Early programming of health and disease: the example of endocrine disruptors

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Autumn meeting BVN – GBN
28/11/2024

- The concept of Developmental Origin of Health and Disease (DOHaD)
- Exposure to EDCs and brain development
- Exposure to EDCs and male sexual differentiation
- Exposure to EDCs and energy balance
- DOHaD and placental epigenome: experimental data

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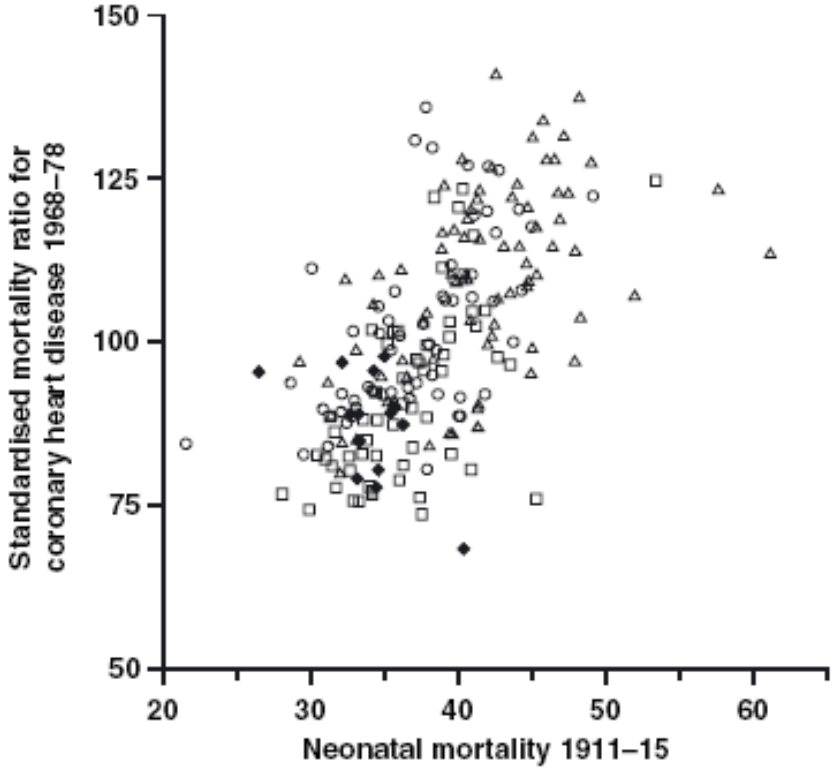
Developmental Origin of Health and Disease (DOHaD)

Barker's hypothesis

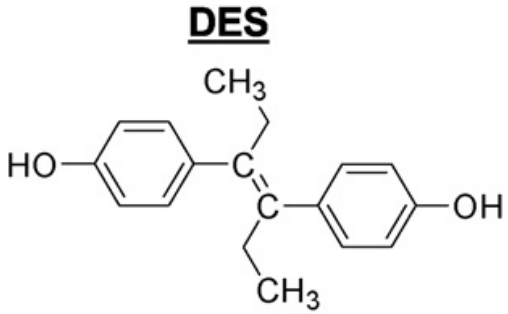


positive geographic correlation for standardized rates for infant mortality from 1921 to 1925 and ischemic heart disease from 1968 to 1978

407 hommes de 59-70 ans		
Poids de naiss. (kg)	Prévalence du synd. mét. (%)	Risque de synd. métab.
> 4.3	6	1
3,9 - 4,3	6	X 2,2
3,4 – 3,8	12	X 4,9
2,9 – 3,3	17	X 8,5
2,5 – 3,2	19	X 8,4
< 2,5	30	X 18,0

Association between low birth weight and increased risk of metabolic syndrome and cardiovascular disease

Developmental Origin of Health and Disease (DOHaD)

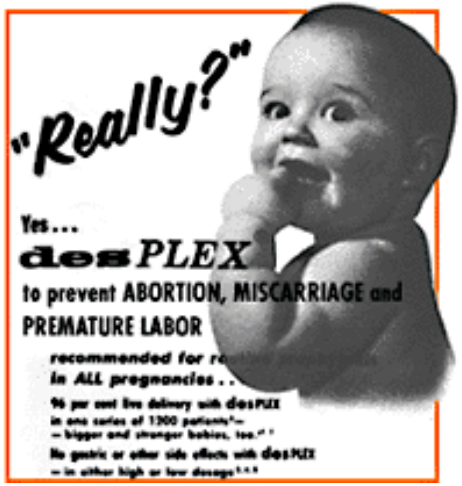


Women:

- Anatomical abnormalities of the reproductive tract (uterus, fallopian tube)
- Decreased fertility

Animal:

- Early puberty
- Ovulatory disorders
- Obesity and metabolic syndrome in adulthood



Developmental Origin of Health and Disease (DOHaD)

Prenatal malnutrition

Barker DPJ et al., 1986, 2005

Intra-uterine growth restriction

Obesity, metabolic syndrome

Metabolism

Bisphénol A

Diéthylstilbestrol

Herbst AL et al., 1971

Alteration of pubertal timing, fertility and neoplasia

Disorders of sexual differentiation

Reproduction

Phtalates

Sharpe R & Skakkebaek NE, 2008

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Stress

Endocrine disruptors

Nutrition

Fetal/Early posnatal periods

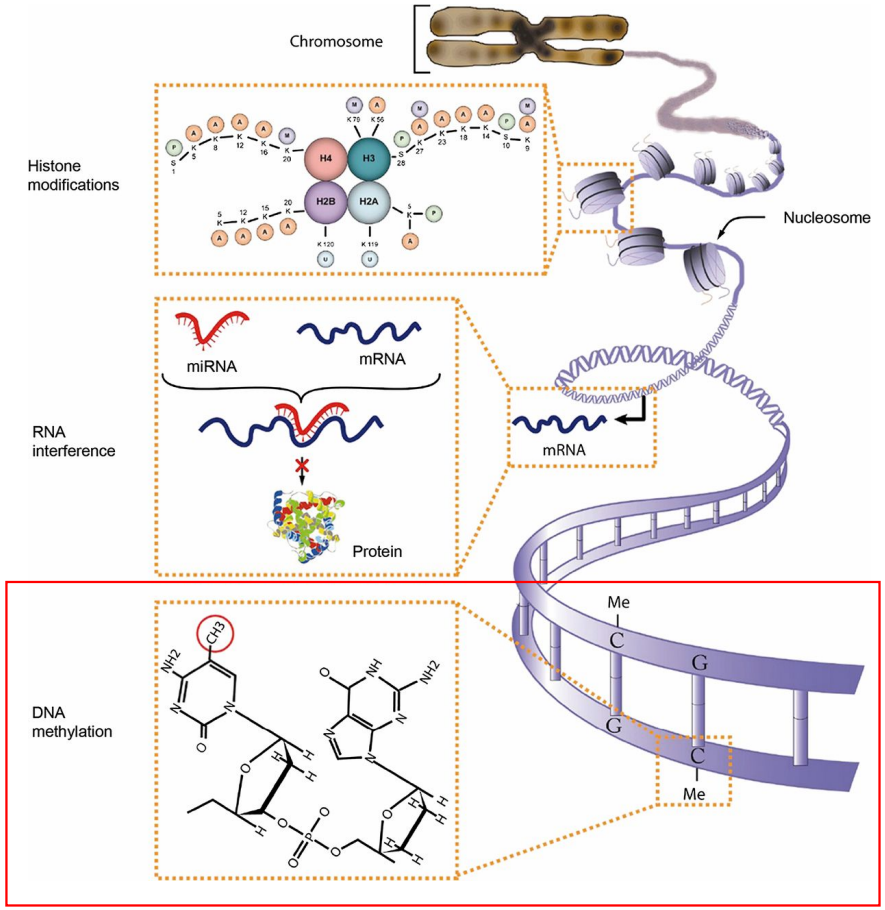
Long and variable latency

EPIGENETIC ?

