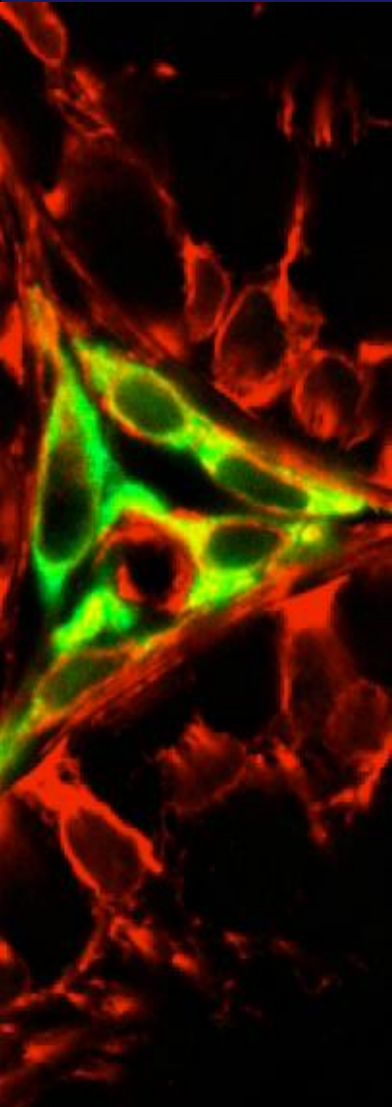


French Senate 2013

# Endocrine disruptors and the decline in male reproductive health

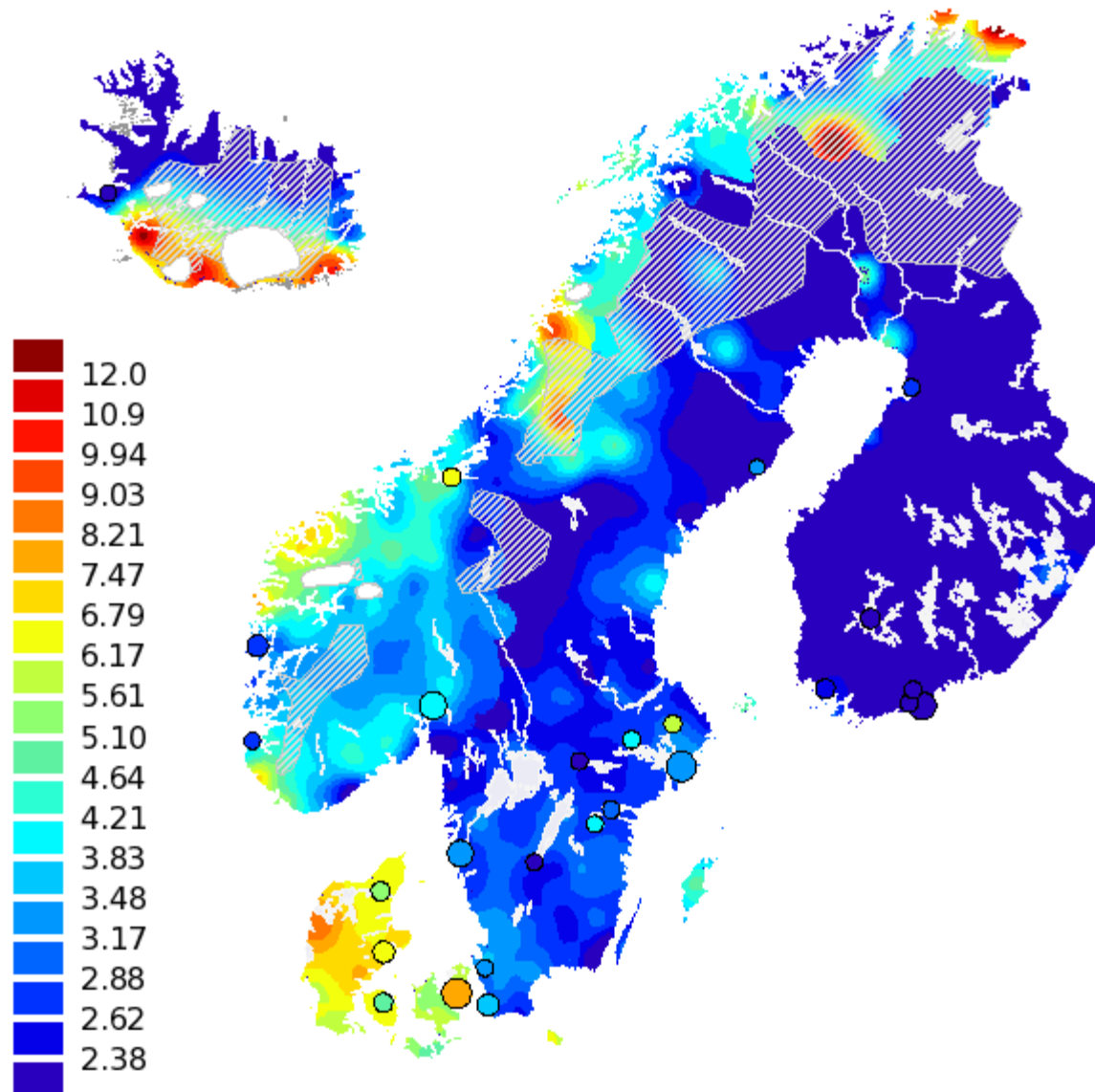
Andreas Kortenkamp, Olwenn Martin  
*Brunel University London*  
*Institute for the Environment*

26 April 2013



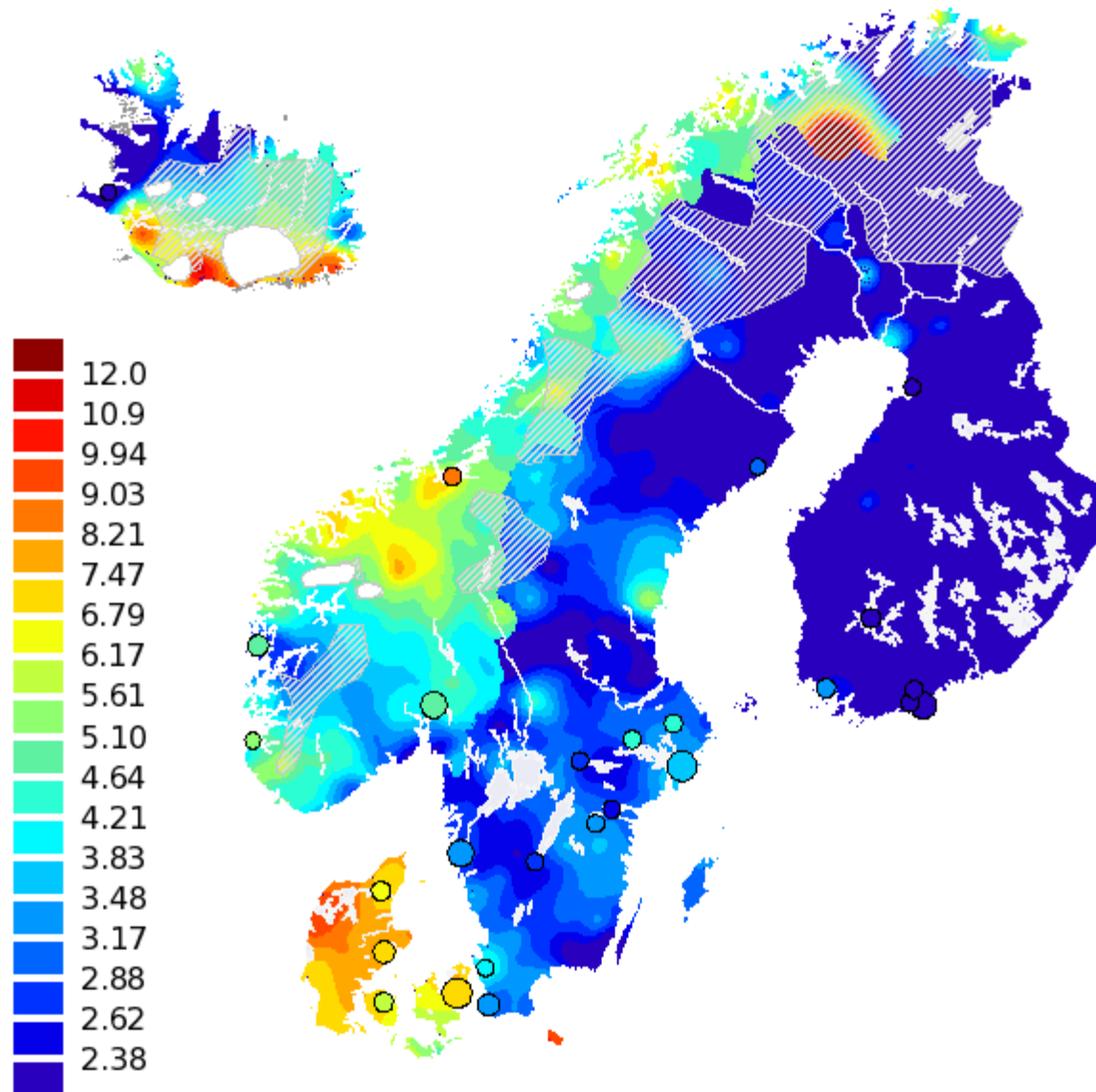
# Testicular cancer, 1970-1976

Incidence / 100,000.



