

PCB-INDUCED NEURODEVELOPMENTAL TOXICITY IN HUMAN INFANTS AND ITS POTENTIAL MEDIATION BY ENDOCRINE DYSFUNCTION *)

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OUTLINE

Neurodevelopmental toxicity of PCBs/PCDDs

- Overview
- Düsseldorf-study – Delay or deficit?
- Duisburg study – Searching for the NOAEL

Endocrine dysfunction as a potential mediator

- The HPT-axis as a target (experiment & epidemiology)
- The HPG-axis as a target (experiment & epidemiology)

Conclusions

Overview: Neurotoxicity of PCBs in Children

Oswego Study (Stewart et al 2003)

- **Source:** Fish from the Great Lakes
- **Exposure:** background (1991/1994)
- cognitive/neurodevelopmental deficit transient (up to 38 months) no effect at 54 months
- **prenatal**

Michigan (Jacobson et al 1990)

- **Source:** fish consumption
- **Exposure:** background 1980
- cognitive deficit (memory, IQ)
- longlasting effects (4, 11 years)
- **prenatal** (cordblood)

North Carolina (Rogan et al 1986)

- **Source:** diet
- **Exposure:** background 1980
- no cognitive deficit
- hypotonia/hyporeflexia transient (up to 24 month)
- **prenatal** (early milk)

Dutch Studies(e.g. Huisman et al 1995)

- **Source:** diet
- **Exposure:** background 1991
- neurodevelopmental delay
- cognitive deficit (42 months) up to 42 months
- **prenatal** (maternal serum)

Düsseldorf/Duisburg

- **Source:** diet
- **Exposure:** background 1993/95 or 2000/2002



Outcome?

PCBs: Neurodevelopmental Delay or Deficit ?

The Düsseldorf Study (*Walkowiak et al., 2001; Winneke et al., 2005*)

- Recruitment of healthy mother-infant-pairs between 1993 and 1995
- PCBs (138, 153, 189) in cordblood and maternal milk at ≥ 2 weeks pp
- Neurodevelopmental assessment at 7, 18 and 30 months using the Fagan test (FTII) and the Bayley Scales of Infant Development (BSID)
- Reassessment using the Kaufman Assessment Battery for Children (K-ABC) at 42 months of age
- Follow-up at 72 months using the K-ABC

