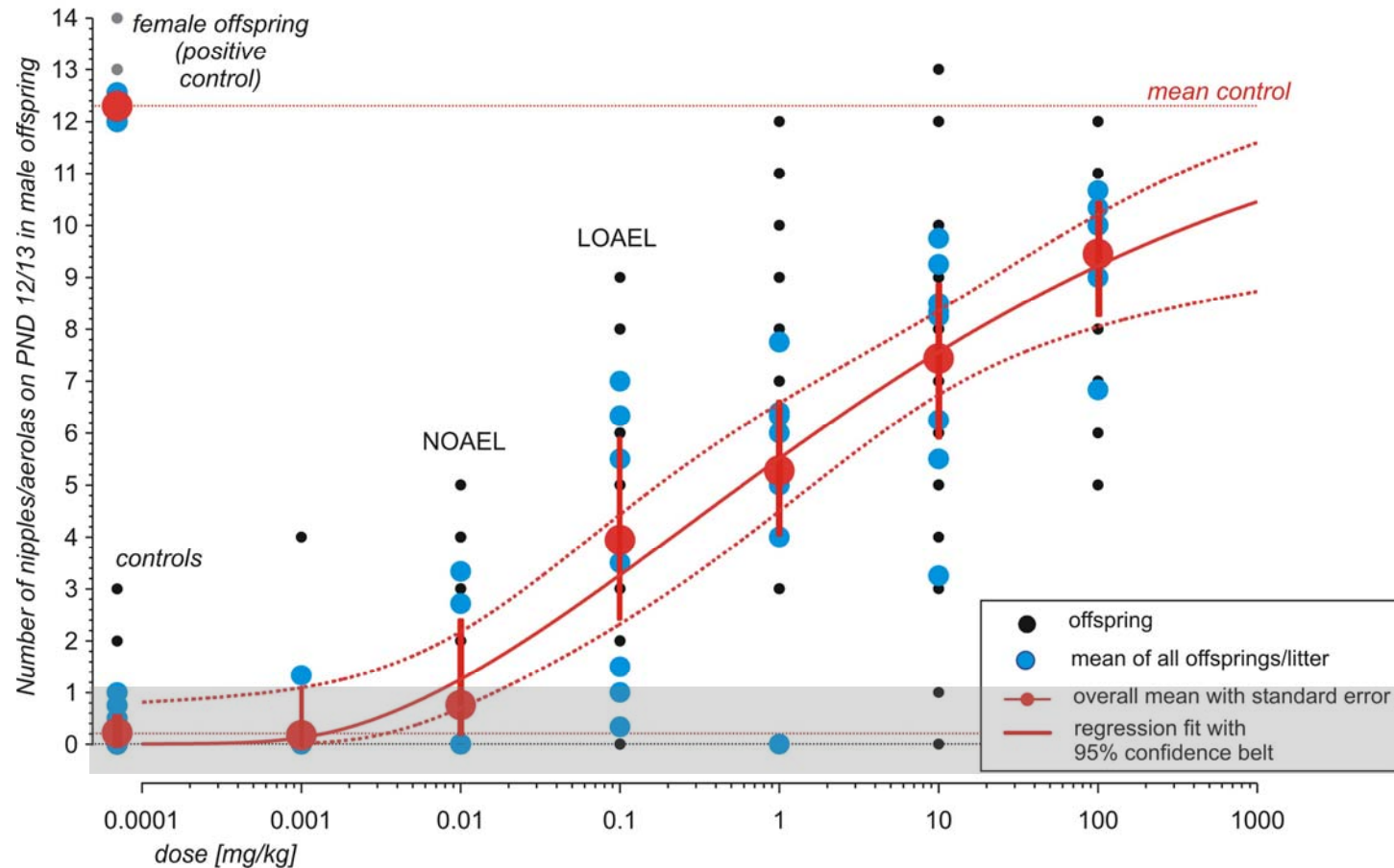
\*Dunnett test, one-sided, alpha=5%, beta=10%