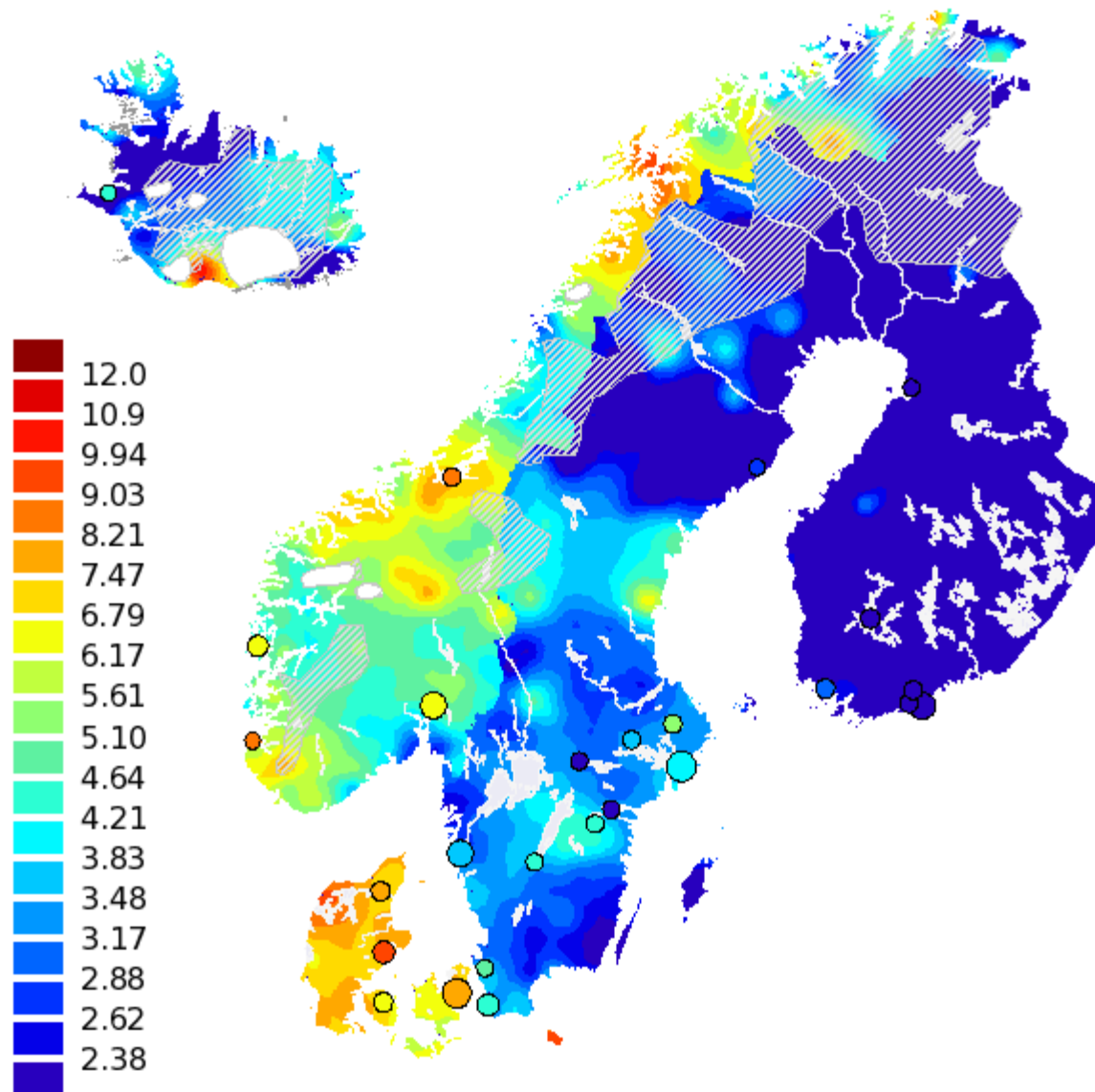
# Testicular cancer, 1974-1979

Incidence / 100,000.



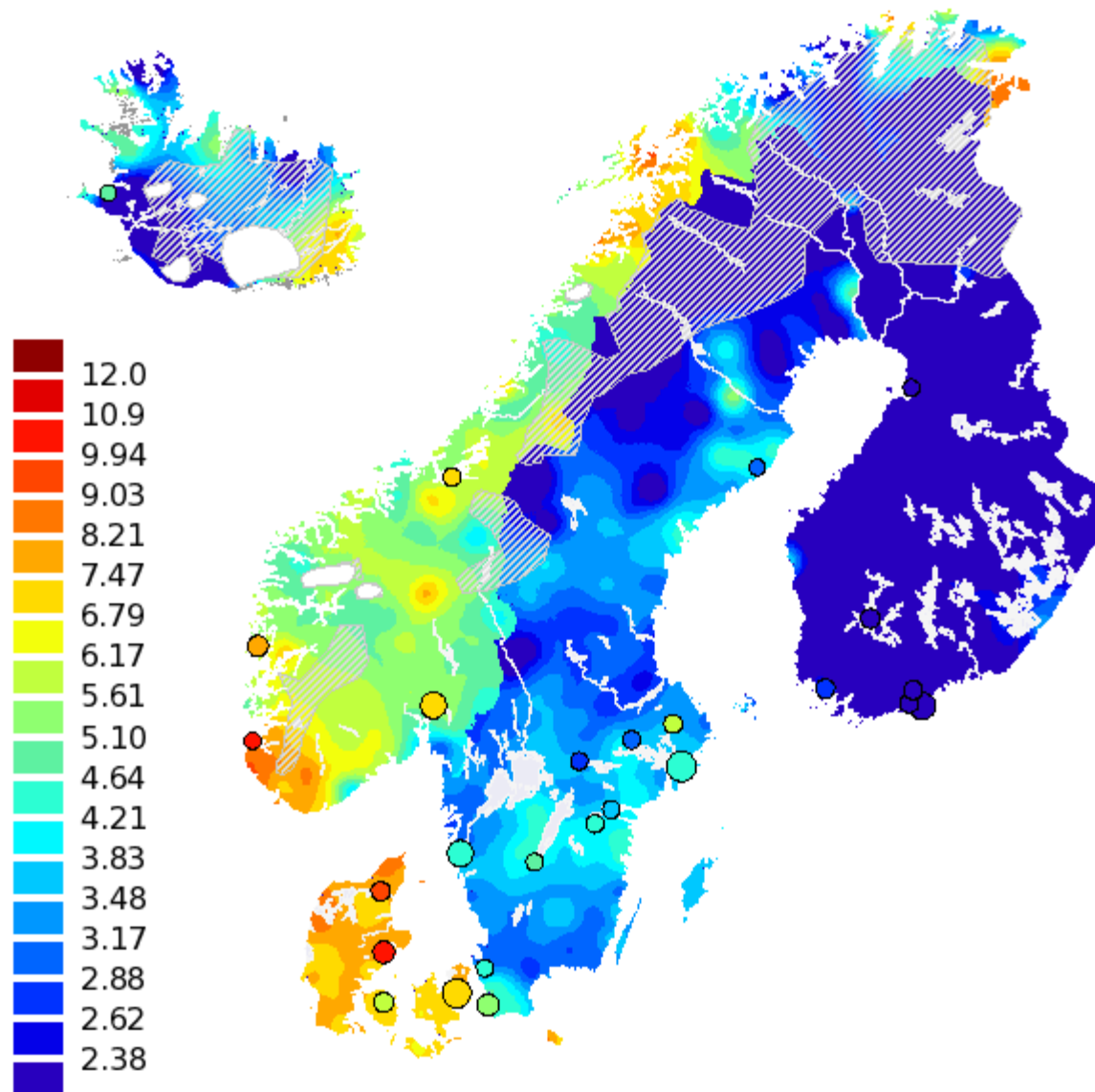
# Testicular cancer, 1977-1982

Incidence / 100,000.



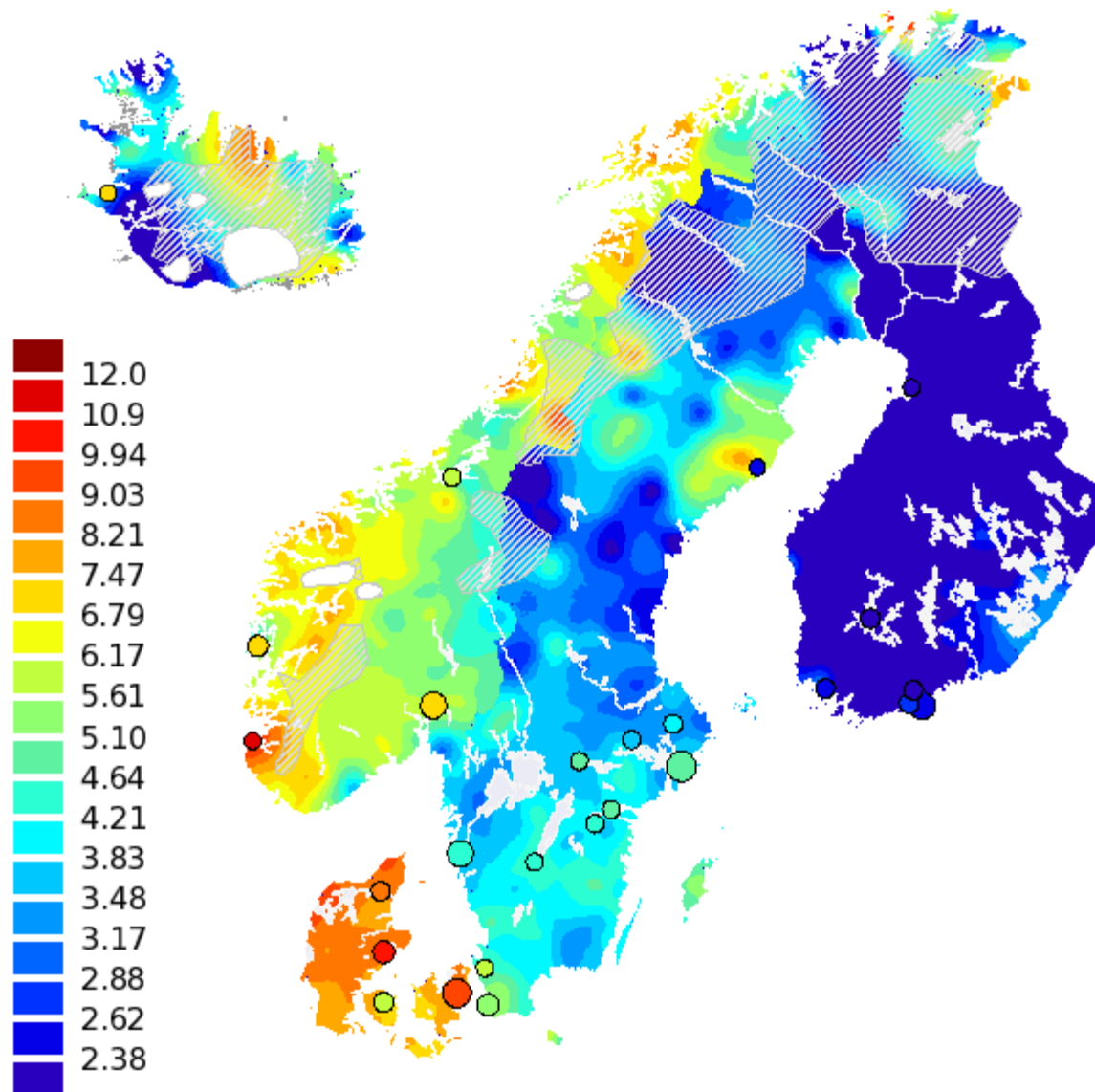
# Testicular cancer, 1980-1985

Incidence / 100,000.