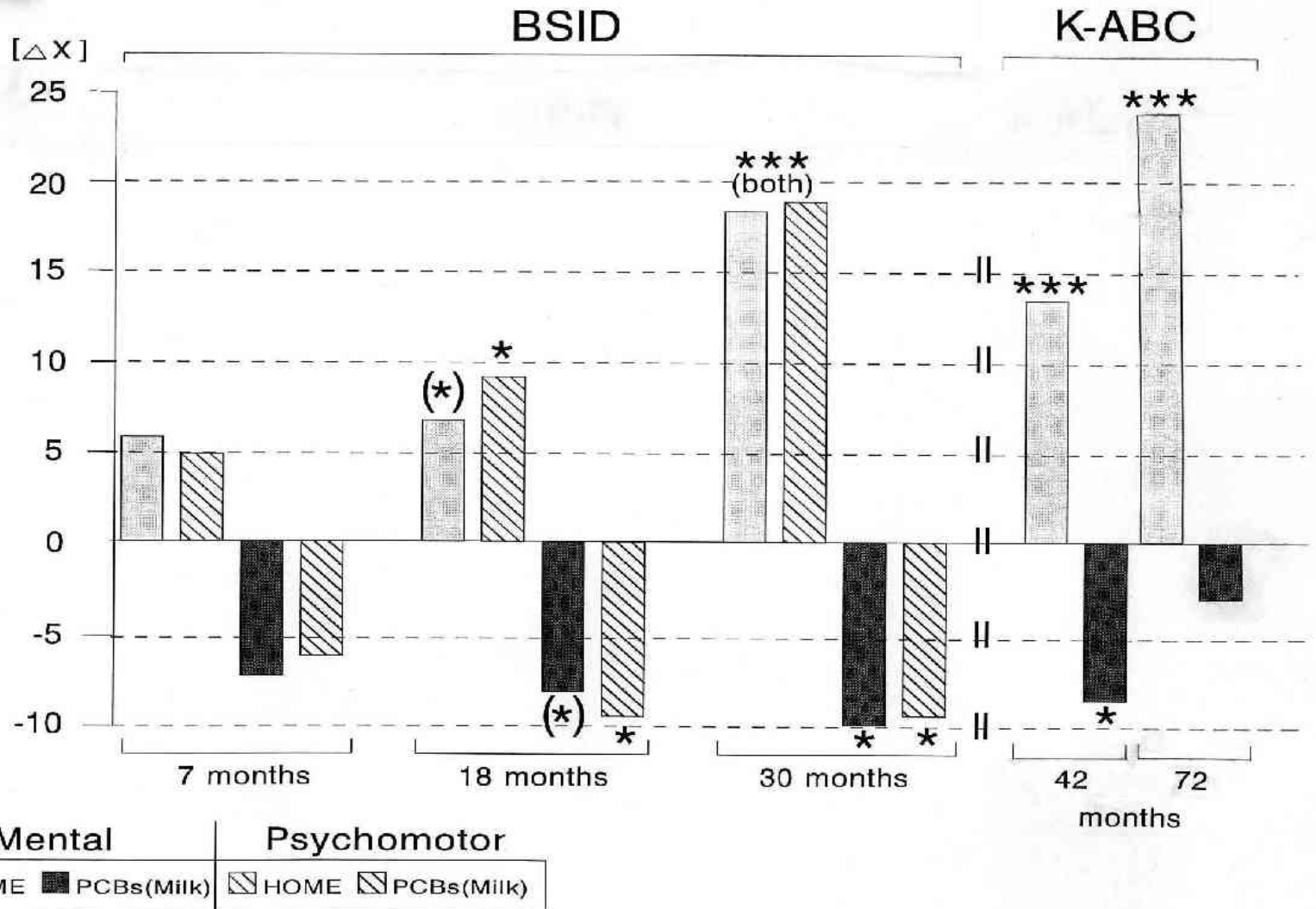
PCB Study Düsseldorf*

Age of Child	PCB-Measurement	Outcome Assessment
At birth	Cordblood	Anthropometry
Week 2	Maternal Milk	Neurology
7 month	-	Fagan Bayley MDI/PDI Vocalization Anthropometry
18 month	-	Bayley MDI/PDI Vocalization Anthropometry HOME
30 month	-	Bayley MDI/PDI Anthropometry
42 month	Serum	Neurology Kaufman ABC Anthropometry HSE/HOME
68 – 72 month		Kaufman ABC

*Walkowiak et al., Lancet 2001; Winneke et al., ETAP 2005

Effect-Sizes for Developmental Outcome in Düsseldorf Study: Inclusion of 72-month Data [5% - 95%]: Delay rather than deficit ?

[Walkowiak et al., 2001; Winneke et al., 2005]



Are there still adverse psychodevelopmental effects
at even lower levels of environmental exposure to
PCDDs and PCBs at 12 and 24
months of age ?

The Duisburg study

Study design (1)

Study type:

- Birth cohort (2000 – 2002) N = 230

Exposure assessment:

- Organochlorines (PCB, PCDD/F)
in blood of pregnant mother (n = 182)
- Organochlorines (PCB, PCDD/F)
in breast milk of mother (n = 149)
- Pb in blood, Cd and Hg
in urine of pregnant mother

Outcome assessment

BSID at 12 and 24 months of age

Comparing the Düsseldorf- and the Duisburg-studies in terms of PCB-concentrations in maternal milk

[Wilhelm et al., 2006]

	N	PCB 138 [ng/g lipids]		PCB 153 [ng/g lipids]		PCB 180 [ng/g lipids]		Σ NDL PCBs [ng/g lipids]	
		P50	P95	P50	P95	P50	P95	P50	P95
Düsseldorf (1993 – 1995)	126	141	235	181	292	85	145	405	679
Duisburg (2000 – 2002)	176	50	109	81	184	42	100	172	377

