

# Hvilke stoffer er hormonforstyrrende? Hvad betyder de for vækst/fertilitet/sygdomme?

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## Formål

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**At vise data, der kan overbevise jer om, at**

- ▶ Den føtale udviklingsperiode er et følsomt vindue for senere udvikling af metaboliske sygdomme og sygdomme i reproduktionsorganer
- ▶ Udsættelse for stoffer med hormonforstyrrende virkning i denne periode kan spille en vigtig rolle for udviklingen af disse sygdomme

## Effektmål

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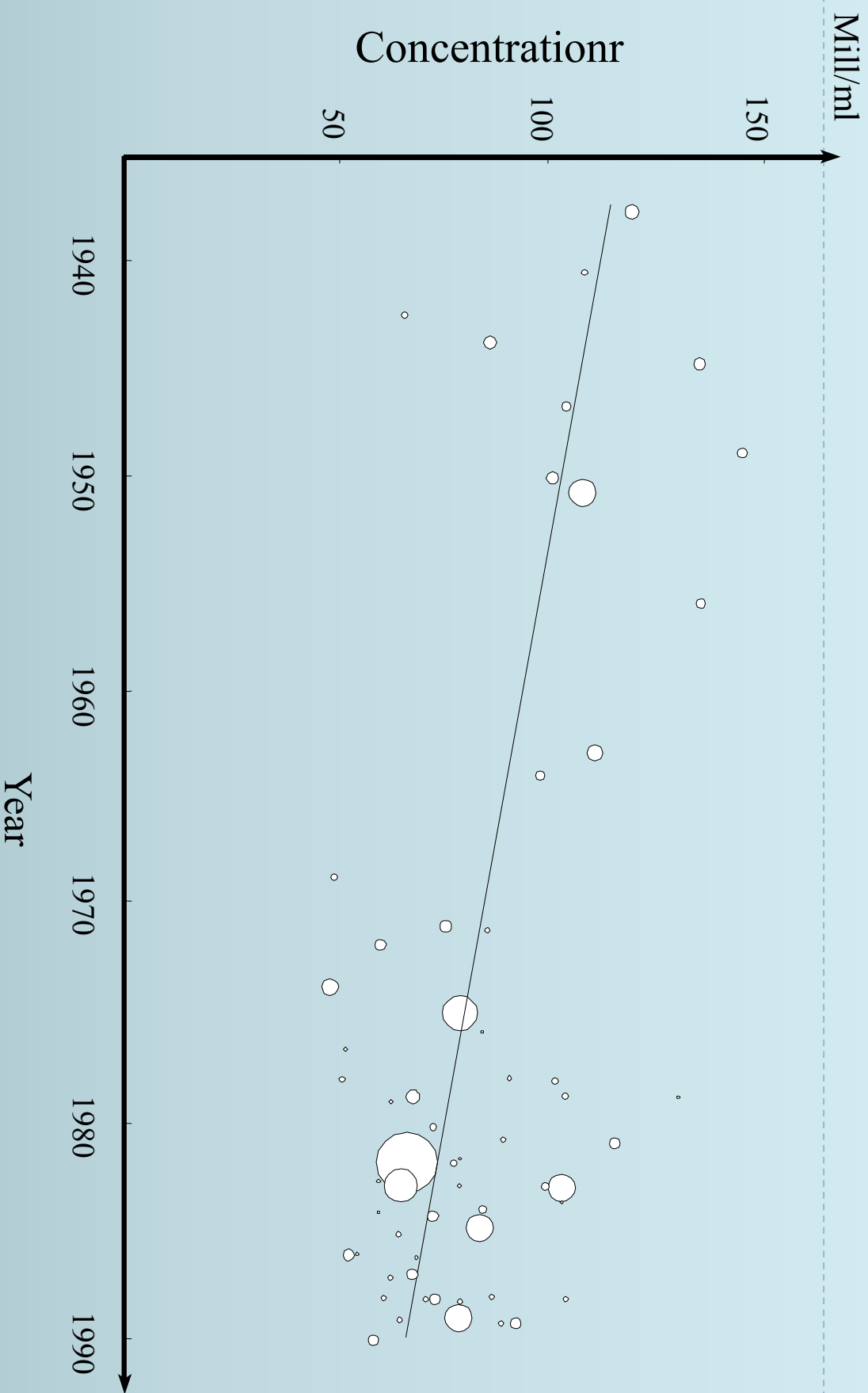
- ▶ **Sædkvalitet**
- ▶ Testicular dysgenesis syndrome
- ▶ Hormonforstyrrende stoffer
- ▶ Fedme

# Sædkvalitet

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- ▶ Volume
- ▶ Koncentration (total sperm count)
- ▶ Morfologi
- ▶ Motilitet

