

Blootstelling aan hormoonverstoorders en mannelijke fertiliteit

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Prevalence of subfertility

¹ U.K., 25-40 yrs. → 1st pregnancy: 13%; 2nd pregnancy: 17%

² The Netherlands, 15-45 yrs. → 10,9%

Endocrine disrupting chemicals (EDC)

WHO: *'An endocrine disruptor 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.'*

'Testicular Dysgenesis Syndrome': prenatal exposure to EDCs is associated with increased risk for low sperm quality, testis cancer, cryptorchidism and hypospadias. ³

Study the relationship between **male subfertility** and exposure to **endocrine disrupting chemicals (EDC)**

Male subfertility → **case-control design**

Case = impaired sperm quality

Control = normal sperm quality

Exposure to EDC's → **human biomonitoring**

Chlorinated and brominated POPs

Heavy metals

Phthalates, bisphenol A, triclosan, perfluors

Recruitment

4 fertility centers in Flanders



Centrum voor
Reproductieve Geneeskunde

Centre for Reproductive Medicine, VUB, Brussels



Leuven University Fertility Center, KULeuven



Universitair Ziekenhuis Gent

Women's clinic, University Hospital, Ghent

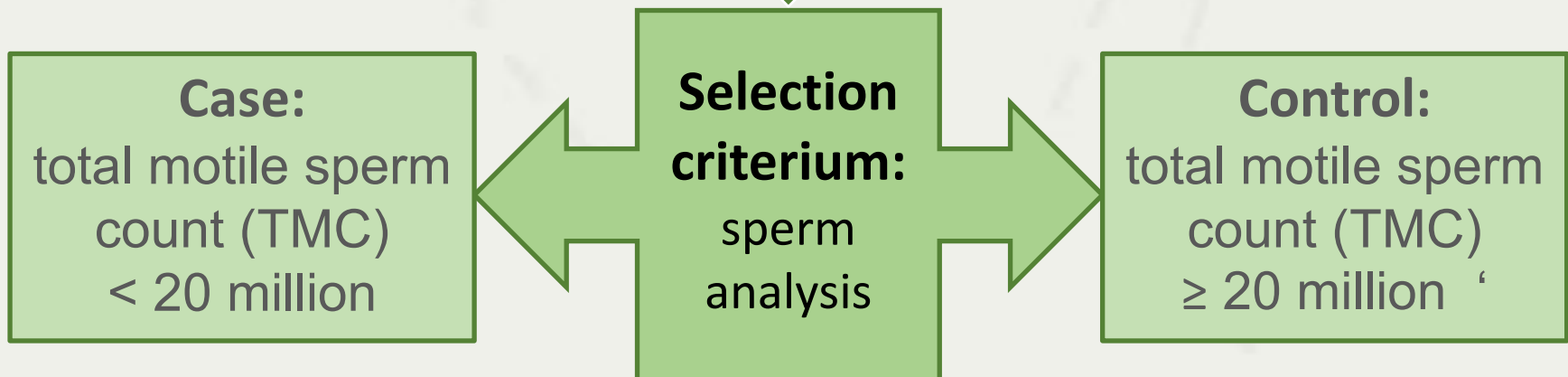


Fertility department, Hospital Oost-Limburg, Genk

Selection of cases and controls

Inclusion criteria:

♂, age < 50 years, BMI \leq 35 kg/m², normal clinical consult, IC



TMC = number of progressive moving sperm cells before capacitation
= volume * concentration in mil./ml * (%A+%B/100)

Study design

Selection of cases and controls

Cases: TMC < 20 mil.

Controls: TMC ≥ 20 mil.

Exposure assessment

Biomarkers of exposure in blood and urine

Logistic regression analysis

Outcome = risk for subfertility, associated with levels of exposure

Exposure assessment

Biomarkers of exposure:

Chlorinated persistent compounds: PCBs, Calux

Chlorinated pesticides: hexachlorobenzene, oxychlorodane,
trans-nonachlor, p,p'-DDE, p,p'-DDT