# Finasteride

Retained nipples of male offspring of female treated rats

Ulla Hass and colleagues

### Finasteride (code 0005-01), study 04-01



Gen. Logit model I with log10-transformation of the dose scale



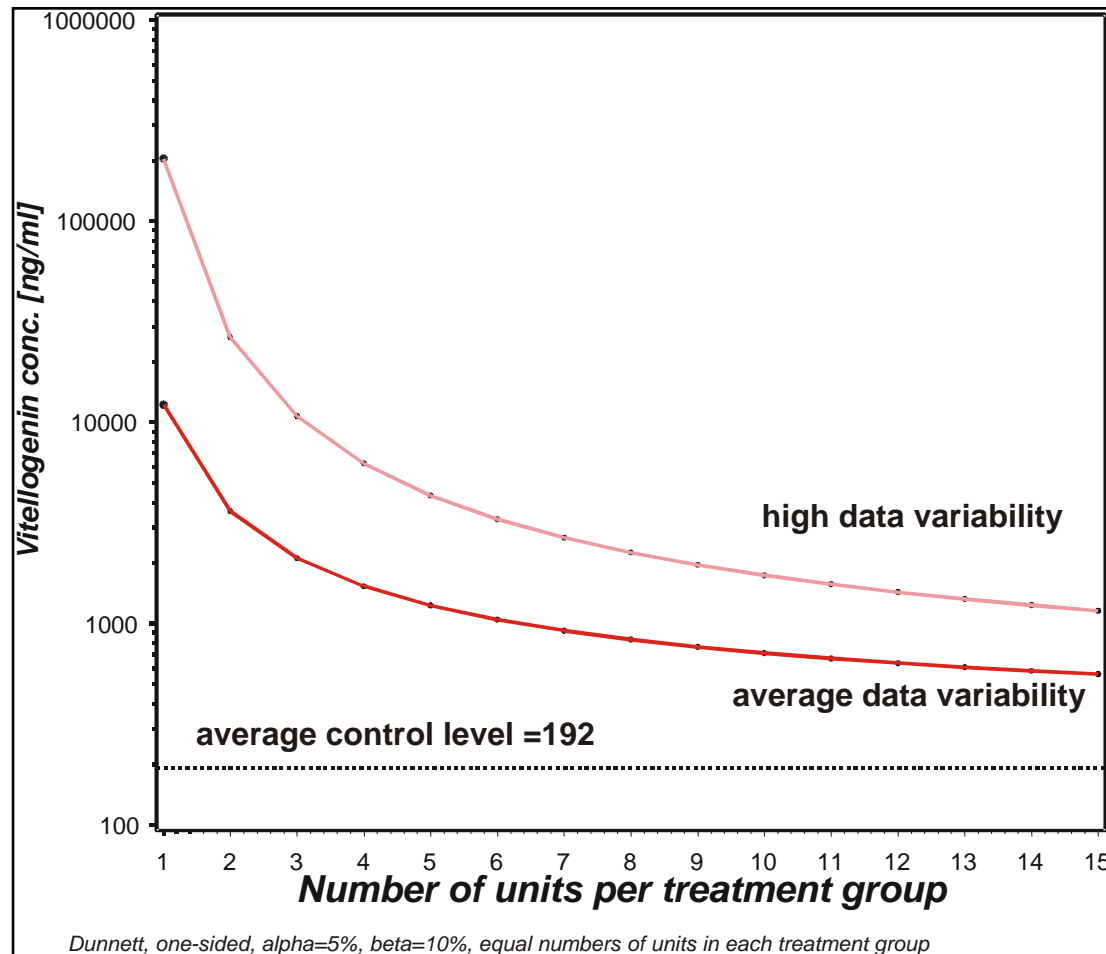
# MSD and number of replicates

Estradiol

Vitellogenin  
induction

Thorpe *et al.*  
2001, EST 35,  
2476


Data analysis:  
Martin Scholze



# NOAEL



# Issues

- 
- Are existing tests sufficiently sensitive to show small effects?
  - Likelihood of overlooking effects?