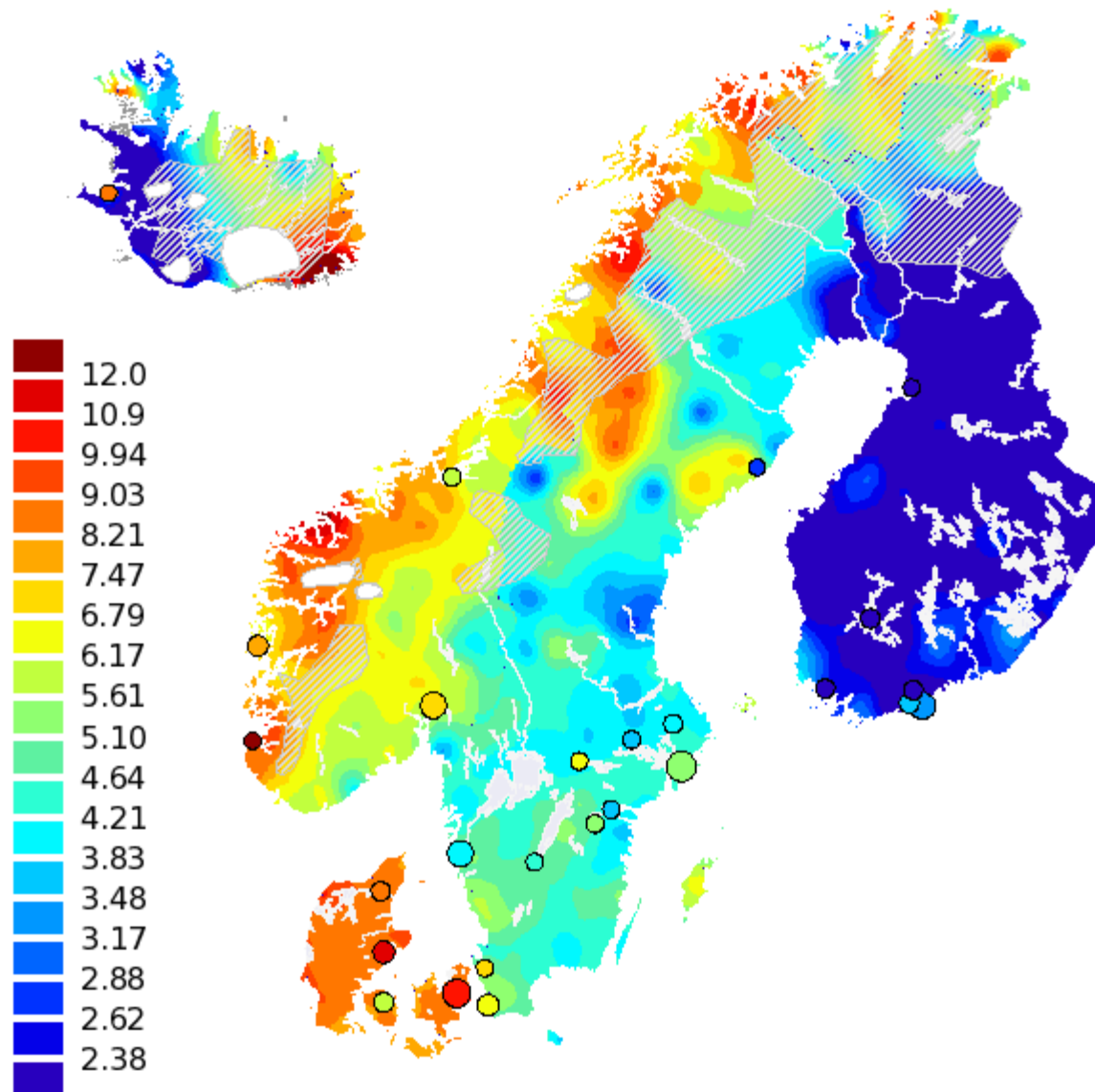
# Testicular cancer, 1983-1988

Incidence / 100,000.



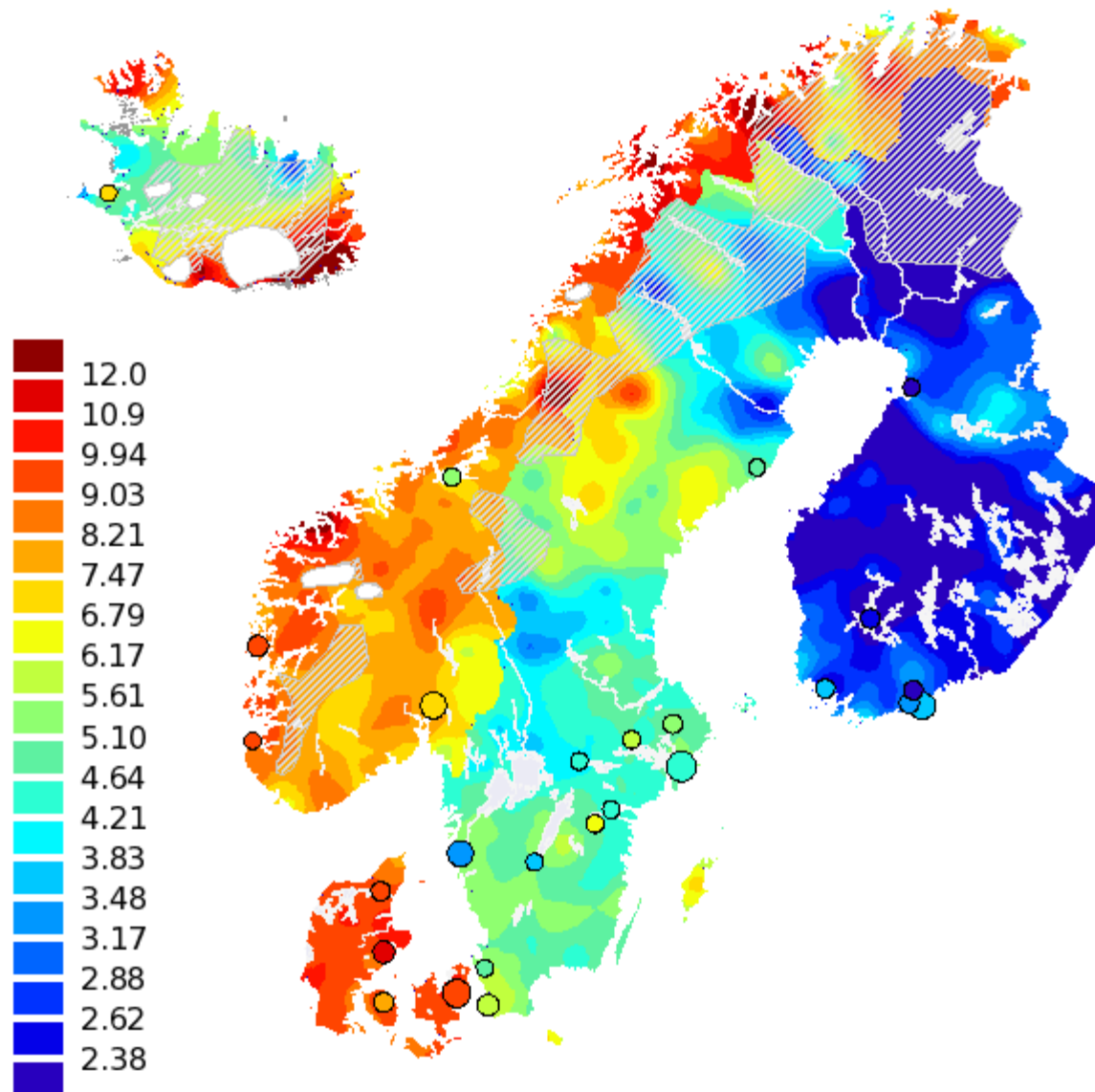
# Testicular cancer, 1986-1991

Incidence / 100,000.



# Testicular cancer, 1989-1994

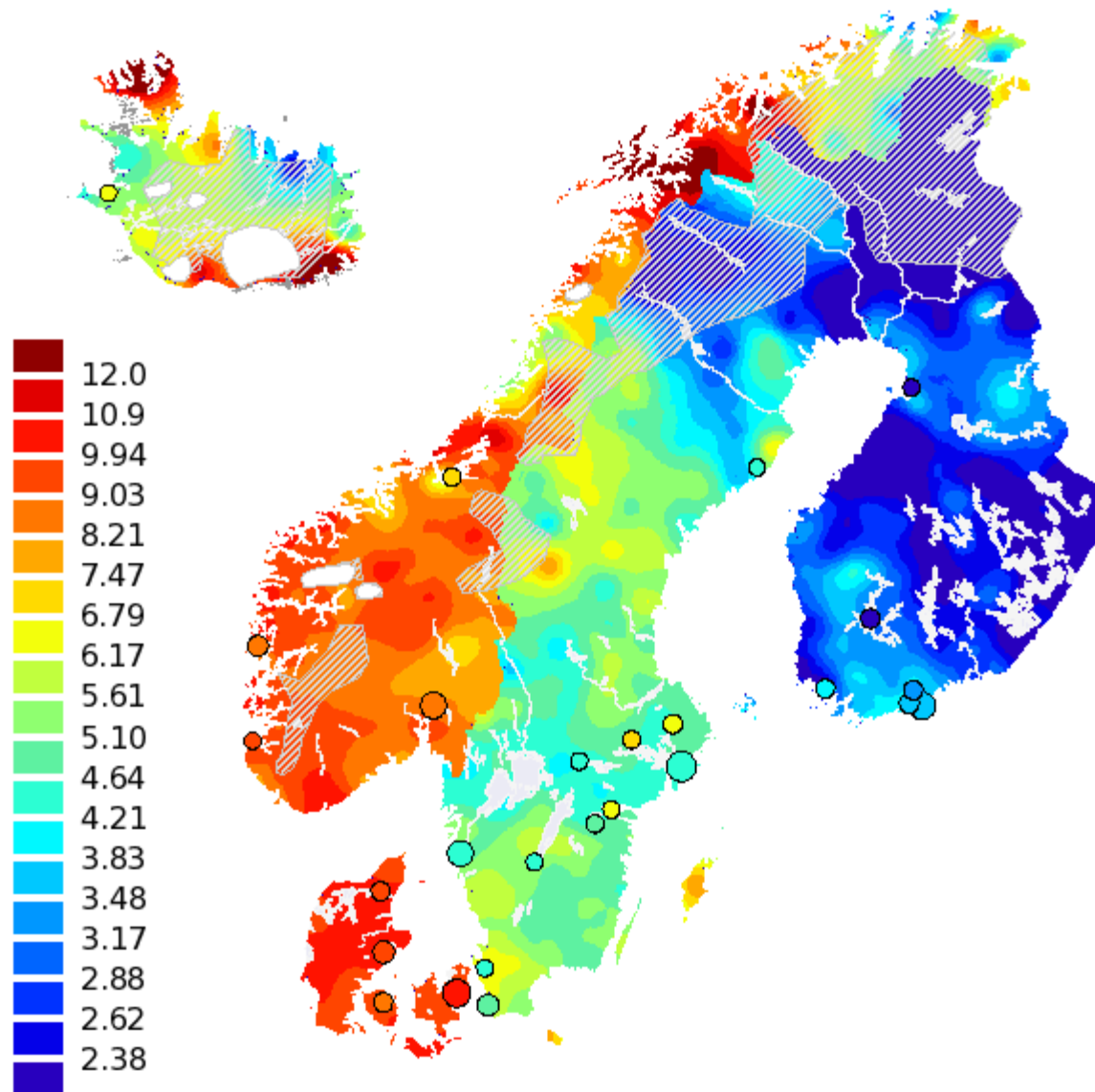
Incidence / 100,000.





