

How to make environment safe to protect reproductive health

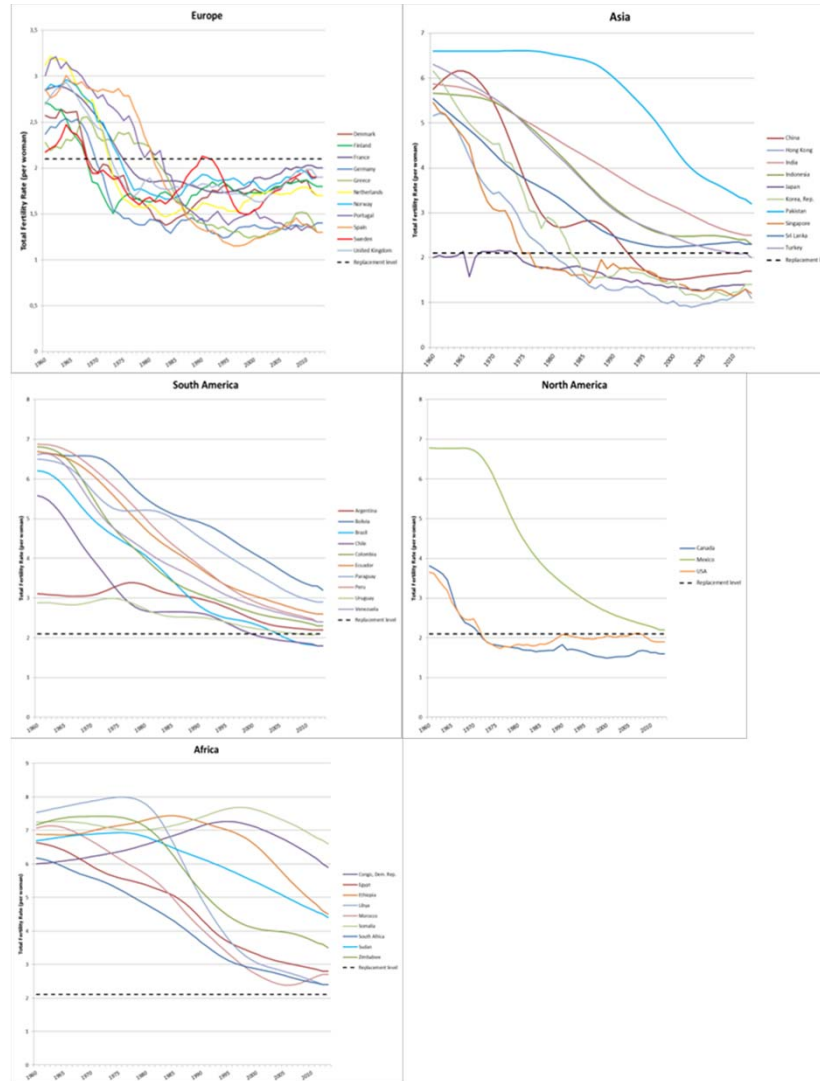
Jorma Toppari

Brussels 2018

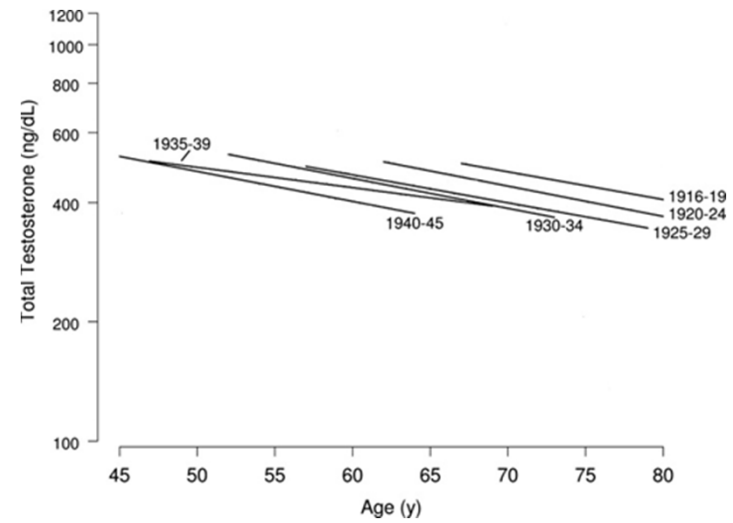
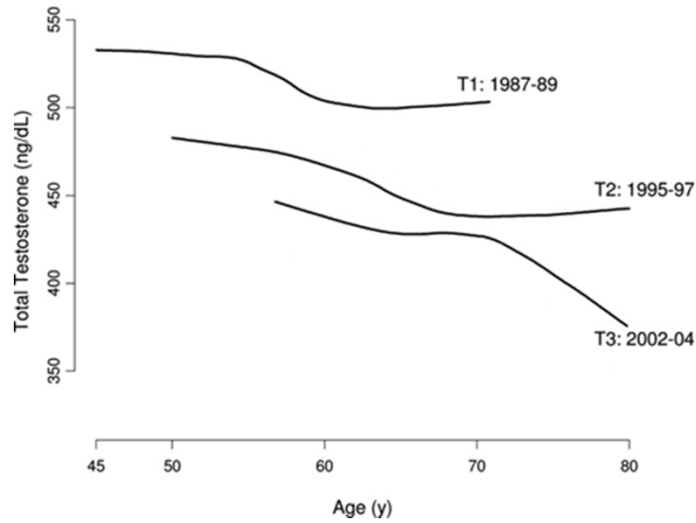
Disclosures

- I have received lecture honoraria from Merck Serono and Novo Nordisk Pharma, during the last 5 years
- Supported by
 - EU, Envir. Reprod. Health, Expored, Eden, DEER
 - Academy of Finland
 - Pediatric Research Foundation
 - Sigrid Juselius Foundation
 - Turku University Hospital and TYKS Foundation
 - Danish Council for Strategic Research
 - Novo Nordisk Foundation
 - NIH
 - JDRF
 - EFSD
 - Danish Innovation Fund