# Implications



Critical assessment of assay sensitivity

Consider larger test groups

# Extrapolations - example: vinclozolin



**Rat (demasculinising effects):**

5 mg/kg body weight/day

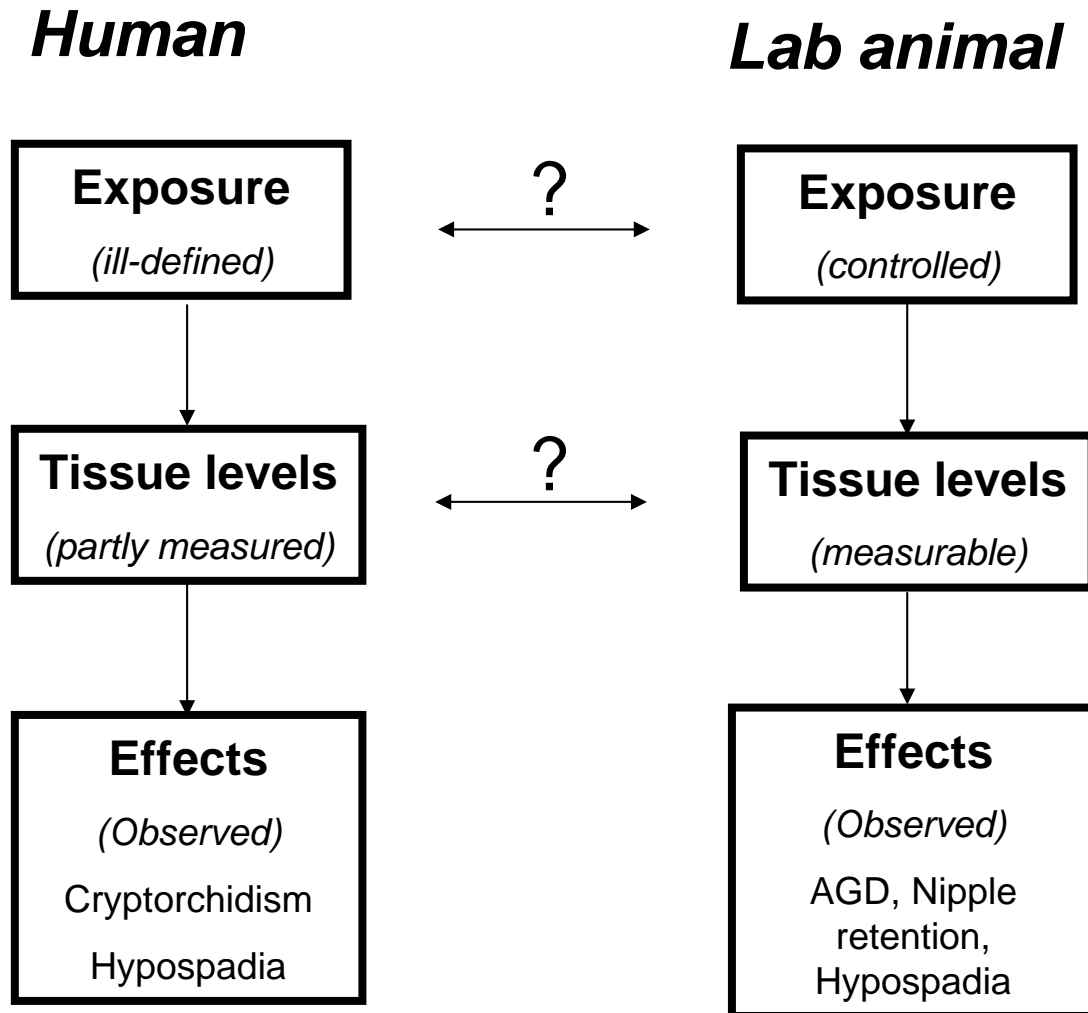
**Human exposure:**

0.005 – 0.01 mg/kg body weight/day

**Margin of Safety:**

200 - 1000

# Extrapolations



# Implications

Critical assessment of uncertainty factors

Introduction of alternative dose metrics



# Known unknowns



- *In vitro* AR antagonists
  - 35 pesticides
  - UV-filter substances (4-MBC, OMC)
  - 1,2,3,6,7,8 HCDD;  
2,3,4,7,8 PeCDF
- Fragmentary exposure information