Puberty / Adult age

Epigenetic mechanims

Definition : heritable changes in gene expression caused by mechanisms that do not depend on changes in DNA sequences



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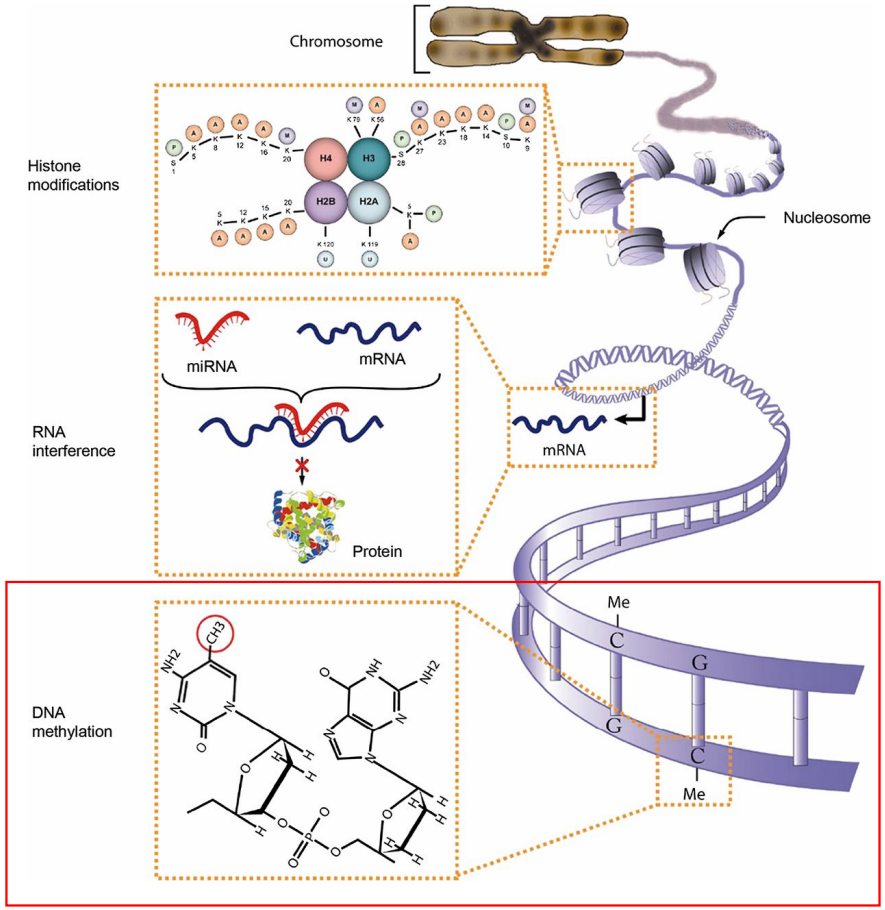
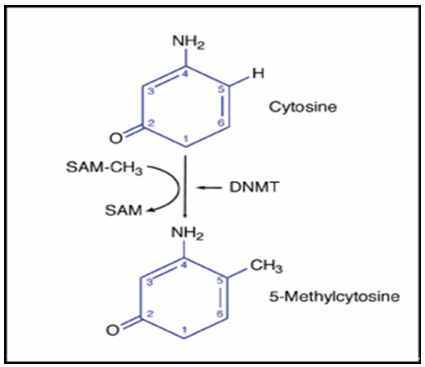
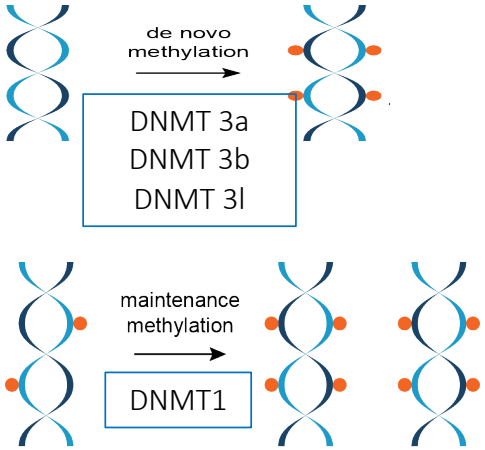
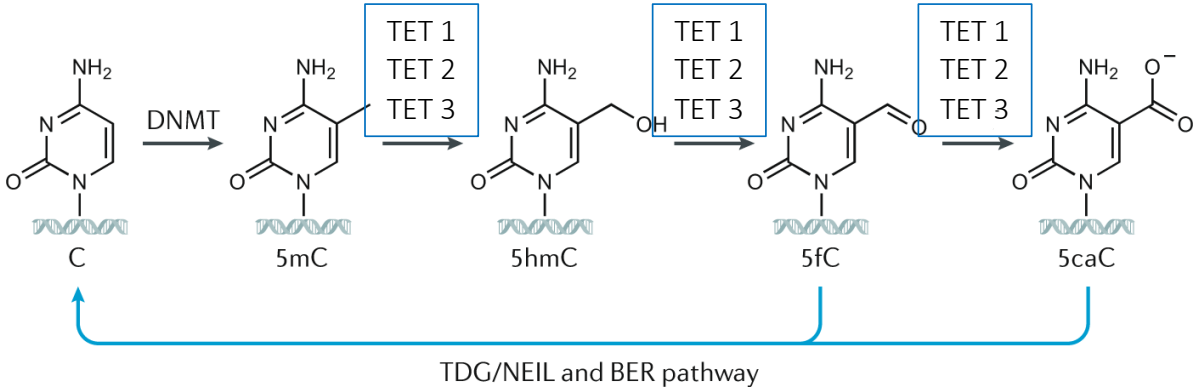