Comparing the Düsseldorf and Duisburg Studies for outcome in terms of BSID MDI [Wilhelm et al., 2006]

Mental Development (BSID)

Age (mo)	N	Mean score (BSID)	Change (%) for doubling of exposure (95% CI)	p-value
Düsseldorf (1993 – 1995)				
18	112	106	-3.9 [-8.7; 1.0]	0.122
30	104	150	-3.3 [-6.9; 0.3]	0.074
Duisburg (2000 – 2002)				
12	106	86	0.5 [-1.4; 2.5]	0.585
24	105	134	0.8 [-1.1; 2.7]	0.402

Summary & Conclusions (1)

- At PCB-levels exceeding 400 ng/g lipids (milk) adverse developmental effects (BSID mental/motor) were found in the **Düsseldorf** study at 30 and 42 months of age
- Adverse effects were no longer seen in the same (smaller) cohort at school age, suggestive of developmental delay rather than deficit; rather strong effects of genetic (maternal IQ) and environmental factors (HOME, social background) emerged at this age, which may have had a superimposing influence
- At PCB-levels below 175 ng/g lipids (milk) adverse developmental effects (BSID mental/motor) were no longer seen in the **Duisburg** study at 12 and 24 months of age, suggestive of some sort of „effect threshold“ between 400 and 175 ng/g lipids for neurodevelopmental adversity (NOAEL).

EXPLANATION

in terms of

ENDOCRINE DYSFUNCTION ?

INTERACTION OF PCBs WITH ENDOCRINE SYSTEMS

(Brouwer et al., 1999)

- Thyroid Hormone System

- Estrogen System

- Androgen System

- Retinoid System

- Corticosteroid System

- and others ??

Thyroid hormones and brain development

Thyroid hormones play an important regulatory role in brain development. Severe hypothyroidism in the fetal and early postnatal period, if untreated, cause cretinism, associated with mental retardation, hearing deficit etc. PCBs/metabolites interfere with TH-function through competitive interaction with TH for binding to transport proteins and/or induction of TH-metabolizing liver enzymes. Thus, the link for TH and PCB neurotoxicity is at least plausible (Porterfield, 1994)

Thyroid hormones are important for the temporal programming and fine tuning of CNS-development, namely

- neuronal proliferation**
- differentiation of neurons**
- neuronal migration**
- myelinization of neurons**

PCBs/PHAHs and TH: Epidemiology (modified from Brouwer et al., 1999)

Expos.	Location	Reference	T4	TSH
PCB	Netherlands	Koopman- Esseboom et al. (1994)	↓	↑
PCBs	Netherlands	Fiolet et al. (1997)	→	NR
PCBs	Germany	Weipert (2000)	↓	↑
PCBs	USA	Longnecker et al. (2000)	→	→
PCB/PCDD	Germany	Wilhelm et al. (2006)	↑	↓

Endocrine effects of PCBs/PCDDs

(Duisburg-study)

- **Thyroid hormones (T3, T4, TSH in cordserum and milk) were measured in the Duisburg-cohort. If anything, associations with PCB/TCDDs were positive. Thus, at these levels of exposure, thyroid functions are not impaired (Wilhelm et al., 2006). The overall evidence in this respect is controversial (Hagmar et al., 2002)**
- **Other than the HPT-axis (thyroid hormones) the HPG-axis (gonadal system) has received little attention in human epidemiological studies, so far.**
- **The emphasis now is on associations between PCBs/PCDDs and gonadal hormones**

Sex Steroids and Brain Development

During development , **sexually dimorphic brain structures and functions** are organized by complex spatially restricted and precisely timed interactions of steroid hormones , growth factors, and neurotransmitters .

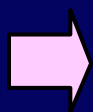
Sexually dimorphic brain structures:

- Parts of the **hypothalamus and the preoptic area (HPOA)**
- Bed nucleus of the stria terminalis (BNST)
- Amygdala

Differentiation of the **cerebral cortex, striatum and hippocampus** - perinatal expression of estrogen receptors and aromatase

Differentiation of **spinal and cranial motoneurons** by androgens

Differentiation of **GFAP-reactive astrocytes** by estradiol - inhibition of proliferation by progesterone



Sex steroid-induced changes in the nervous system are mostly permanent (organizational) during development and transient (activational) in adulthood.