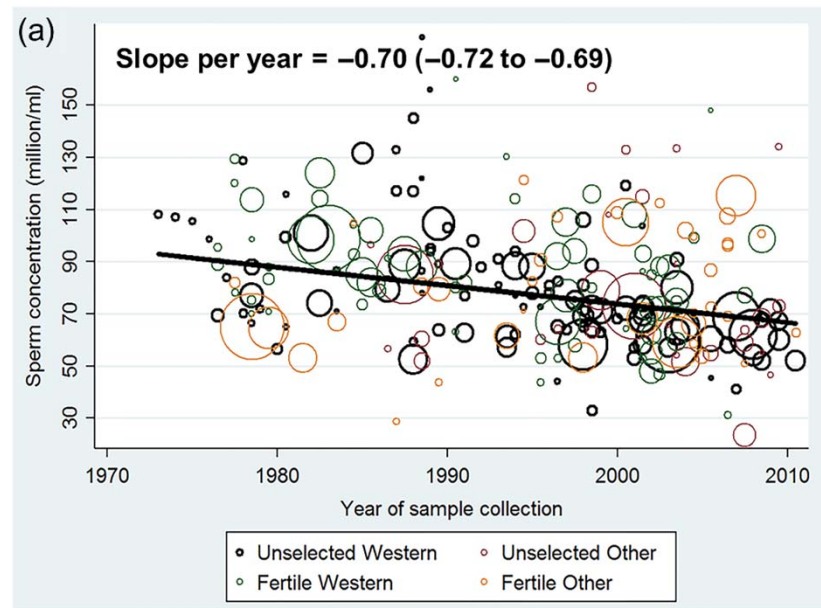
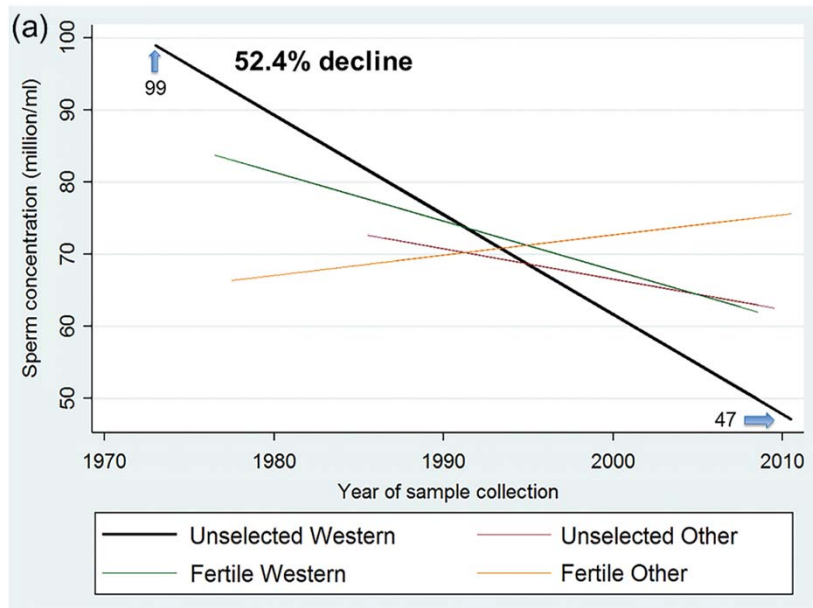
Fertility rates decline globally