# Fald i sædkvalitet?



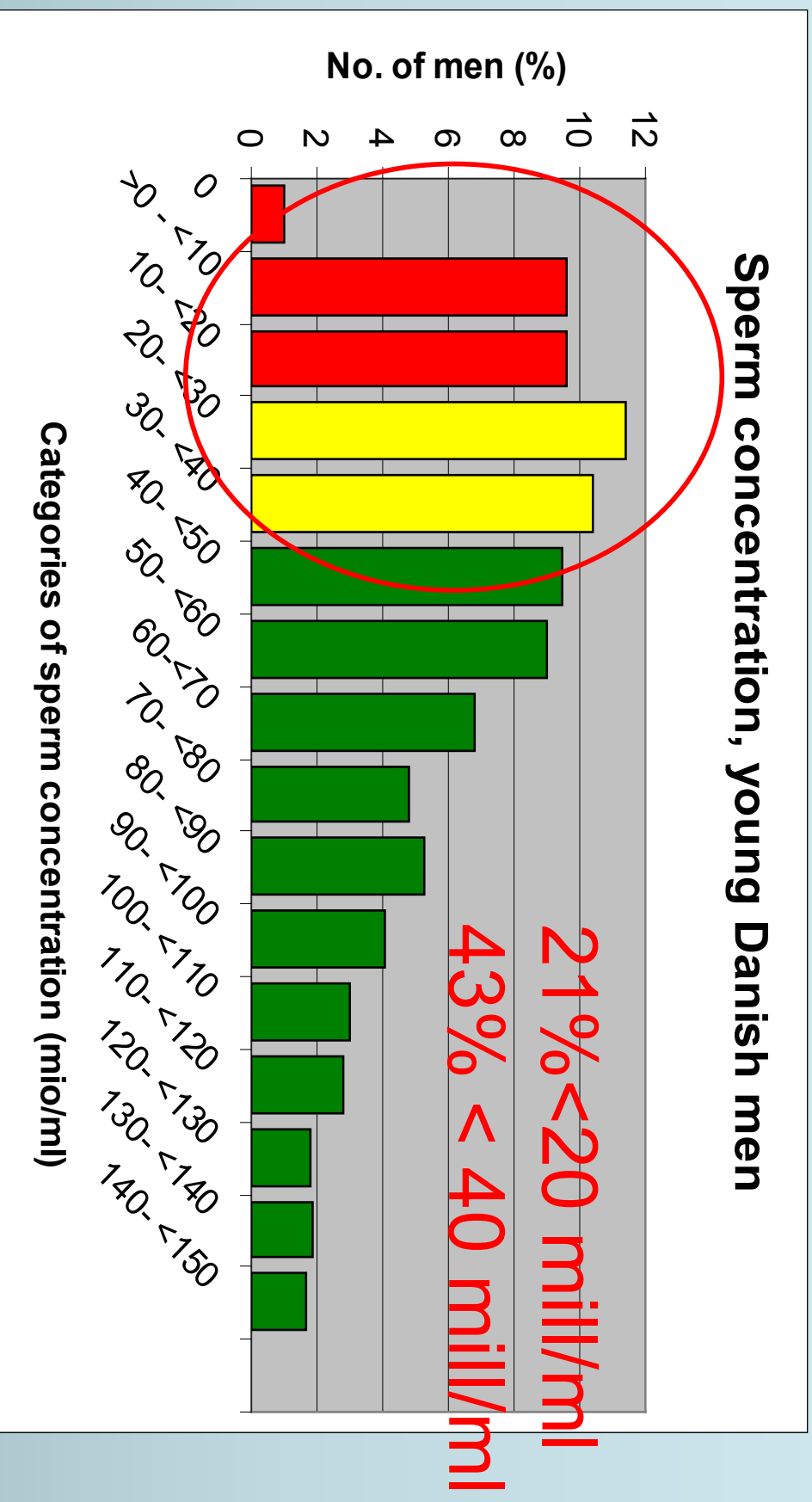
## Problemer ved disse studier

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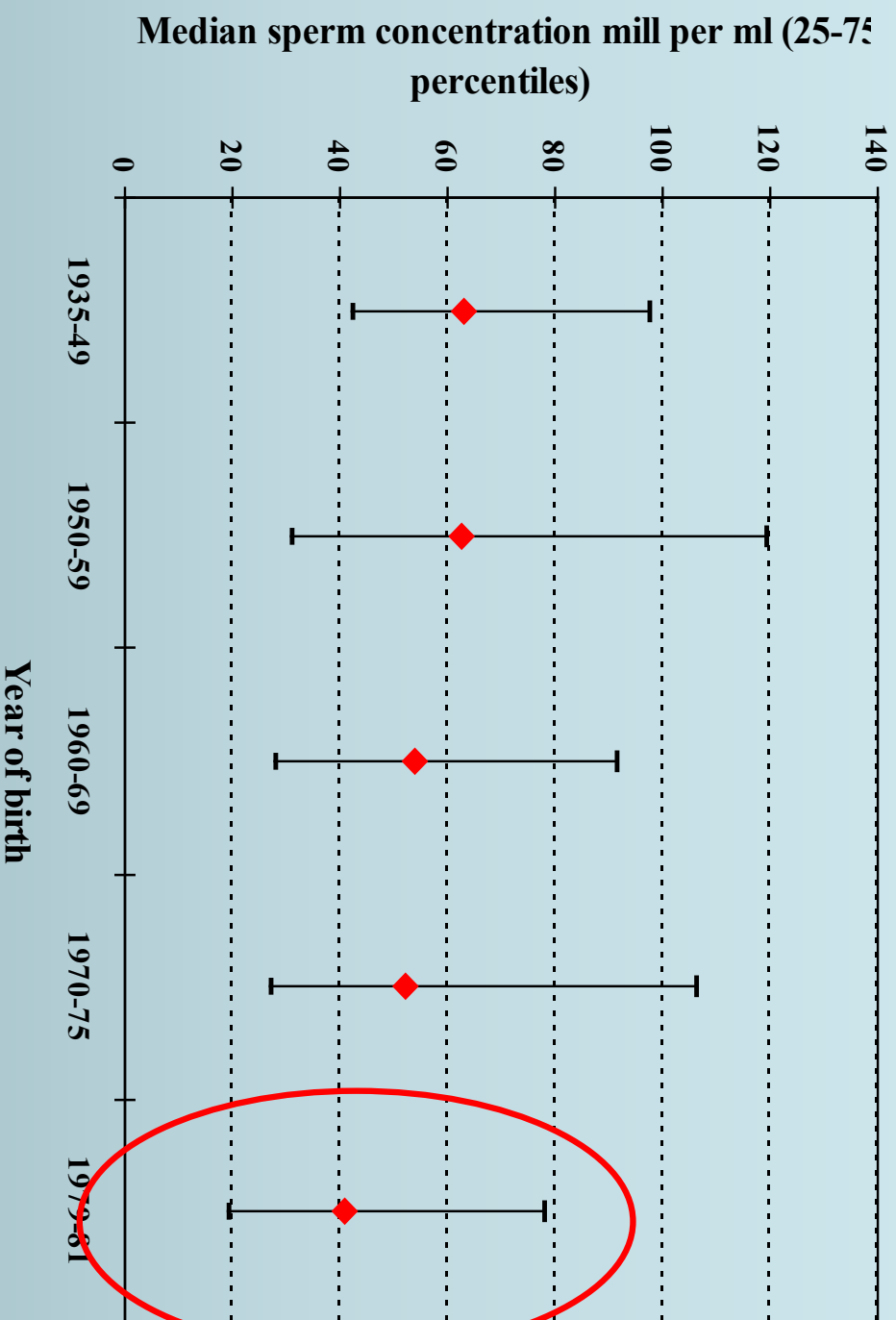
- ▶ Deltagerprocent lav
- ▶ Abstinens tid
- ▶ Betydelig biologisk variation (inter- og intraperson)
- ▶ Tid mellem eksponering og prøveopsamling
- ▶ Standardisering af metoder til vurdering af sædkvalitet (volumen, koncentration, morfologi, bevægelighed)

# Værnepligtige

## Sperm concentration, young Danish men



# Fødselskohorteffekter i sædkvalitet



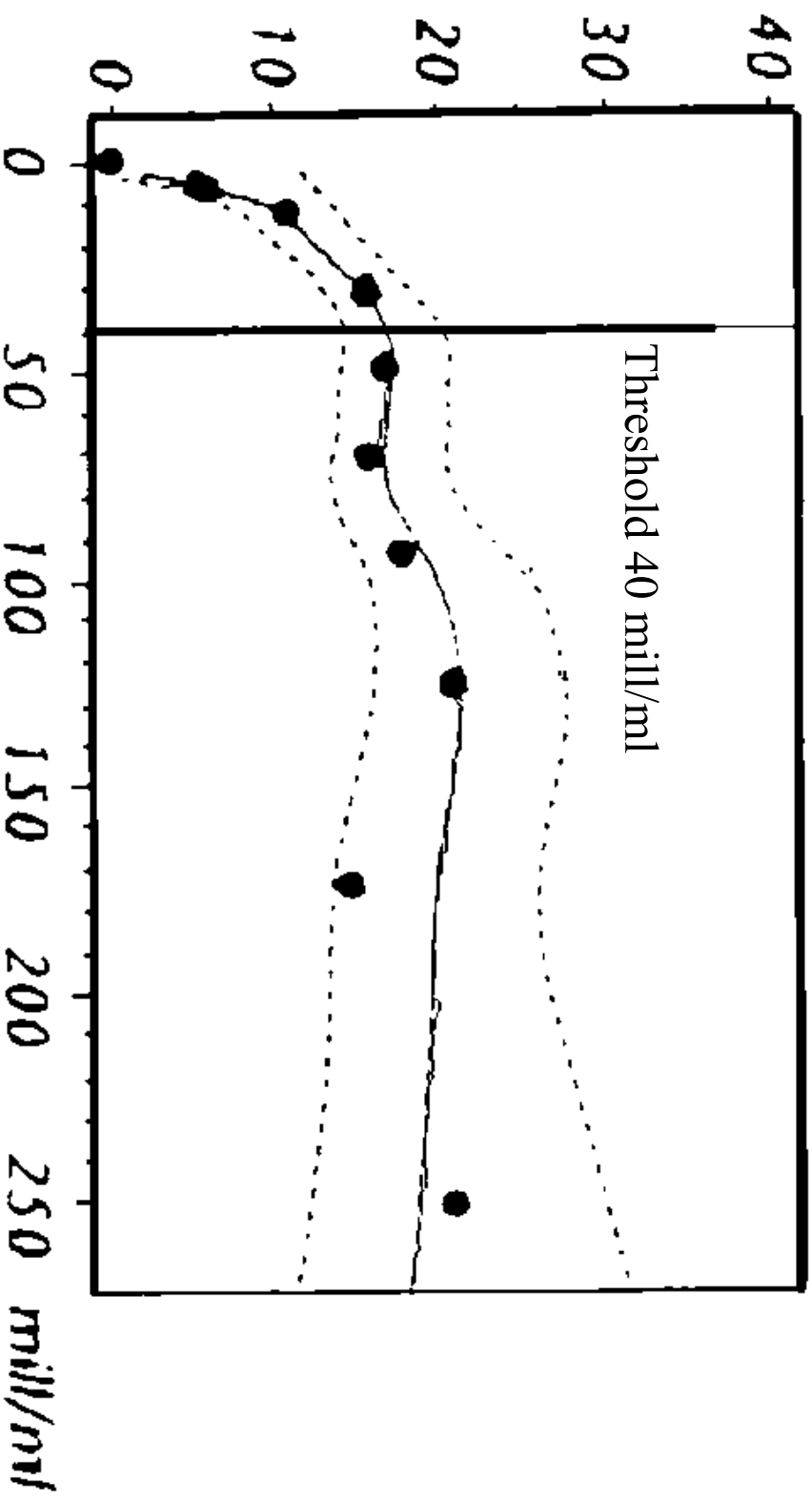
*Bonde et al. Scand J Work Environ Health. 1998.*



