# ENDOCRINE ACTIVE SUBSTANCES : HUMAN HEALTH EFFECTS

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# Where did it all begin?

WWF Wingspread Conference 1991

“Many compounds introduced into the environment by human activity are capable of disrupting the endocrine system of animals, including fish, wildlife, and humans. Endocrine disruption can be profound because of the crucial role hormones play in controlling development.”

Colborn & Clement 1992

# Explosion of knowledge on potential actions & interactions of endocrine active substances

- Initial focus on substances with oestrogenic activity
- Rapidly followed by interest in (anti-) androgenic, progestogenic and thyroid activity
- A single substance can be agonist or antagonist (complete or partial) depending on concentration and presence of competitors
- MOA via binding of ligands to the superfamily of nuclear hormone receptors (ER, AR, PR,TR) located in the cytosol, which then translocate to the nucleus to interact with DNA
- MOA via interference with steroid hormone metabolism

# Explosion of knowledge on potential actions & interactions of endocrine active substances

- Interactions of endocrine active substances with many other receptors (nuclear, membrane, mitochondrial)

- Role of cross-talk between receptors and between signal transduction pathways

| Receptors | Functions |
| --- | --- |
| Aryl hydrocarbon receptors (AhR) | Cell proliferation, differentiation, ovarian aromatase expression |
| Constitutive androstane receptors (CAR) | Xenobiotic & steroid metabolism |
| Pregnane X receptors (PXR) | |
| Peroxisome proliferator-activated receptors (PPAR) | Lipid and glucose metabolism |
| Retinoid X receptors (RXR) | Multiple roles in development and homeostasis |
| Glucocorticoid receptors (GR) | Development, metabolism, immune response |
| Mineralocorticoid receptors (MR) | CNS function |
| G-protein coupled ER1 (GPER) | Cardiovascular function, body wt |

# Possible outcomes of human exposure to endocrine active substances

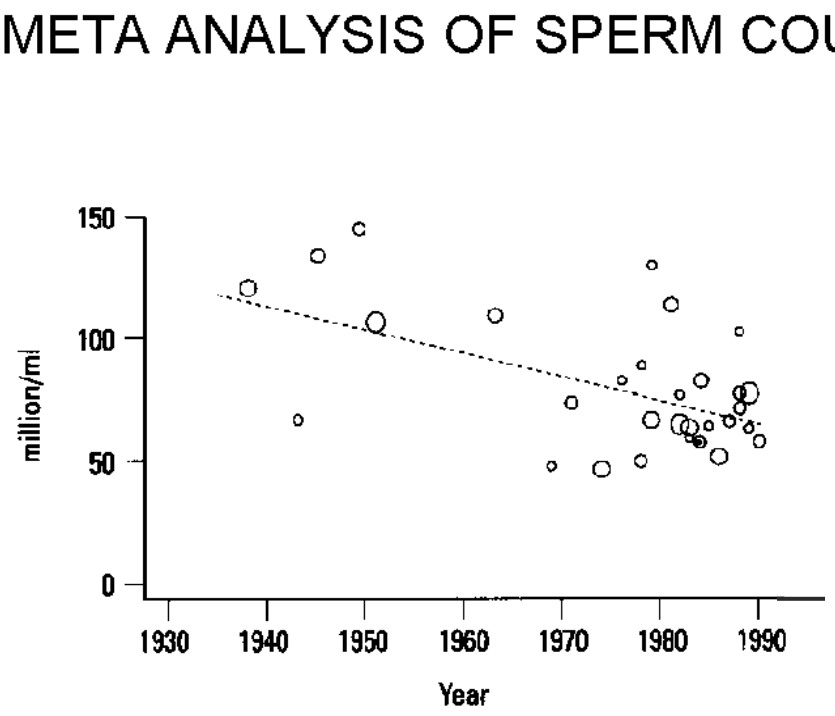
- Effects on sperm quality
- Male reproductive tract abnormalities
- Female reproductive tract abnormalities
- Precocious puberty
- Changes in circulating hormone levels
- Menstrual cycle disturbances
- Effects on sexual desire, potency
- Effects on fecundity and fertility
- Alterations in sex ratio of offspring
- Polycystic ovary syndrome, endometriosis

# Possible outcomes of human exposure to endocrine active substances

- Shortened lactation
- Gynecomastia
- Cancer — testis, prostate, breast, uterus & thyroid
- Effects on the thyroid system
- Effects on neurodevelopment
- Effects on the immune system
- Effects on the adrenal system
- Effects on gastrointestinal tract hormones
- Obesity and associated type II diabetes
- Cardiovascular disease