But...

toxic cocktail

...and the impact of climate change on human health and the environment

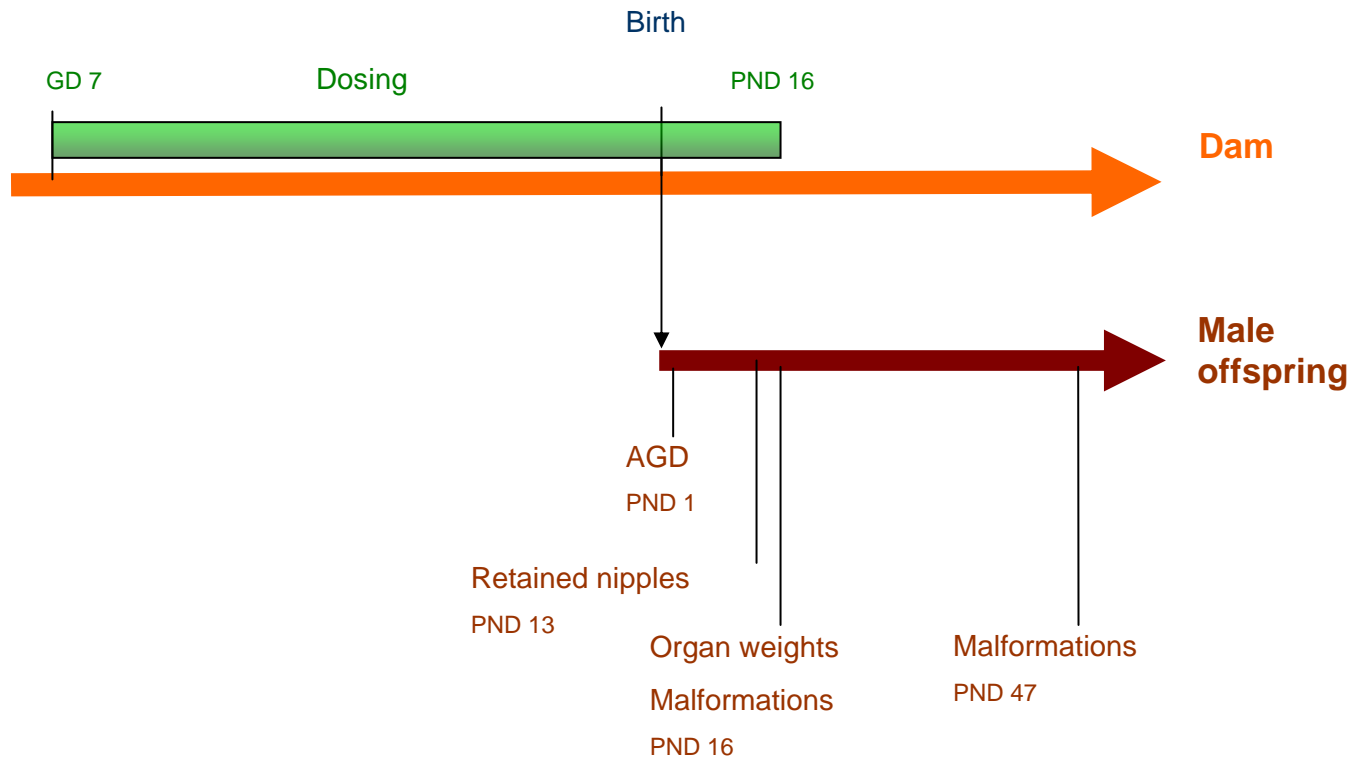
# “Toxic cocktails”