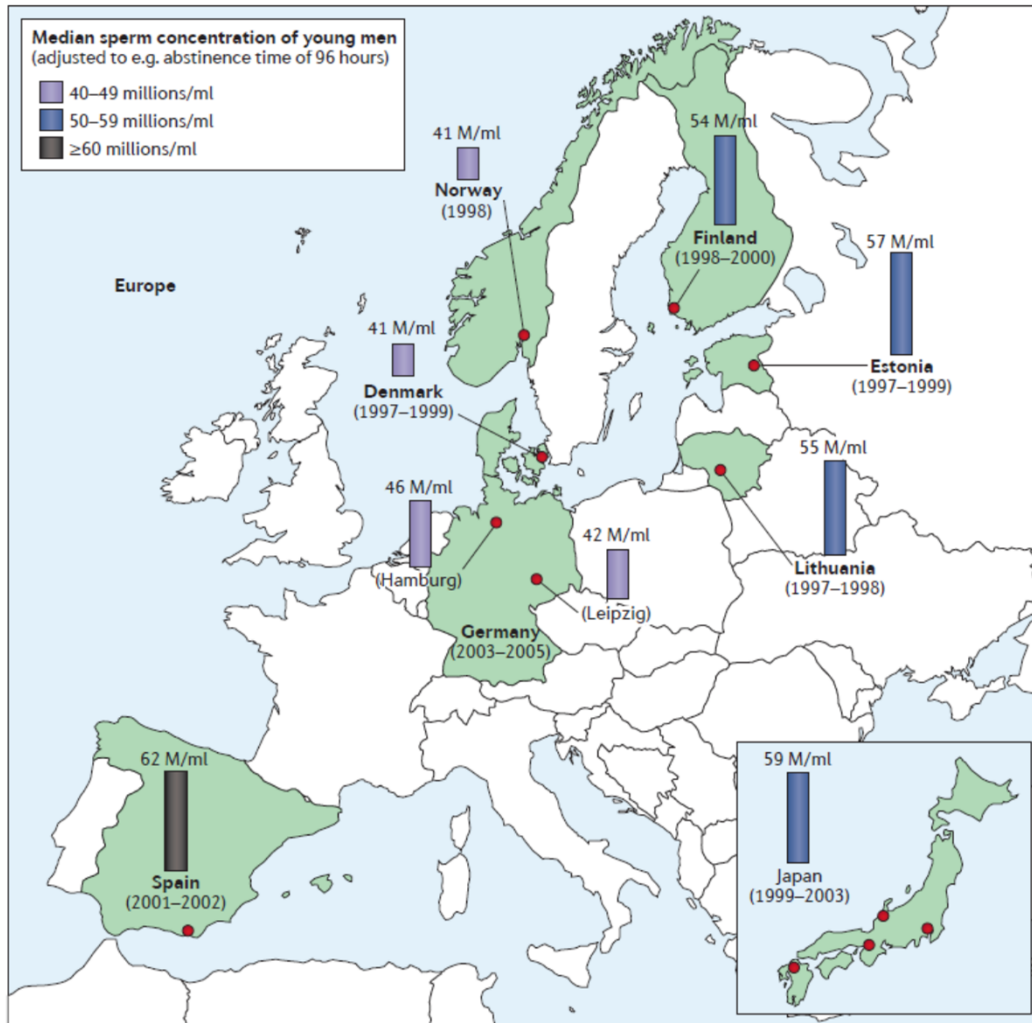


Testosterone levels have declined



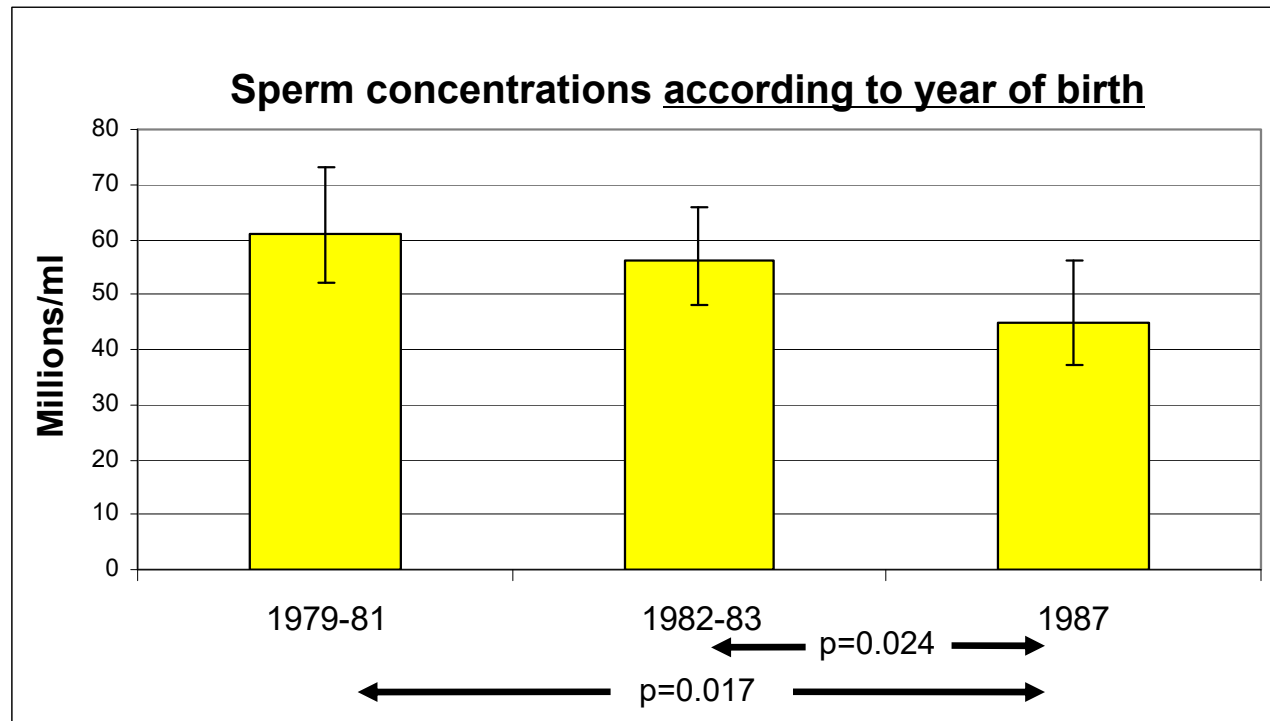
Sperm counts have declined





Virtanen, Jorgensen, Toppari
Semen quality in the 21st century
Nature Reviews Urology 2017

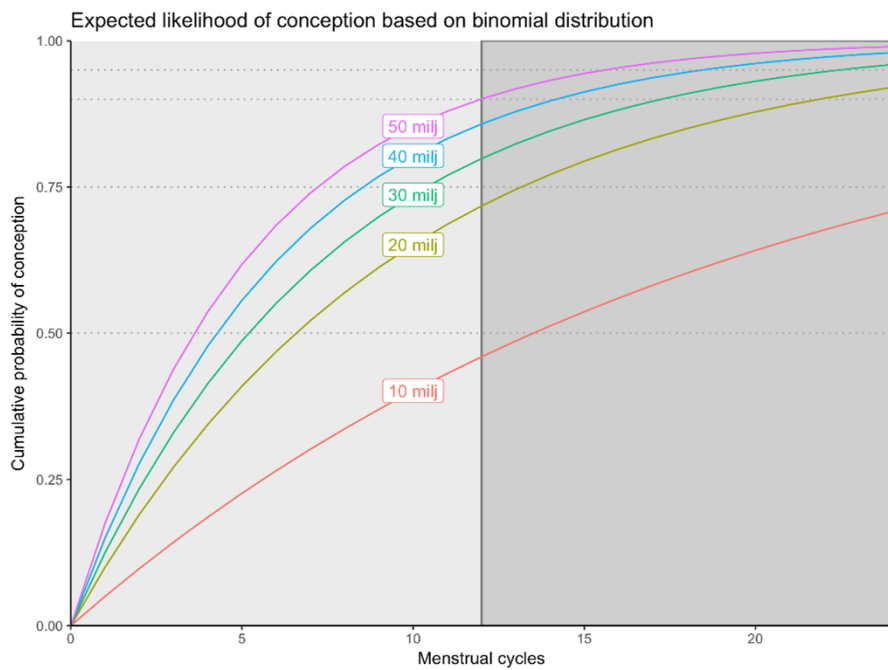
Young men from the Finnish general population



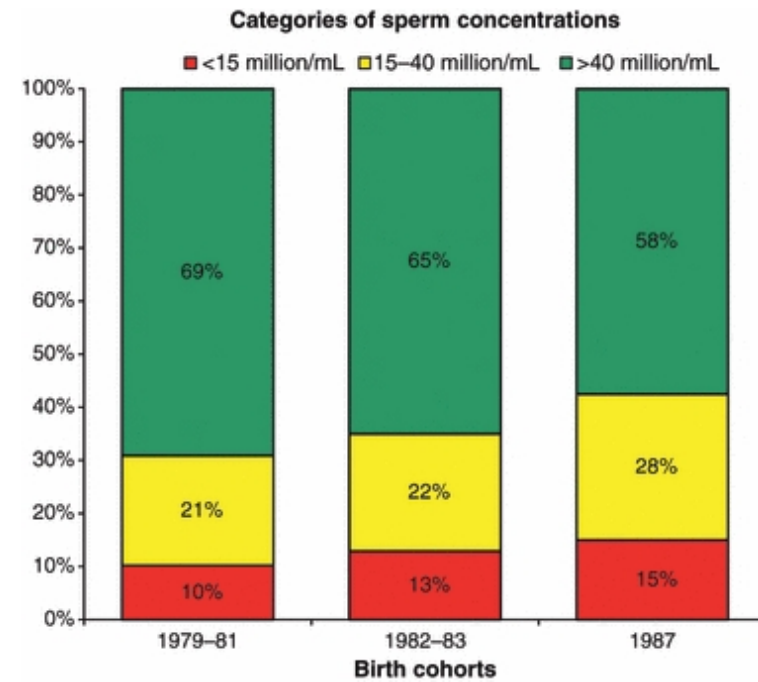
Adjusted for duration of ejaculation abstinence