# Trends in sperm quality

*61 studies, 15000 men, mean counts halved over time*




Carlsen et al, 1995 BMJ 305:609

# Decreasing sperm quality: where are we now?

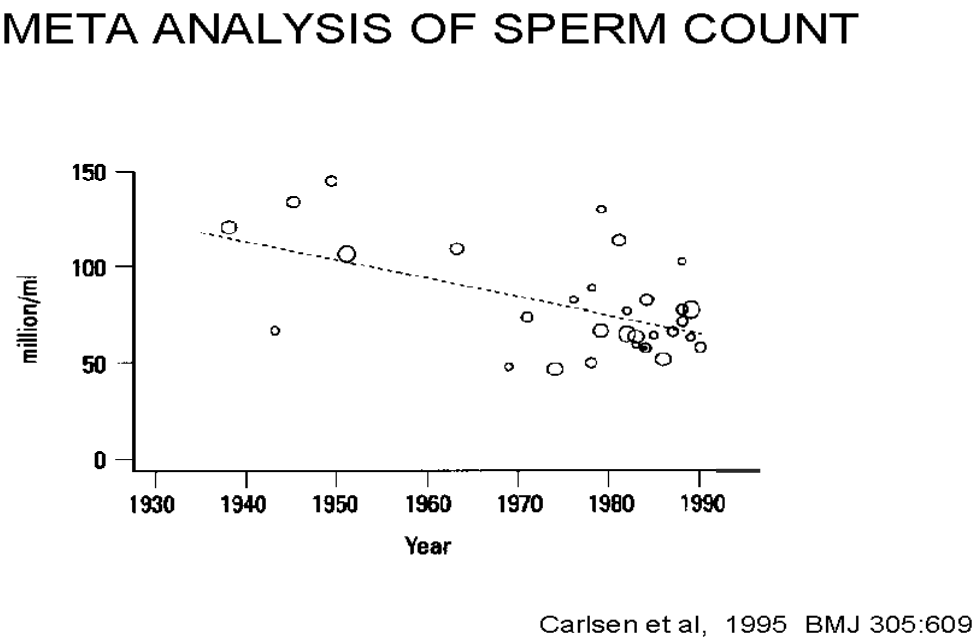
***Merzenich et al. BMC Public Health 2010, 10:24***

*Many potential influences and confounders in sperm studies: meta-analysis should be interpreted with caution*

- Geographical variation (most of early studies were from USA)
- Ethnic variation (not known)
- Differing study designs
- Differing methodological standards
- Selection bias (all self-selected volunteers, some proven fertility, some unknown fertility)
- Age (not considered in the meta-analysis)
- Duration of sexual abstinence (34% did not comply with 3-5 day reqt)

# Decreasing sperm quality: where are we now?

- The negative regression in Carlsen et al. is attributable to 21% of the studies and 12% of the volunteers from pre-1970
- The 1970-1990 studies show an increase in sperm counts over time

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# Decreasing sperm quality: where are we now?

*Subsequent studies published since 1992 show:*

- Sperm counts vary widely between and within countries
- Geographically close countries show very wide differences (e.g. Denmark vs Finland, Latvia, Estonia)
- Some studies support a decline (Paris, Scotland), some show no decline (Toulouse), some show increase (NY, Minnesota, California)