**Can chemicals that are safe on their own “gang” up when they meet in our bodies?**

**Effects predictable?**

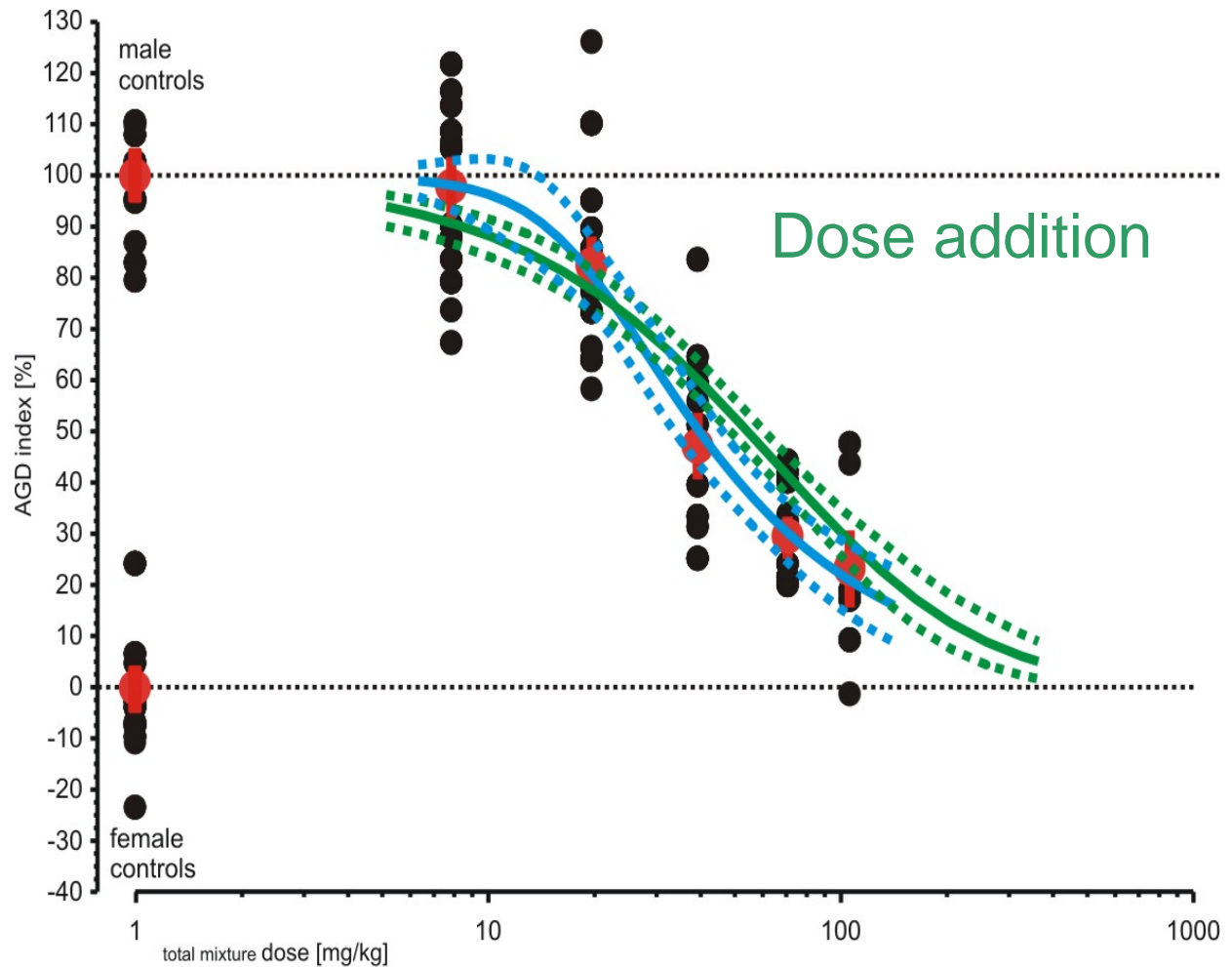
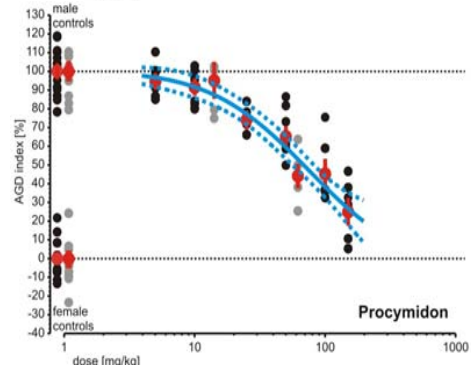
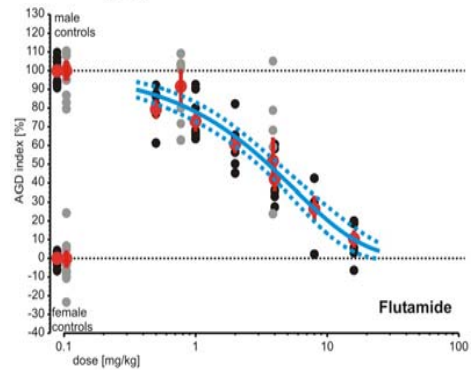
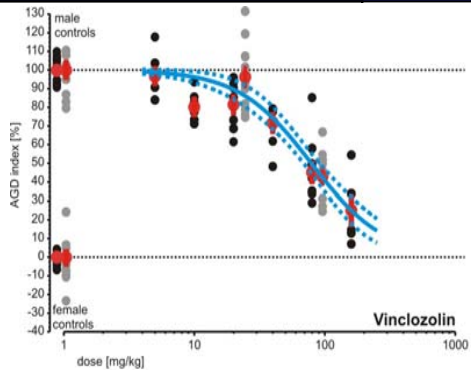
# Developmental toxicity