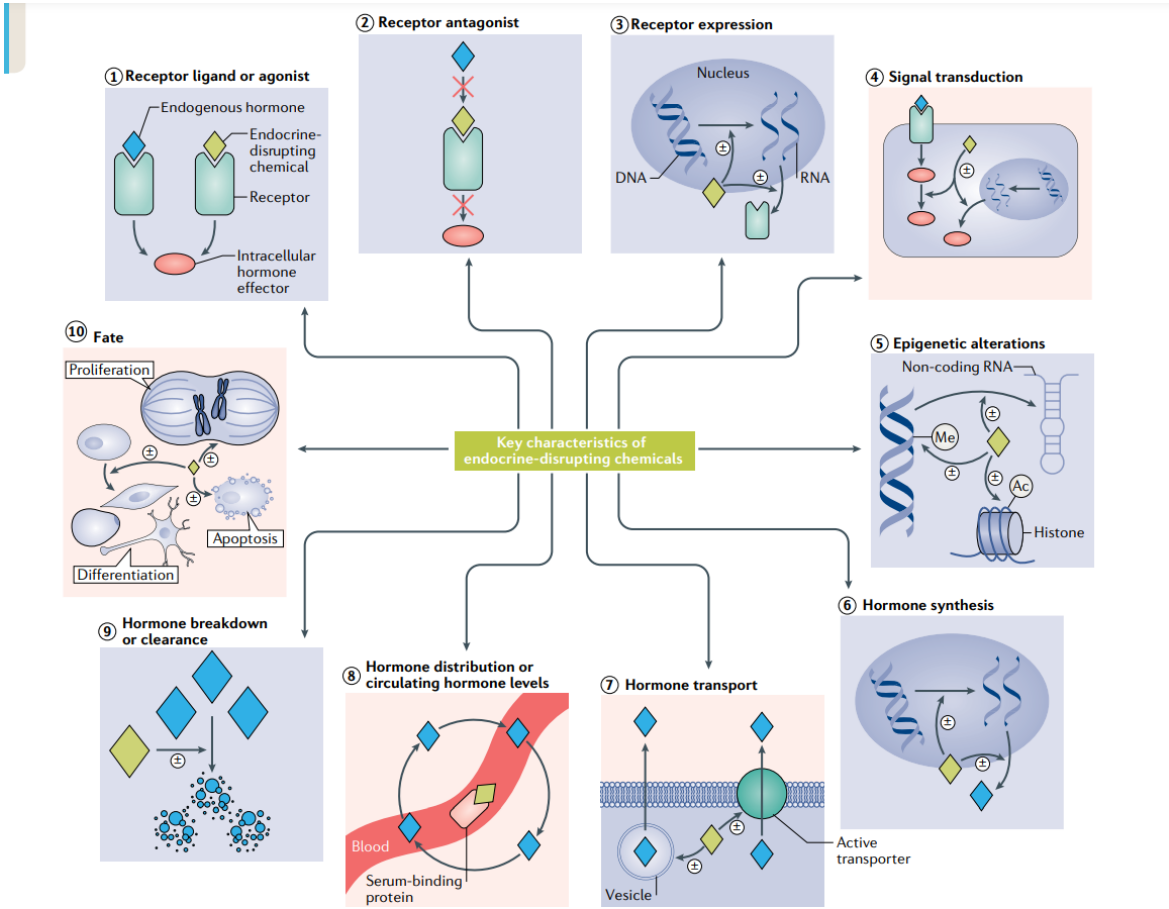




EDCs: definition

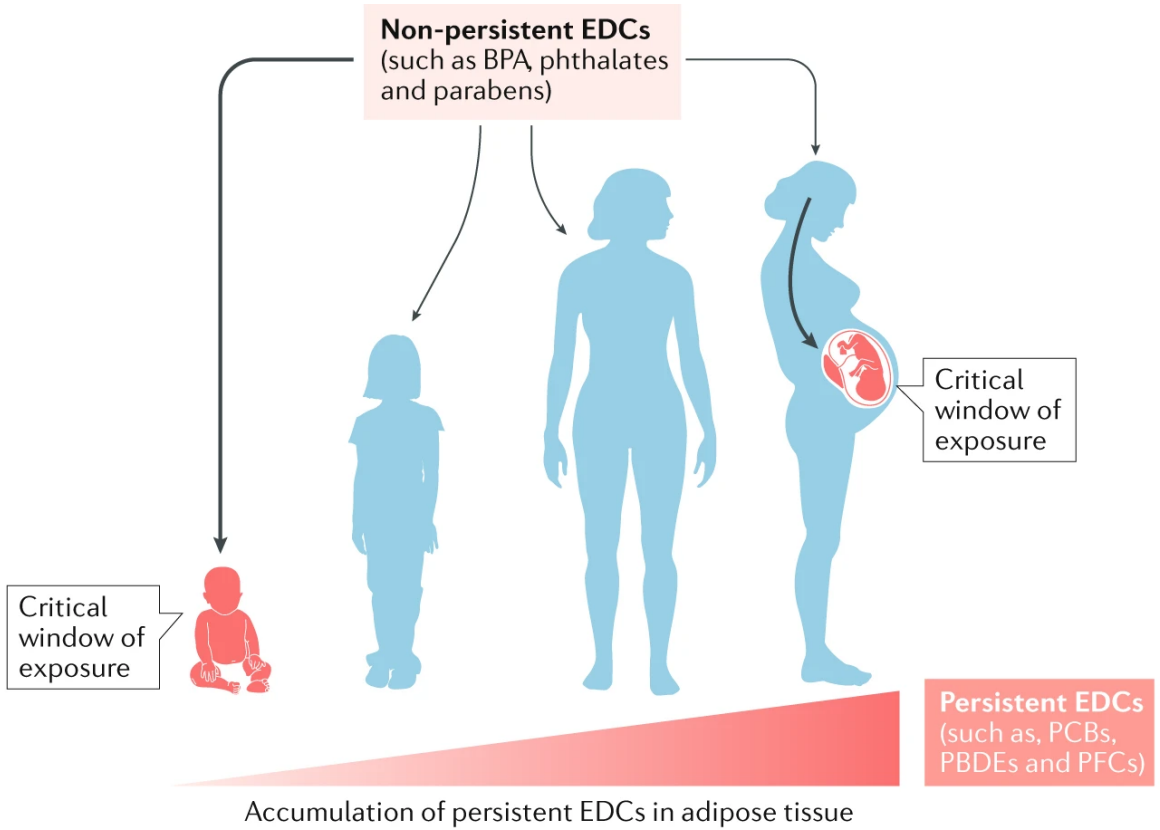
Organisation mondiale de la santé

« …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…»



