Exposure to endocrine disrupters at low doses – implications for testing and risk assessment

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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

**Estradiol**

**Vitellogenin induction**

Data analysis: Martin Scholze

- Estimated minimal effect = 192
- Minimal detectable significant effect* = 510

* Dunnett test, one-sided, alpha=5%, beta=10%
Retained nipples of male offspring of female treated rats

*Ulla Hass and colleagues*

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**Finasteride**

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

![Graph showing the number of nipples/germ cells on PND 12/13 in male offspring versus dose in mg/kg](image)

- **Female offspring (positive control)**
- **Mean control**
- **NOAEL**
- **LOAEL**

**Gen. Logit model l with log10-transformation of the dose scale**
Estradiol
Vitellogenin induction
Thorpe et al. 2001, EST 35, 2476

Data analysis: Martin Scholze

MSD and number of replicates

Number of units per treatment group

Vitellogenin conc. [ng/ml]

average control level =192
high data variability
average data variability

Dunnett, one-sided, alpha=5%, beta=10%, equal numbers of units in each treatment group
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

**Human**

- Exposure (ill-defined)
- Tissue levels (partly measured)
- Effects (Observed)
  - Cryptorchidism
  - Hypospadia

**Lab animal**

- Exposure (controlled)
- Tissue levels (measurable)
- Effects (Observed)
  - AGD, Nipple retention, Hypospadia
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 cocktails”

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

Effects predictable?
Developmental toxicity

Experimental design

- GD 7
- Dosing
- PND 16
- Birth
- AGD
- PND 1
- Retained nipples
- PND 13
- Organ weights
- Malformations
- PND 16
- Malformations
- PND 47

Dam

Male offspring
Androgen receptor antagonists produce mixture effects
Hass et al. 2007 EHP 115 Suppl 1, 122

Dose addition
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