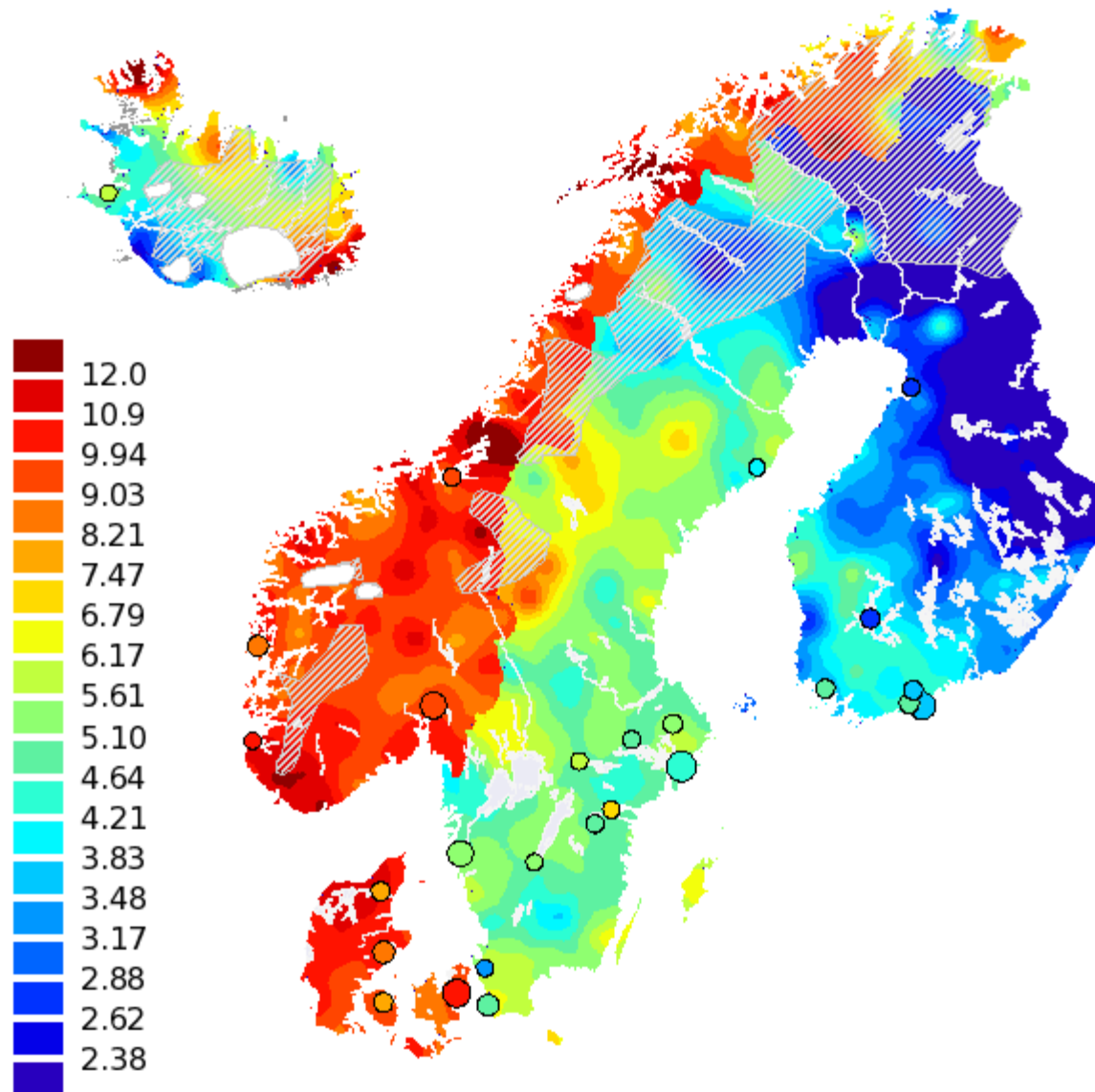
# Testicular cancer, 1992-1997

Incidence / 100,000.



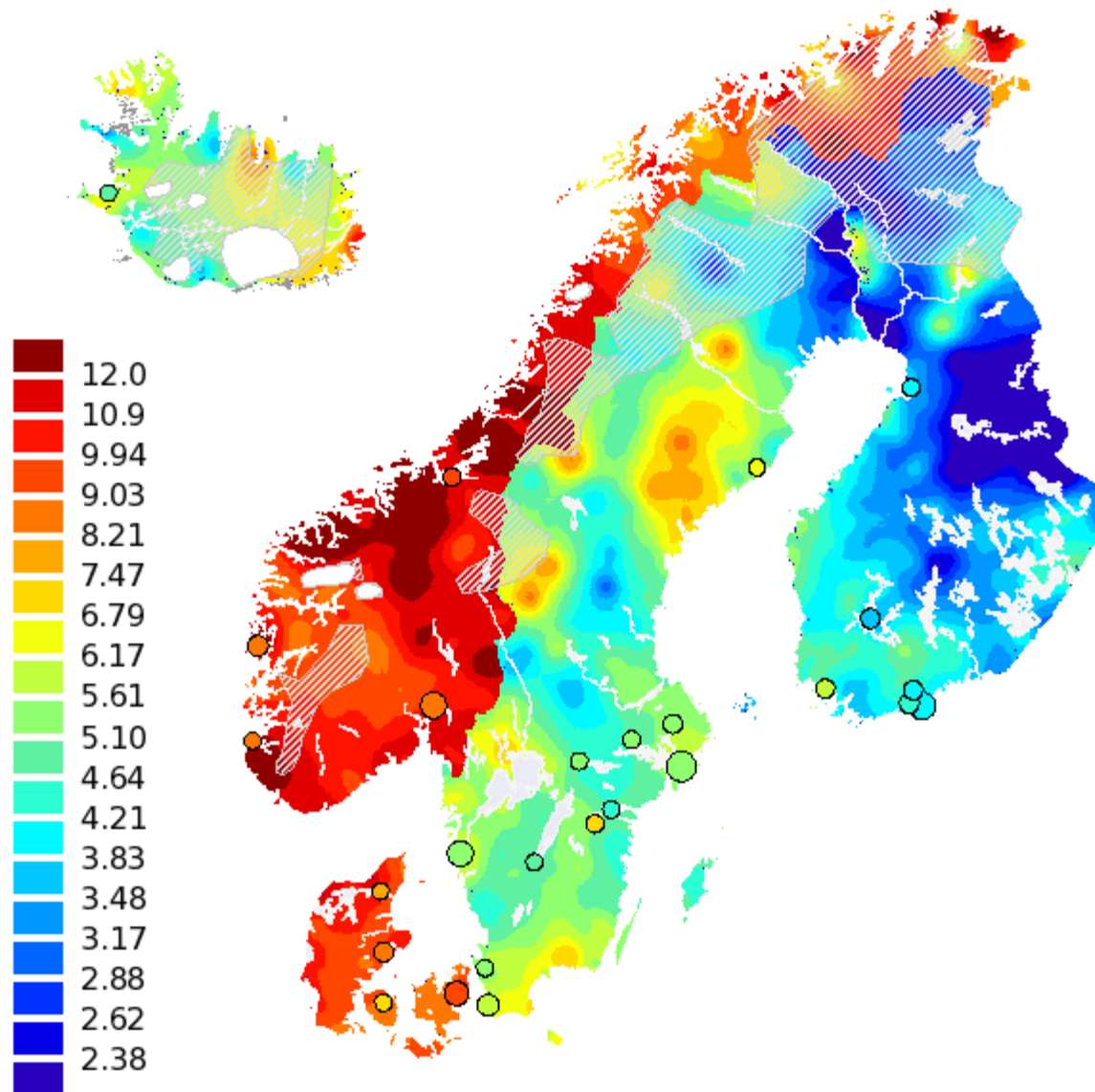
# Testicular cancer, 1995-2000

Incidence / 100,000.

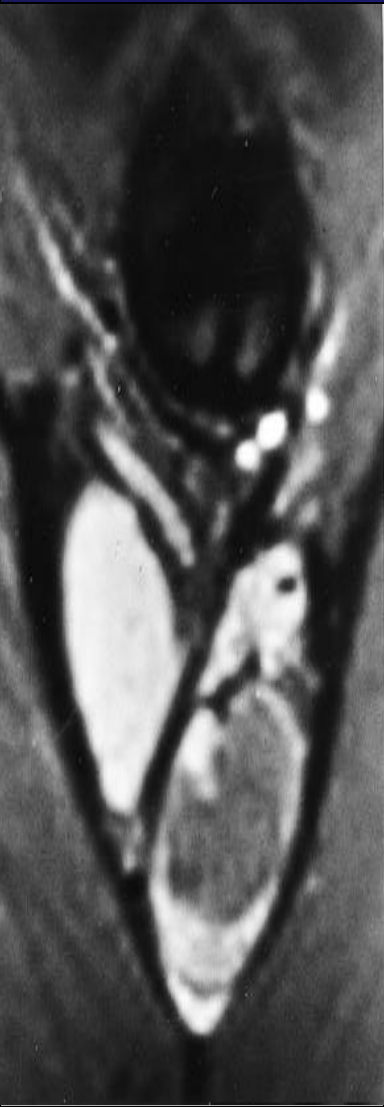


# Testicular cancer, 1998-2003

Incidence / 100,000.

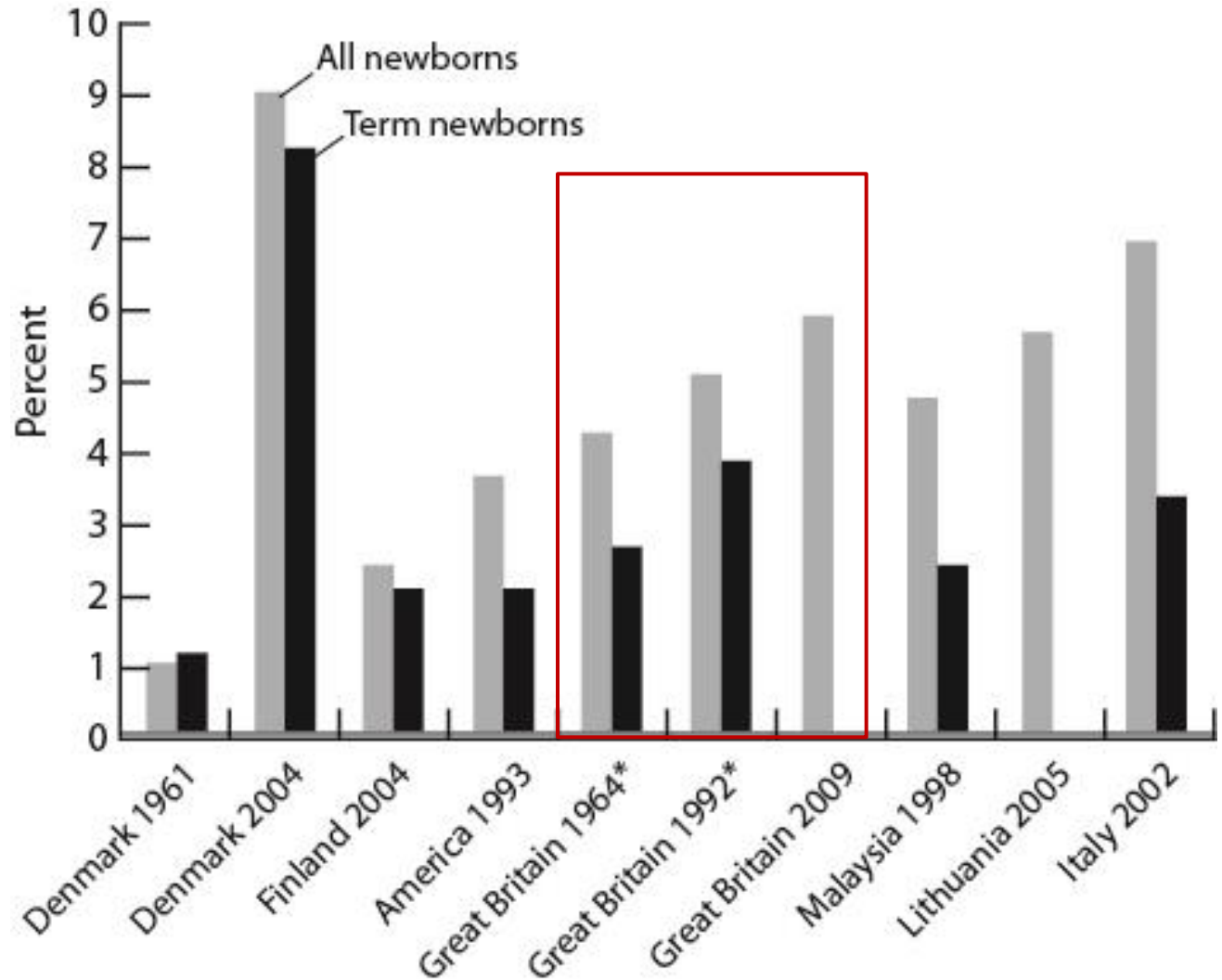
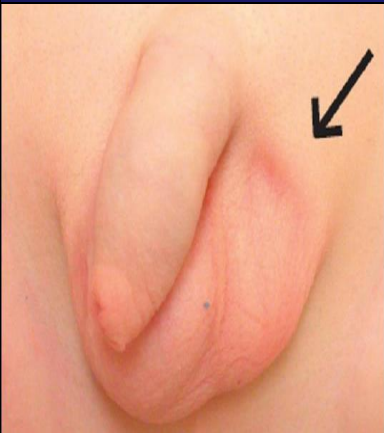