La Merril et al Nat Rev Endo 2020

EDCs: critical windows of exposure

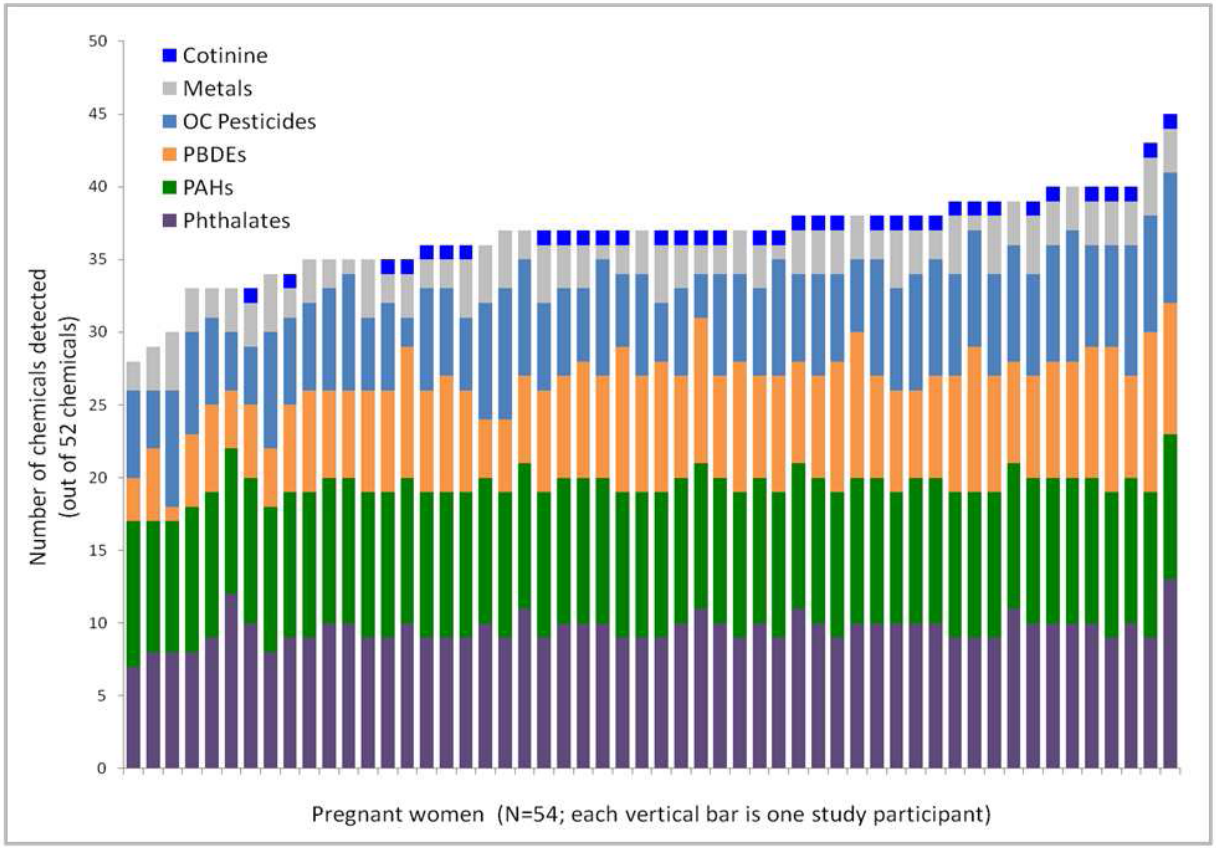


Fetal and neonatal exposure to EDCs

- Placental transfer
- Maternal milk

Lopez-Rodriguez et al. Nature Rev. Endo 2021

Critical windows of exposure to EDCs



Woodruff TJ
EHP 2011

Mean detected levels in pregnant women : 37

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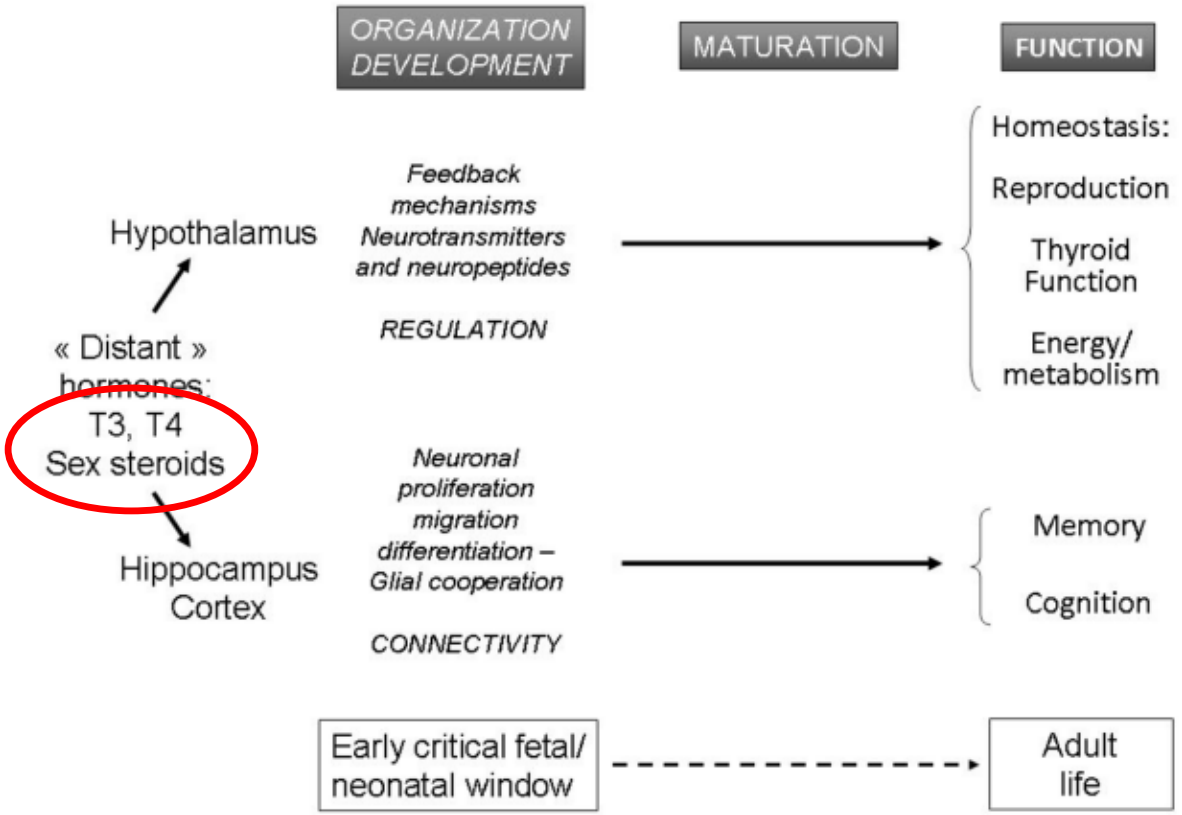
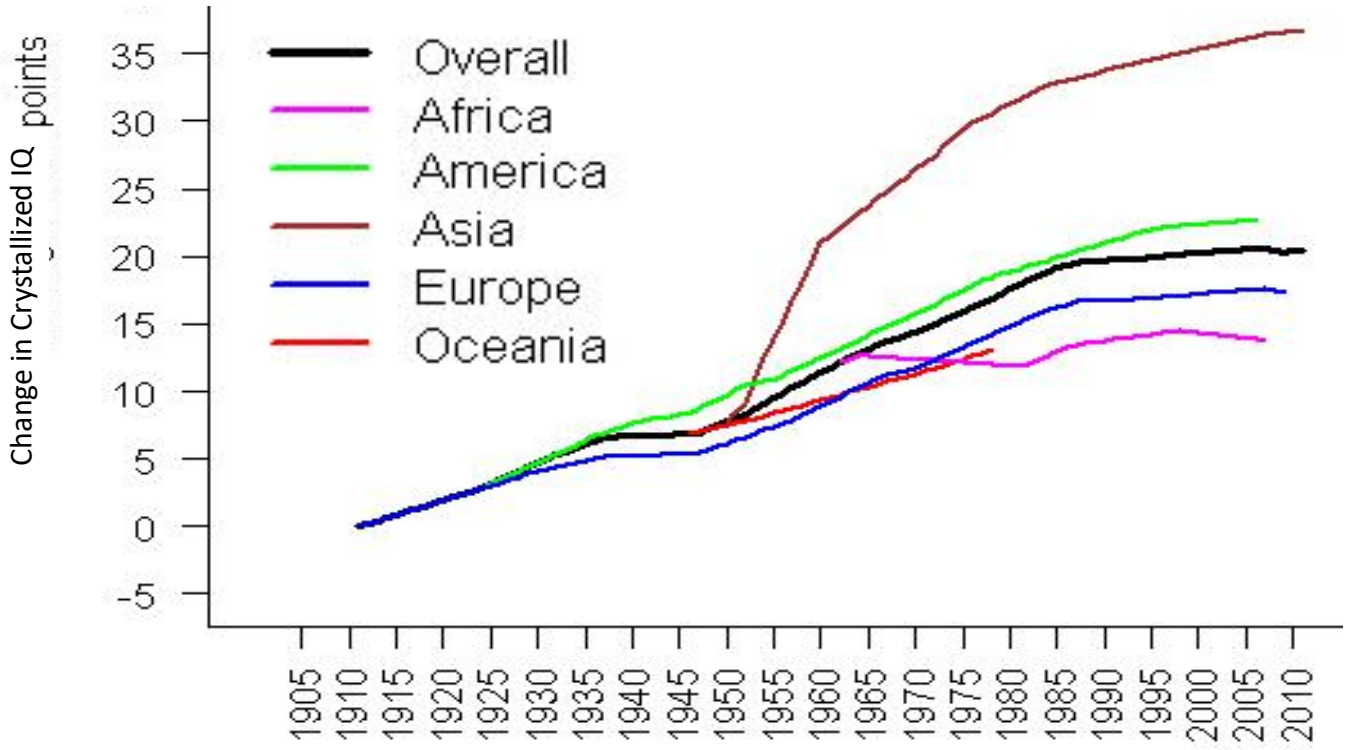
EDCs and brain development