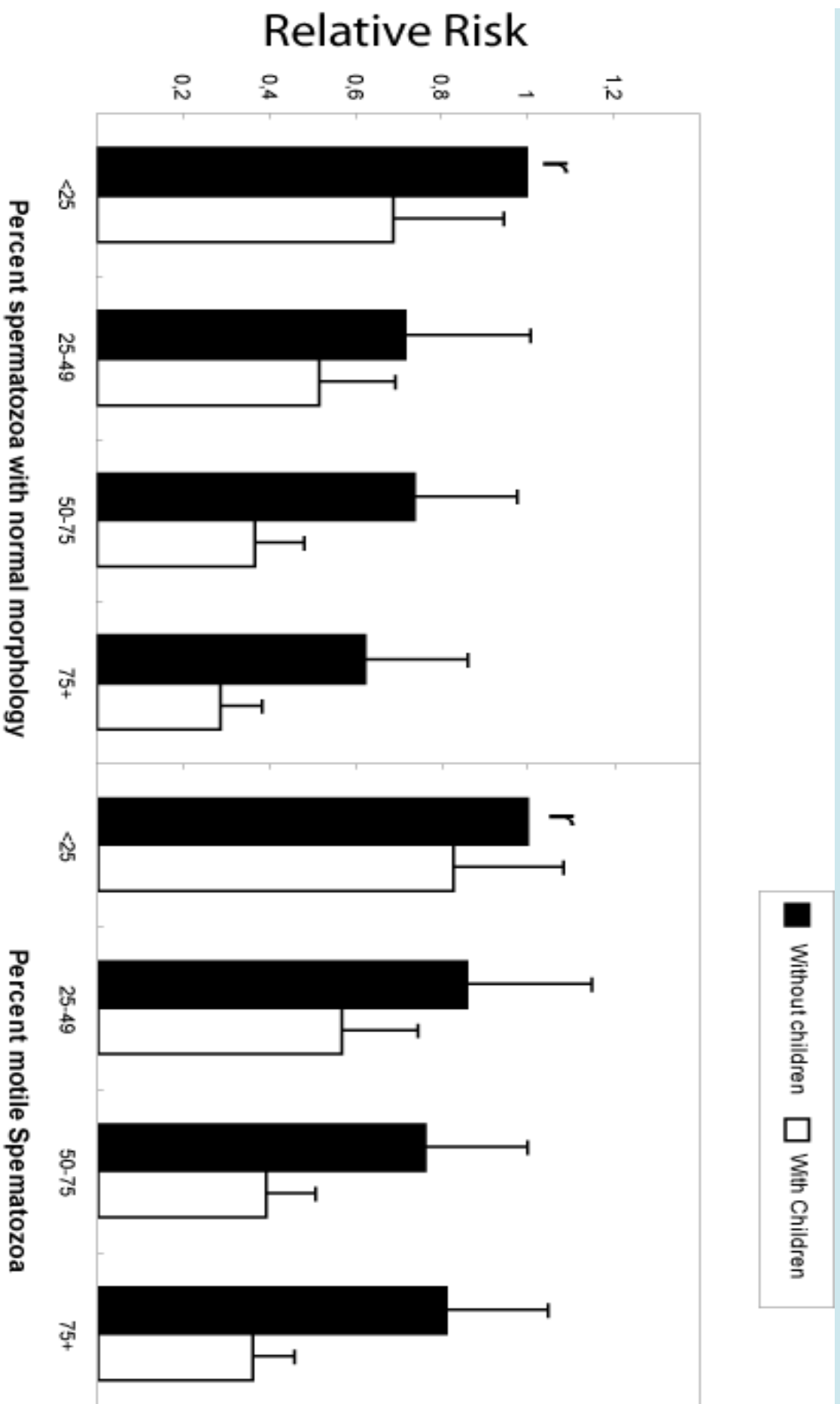
Skal vi være bekymrede og faldet i sædkvalitet?

”..... Vi har jo kun brug for en sædcelle til befrugtning.....”

# Sandsynlighed for graviditet i en cyklus sammenholdt med sædkoncentration



# Sædkvalitet og mortalitet

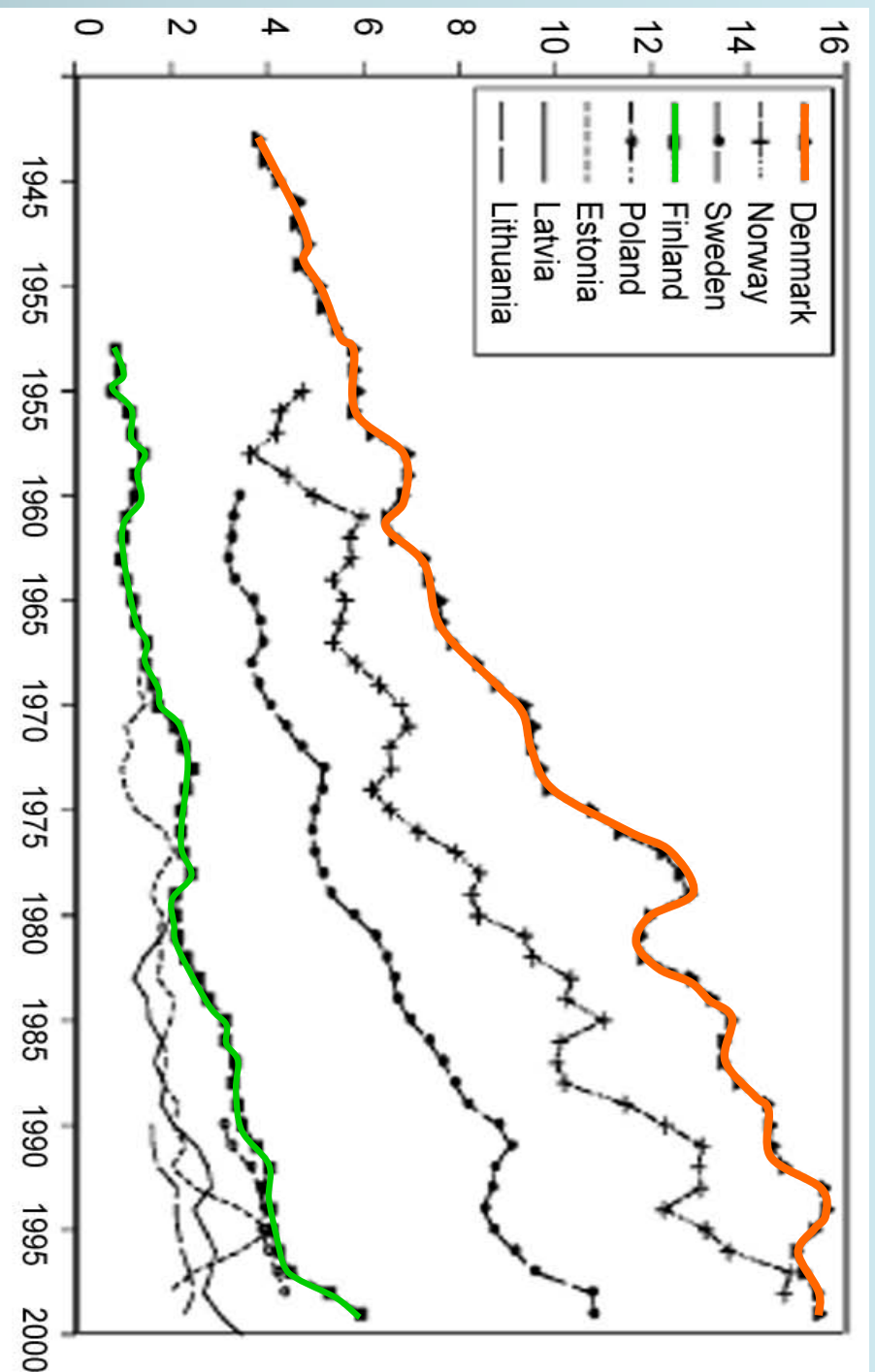


## Effektmål

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- ▶ Sædkvalitet
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- ▶ Fedme