***Merzenich et al. concluded:***

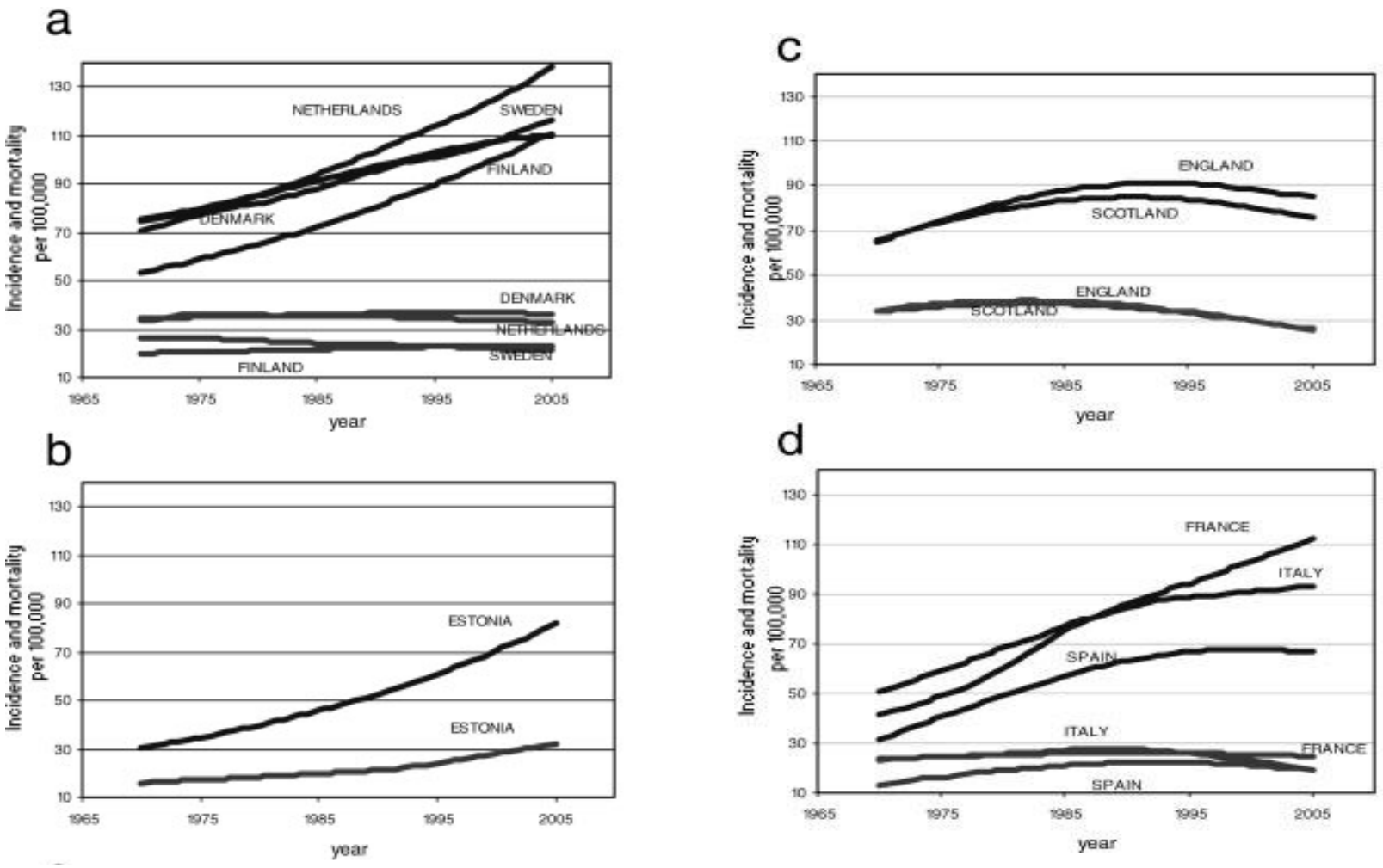
*Population-based, prospective studies needed to assess time-trends*

# Sperm quality: conclusions

- Examples from occupational exposure studies support a conclusion that man-made chemicals can induce changes in human semen quality
- Studies of decreased semen quality have not measured exposures to endocrine active substances
- Difficult to infer from these studies that the outcome measured is related to an endocrine mechanism
- Not been shown that endocrine active substances are having an effect at the level of the general population

# Trends in breast cancer

***Sant et al Int J Cancer 119 2417-2422, 2006***



# Breast cancer : where are we now?

- Increasing incidence of breast cancer in many industrialised countries since 1940s
- Migrants from low to high incidence area progress to showing high incidence
- Compatible with environment and lifestyle influences
- Oestrogens play known role in risk of breast cancer
  - early menarche, late menopause
  - no children, late age at first birth, never lactated
  - Oral contraceptive use, HRT use
  - postmenopausal obesity

# Breast cancer : where are we now?

- **Role of organochlorine compounds**

  *(measured in serum or adipose tissue)*

  - Most studies lack statistical power
  - PCBs: many studies, inconsistent results, some indicate specific PCBs may play a role
  - *o,p'*-DDT (oestrogenic) and *p,p'*-DDE (anti-androgenic): many studies, no consistent association
  - Chlordane, dieldrin, hexachlorobenzene, β-hexachlorocyclohexane, mirex, TCDD: few studies, some negative, some borderline associations

# Breast cancer : conclusions

- Known risk factors
  - Cumulative lifetime's exposure to oestrogens
  - Genetic/familial factors
  - Alcohol consumption
  - Ionising radiation
  - Benign breast disease
- Organochlorines: Biologically plausible but no strong evidence to support a causal role
- Role of early exposures during breast development unstudied

# Thinking outside the box

**What connects**
**masculinisation of female whelks (imposex)**
**and obesity?**

# Imposex in the common whelk


**What connects imposex in whelks and obesity?**

# Tributyltin (TBT)

## Gastropods & molluscs: aromatase inhibitor

## ligand for RXR

# Obesity

***Grun & Blumberg Mol Cell Endocrinol 2009, 304 19-29***

- Obesity = more adipocytes, increased lipid content
- Both these regulated by PPARγ-RXR heterodimers acting as ligand sensors for lipophilic hormones and dietary fatty acids
- Pharmaceutical PPARγ agonists thiazolidinediones used to treat diabetes cause persistent weight gain
- Organotins TBT and TPT are PPARγ and RXR agonists
- Prenatal TBT induces adipogenesis in mice