# Testicular germ cell cancers



- Within 30 years **3-4 fold** increases in Scandinavia
- Not due to improved diagnosis or genetics
- Smoking not associated with risks

# Cryptorchidism

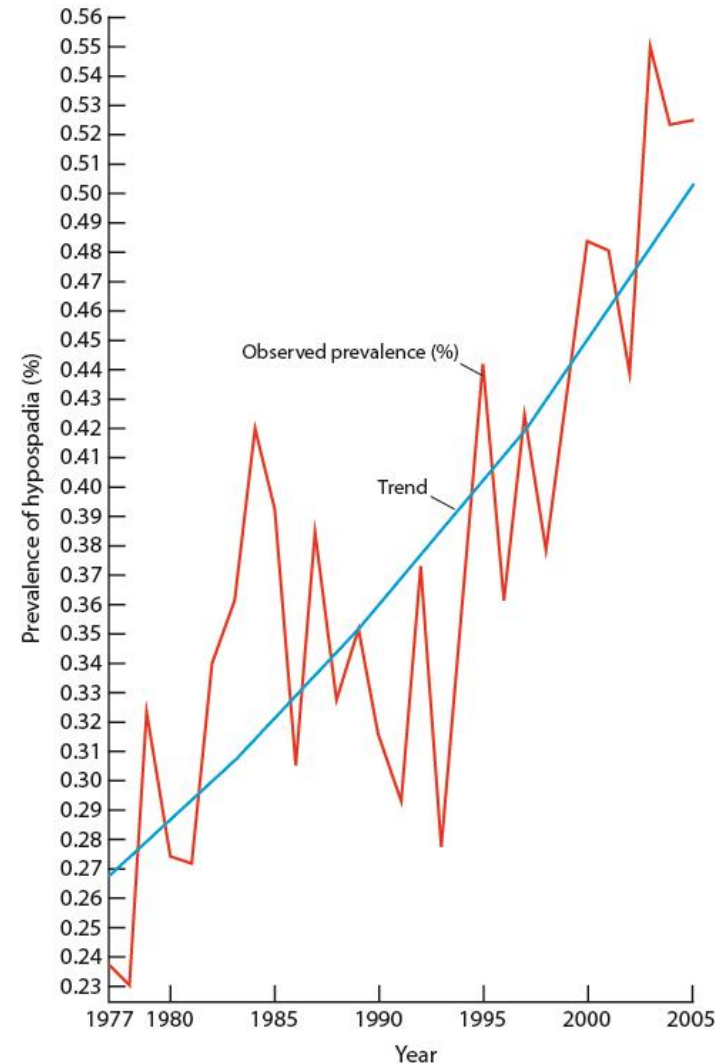


**WHO, UNEP (2013)**  
State of the Science  
of Endocrine  
Disrupting  
Chemicals 2012

# Hypospadias

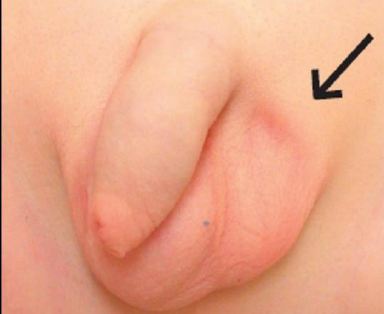


Prevalence of  
hypospadias  
among new-born  
boys in Denmark  
1977 - 2005



**WHO, UNEP (2013)**  
State of the Science  
of Endocrine  
Disrupting  
Chemicals 2012

# Testicular dysgenesis syndrome



- Skakkebaek (2001): **Common foetal origin** of testicular germ cell cancers, cryptorchidisms and hypospadias
- Diminished androgen action in foetal life
- Negative impact on Sertoli and Leydig cells with **irreversible** consequences in adult life
- Proposes an **environmental component** (exposure to antiandrogens)

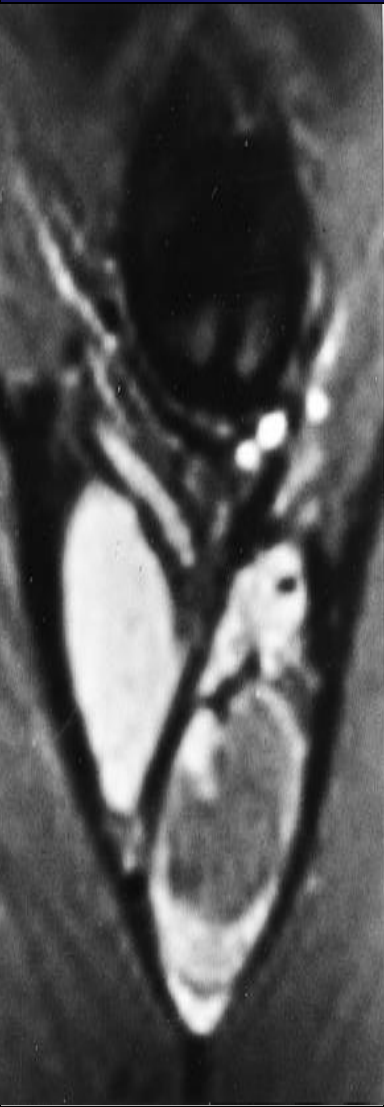
# Anti-androgens – experimental studies

- *In vitro* screening and QSAR
  - Many estrogens are AR antagonists
  - Suppression steroidogenesis
  - QSAR: 8% of all chemicals AR antagonists
- *In vivo* studies
  - Certain phthalates
  - Azole pesticides
  - PBDE
  - TCDD (different mechanism)



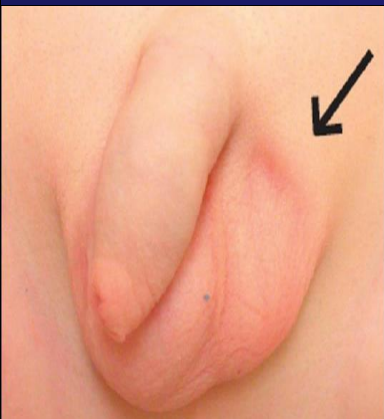


# Testicular germ cell cancers



- **Epidemiology (8 studies):** Associations
  - with DDE/DDT (3 studies)
  - certain PCBs (3 studies – 1 reported lack of assoc)
  - PBDEs (1 study)
  - certain organochlorine pesticides (3 studies)
- **No information** about association with anti-androgenic EDC (e.g. phthalates, azole fungicides etc)
- **No information** about combination effects
- **Lack of animal model** for the detection of testicular carcinogens

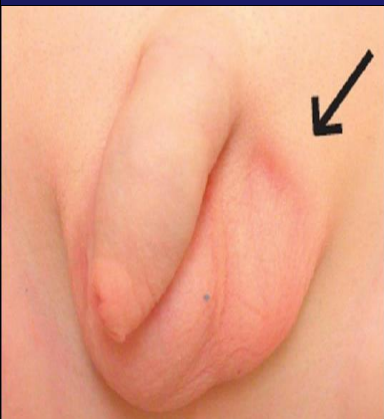
# Cryptorchidisms, hypospadias



Indirect exposure measurements in epidemiology - association with **occupational pesticide exposures**

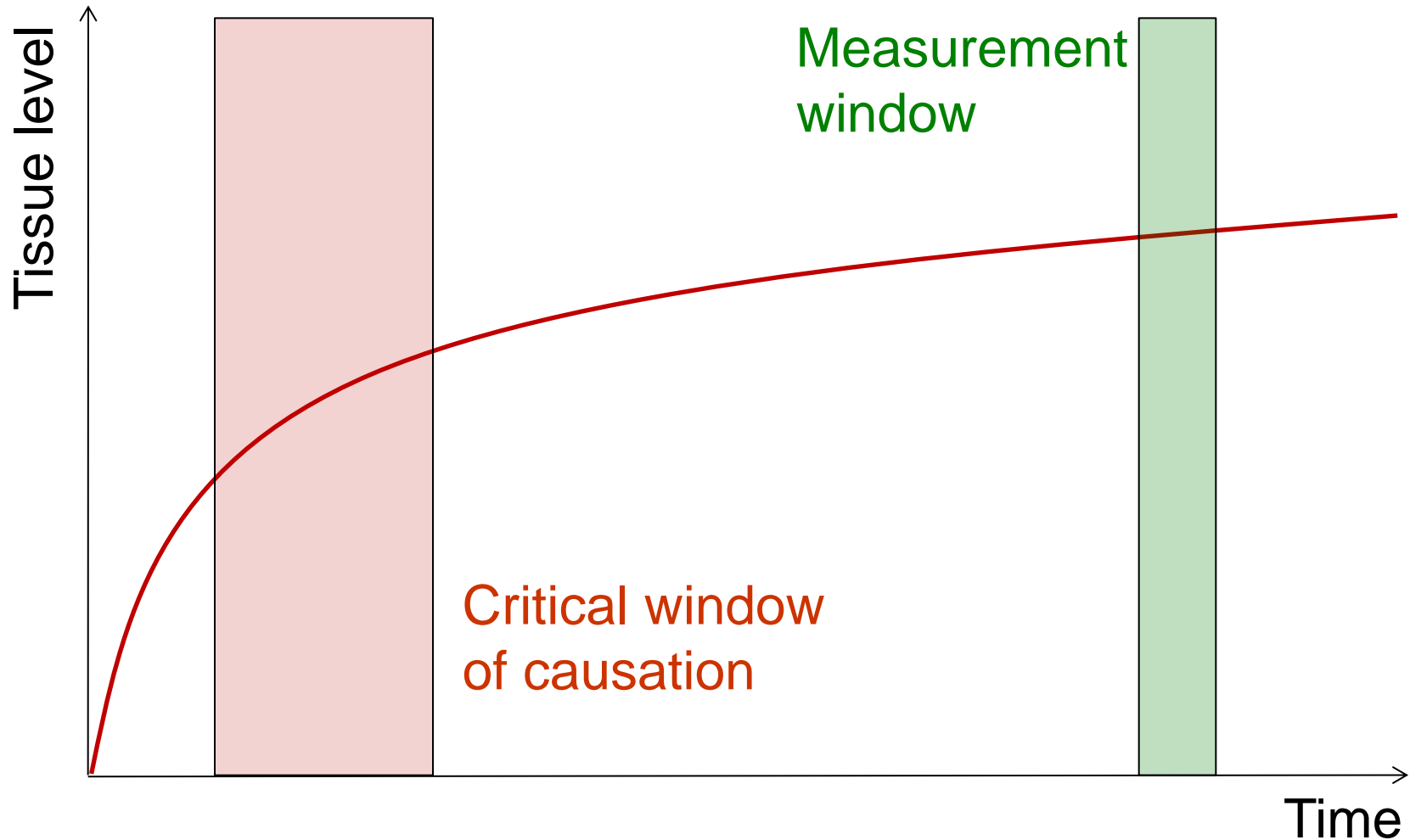
- Working in farming
- Areas of high pesticide use
- Complex, undefined occupational pesticide exposure (greenhouses)
- Not limited to single observations (*7 studies*)