# Trends i testis cancer incidence



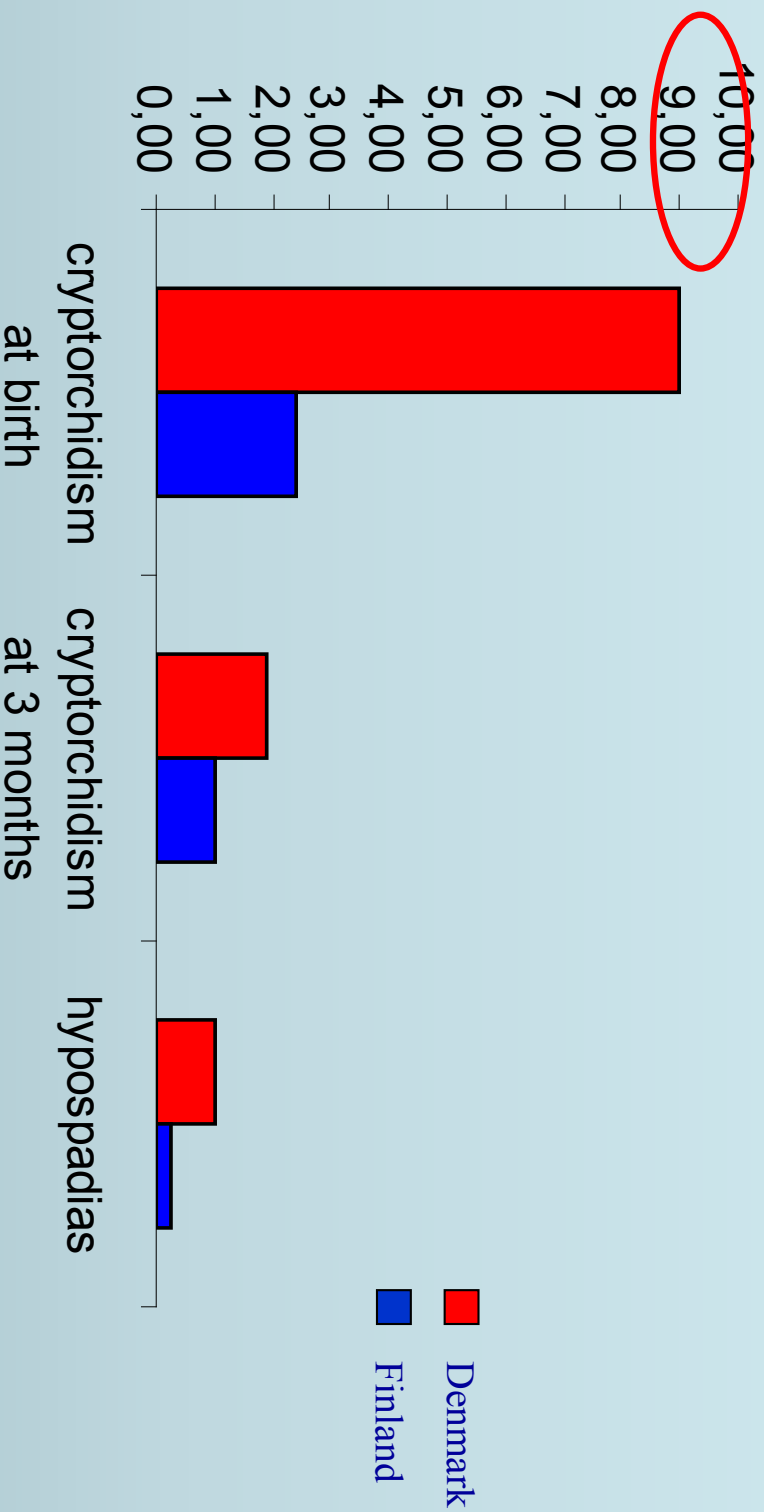
## Testis cancer hos immigranter

Relativ risiko (RR) for testiscancer ifht danske mænd

- ▶ 1. generationsindvandrere  
RR = 0.37 (0.31-0.43)
- ▶ 2. generations indvandrere  
RR = 0.88 (0.51-1.53)

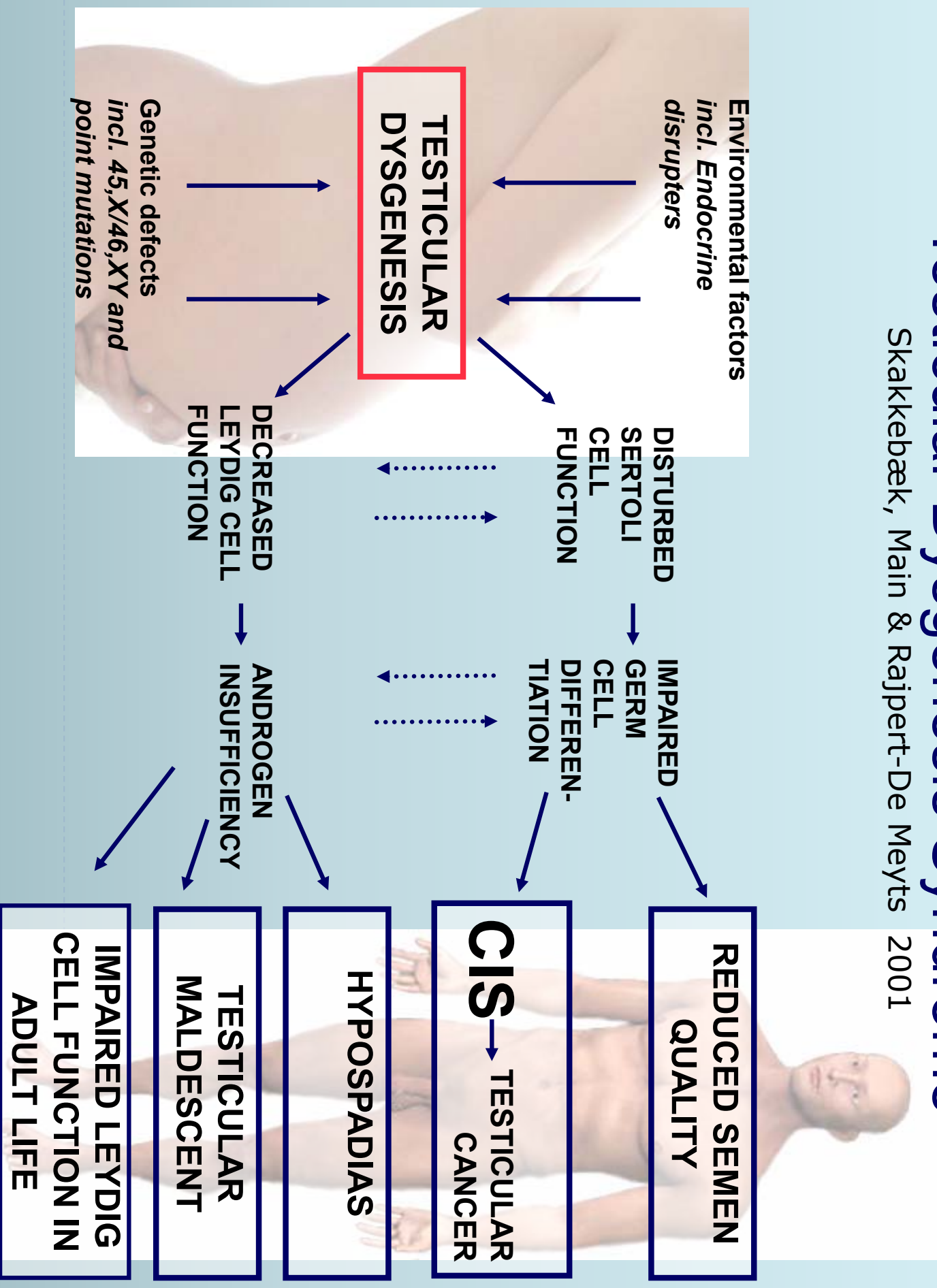
# Forskelle i anomaliteter i kønsorganer hos danske og finske drenge

- Standardized protocols!!



# Testicular Dysgenesis Syndrome

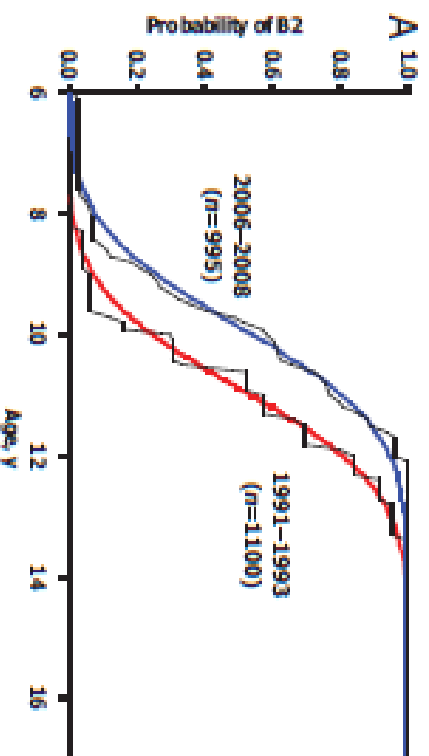
Skakkebaek, Main & Rajpert-De Meyts 2001



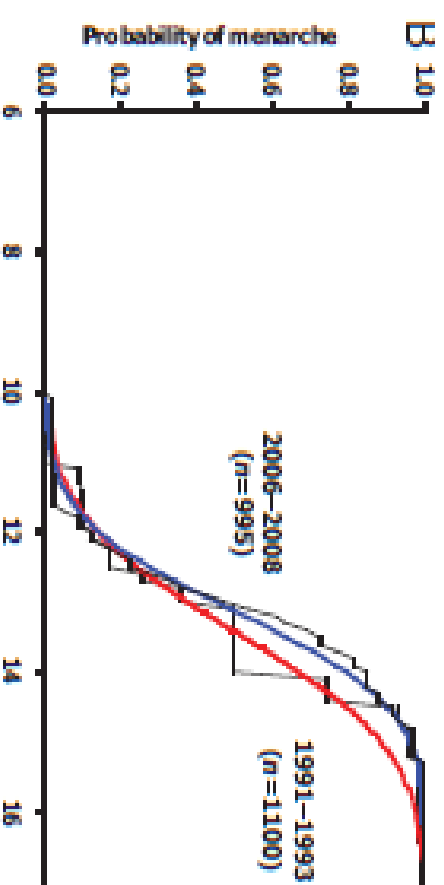


# Trends i kvindelig reproduktion?

- ▶ Svært at måle, da det kræver mere invasive studier
- ▶ PCOS, endometriose og aborter er måske stigende men måske diagnose bias
- ▶ Brystkræftincidens stigende
- ▶ Pubertet og brystudvikling tidligere



Breast development



Menarche

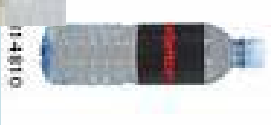
## Effektmål

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- ▶ Testicular dysgenesis syndrome
- ▶ **Hormonforstyrrende stoffer**
- ▶ Fedme