PCBs and Steroid Hormones

- Delayed **sexual maturation** (Lundkvist 1990)
- **Gonad weights, sperm production** (z.B. Gellert 1978; Hansen et al. 1992; Jansen et al. 1993; Cooke et al. 1996, Faqiet al. 1998)
- **Hormone concentrations** in serum (z.B. Yeowell et al. 1987; Vincent et al. 1992; Hany et al. 1999; Lilienthal et al. 2000; Kaya et al., 2002)
- **Metabolism** of steroids (Haake-McMillan & Safe 1991)
- **Estrogen receptors** and ER-dependent **functions** (Nesaretnam et al. 1996 und 1997)
- Reduced **activity of aromatase** *in vitro* (Drenth et al. 1996) und *in vivo* (Hany et al. 1999)

Sex- dependent neurotoxicity

- Impairment of **delayed spatial alternation** in PCB-exposed female rats (Schantz al. 1995)
- Reduced amplitudes in scotopic **electroretinogram** in PCB-exposed female rats (Kremer et al. 1999)

Duisburg Study design (2)

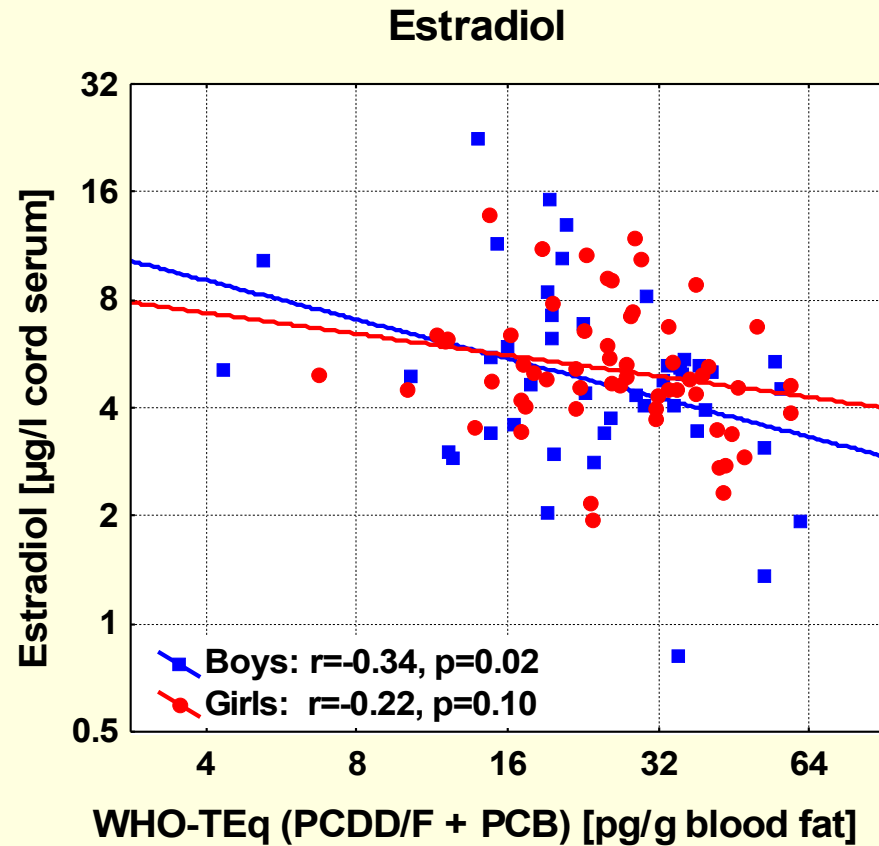
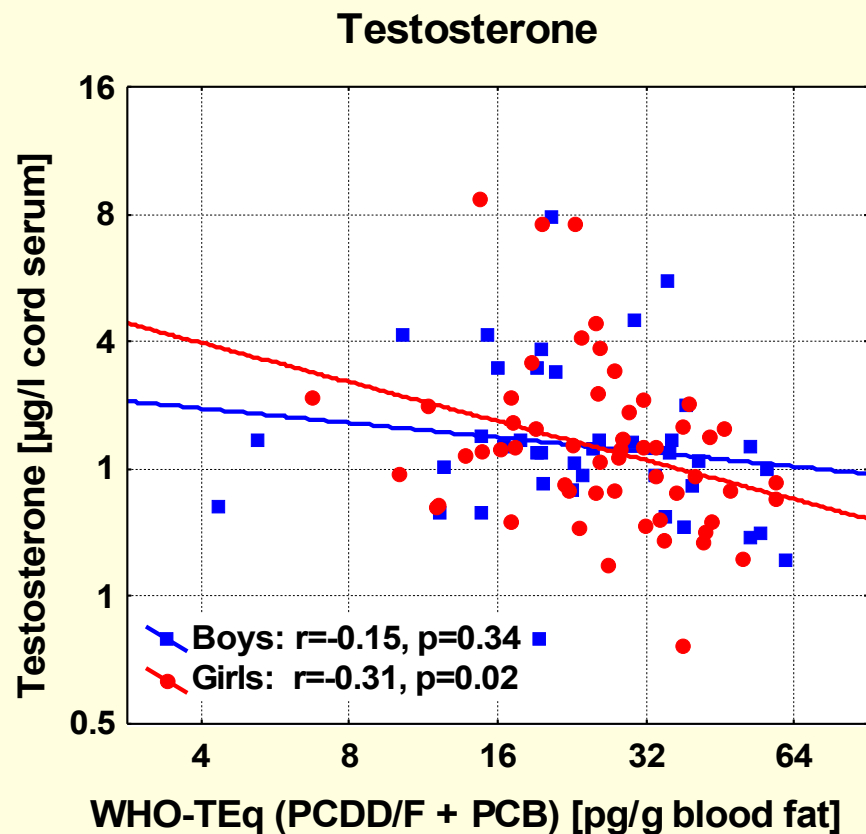
Outcome variables:

- Testosterone and estradiol in serum of pregnant mothers and cord serum

Study size:

- 104 newborns (in 2000 - 2002)
with the complete set of measurements

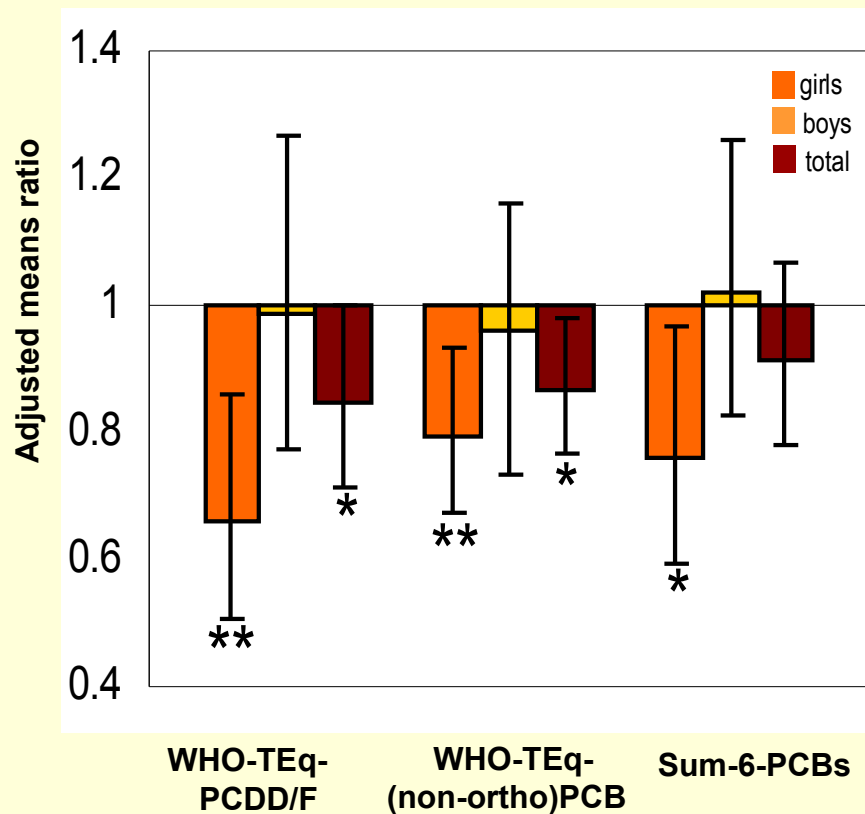
WHO-TEq-PCDD/F+PCB levels in maternal serum and testosterone and estradiol levels in cord serum