Jørgensen et al 2011, IJA

Semen quality in Finland

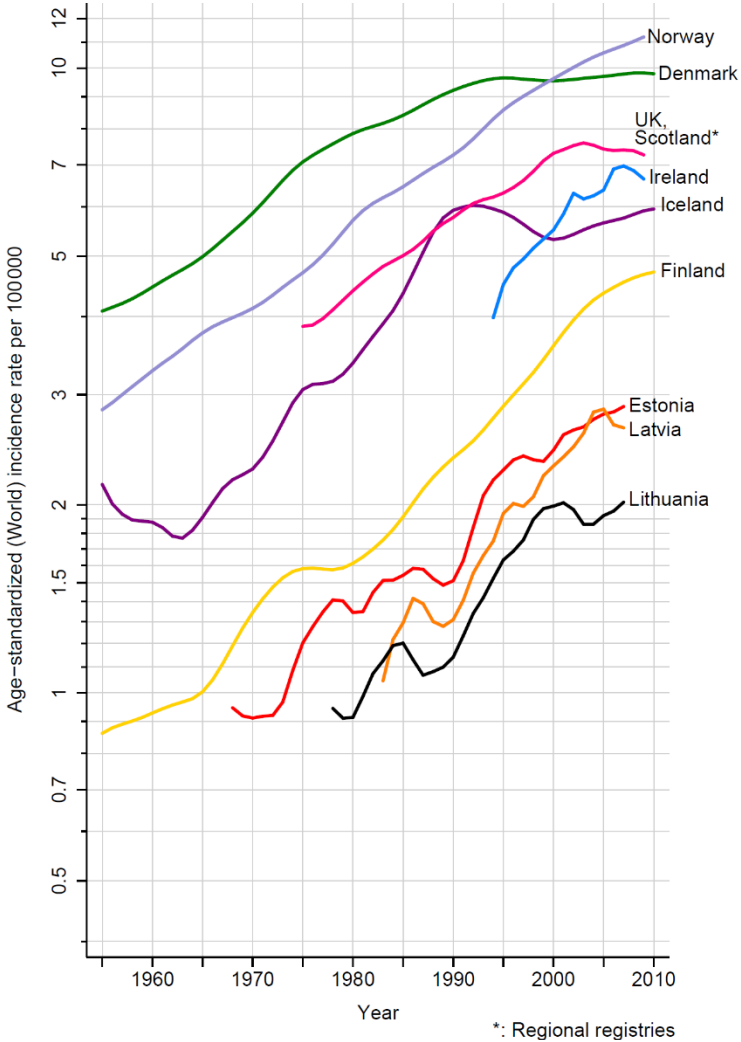


According to Bonde et al. 1998 Lancet



Jørgensen et al. 2011 Int J Androl

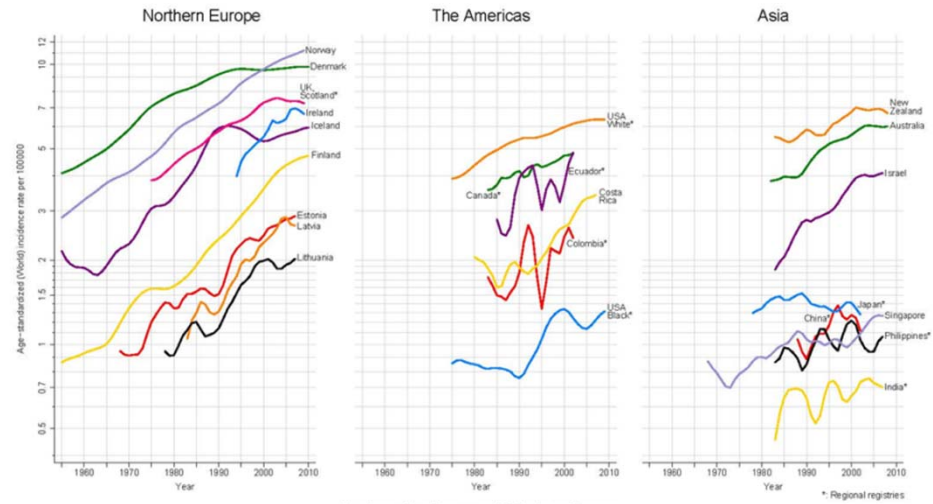
Trends in testicular germ cell cancer



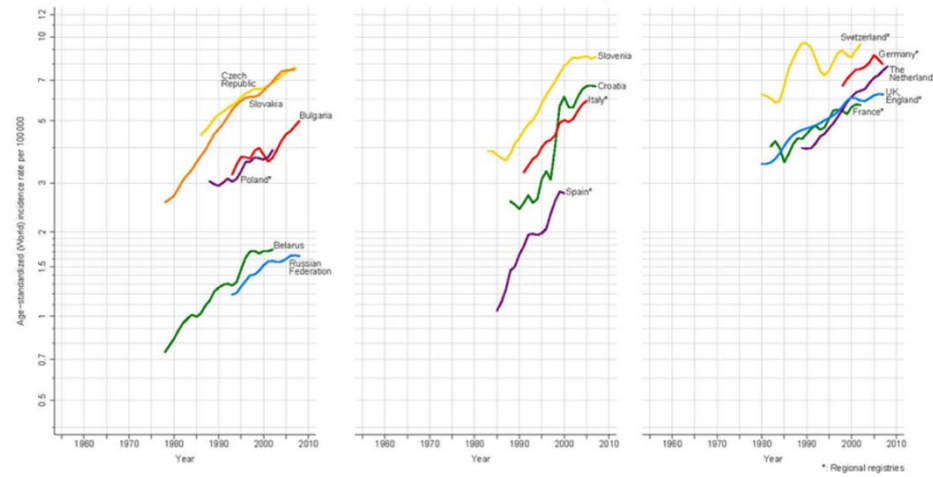
Northern Europe

Modified from Znaor et al, European Urology, 2014

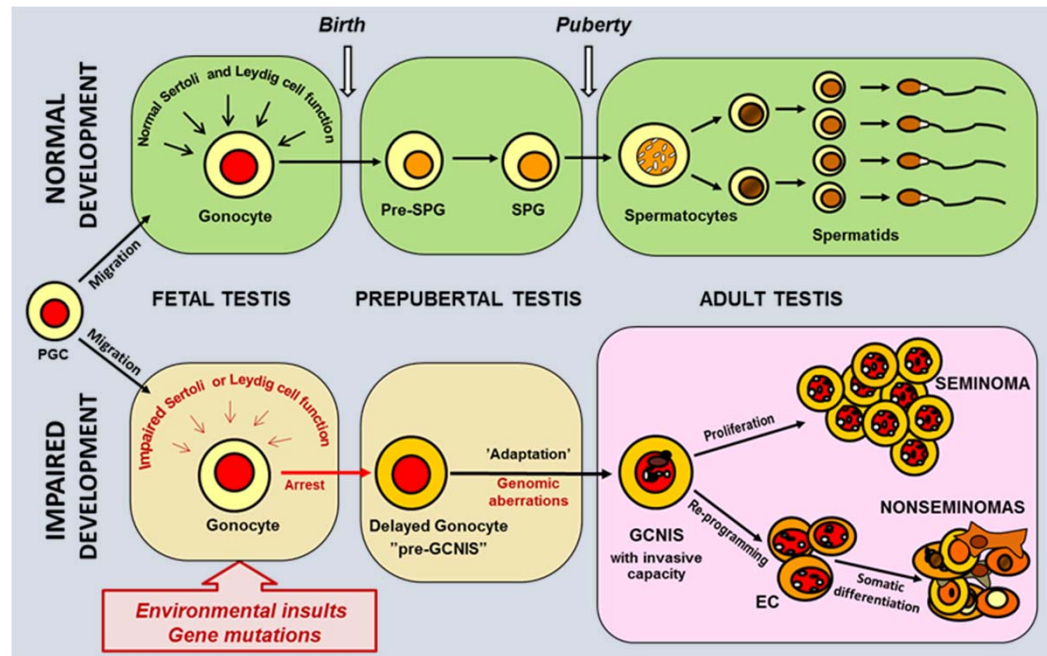
Testicular cancer: Trends in age-standardized (World) incidence rate per 100000