# Cryptorchidisms, hypospadias

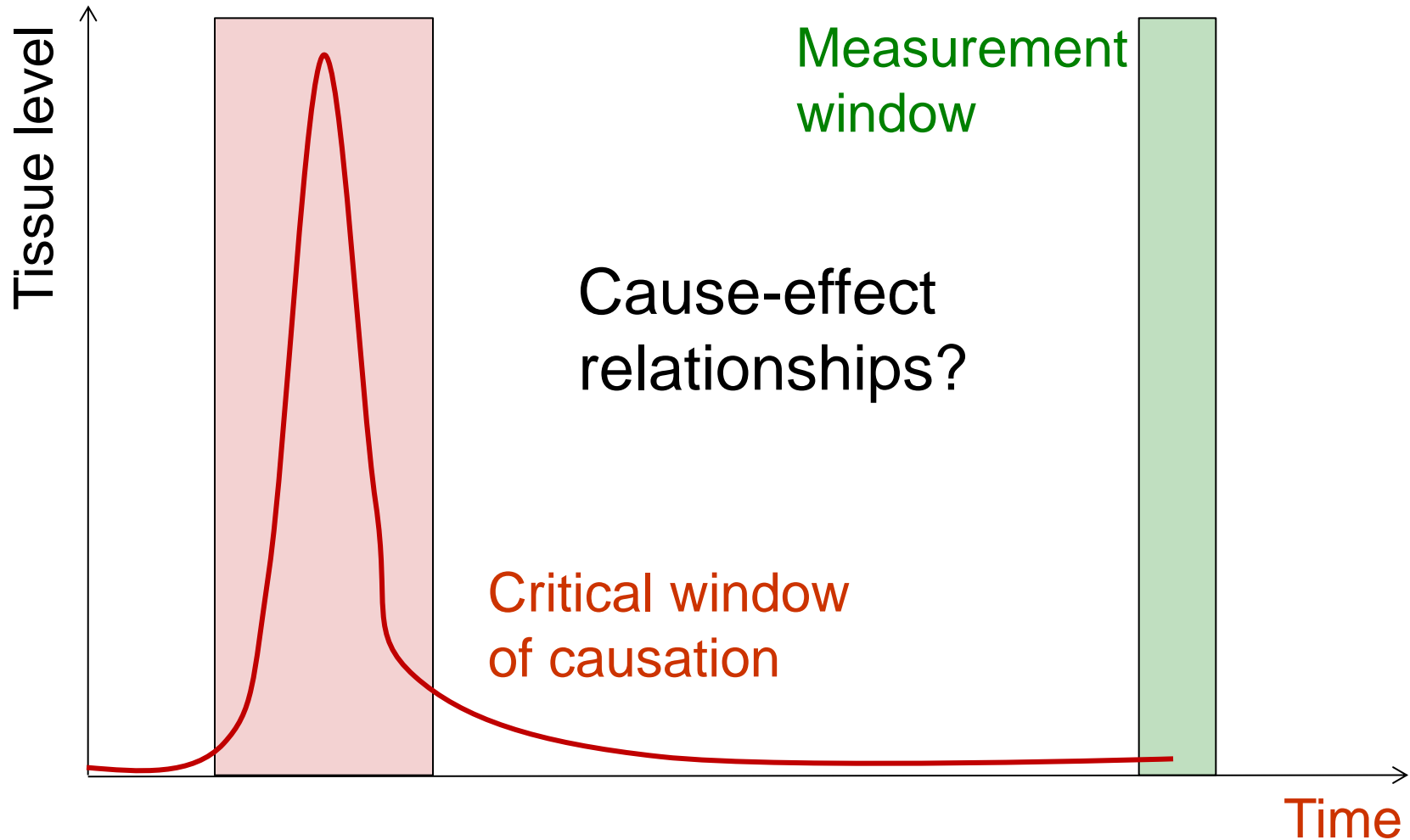


- **No single EDC shows strong associations** with risk of cryptorchidism and hypospadias
- For cryptorchidisms: Indications of **cumulative effects**
  - **Sum of PBDEs in mother's milk**
  - **Sum of organochlorine pesticides in mother's milk**
  - **Total estrogenicity in placenta extracts**

# Challenges: Critical windows



# Challenges: Critical windows



But...

# Toxic cocktail

Chemicals that are safe on their own can gang up when mixed in your body. EPA's Toxics reports

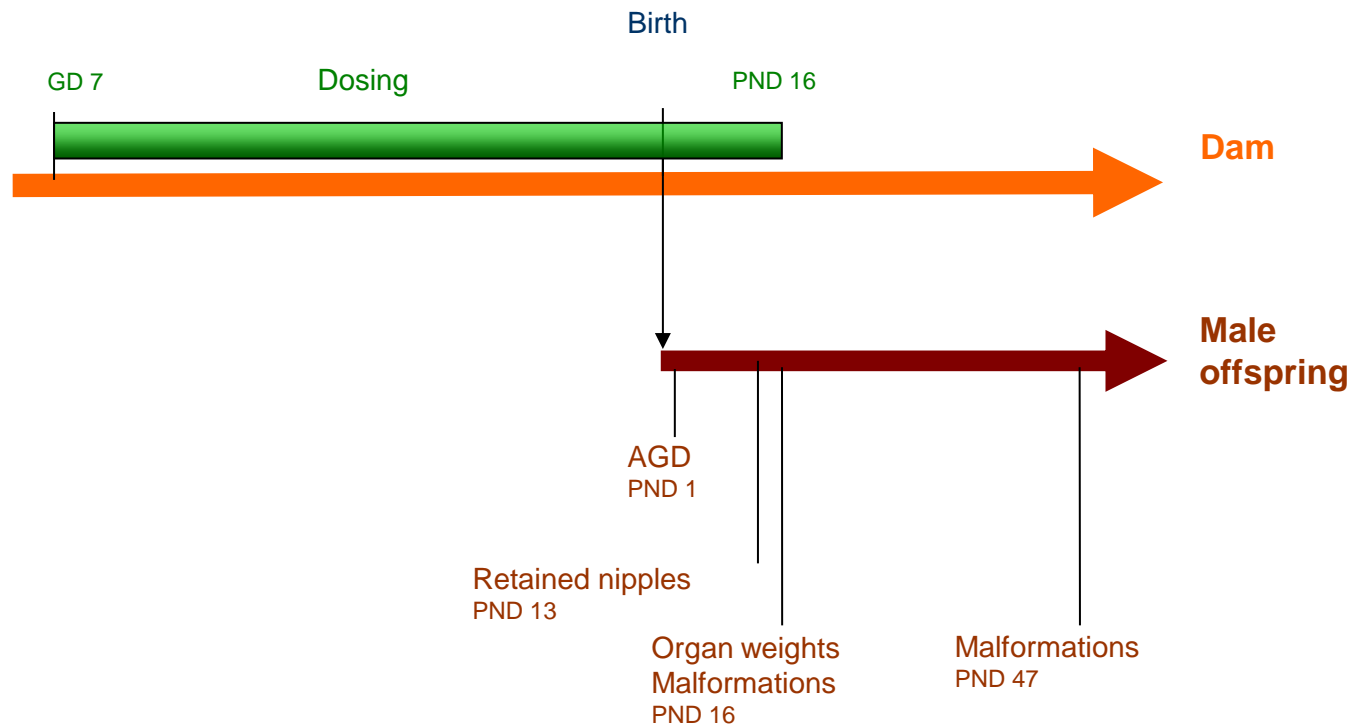
# Challenges: combined exposures

- Do we face a situation where exposure to numerous chemicals, each at innocuous levels, makes an impact?
- How do antiandrogens work together?
- Do they produce joint effects at low levels?



# Developmental toxicity model in the rat

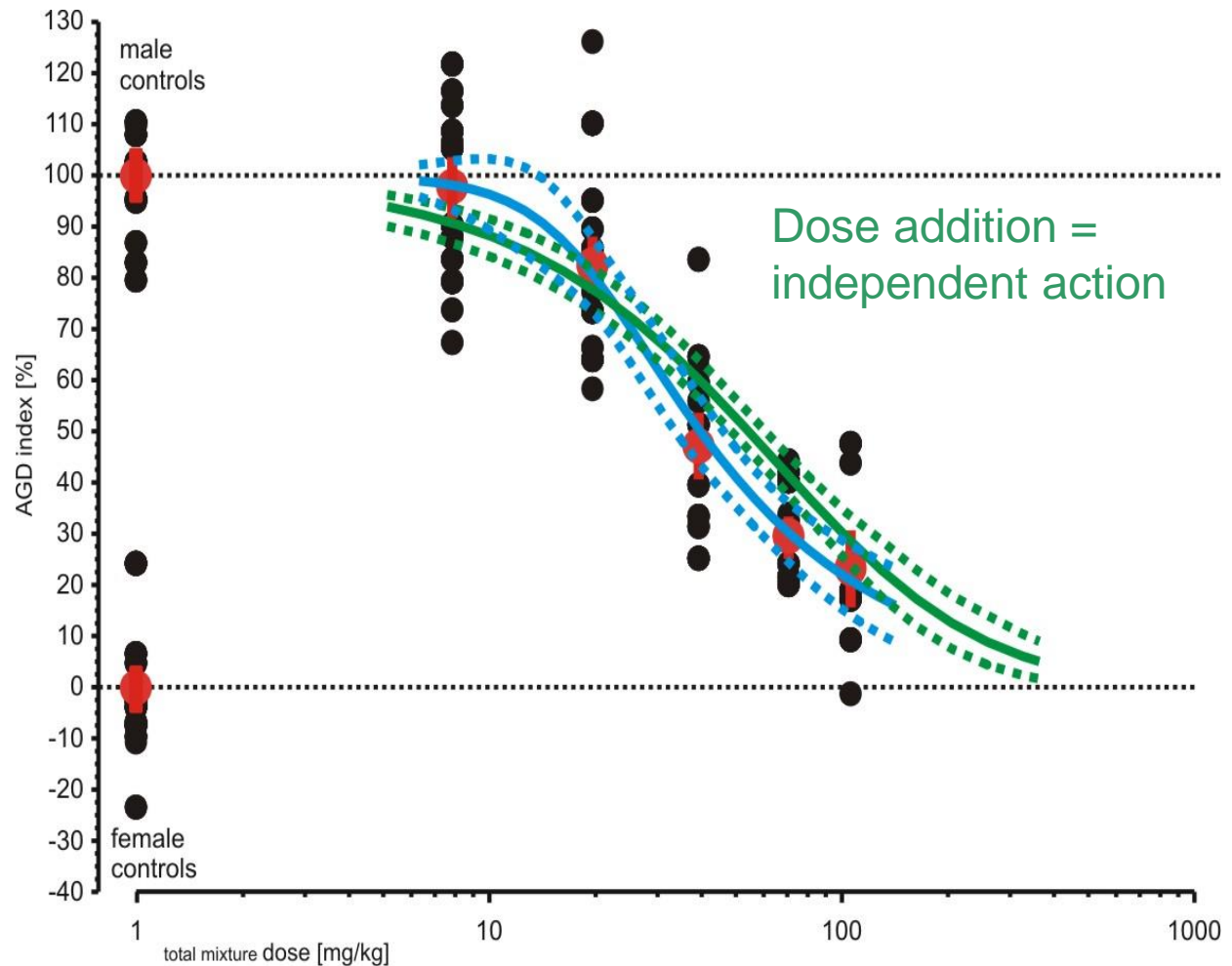
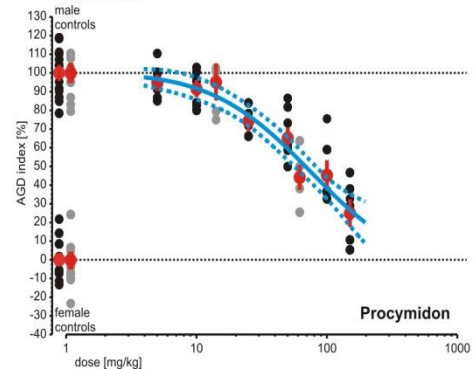
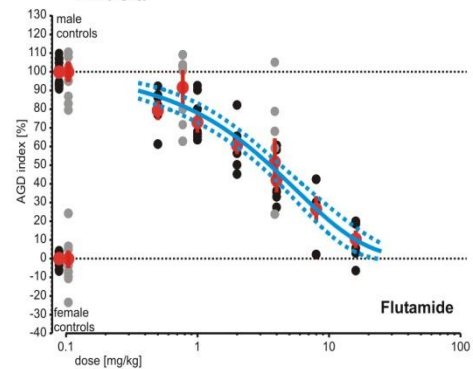
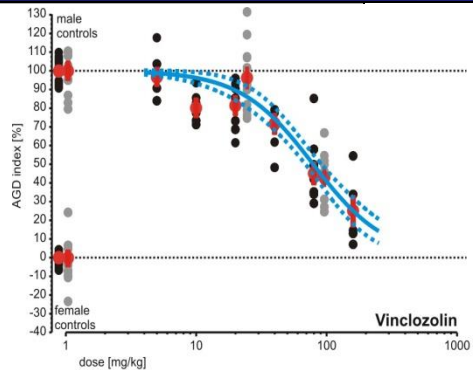
## Experimental design