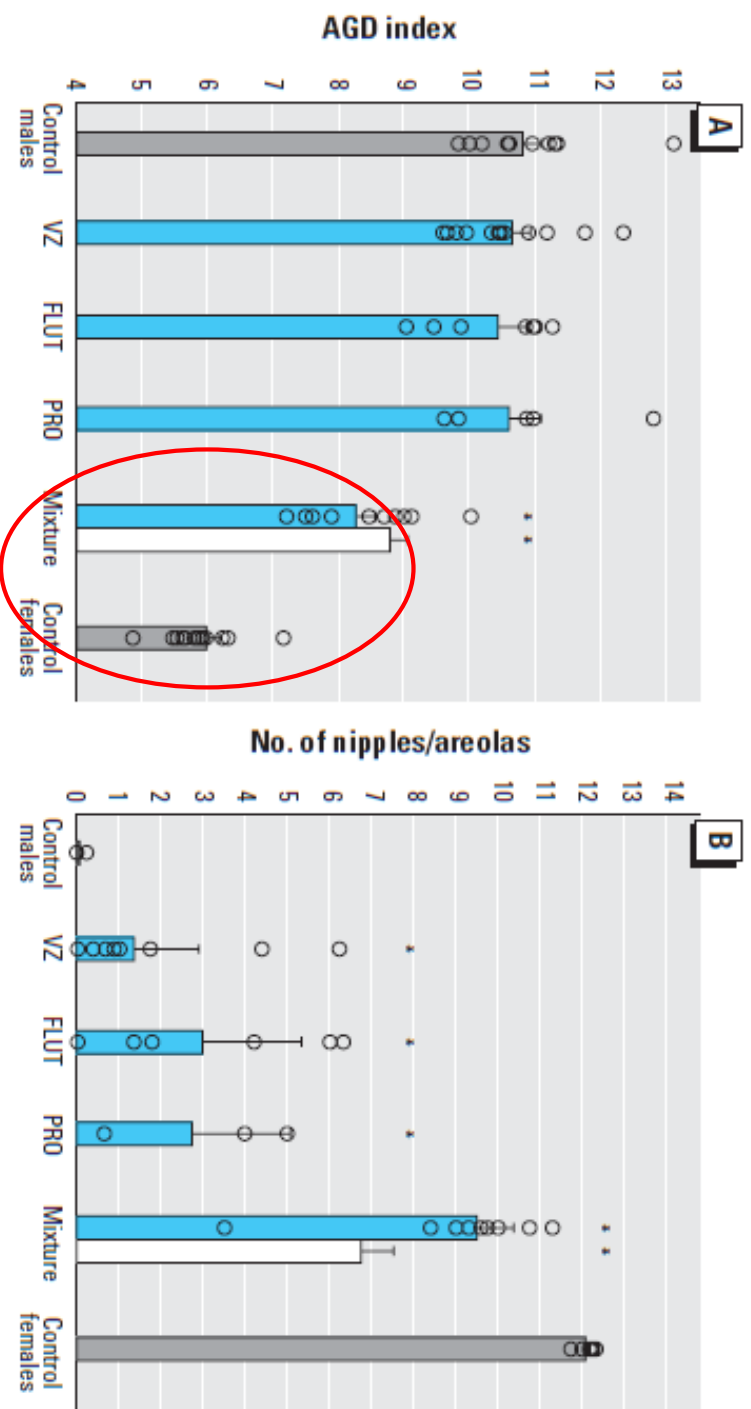
# Hormonforstyrrende stoffer

Udsættelse for miljøkemikalier med hormonforstyrrende virkning især som foster kan medføre senere problemer med den mandlige forplantningsevne



- ◆ Polychlorerede biphenyler (PCBer)
- ◆ DDT/DDE
- ◆ Perfluorinerede oktanolforbindelser
- ◆ Phthalater
- ◆ Bisphenol A
- ◆ **Mixture effects!**

# Mixture effekter



**Figure 3.** Mixture effects on AGD (A) and NR (B) at low doses of individual mixture components. Results shown are group mean  $\pm$  95% confidence belt for control males and females (gray), individual doses of 24.5 mg/kg vinclozolin (VZ), 0.77 mg/kg flutamide (FLUT), and 14.1 mg/kg prycymidone (PRO) (blue), the combined mixture dose of 39.37 mg/kg (blue), and the predicted mixture effect (white). Open circles represent litter means.

\*  $p < 0.05$  compared to control.

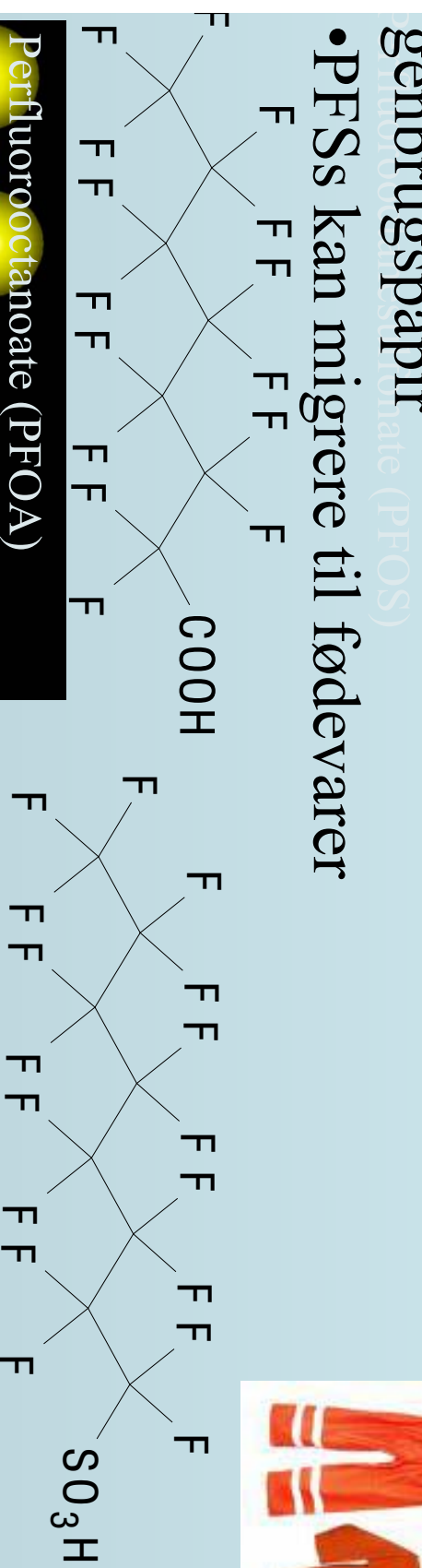
## Udsættelse for DES som foster øger risiko for:

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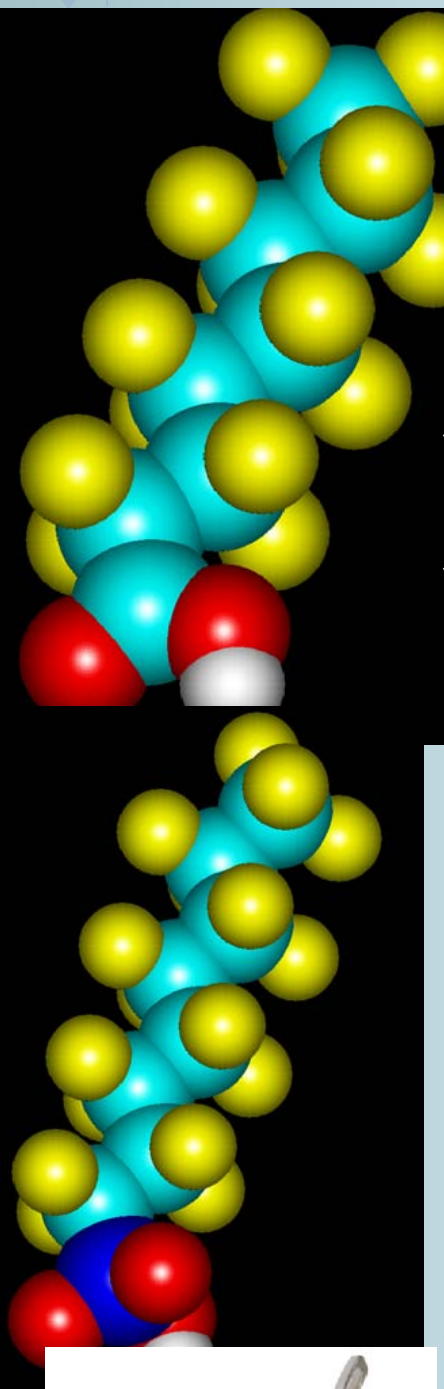
- ▶ Misdannelser i mandlige kønsorganer
- ▶ Misdannelser i kvindelige kønsorganer
- ▶ Nedsat sædkvalitet?
- ▶ Testis cencer?
- ▶ Nedsat kvindelig fertilitet
- ▶ Tidlig menopause
- ▶ Uregelmæssig menstruation
- ▶ Tidlig menopause
- ▶ Nedsat fertilitet hos børnebørn (piger)

# Perfluorinated compounds

- PFSs er vand og smuds afvisende
- Anvendt i stigende grad til genbrugspapir
- PFSs kan migrere til fødevarer