-----Eastern, Southern and Western Europe-----

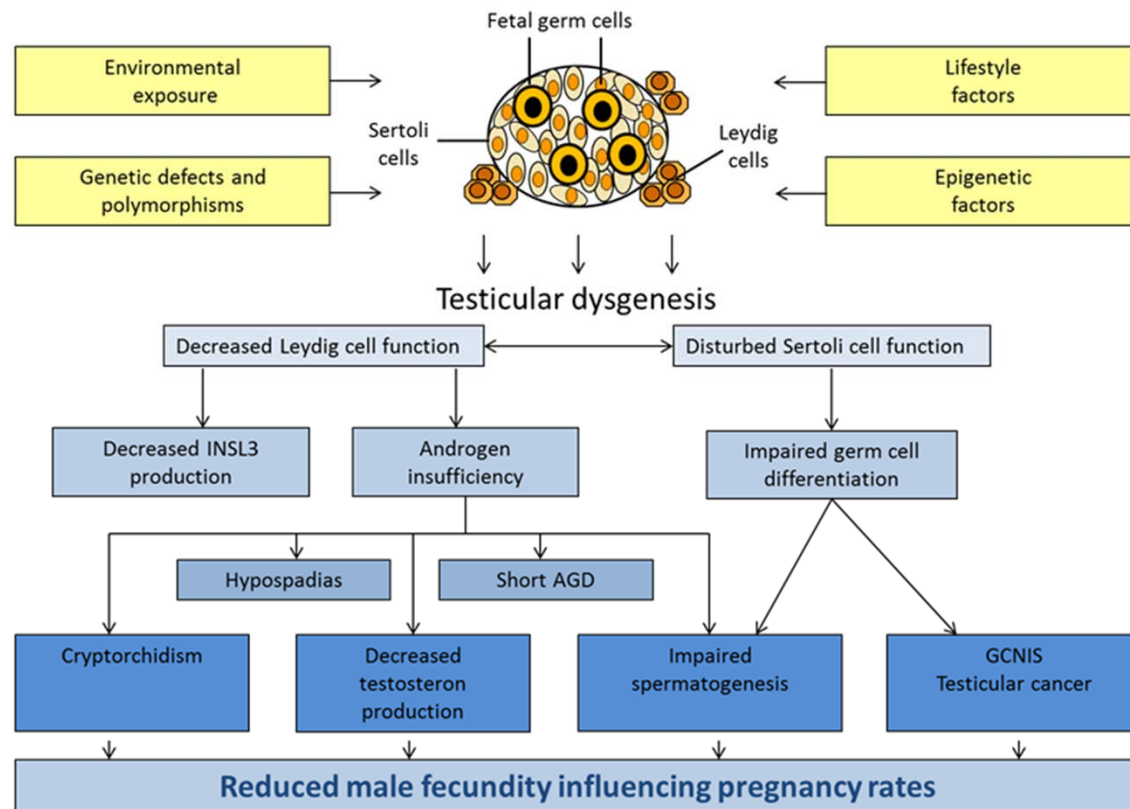


* Regional registres



Skakkebaek et al. Physiol Rev 2016

Fetal origin of adult testicular problems: The Testicular Dysgenesis Syndrome (TDS) Hypothesis



Skakkebaek et al. Physiol Rev 2016



4957 families
2562 boys

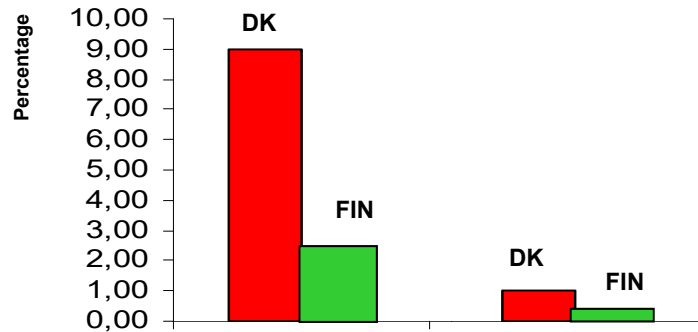


Danish-Finnish Birth Cohort Study

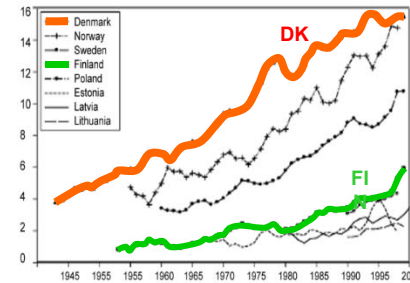
- All newborn boys of volunteer mothers (born 1997 -1999)
 - Questionnaire during pregnancy
 - Clinical examinations
 - All boys: At birth and at 3 months of age
 - Cases and controls: Also at 18 months of age
 - Biological samples
 - Blood sample at 10 - 15 gestational weeks
 - Placenta
 - Breast milk (4-8 weeks after birth)
 - Blood sample at 3 months of age

Testicular germ cell cancer: Association with other reproductive disorders

Prevalence of genital malformations in boys

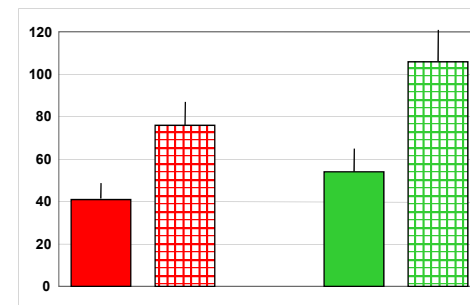


Boisen et al. Lancet 2004; JCEM 2005



Testis Cancer (*Richiardi et al. 2004*)