Brominated persistent compounds: PBDEs, HBCD

Heavy metals: Pb, Cd, Mn, Cu

Perfluor compounds: PFOS, FPOA

Plastic compounds: phthalate metabolites, BPA

Personal care products: triclosan

Selection of cases and controls

	1 st sperm analysis: TMC < 20	1 st sperm analysis: TMC ≥ 20
2 nd sperm analysis: TMC < 20	n = 40	n = 14
2 nd sperm analysis: TMC ≥ 20	n = 8	n = 80
2 nd sperm analysis: none	n = 15	n = 6
Study group:	77 cases	86 controls

associations between exposure and sex hormones

associations between exposure and sperm quality

Sperm quality

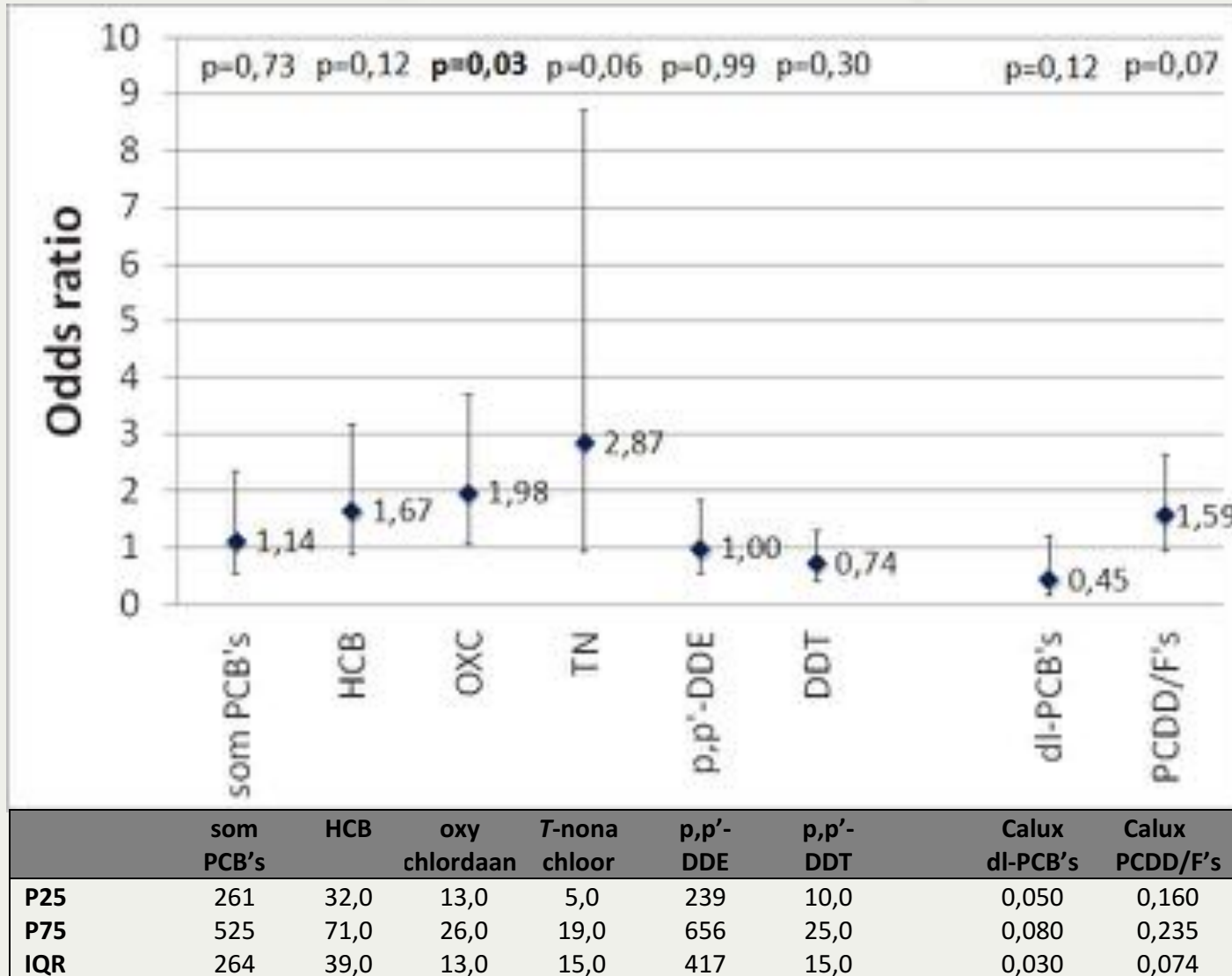
	Controls (n=86)	Cases (n=77)	p-value
<u>1st sperm analysis</u>	n=86	n=77	
Sperm conc. (mil/mL)	55.7 (32.6 – 102)	6.9 (3.3 – 17.2)	<0.0001
Motility: %A + %B	58.2 (14.3)	31.4 (18.7)	<0.0001
Morfology: % normal	3.1 (2.0 – 4.0)	0.2 (1.0 – 4.0)	<0.0001
Total Motile Count, TMC (mil)	105 (53.2 – 199)	3.3 (1.5 – 15.4)	<0.0001
Period of abstinence (days)	3.1 (2.0 – 4.0)	2.4 (2.0 – 3.0)	0.30
<u>2nd sperm analysis</u>	n=80	n=40	
Sperm conc. (mil/mL)	67.0 (40.5 – 107)	10.2 (4.2 – 25.0)	<0.0001
Motility: %A + %B	59.9 (12.7)	40.4 (20.5)	<0.0001
Morfology: % normal	6.2 (7.0 – 11.0)	0.3 (2.0 – 7.0)	0.0002
Total Motile Count, TMC (mil)	122 (60.0 – 202)	6.5 (3.5 – 23.0)	<0.0001
Period of abstinence (days)	2.5 (3.0 – 4.0)	3.5 (3.0 – 5.0)	0.30