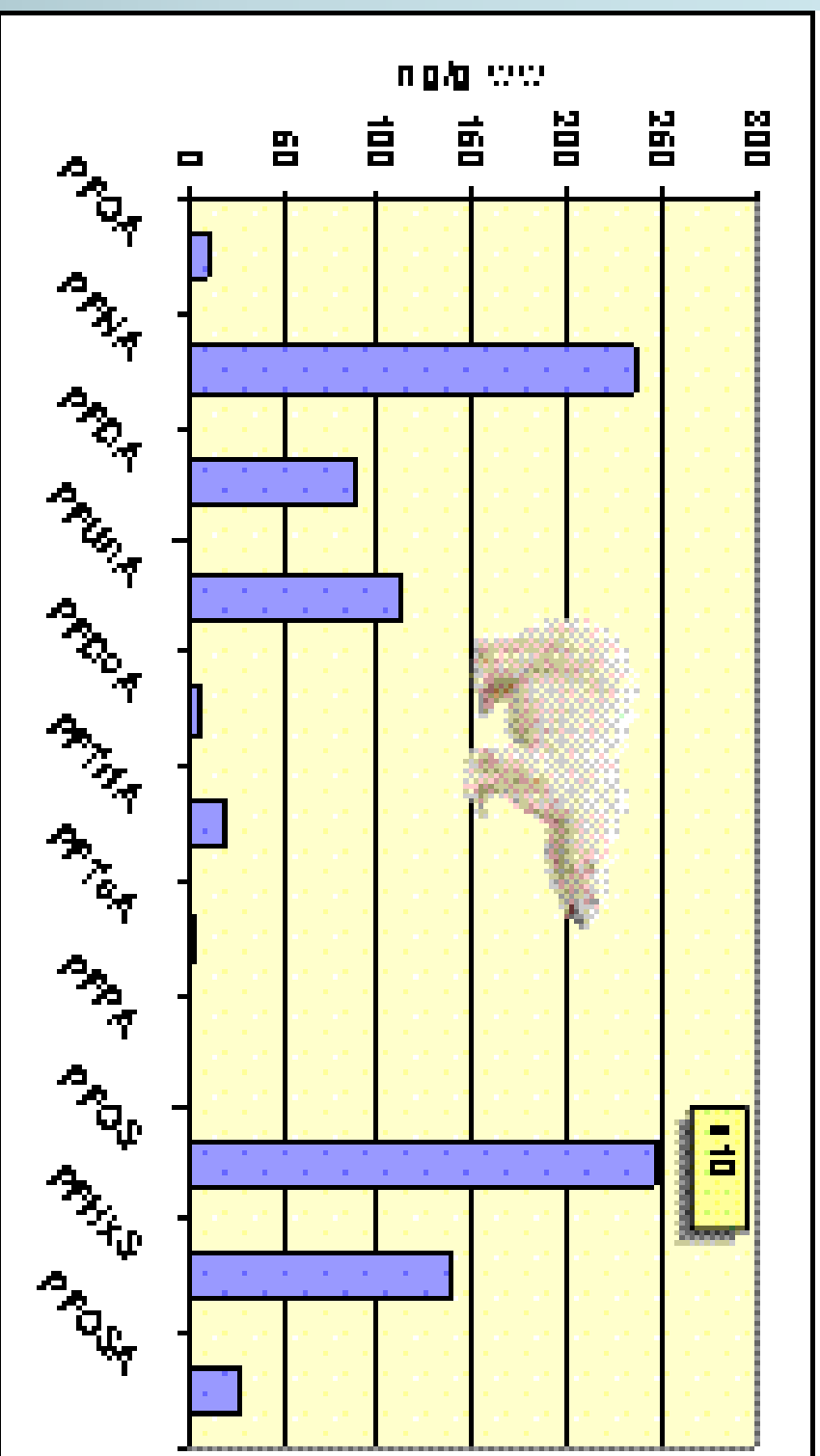


Perfluorooctanoate (PFOA)



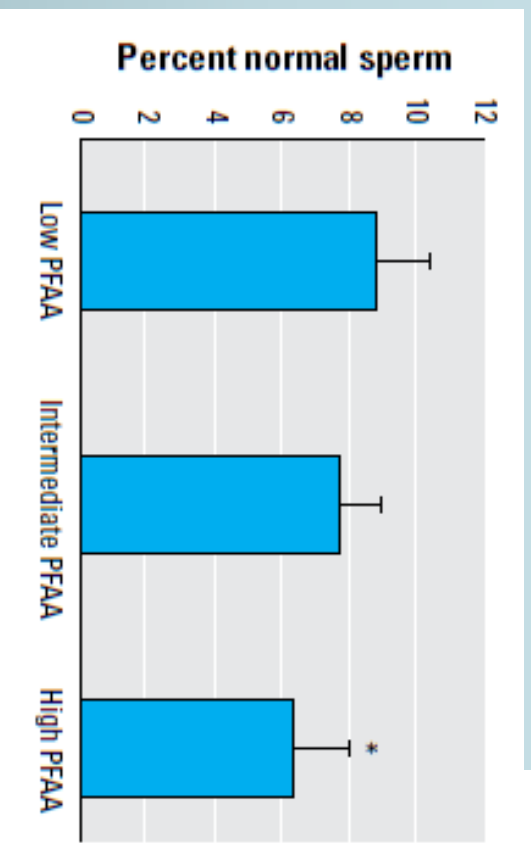
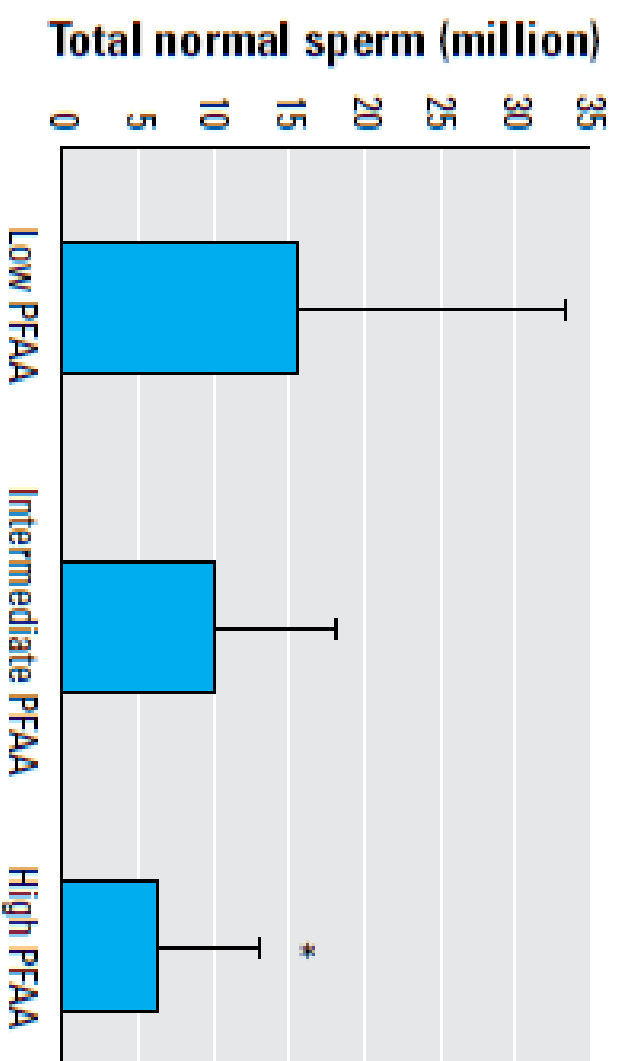
# Isbjørne

PFAS i lever fra 29 grønlandske isbjørne  
(gen.)



Smidnick et al. 2005

# PFAA og sæd kvalitet hos danske værnepligtige





# Infertilitet og PFOA/PFOs

**Table II Estimated OR for infertility (TTP >12 months) and FOR according to plasma concentrations of PFOS or PFOA (ng/ml) in early pregnancy<sup>a</sup>**

Exposure	No. of planned pregnancy	Infertility		OR (95% CI) <sup>b</sup>	FOR (95% CI) <sup>c</sup>
		Per cent			
PFOS (ng/ml)					
6.4–26.0	293	10.6		1.00	1.00
26.1–33.3	305	15.4		1.70 (1.01, 2.86)	0.70 (0.56, 0.87)
33.4–43.2	317	19.5		2.34 (1.40, 3.89)	0.67 (0.53, 0.84)
≥43.3	317	18.6		1.77 (1.06, 2.95)	0.74 (0.58, 0.93)
P-value for trend <sup>d</sup>				0.025	0.002
PFOA (ng/ml)					
<LLOQ–3.91	293	8.9		1.00	1.00
3.91–5.20	308	18.2		2.06 (1.22, 3.51)	0.72 (0.57, 0.90)
5.21–6.96	315	15.5		1.60 (0.93, 2.78)	0.73 (0.58, 0.92)
≥6.97	316	21.5		2.54 (1.47, 4.39)	0.60 (0.47, 0.76)
P-value for trend <sup>d</sup>				0.006	<0.001

<sup>a</sup>The activities were significant for menarche.