Sperm concentrations in DK and FIN



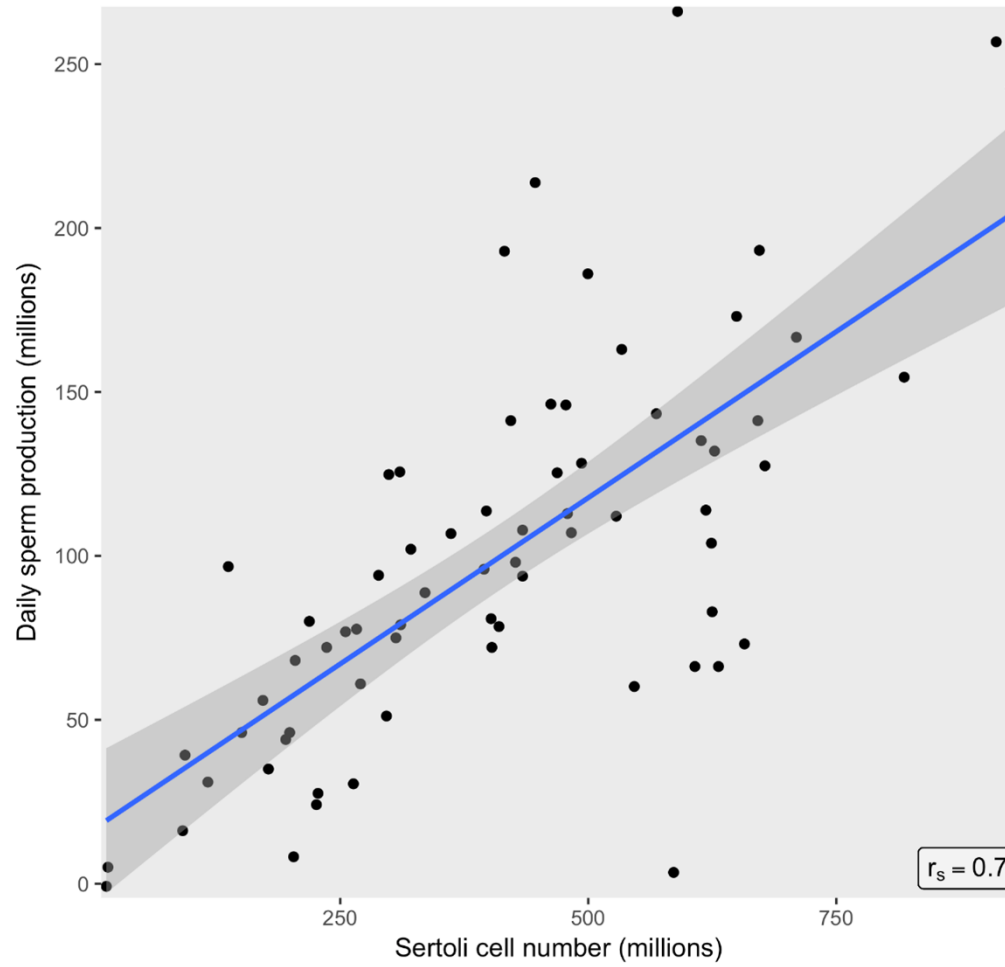
Denmark

Finland

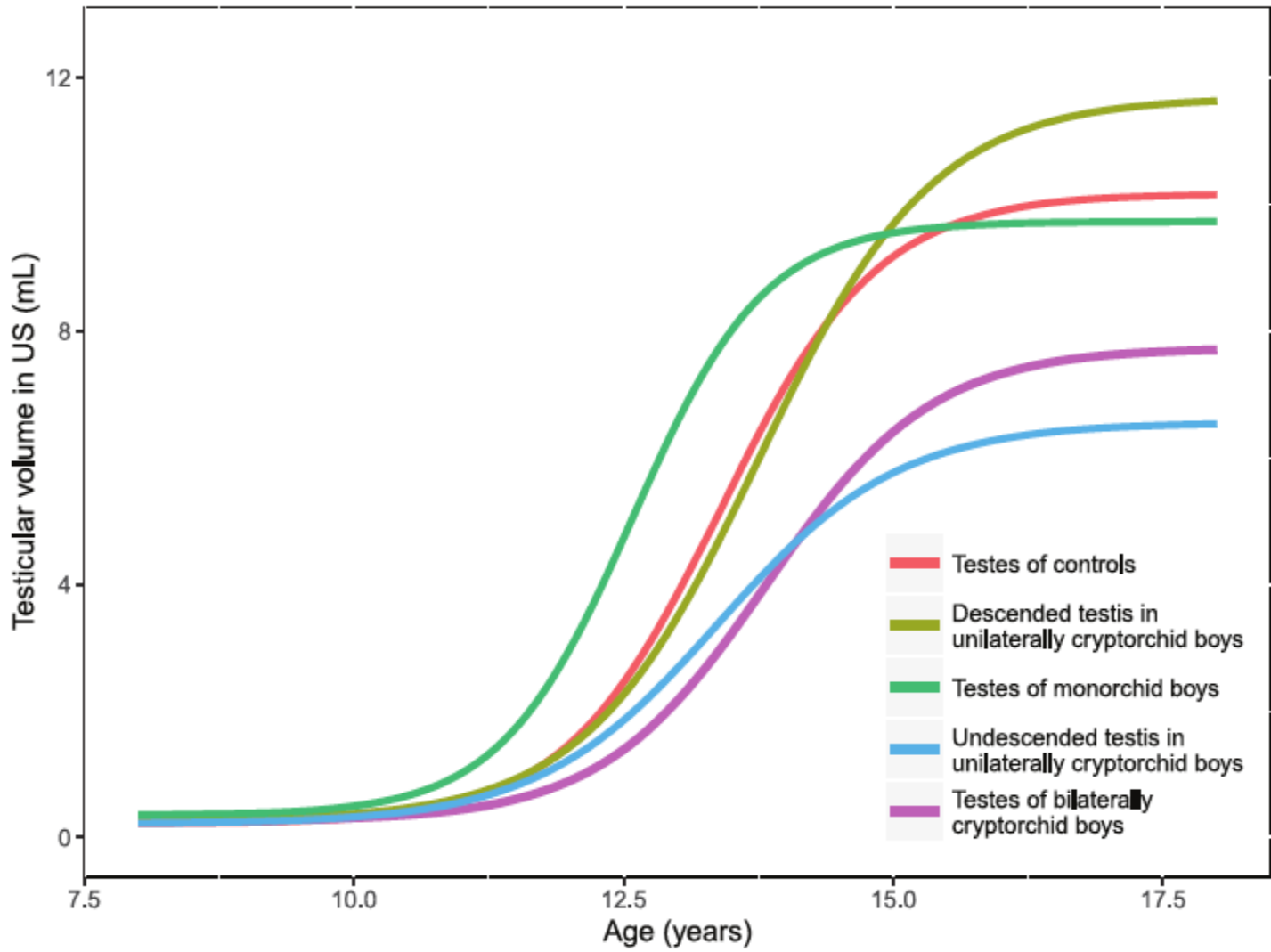
Young unselected men
 Fertile men

Jørgensen et al. Hum Reprod 2001; 2002

Sertoli cell number determines the sperm output



Johnson et al. 1984 Biol Reprod



Sadov
JCEM
2016

Exposure to anti-androgens

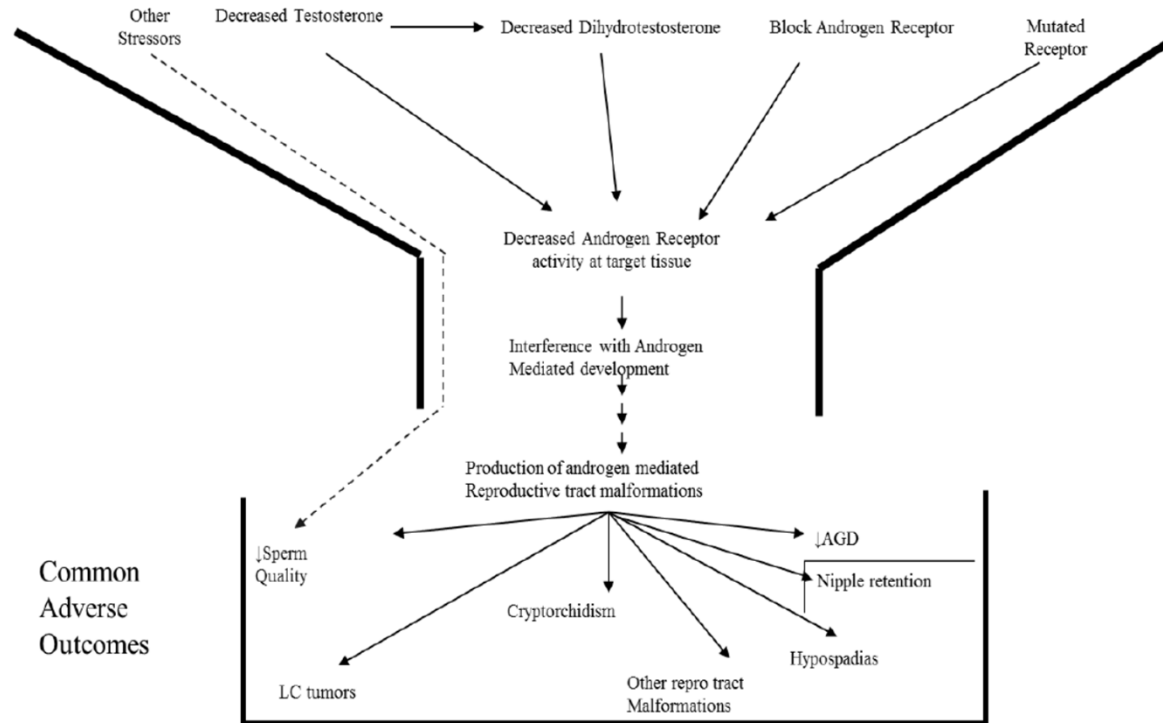
- Hypospadias
- Cryptorchidism
- Nipple retention
- Shortened anogenital distance
- Dysgenetic testicular structure
- Impaired spermatogenesis