# Assessment and prediction (1)

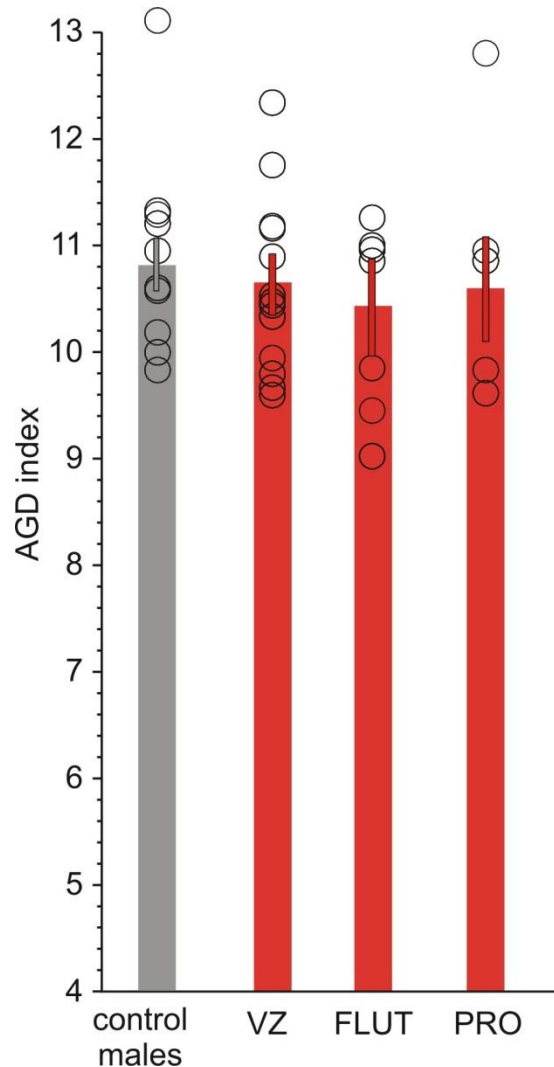
Hass *et al.* 2007 EHP 115 Suppl 1, 122



# Comparing mixture effects with those of components

Similarly acting chemicals:  
Something from “nothing”

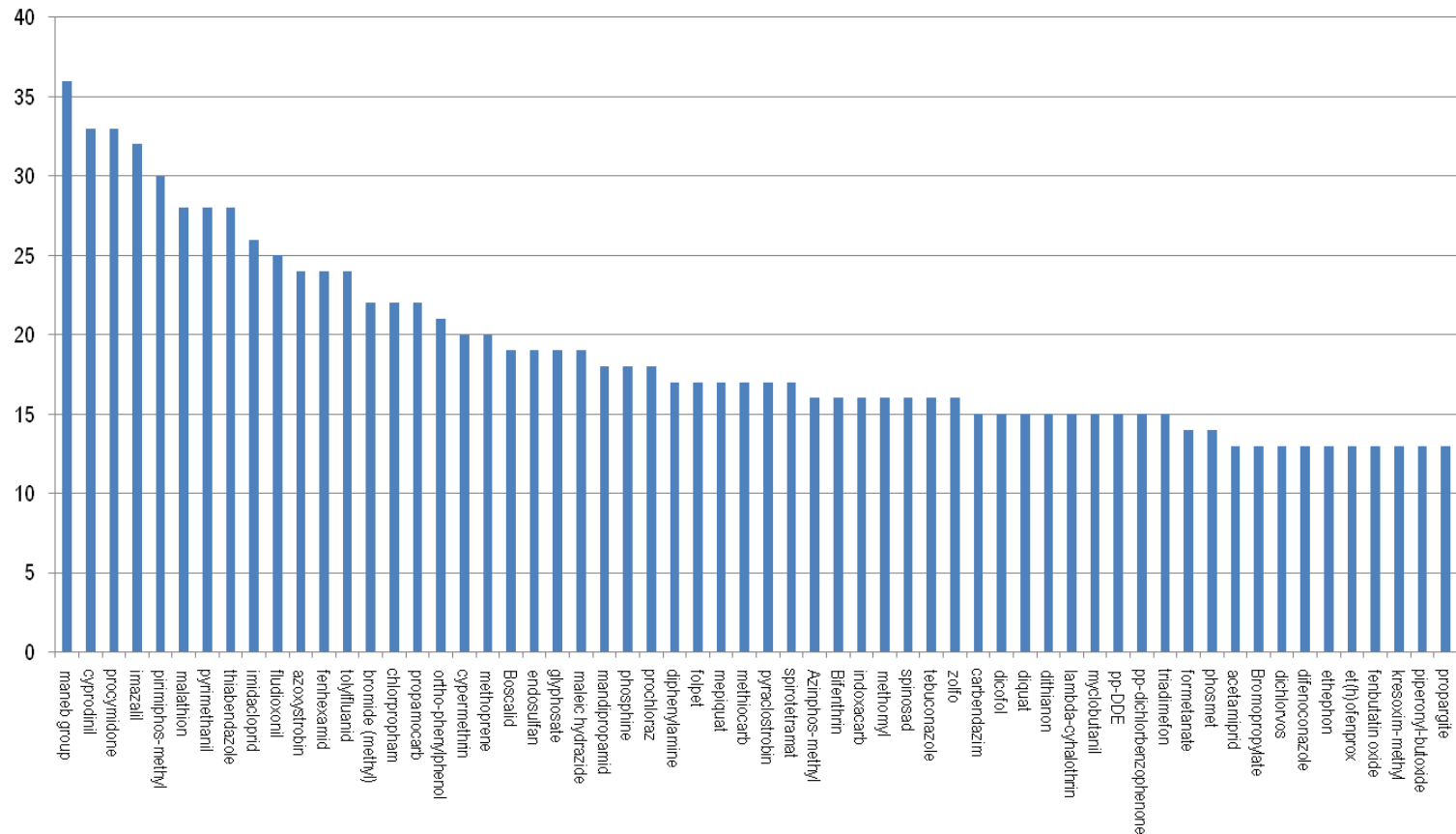
Hass *et al.* 2007,  
EHP **115** (Suppl 1),  
122



# Searching for antiandrogens: pesticides

Pesticides  
in the EU,  
ranked  
according  
to usage

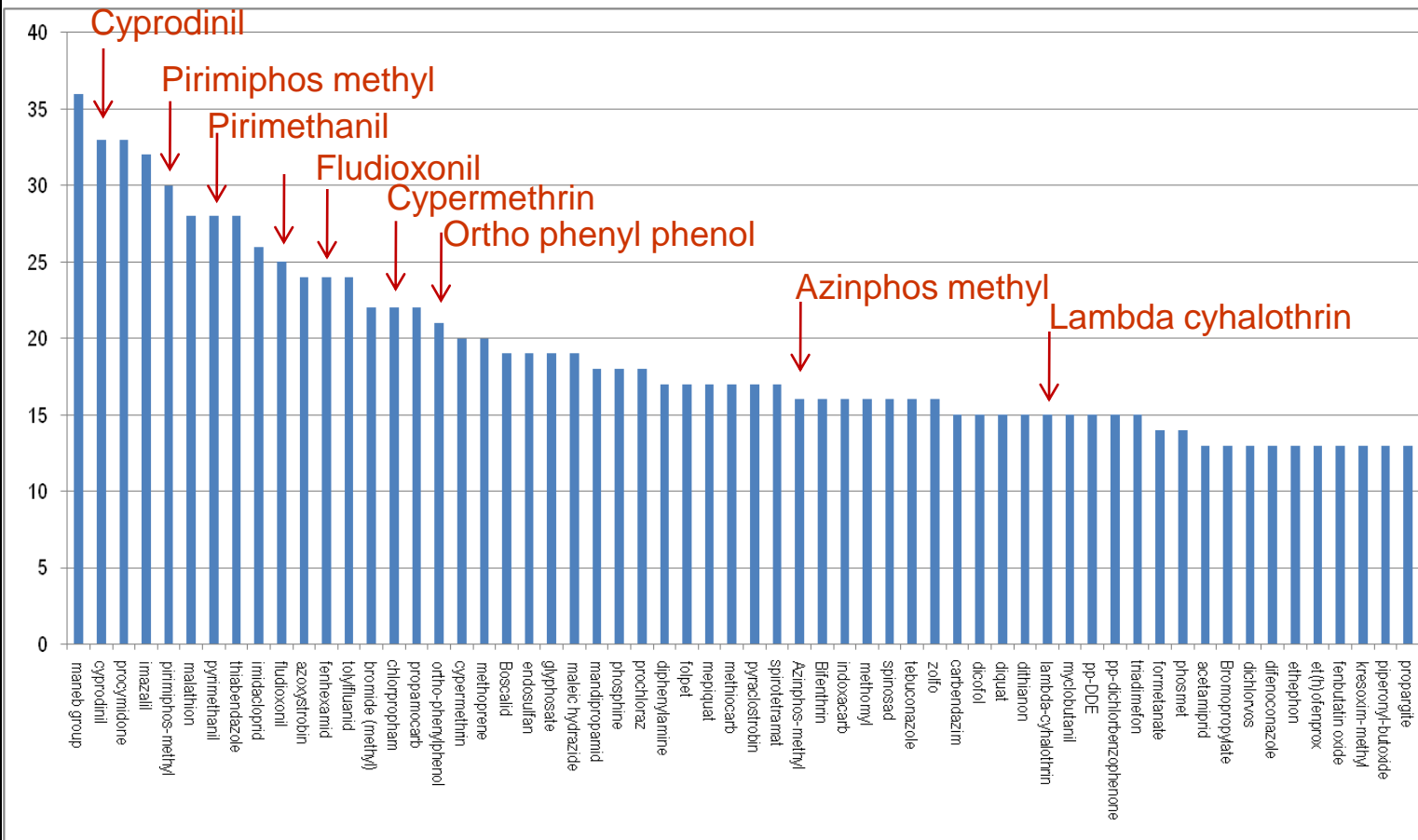
Orton *et al.* 2011  
Environ. Health  
Perspect. 119,  
794-800



# Pesticide intakes rank order (EU)

Pesticides in the EU, ranked according to usage

Orton *et al.* 2011  
 Environ. Health Perspect. 119,  
 794-800



# EDC regulation

- Do endocrine disruptors pose risks comparable to those of
  - Carcinogens
  - Mutagens
  - Reproductive toxicants
- Features:
  - Irreversibility
  - Harm to subsequent generations

# EDC regulation: Three elements

What is an endocrine disrupter?