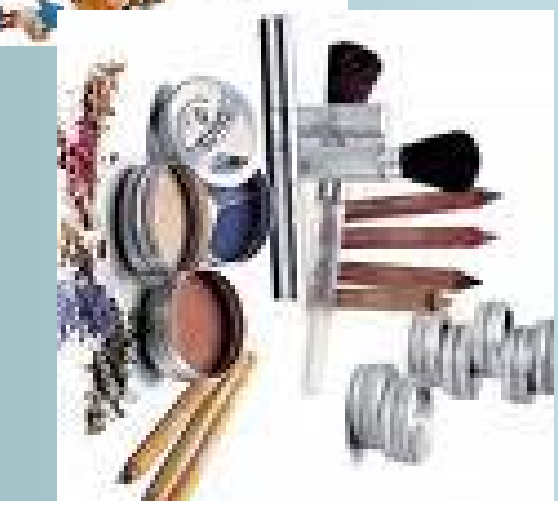
<sup>b</sup>OR

<sup>c</sup>FOR

<sup>d</sup>P

# Phthalater

- ▶ Multifunktionelle kemikalier
- ▶ Holder på farve i kosmetikprodukter
- ▶ Opløsningsmiddel til maling, lim og insektspray
- ▶ Blødgør plastic og medicinsk udstyr inkl. blodposer, dialysekatetre
- ▶ Findes i luft, mad og drikkevand!



## Næsten alle har phthalater i urin

<b>Mono phthalates</b>	<b>% of maternal urine in pregnancy</b>	<b>% of placenta homogenate</b>	<b>% of breast milk</b>
<b>mMP</b>	50	54	95
<b>mEP (mEHHP)</b>	98	100	100
<b>mBP</b>	97	100	100
<b>mIBP</b>	74		
<b>mBZP</b>	94	58	100
<b>mEHP (mEHHP, mEOHP)</b>	78 (98,94)	100	100
<b>mOP</b>		0	
<b>mCPP</b>	69		
<b>mINP</b>		0	100

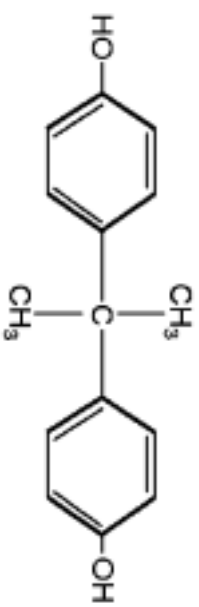
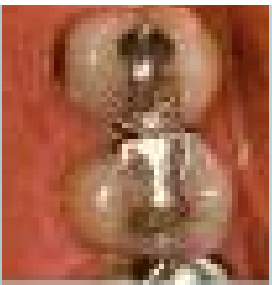
# For tidligt fødte børn

**Table 1.** Distribution of the urinary concentrations of phenols ( $\mu\text{g/L}$ )<sup>a</sup> in hospitalized premature infants.

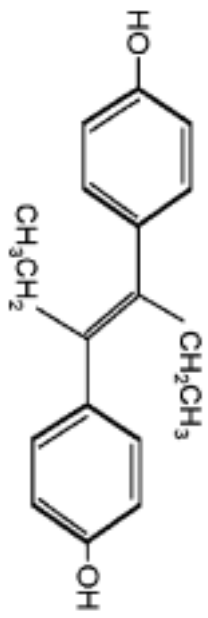
Compound	Species	No. of infants	No. < LOD	Geometric mean (SD)	Median	Range		NIHANES 2003–2004 <sup>b</sup>	
						Minimum	Maximum	Median	95th percentile
BP-3	Total	42	2	3.4 (4.8)	2.4	< LOD (0.4)	176	17.2	227
	Free	36	17	NA	NA	< LOD (0.4)	4.1		
BPA	Total	41	0	30.3 (5.2)	28.6	1.6	946	3.7	16.0
	Free	37	3	1.8 (3.2)	1.7	< LOD (0.4)	17.3		
MePB	Total	41	0	203 (4.7)	243	10.1	4,010	43.9 <sup>c</sup>	680 <sup>c</sup>
	Free	34	0	32 (4.9)	23	2.2	515		
PPB	Total	42	0	16.8 (4.9)	17.0	1.3	1,360	9.1 <sup>c</sup>	279 <sup>c</sup>
	Free	37	0	2.6 (5.2)	1.7	0.3	171		
TCS	Total	42	34	NA	NA	< LOD (2.3)	16.7	5.9	148
	Free	37	36	NA	NA	< LOD (2.3)	3.4		

# Bisphenol A (BPA)

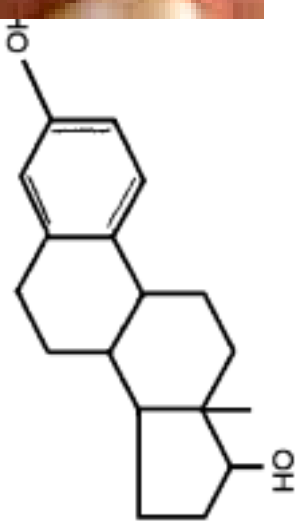
**Produktion mere end  
6.5 mill ton**



Bisphenol A



Diethylstilbestrol (DES)