Parent et al 2011

EDCs and brain development

Increasing of IQ is stopped from 1980

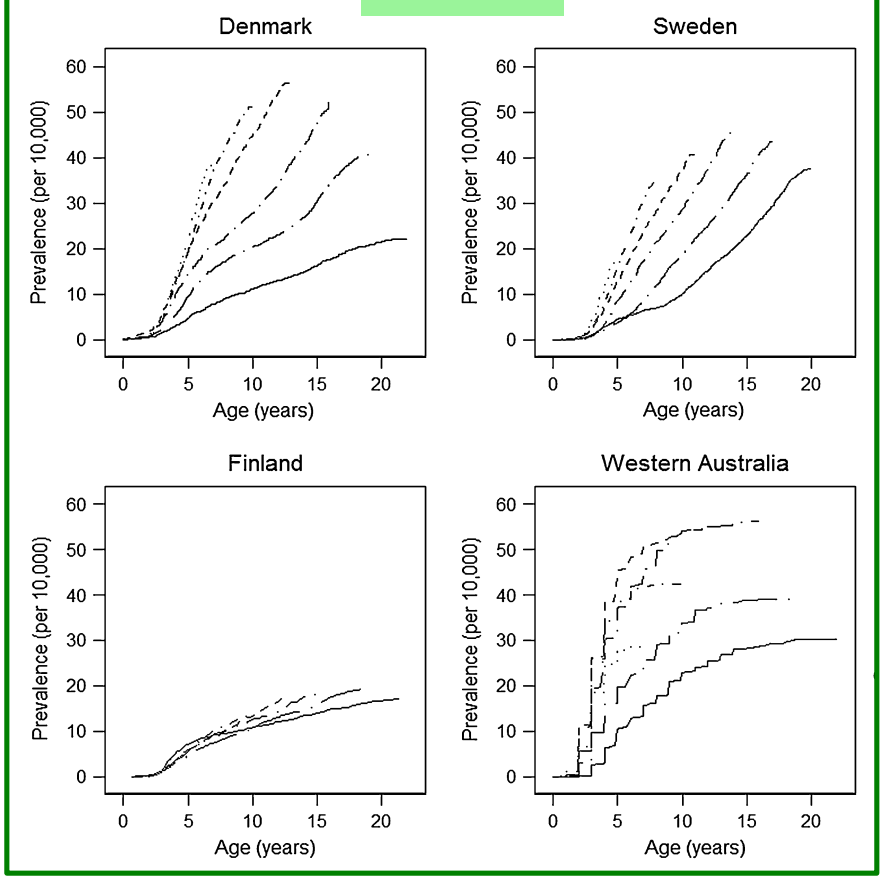


A meta-analysis (219 studies)
Of the "FLYNN EFFECT"

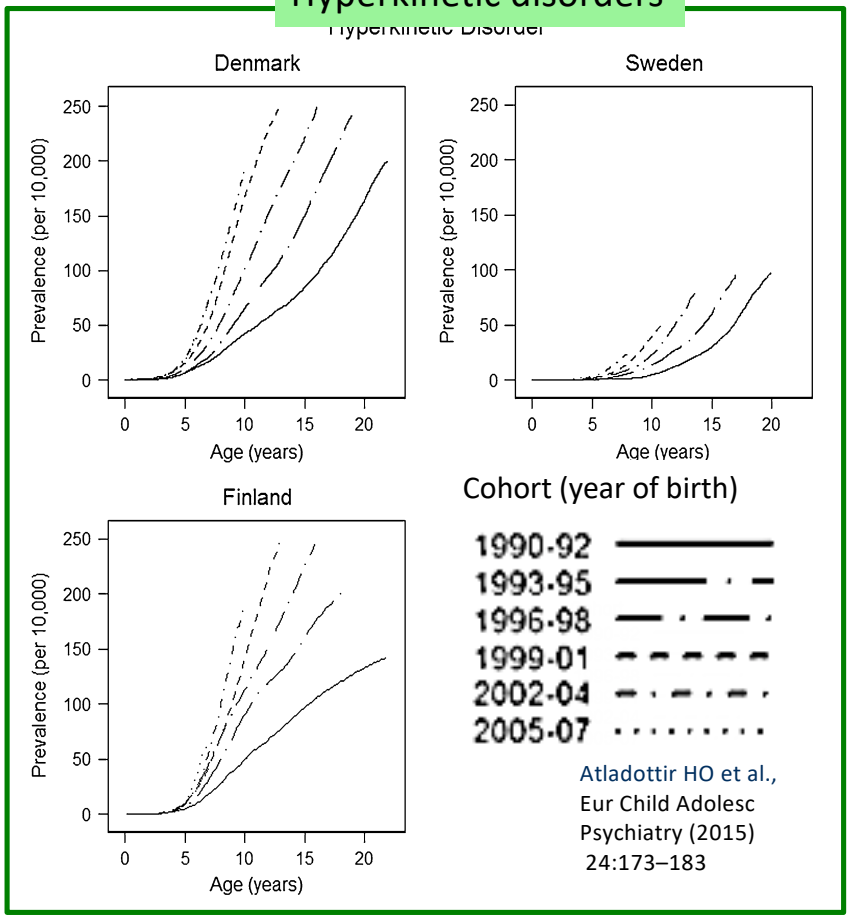
Pietschnig and Voracek, 2015

EDCs and brain development

Autisme



Hyperkinetic disorders

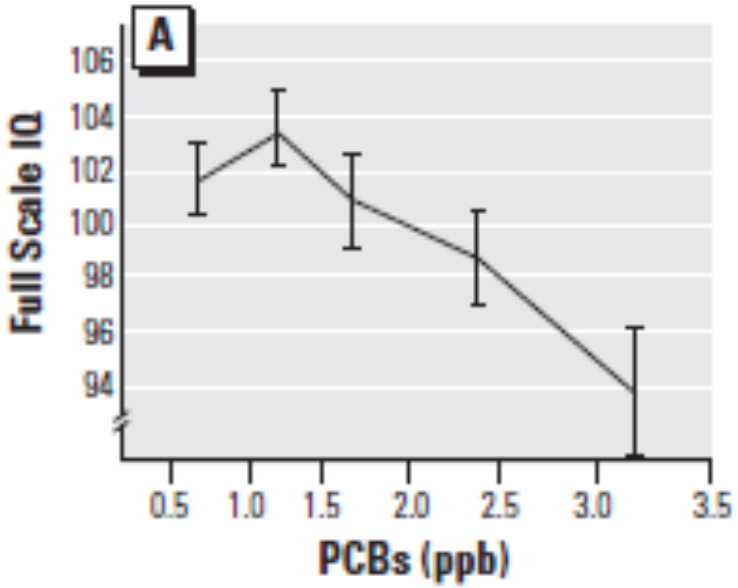


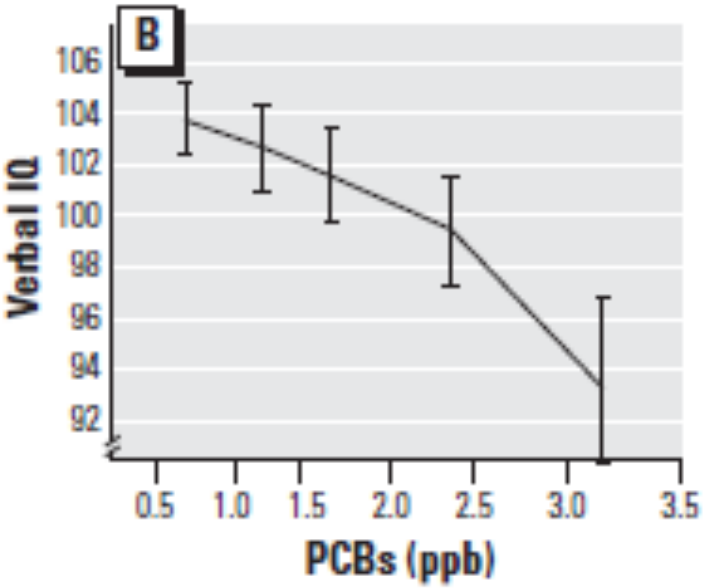
Atladottir HO et al., Eur Child Adolesc Psychiatry (2015) 24:173–183

EDCs and brain development

9 years after exposure to PCBs during his fetal life, this child has lost 10 points of IQ

Stewart et al., Environmental Health Perspectives 2008,116:1416–22





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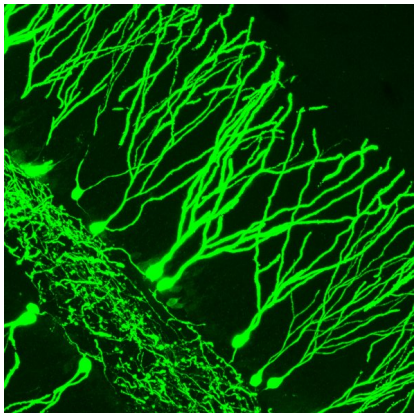

3 weeks after exposure to PCBs during fetal and neonatal life, neurons of this mice showed abnormal development