## Experimental design



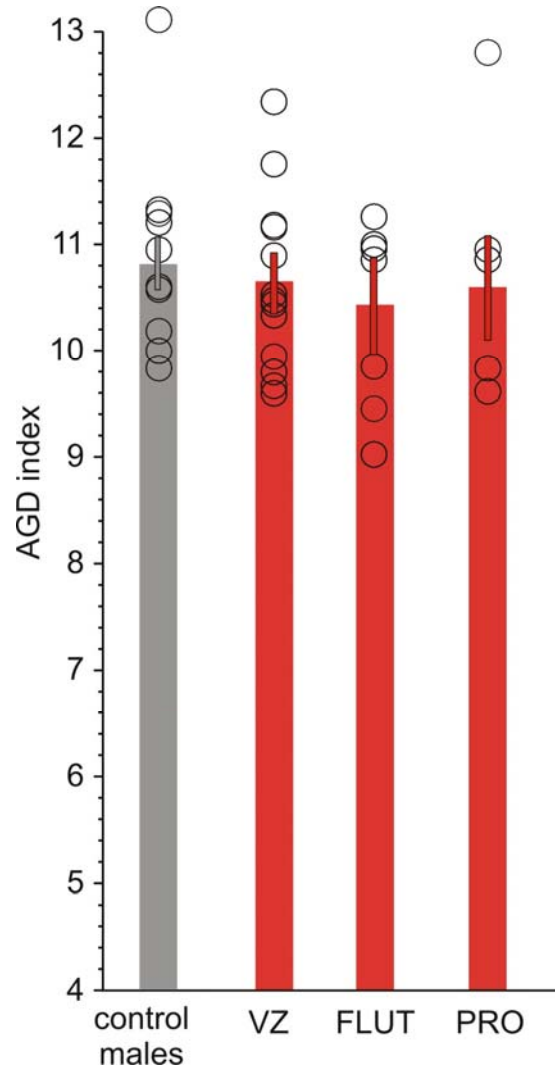
# Androgen receptor antagonists produce mixture effects