Estradiol

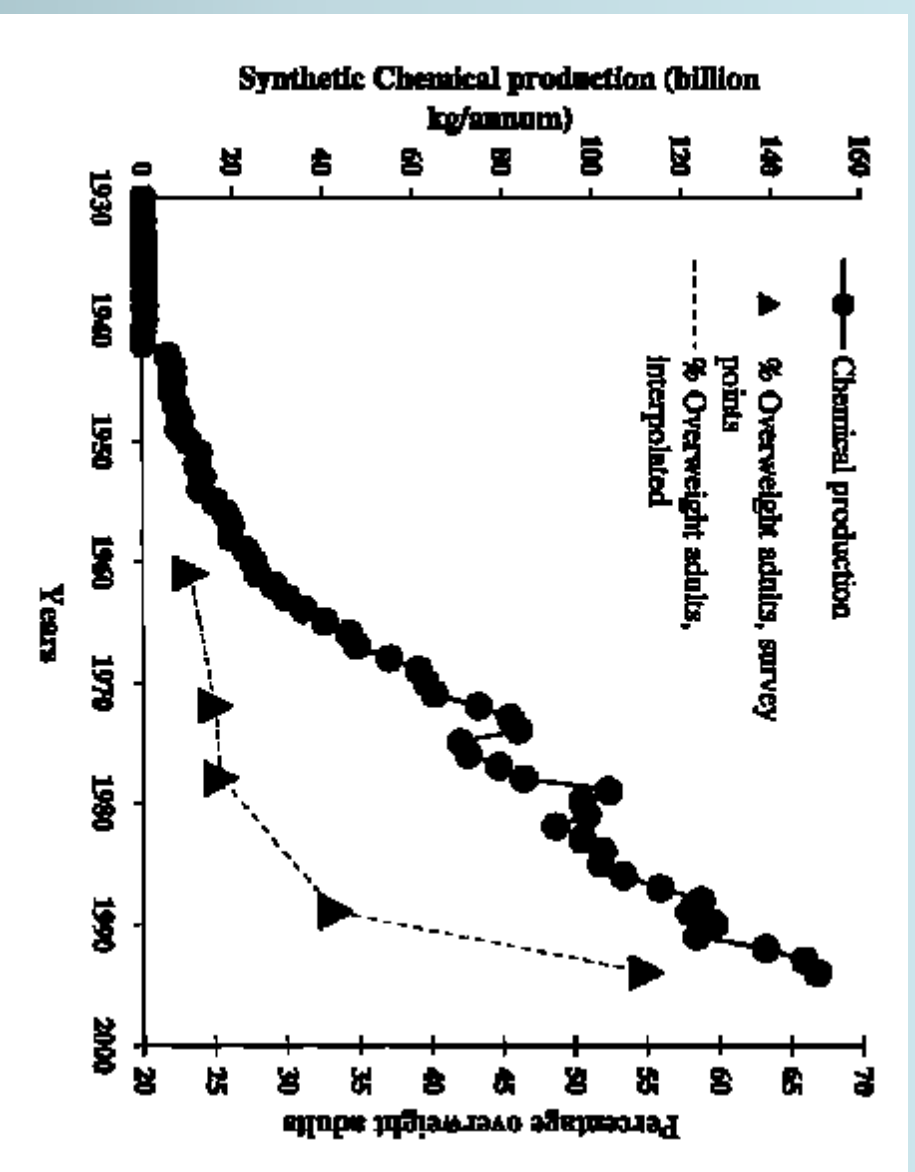


## Effektmål

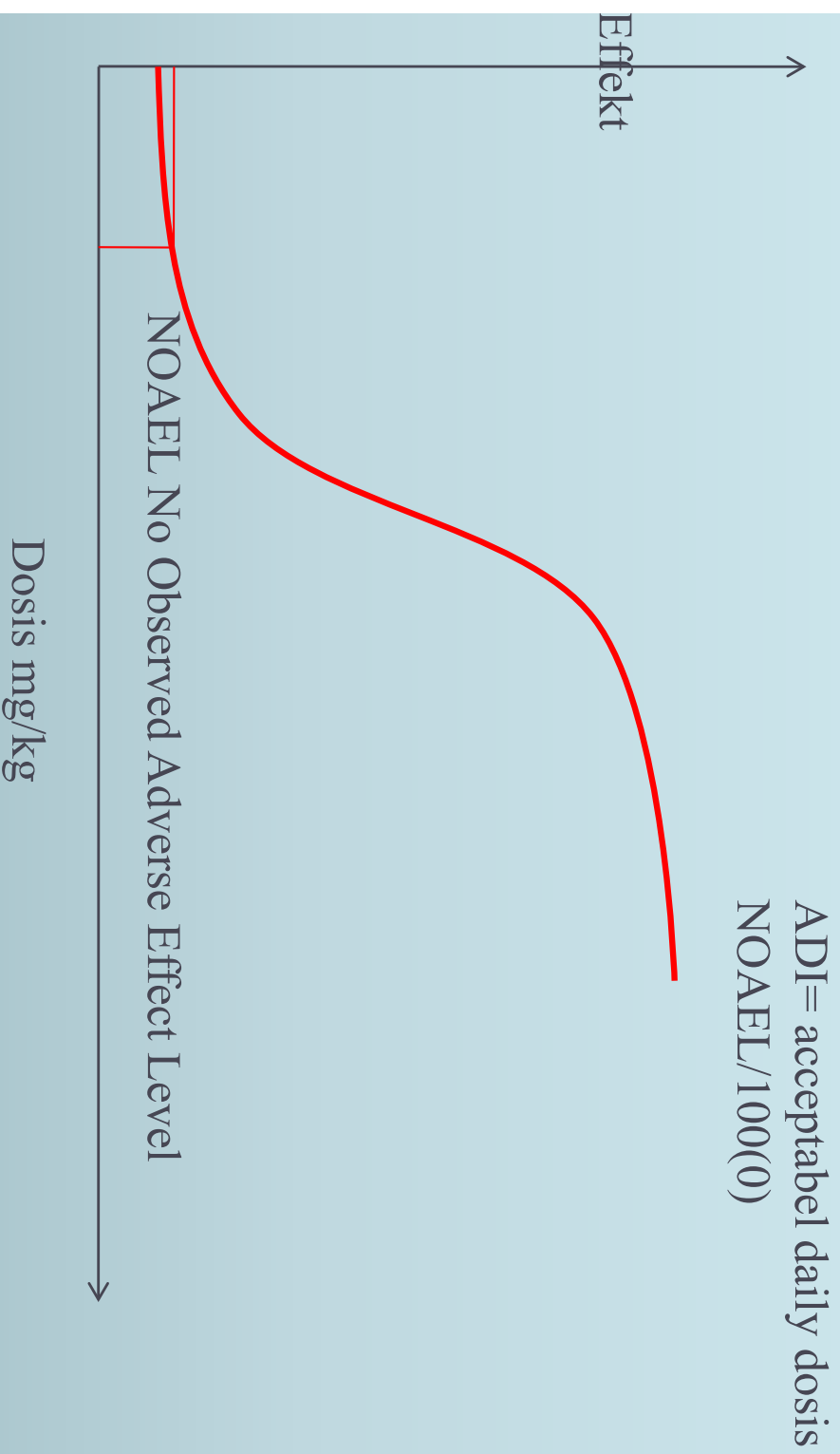
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- ▶ Pubertet
- ▶ Sædkvalitet
- ▶ Testicular dysgenesis syndrome
- ▶ Hormonforstyrrende stoffer
- ▶ **Fedme**

# Udvikling af produktion af kemiske stoffer og fedme

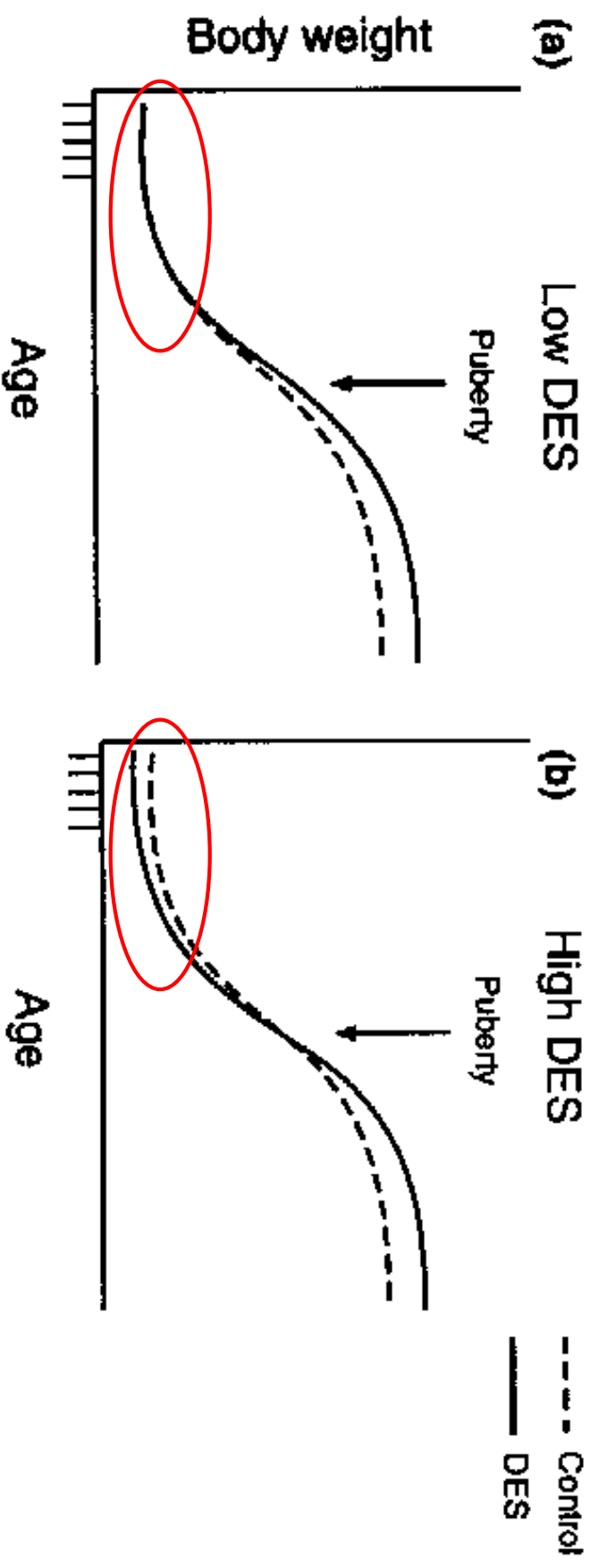


# NOAEL and ADI



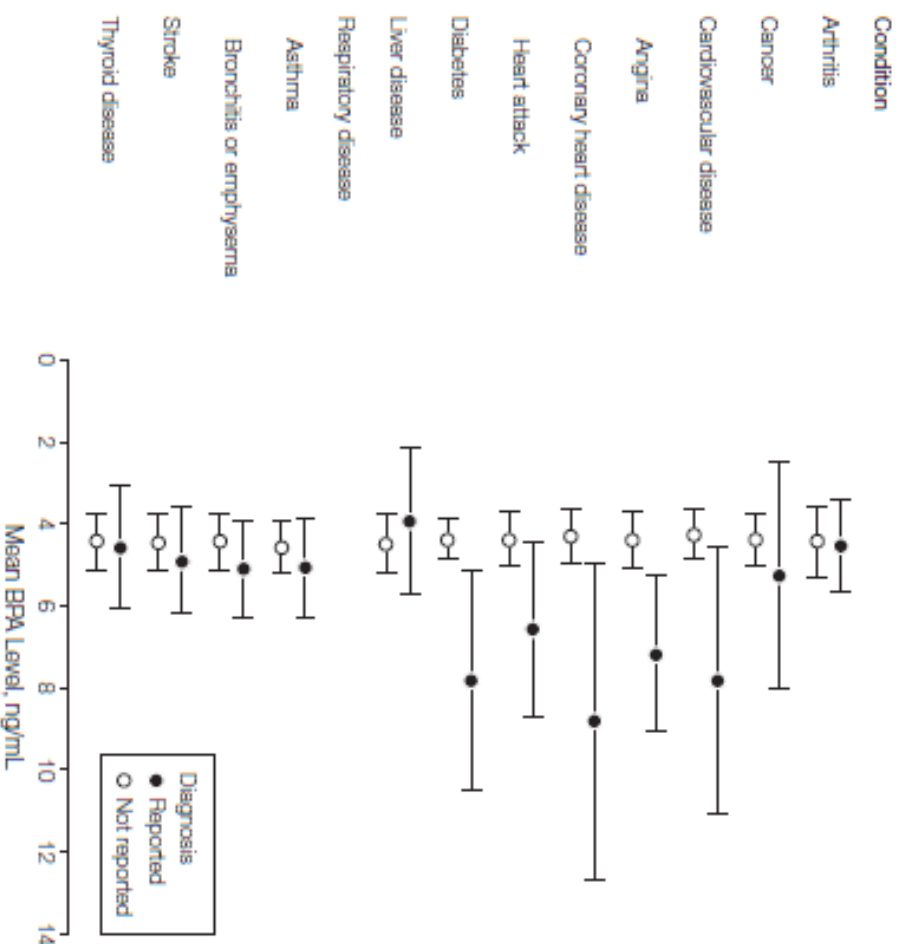


# DES i dyreforsøg



# NHANES og BPA

**Figure.** Estimated Mean Bisphenol A (BPA) Concentrations in Relation to Reported Diseases and Conditions



Estimates adjusted for age and sex. Error bars indicate 95% confidence intervals.

# NHANES og phthalat