Patient characteristics

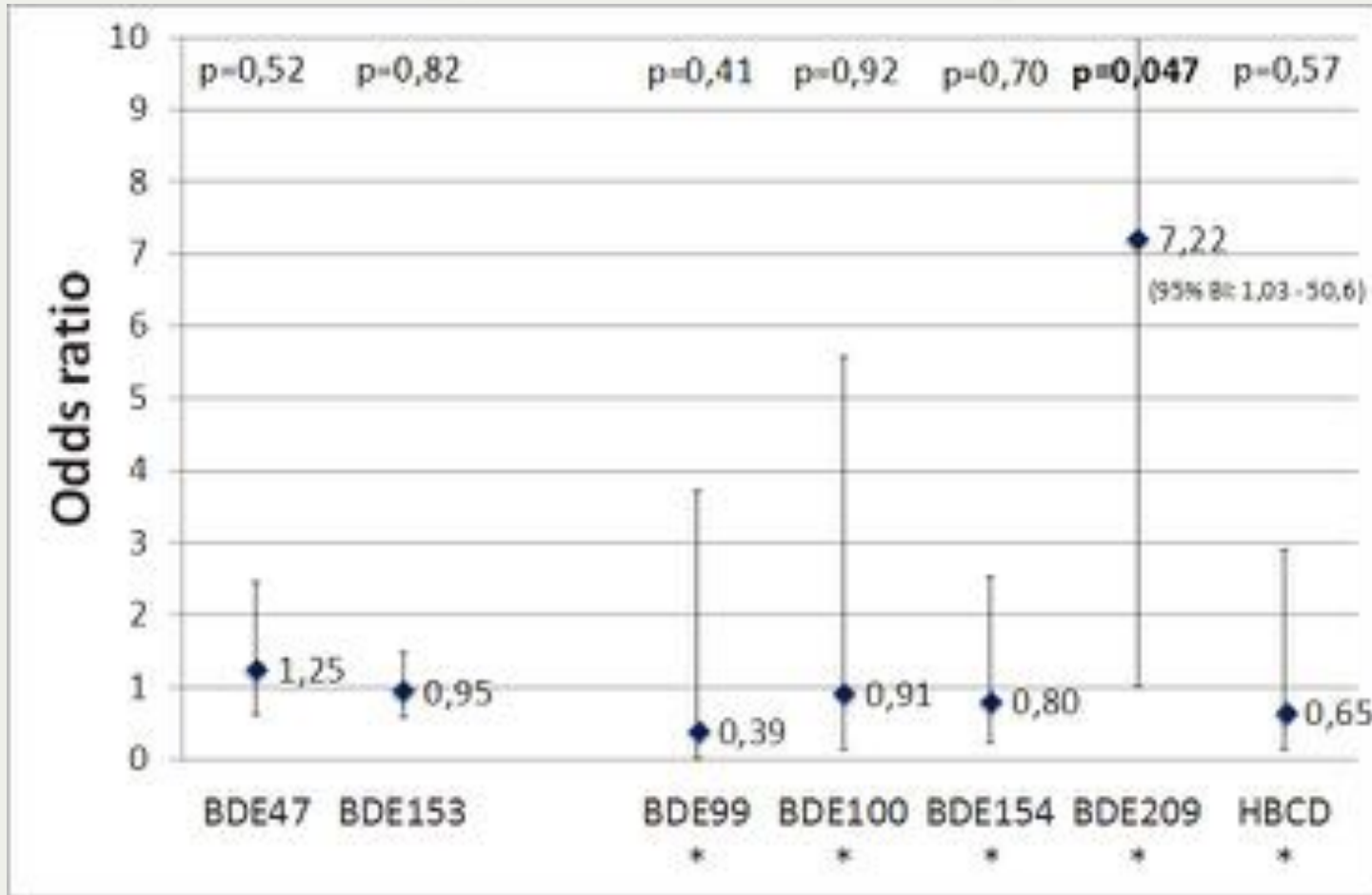
	Controls (n=86)	Cases (n=77)	p-value
Age (years)	33.5 (30.0 – 38.0)	31.9 (29.0 – 35.0)	0.06
BMI (kg/m ²)	24.5 (22.5 – 26.3)	25.5 (23.1 – 27.7)	0.07
% daily smokers	12.8%	20.0%	0.36
% higher education	52.9%	51.4%	0.87
% daily alcohol drinkers	11.8%	1.4%	0.03
Caffeine intake (units/week)	8.9 (7.0 – 21.9)	10.2 (7.0 – 21.9)	0.97
Heavy physical act. (h/week)	0.0 (0.0 – 5.0)	0.1 (1.0 – 9.0)	0.03