Anti-androgens

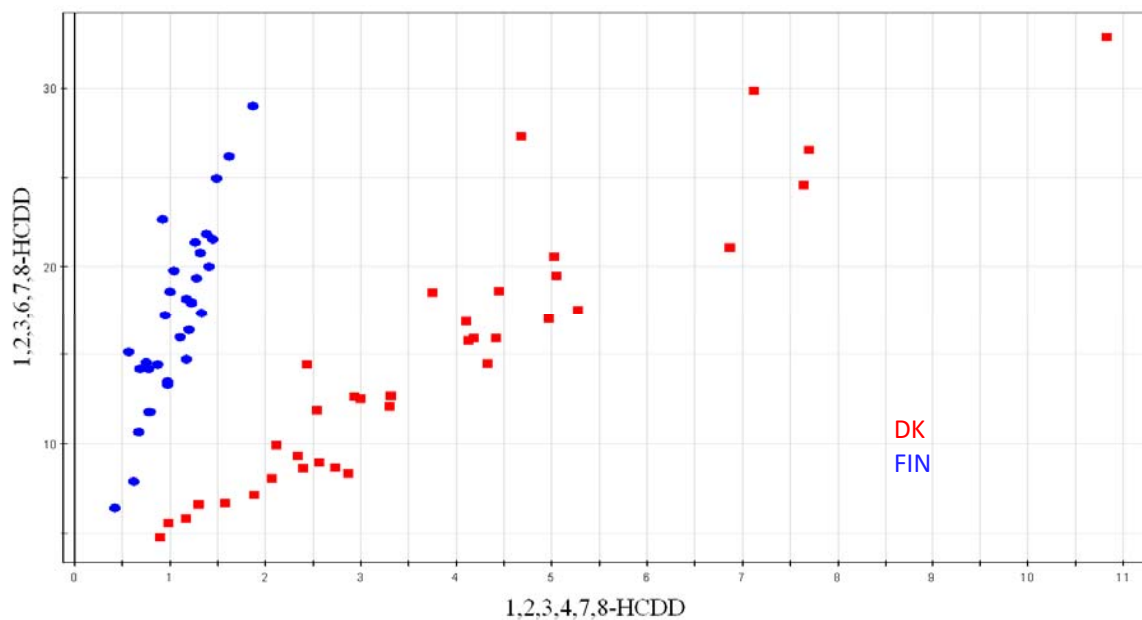
- Effects are additive
- Compounds at levels way below their NOAEL show effects
- E.g., vinclozolin, procymidone, prochloraz, p,p'DDE, and DBP together can cause hypospadias in 100 % of pups when 0% of pups show hypospadias after single chemical exposure

Phthalates and Cumulative Risk, NRC 2008

Fetal Androgen Insufficiency

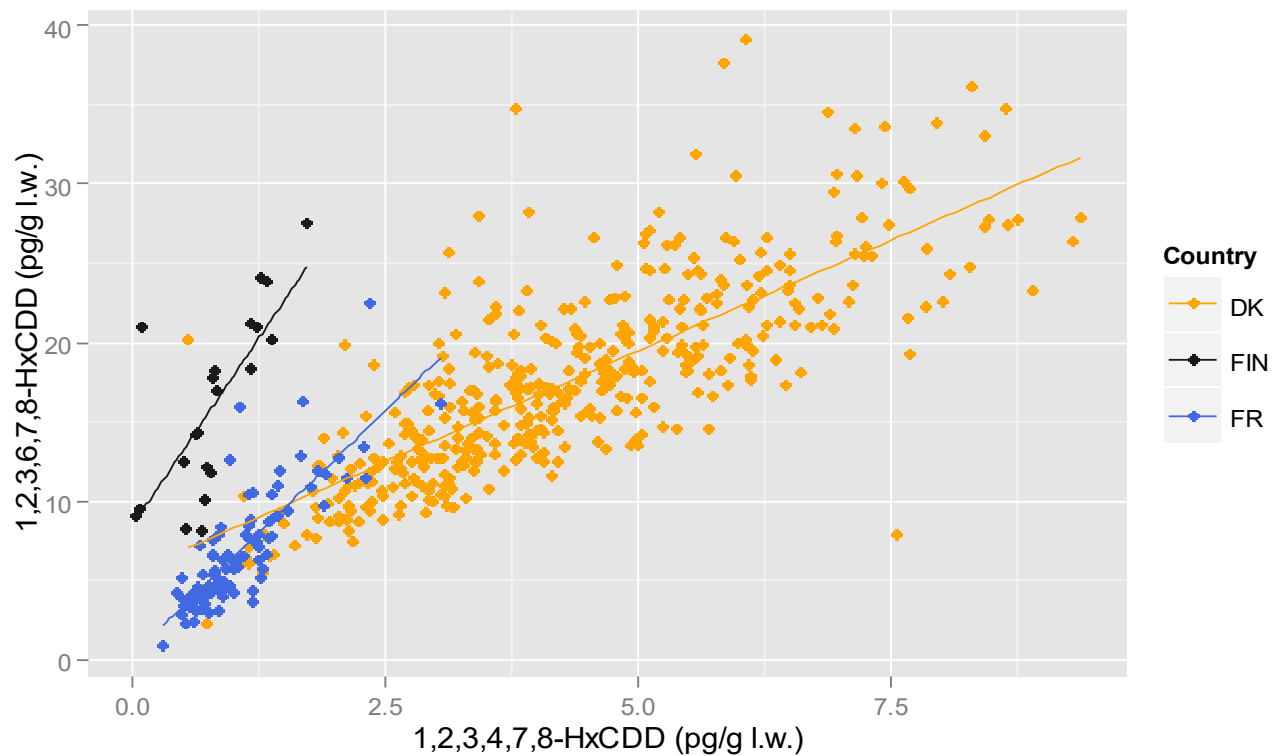


Distinct Chemical Signatures of Danish and Finnish Breast Milk: dioxins



Krysiak-Baltyn et al., Int. J. Androl. 2010

Validation of national chemical fingerprints of pollution



J.P. Antignac et al, **Country-specific chemical signatures of persistent organic pollutants (POPs) in breast milk of French, Danish and Finnish women** Environmental Pollution, Volume 218, 2016, 728–738