**Definition** (what is it you want to deal with?)

**Tests** (do you have the tools to identify an EDC?)

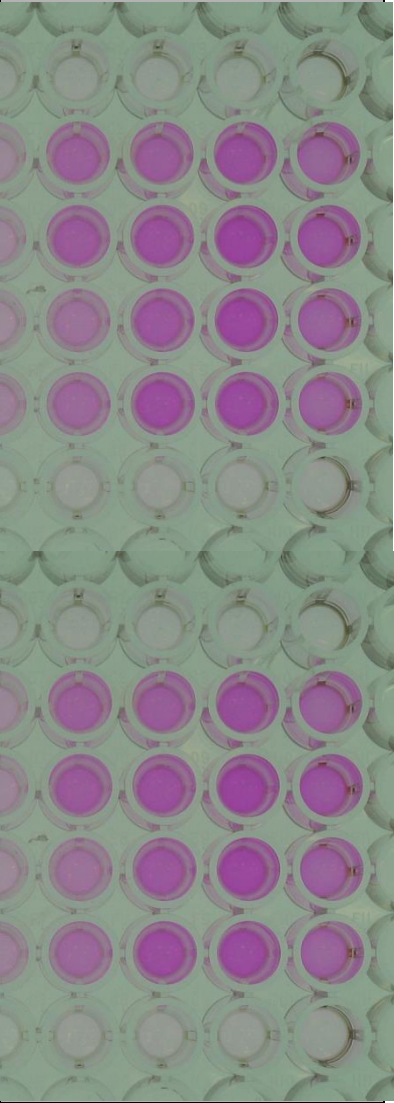
**Criteria** (how to translate test outcomes into regulatory decisions?)

# Definition

- WHO/IPCS definition
- “An endocrine disrupter is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations.”
- Does not define the endocrine system
- **Adversity** – whole animal tests
- Endocrine **mode of action**



# Tests for identifying ED properties

- 
- Have to rely on validated and internationally agreed test methods (OECD/OCDE)
  - This **severely limits** the range of ED effects that can currently become subject to regulation



# ED testing



Current testing requirements  
OECD Conceptual Framework

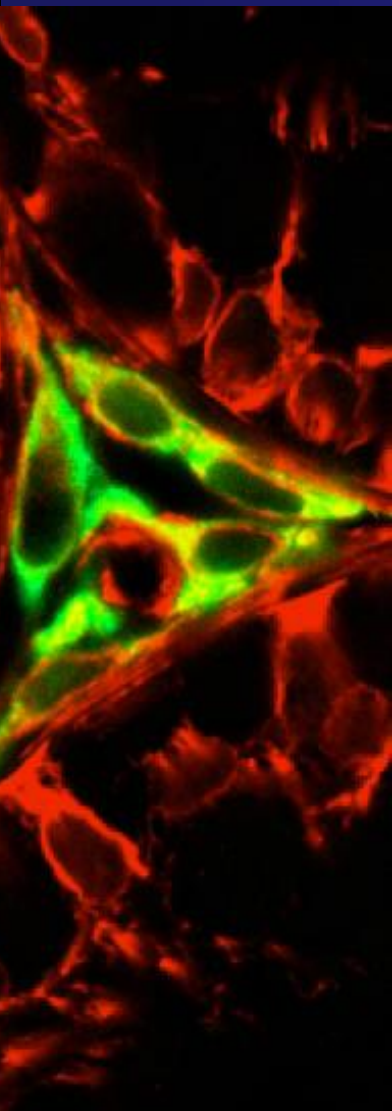
guidance is not yet drafted or  
those included in the Detailed  
Review Paper

Other receptors /pathways

# Tests – general principles

- 
- Demonstrate **adverse** effects in **whole** organisms – *Level 5 OECD*
  - Capture an **endocrine mechanism** – *Level 2 OECD*

# Tests: PPPR – Human toxicology



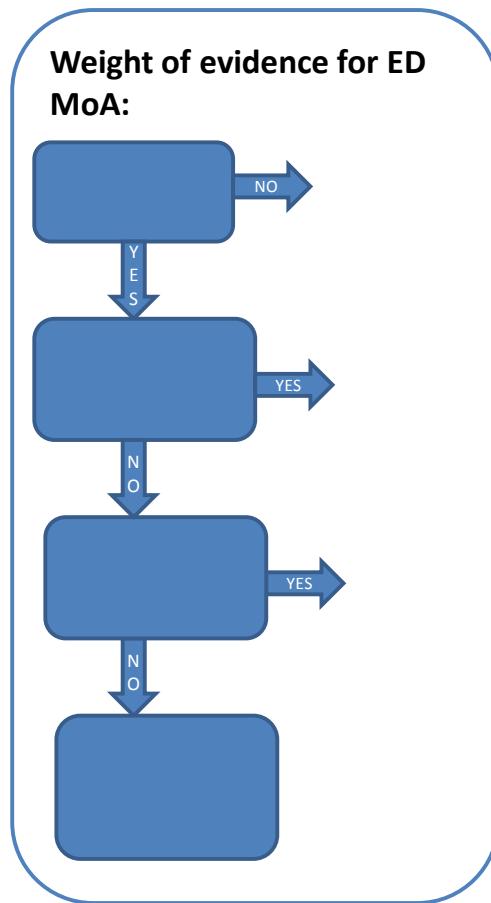
- **Update** Commission Regulations on data requirements for pesticides
- **Minimum requirements for EDC identification**, achievable immediately:
- Addition of endpoints relevant to ED in reproductive toxicity studies
- Two-generation repro (TG 416) or extended one-generation (draft TG 433)
- OECD Level 2 assays (to establish MoA)
- EU 283/2013 has been updated

# Proposed decision tree

- **Stage 1: Evaluation of evidence for ED properties**
  - *Adversity*
  - *Mode of action*
- **Filter**

# Proposed decision tree

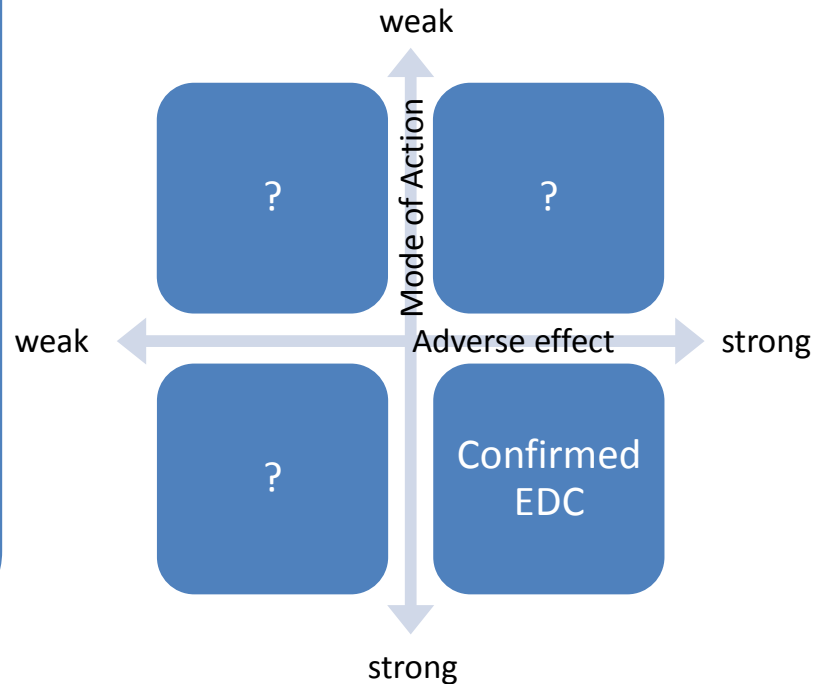
Adversity  
and MoA  
considered  
in parallel



## Weight of evidence for adversity of effect

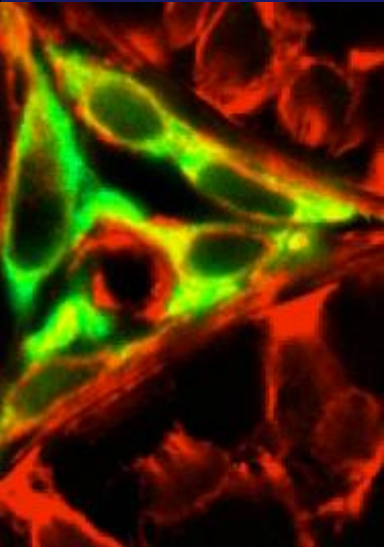
Criteria:

- 1
- 2
- 3
- 4



# Proposed decision tree

- **Stage 2: Evaluating human and wildlife relevance**
- Apply **weight of evidence approaches** (*to be worked out*)
- Assume relevance in the absence of appropriate scientific data
- **Filter**



# Proposed decision tree

- **Stage 3: Toxicological evaluation**
  - Potency
  - Lead toxicity
  - *Severity*
  - Specificity
  - *Irreversibility*
  - **No criterion decisive:** no substance should leave the decision tree at this stage
  - In line with weight of evidence approaches: consider **all the evidence**
  - **Do not filter**

# Proposed decision tree

- **Stage 4: Final decision, classification and categorisation**
- PPPR: cut-off
- REACH: authorisation required
- **Weight of evidence approaches to be worked out**
- **Case-by-case** decisions necessary





# Recommendations

- Implementation of **test methods** as part of information requirements
- Further development of **guidance documents** for the interpretation of test data
- Develop **weight of evidence procedures** for criteria “adversity” and “mode of action” in an inclusive, but not mutually exclusive, way
- Create regulatory categories that **stimulate the provision of data**



# Acknowledgements

- European Commission
- EDEN project
- CONTAMED project



*contamed*

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- Prof Elizabeth Hill (Uni Sussex)

Thank you