AS Parent et al, Eur J Neurosci 2017

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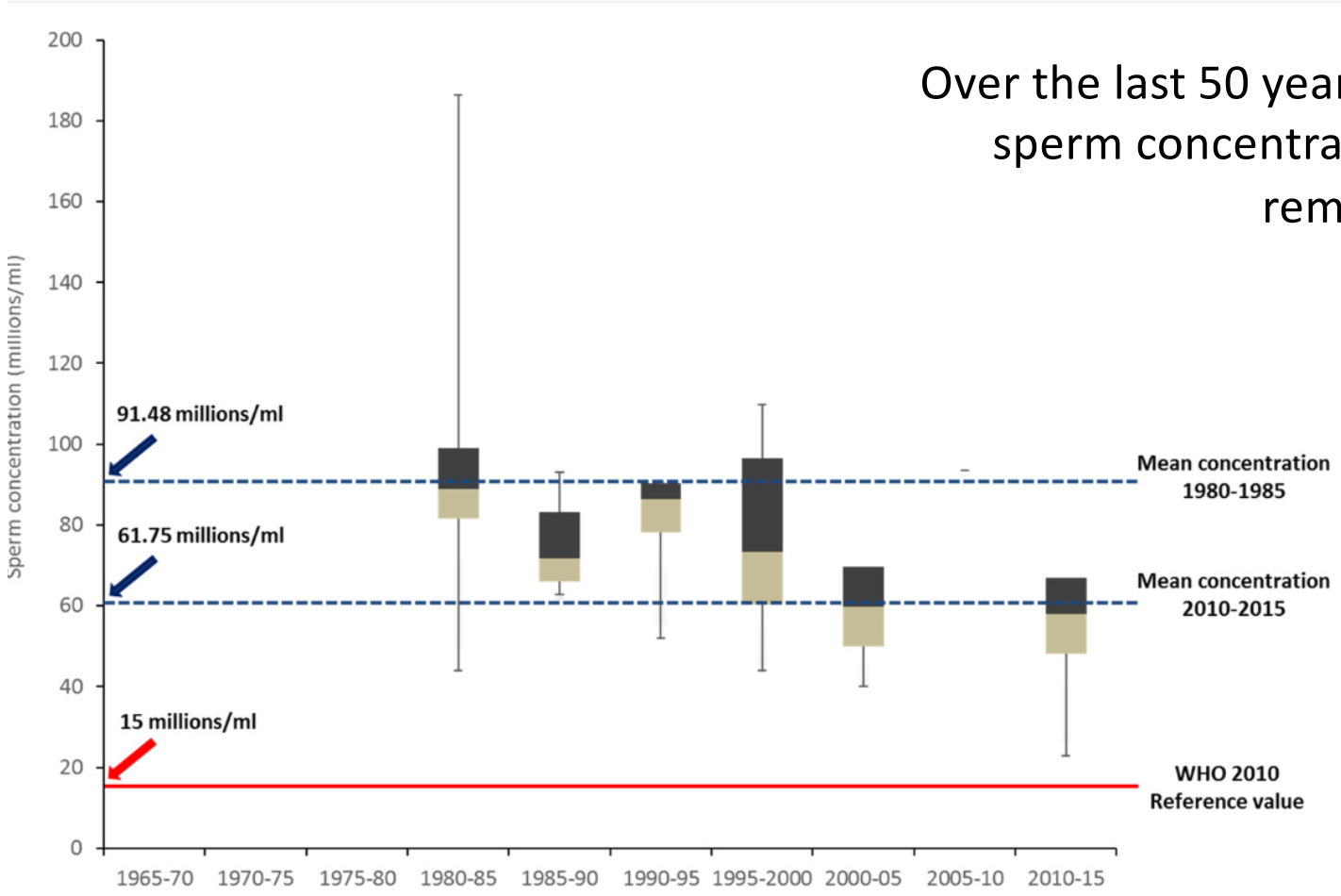
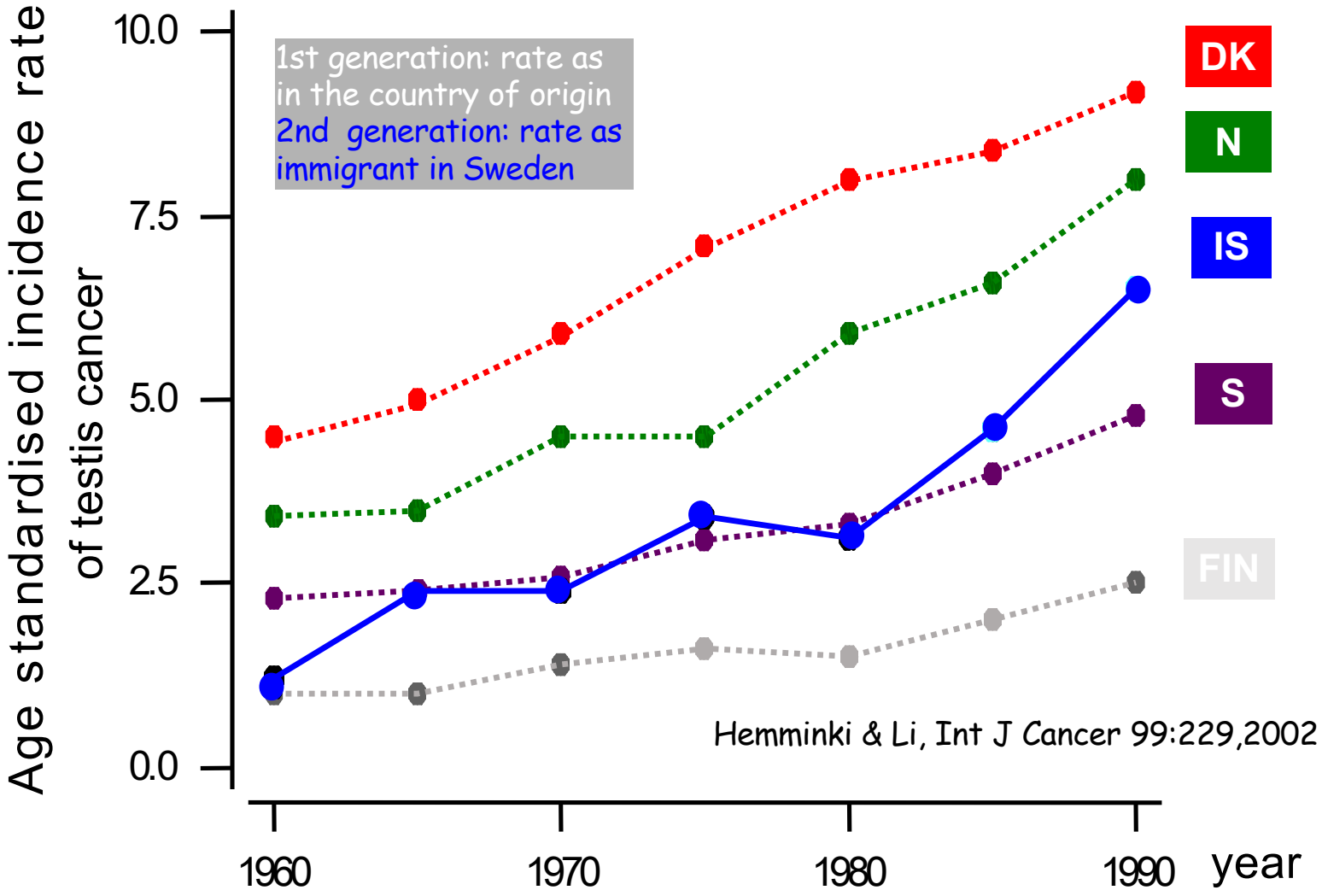
EDCs and sexual differentiation



Over the last 50 years, the 32.5% decrease in sperm concentration in men has been remarkable.