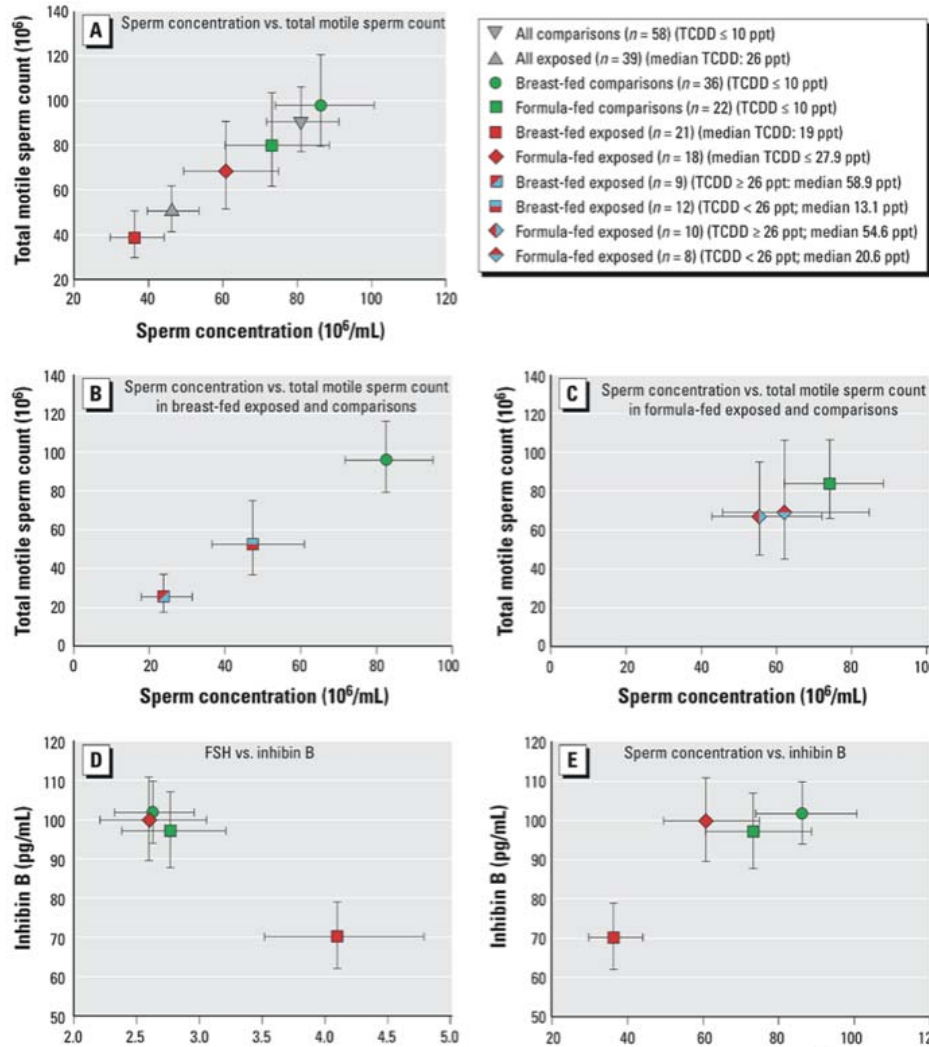
What to do?

- Get rid of persistent organic pollutants – Stockholm convention
- Identify anti-androgenic chemicals and regulate
 - QSAR
 - *in vitro*
 - *in vivo* (vinclozolin would not be identified without *in vivo* experiments)
 - Consider always mixture effects
- Protect development – young men and women, children
- Do not wait proof of human effects
- Avoid unknown risk if possible (would you drink unknown liquid from an unlabeled bottle?)

Thanks

- University of Turku
 - Helena Virtanen
 - Sergey Sadov
 - Jaakko Koskenniemi
 - Antti Perheentupa
 - Wiwat Rodprasert
 - Mirja Nurmio
 - Johanna Järvi
- Supported by
 - EU, Envir. Reprod. Health, Expored, Eden, DEER
 - Academy of Finland
 - Pediatric Research Foundation
 - Sigrid Juselius Foundation
 - Turku University Hospital
 - Danish Council for Strategic Research
 - Novo Nordisk Foundation
- Rigshospitalet, Copenhagen
 - Niels E. Skakkebæk
 - Katharina M. Main
 - Kirsten Boisen
 - Ida Norgil Damgaard
 - Niels Jorgensen
 - Marlene Dalgaard
 - Christine Wohlfahrt-Veje
 - Anders Juul
 - Anna-Maria Andersson
 - Ewa Rajpert-De Meyts
- Inst. Health and Welfare, Kuopio
 - Hannu Kiviranta
 - Terttu Vartiainen
- GSF, Munich
 - Heqing Shen
 - Karl-Werner Schram

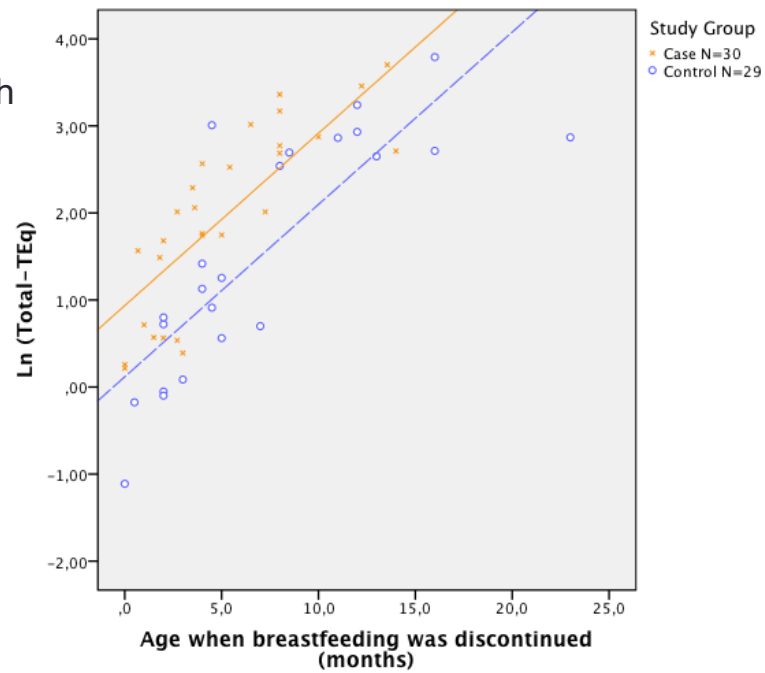
Dioxin exposure pre- AND post-natally affects sperm numbers



Mocarelli et al EHP
119:713-718 2011

PCBs & Dioxins

Koskenniemi et al. Env Health
2015



Prenatal

Breast milk

Diet

Main et al.,
EHP 2007

Polybrominated flame retardants