Data are percentages for categorical variables and geometric means (p25-p75) for continuous variables

Chlorinated POPs



Brominated POPs

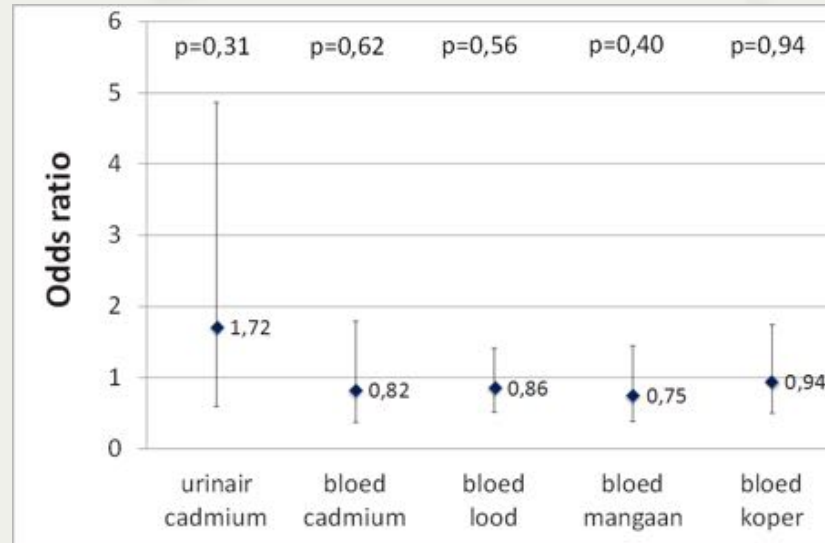


	BDE47	BDE153	BDE99	BDE100	BDE154	BDE209	HBCD
P25	10	15	LOQ:	LOQ:	LOQ:	LOQ:	LOQ:
P75	26	35	2 ng/l	2 ng/l	2 ng/l	40 ng/l	15 ng/l
IQR	15	20					