Sengupta 2017, Hum Exp Toxico

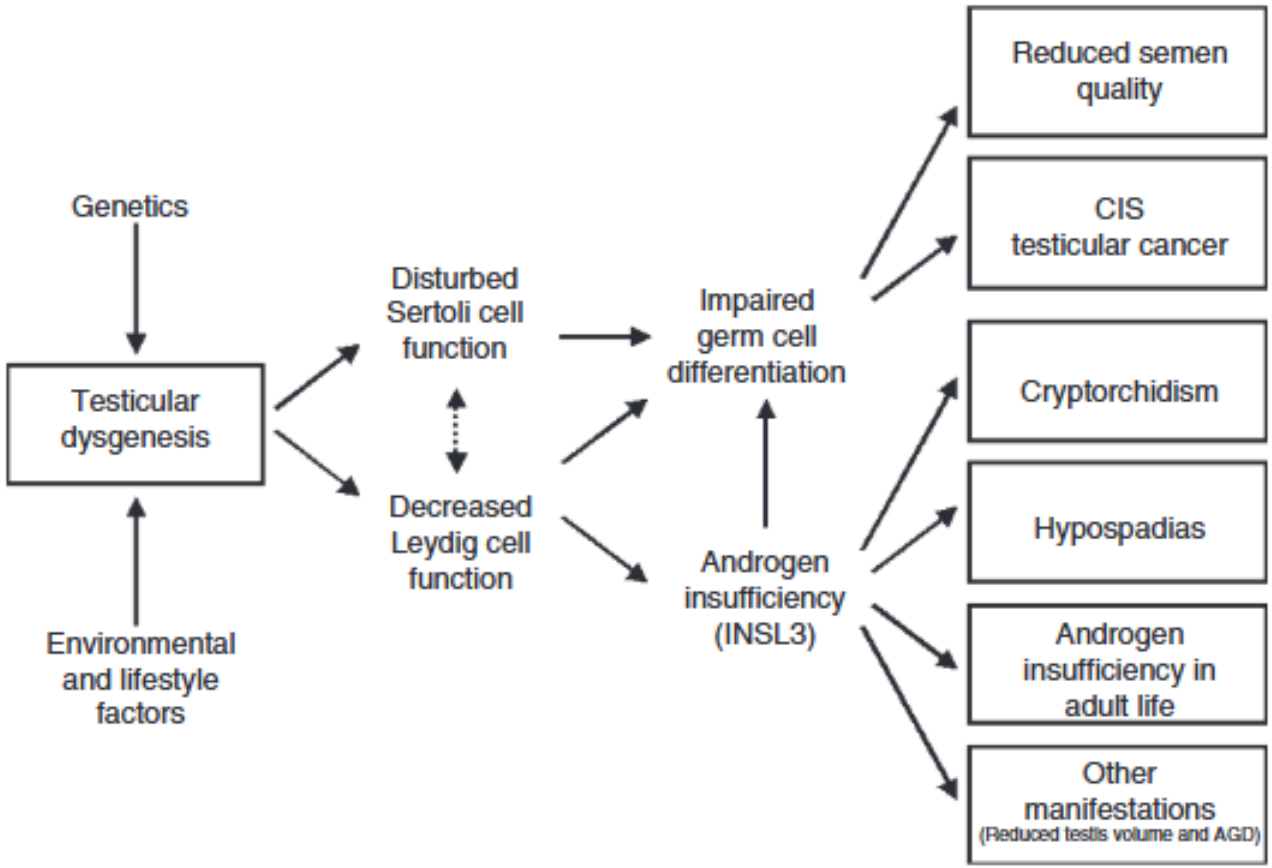
EDCs and sexual differentiation



- Increased incidence of testis cancer
- Second generation of immigrants to Sweden: same incidence as in Sweden

= > Fetal determinism ?

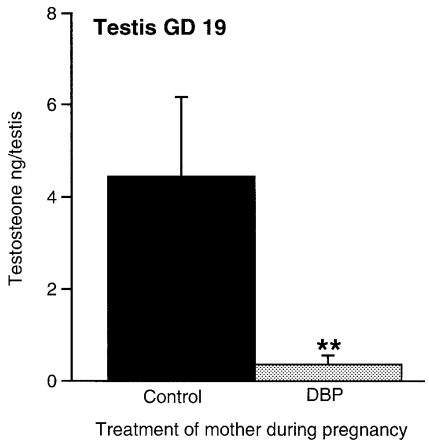
EDCs and sexual differentiation



Skakkebaek, Rajpert-DE Meyts and Main K 2001

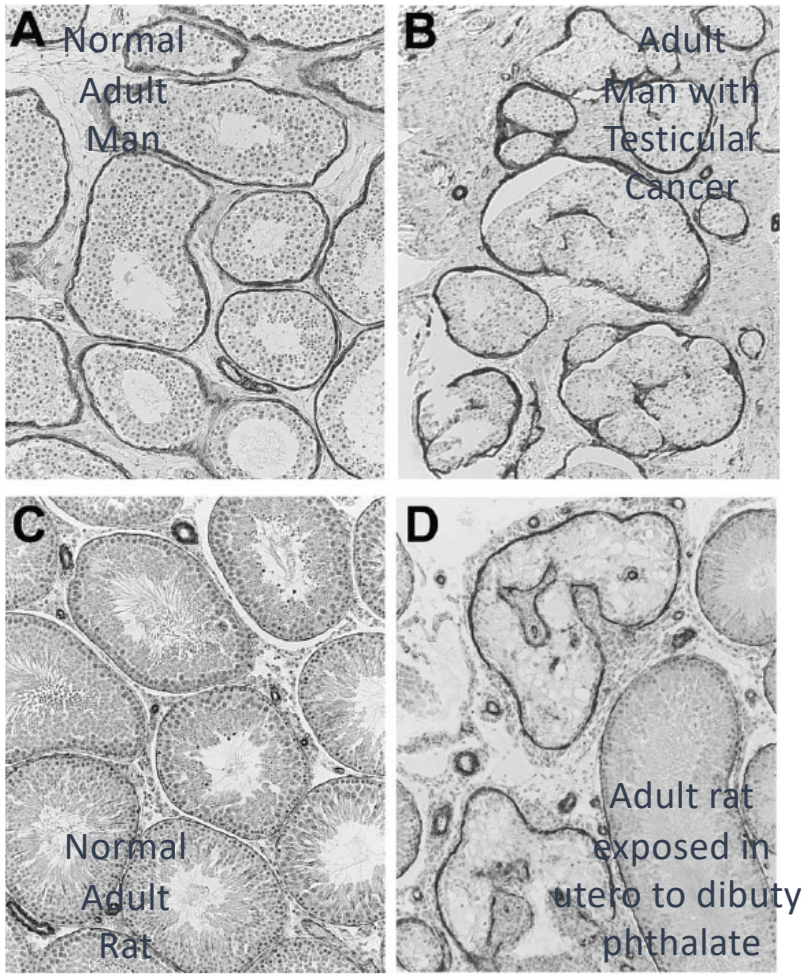
EDCs and sexual differentiation

TDS like condition after fetal rat exposure to phtalates (GD13-GD21)



	Control	DBP exposed
N	10	10
Fertile	9	2
Hypospade	0	6
Cryptorchidie	0	2 (bilat), 8 (unila)

Fisher et al 2003



Sharpe 2006

EDCs and sexual differentiation

Boys from mother with elevated prenatal exposure to phtalates had shorter anogenital distance