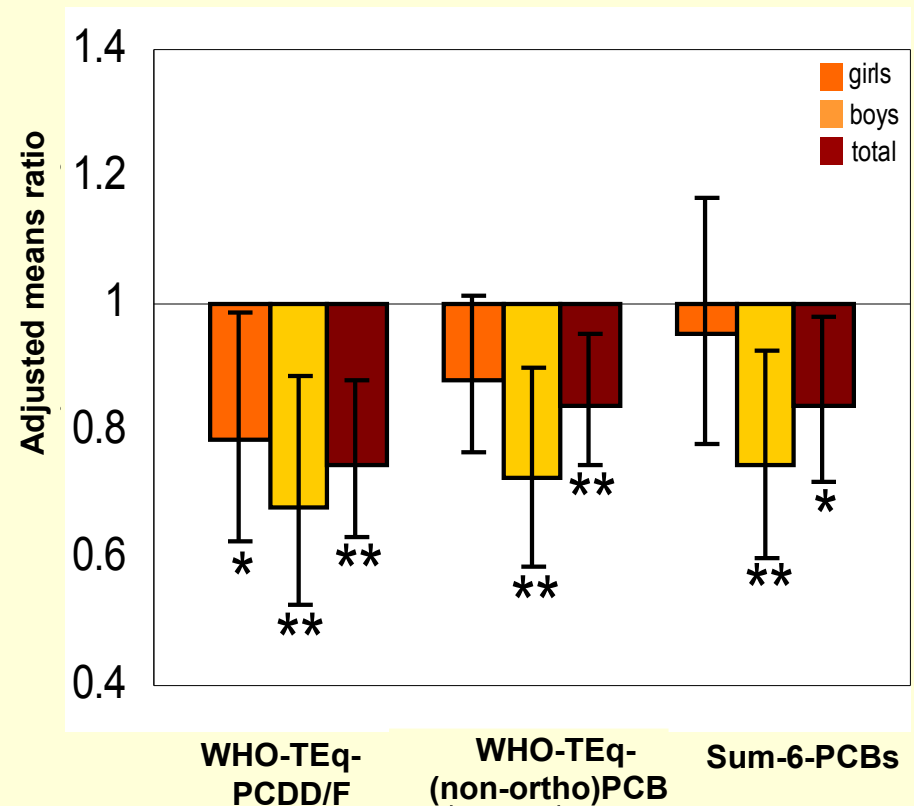
Organochlorines in maternal blood fat and sex-steroid levels in cord serum

Confounder adjusted means ratios (MR) of hormone concentrations with 95% confidence limits by doubling of organochlorine exposure

Testosterone



Estradiol



Summary & Conclusions (2)

- **Robust negative associations were found between sex hormones in cordserum and organochlorines in maternal serum & milk at low environmental levels; nothing for Pb, Hg, Cd and very little for DDE**
- **There was a tendency for these associations to be stronger for dioxins/DL-PCBs than for NDL-PCBs (AhR-mediation??)**
- **These effects correspond to what has been found in experimental animals; human data appear to be lacking, so far (except for modification of gender specific play behavior in Dutch children)**
- **The differential effects for testosterone and estradiol in boys and girls cannot easily be explained at present and need to be confirmed**
- **It is important to clarify the mechanistic basis of the findings, as well as their adversity in terms of longterm consequences for (psycho)-sexual development.**

*Thank you for your
attention !*