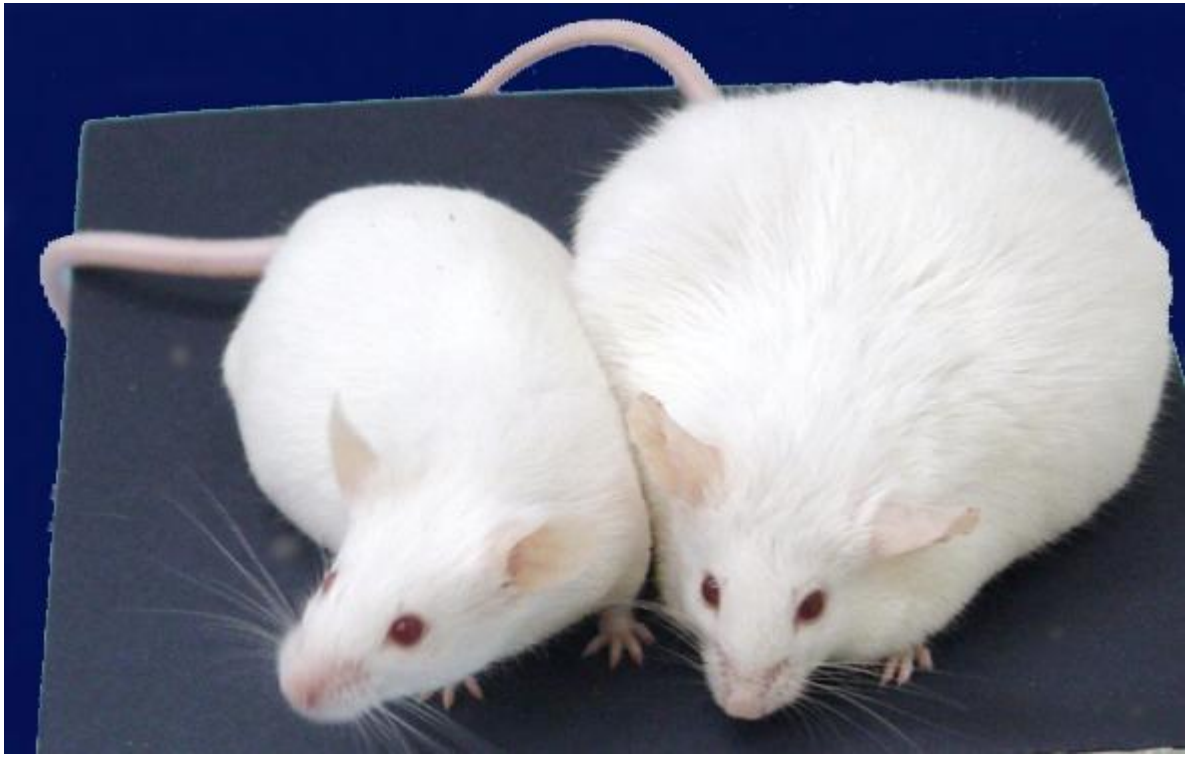
# Obesity

- In contrast PPARα agonists are hypolipidaemic and reduce adipocytes
- Environmental and dietary PPARα agonists
  - DEHP
  - PFOA
- *How could these possibly induce obesity?*
  - MEHP (main DEHP metabolite) is a PPARγ agonist
  - Fetal/perinatal exposure to DEHP or PFOA reduces androgen synthesis ⇨ obesity
  - PFOA ⇨ low birth weight ⇨ increased risk of obesity

# Obesity & oestrogens

***Newbold et al. Mol Cell Endocrinol 2009, 304 84-89***

*Effects of DES (1 µg/kg/d, d1-5 neonatally ) at 4 months in females*



# Obesity & oestrogens

- DES mice had raised serum leptins and insulin, and showed altered glucose metabolism
- Equipotent (in uterotrophic assay) amounts of other oestrogens, oestradiol and genistein also resulted in obesity in mice
- A study of association between weight gain in first week of life and adult overweight in 653 European Americans showed increase of borderline significance in OR if soy-fed

***Stettler et al. Circulation 2005, 111 1897-1903***

# Obesity: conclusions

- Oestrogens and other endocrine active substances have the potential to influence early programming of risks for obesity and diabetes by
  - Effects on adipocyte differentiation
  - Effects on molecular and metabolic control of weight homeostasis

# Human health : overall conclusions

- Clear human evidence of adverse effects of endocrine active substances relates to high exposures
- No clear evidence of effects of endocrine active substances at a general population level
- With possible involvement of many receptors, pathways and their interactions, can anticipate
  - Risk assessment for humans will be complex
  - Cumulative effects from similarly acting substances (both additive and antagonistic)
  - Target organ, functional and pathological surprises!