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



# Something from “nothing”

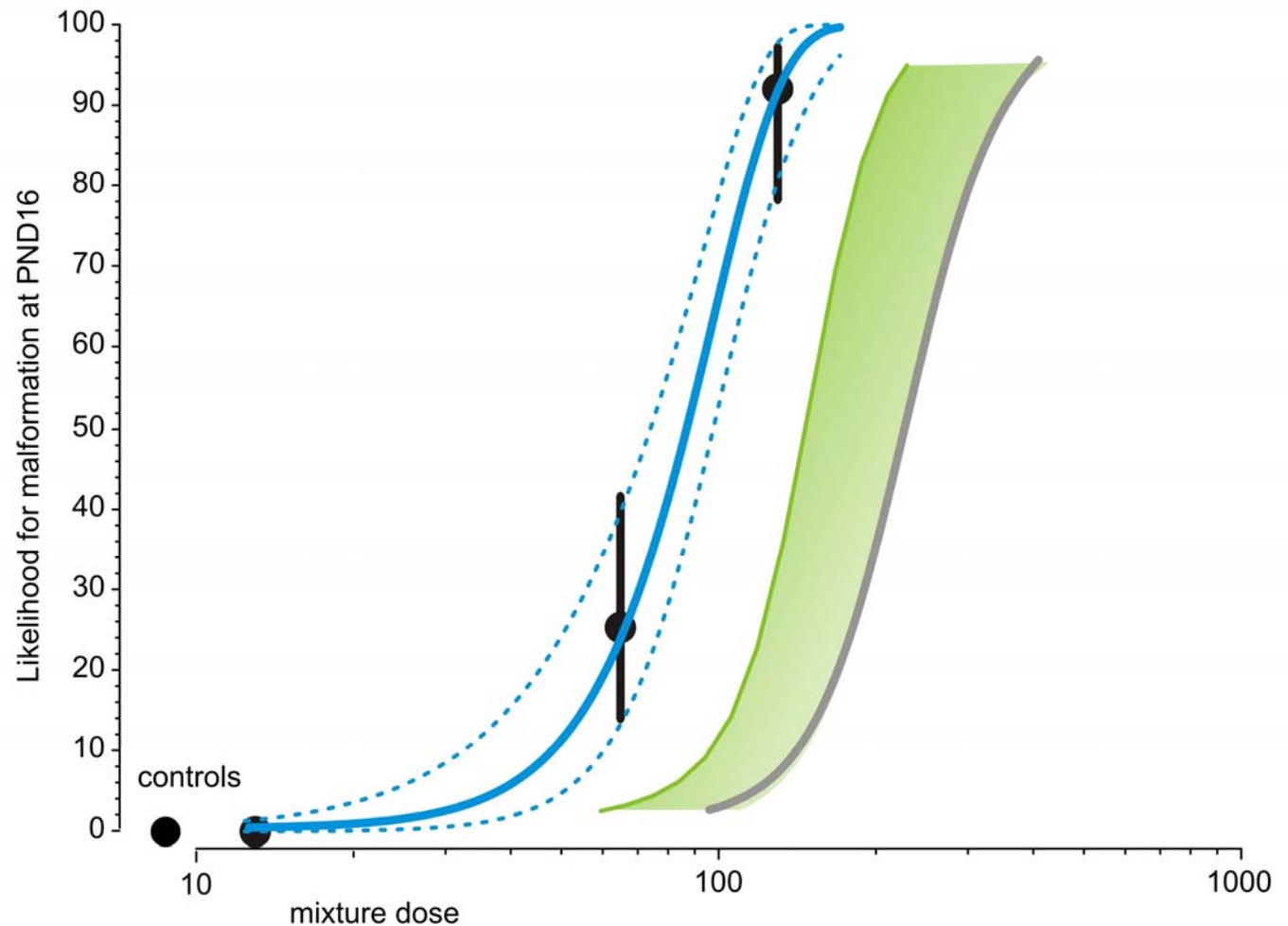
Hass *et al.*  
2007, EHP  
115 (Suppl 1),  
122



# Penile malformations

Finasteride  
Vinclozolin  
DEHP  
Prochloraz

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



# Implications

- Presumed low effects of chemicals judged in isolation are uninformative



Thank you