* Binary analysis

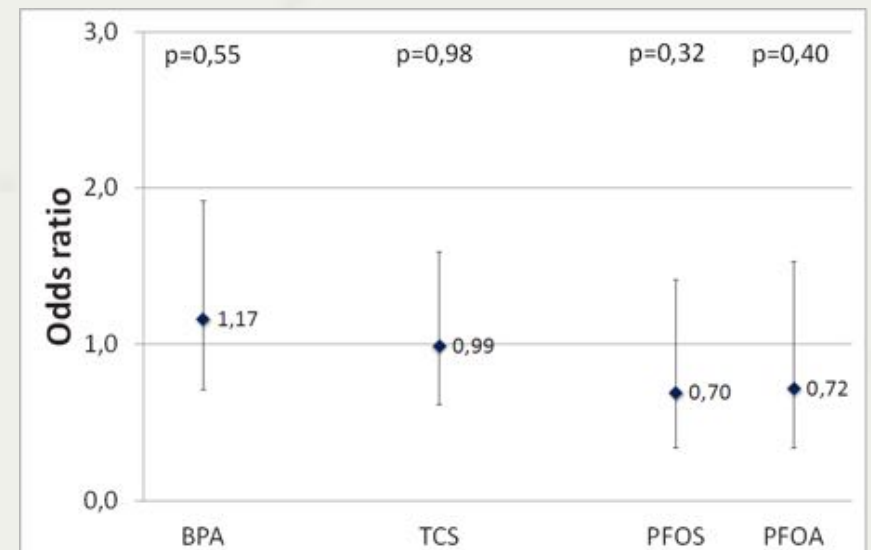
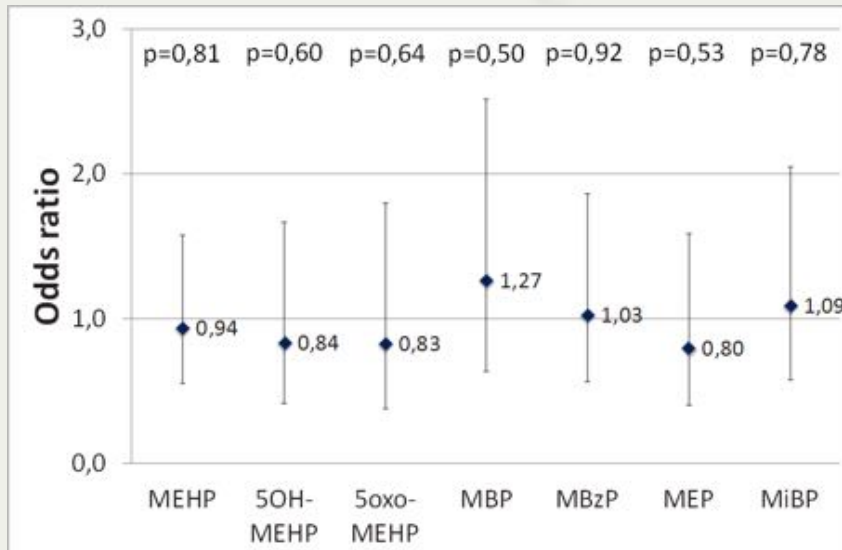
Other chemicals

Heavy metals



Bisphenol A,
triclosan,
perfluors

Phthalates



Chemical exposure and hormone levels

- Phthalates (MEHP): negatively associated with inhibine B
- Triclosan: negatively associated with inhibine B

- Phthalates (MiBP): positively associated with LH
- Triclosan: positively associated with LH

- *Hypothesis:*
 - *Toxic effect on Sertoli cells → inhibine B ↓*
 - *Toxic effect on Leydig cells → via feedback → LH ↑*

Chemical exposure and sperm quality

- Negative associations between biomarkers for exposure to chlorinated and brominated POP's and male fertility
- *Hypothesis:*
Accumulated exposure (life-long, possibly prenatal)
→ chronic effect: male fertility

Chemical exposure and hormone levels

- Negative effects on male hormone synthesis
- *Hypothesis:*
Short-term exposure (order of magnitude: days-weeks)
→ acute, reversible (?) effects: hormone levels in serum

Conclusions and policy interpretation

Male case-control study

- Both historical and 'new emerging' chemicals are associated with endocrine disruption
- Importance of ACTION:
 - policy measures
 - personal measures through sensibilisation / information
- Importance of MONITORING
 - prospective studies: birth cohorts
 - registration and coupling of data

Flemish government

Partners of 4 fertility centers

Prof. T. D'Hooghe; KU Leuven

Prof. H. Tournaye; VUB

Prof. W. Ombelet, dr. A. Vandendael; ZOL

Prof. P. De Sutter, prof. J-M Kaufman; UGent

Partners of Steunpunt M&G

Prof. T. Nawrot, Dr. B. Cox; UHasselt

Prof. W. Baeyens; VUB

Prof. N. Van Larebeke; UGent

Prof. A. Covaci; UA

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**Human exposure to endocrine disrupting chemicals and fertility:
A case-control study in male subfertility patients**  CrossMark

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 milieu en
gezondheid

Eindrapport

**Associatie tussen milieublootstelling en fertiliteit:
een case-control studie bij subfertiele mannen en
een interim analyse bij subfertiele vrouwen.**

denhonde

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