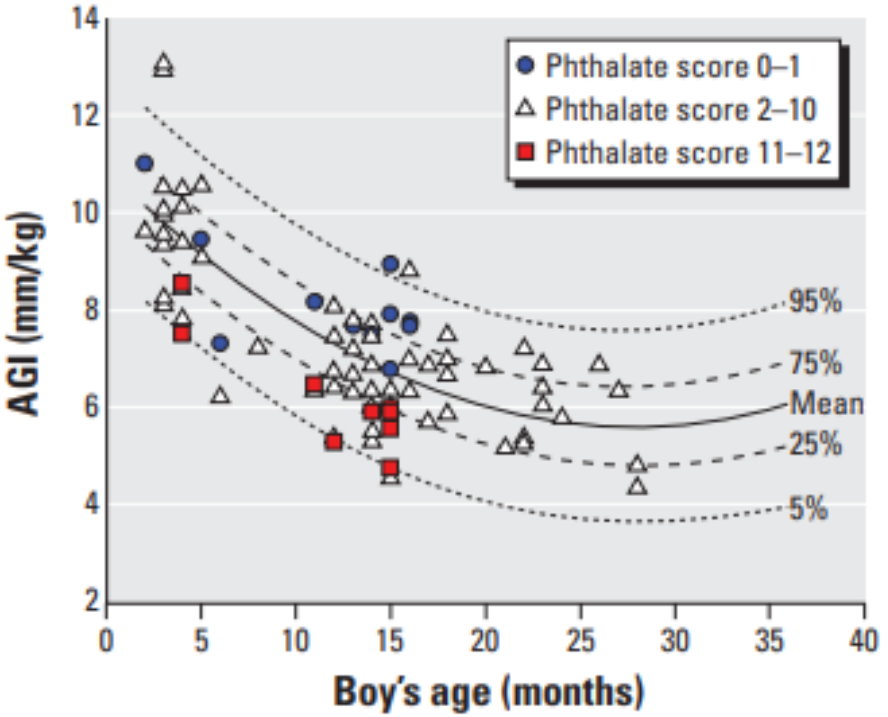
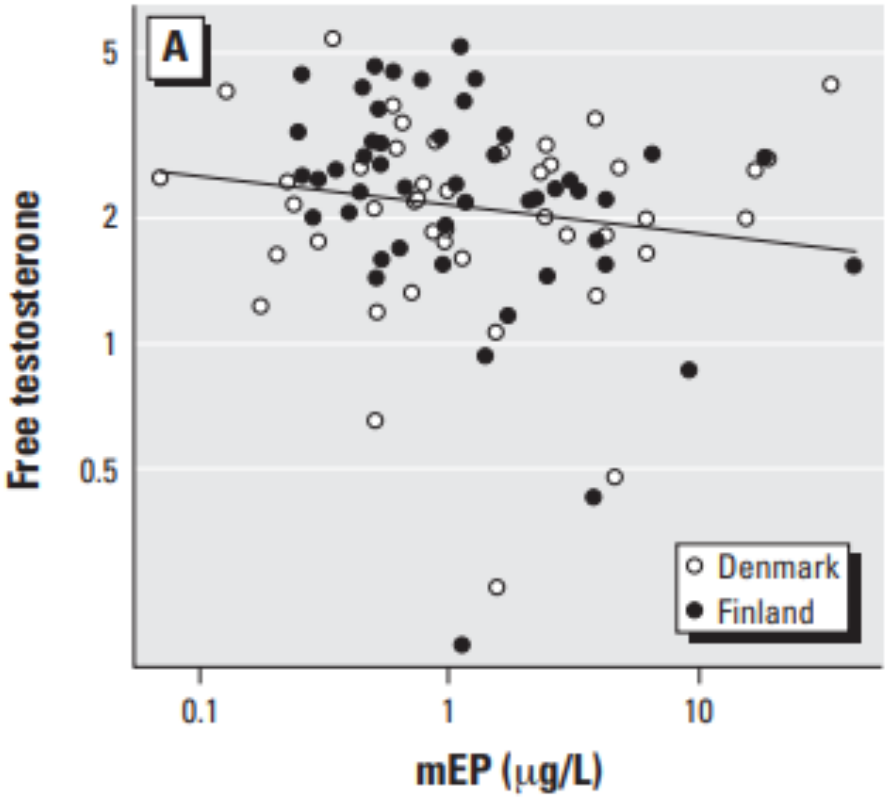


Figure 1. Mean AGI (mm/kg) in relation to boys' age at examination (months).

Swan et al 2005

Free testosterone levels in boys negatively correlated with phtalates levels in breast milk



Main et al 2006

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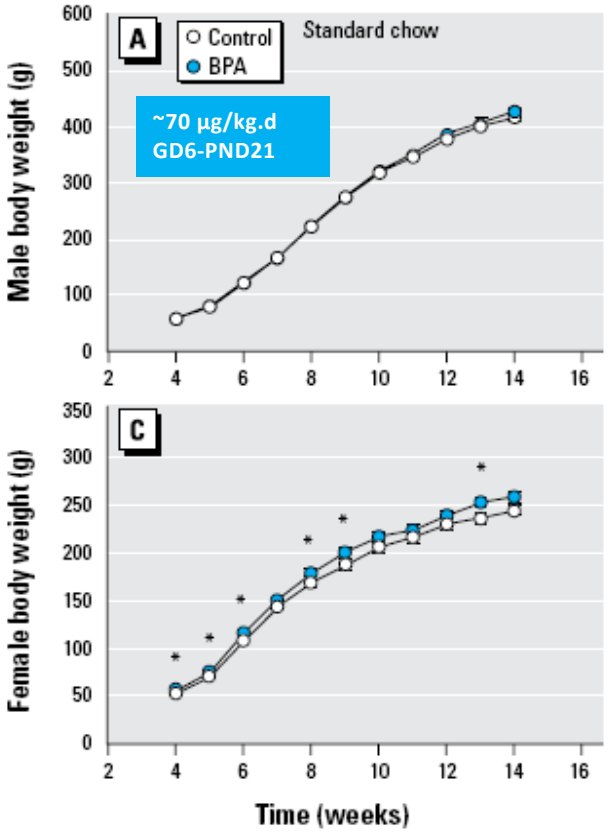
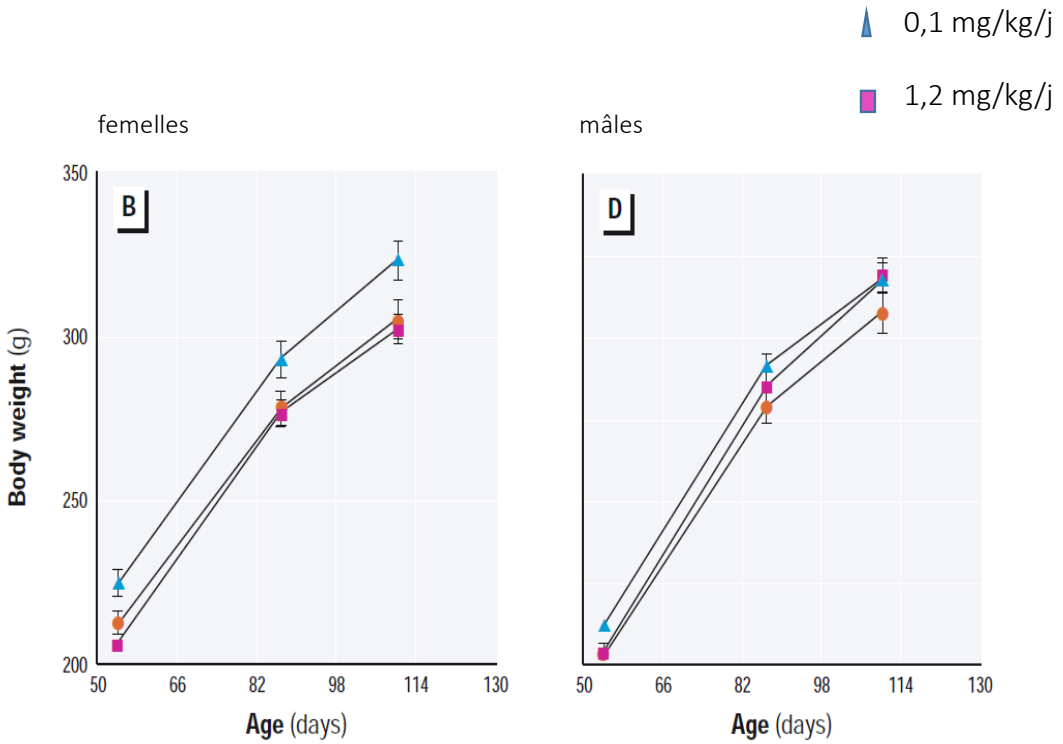
EDCs and energy balance

Obesity in female adult rat exposed during gestation and lactation to BPA

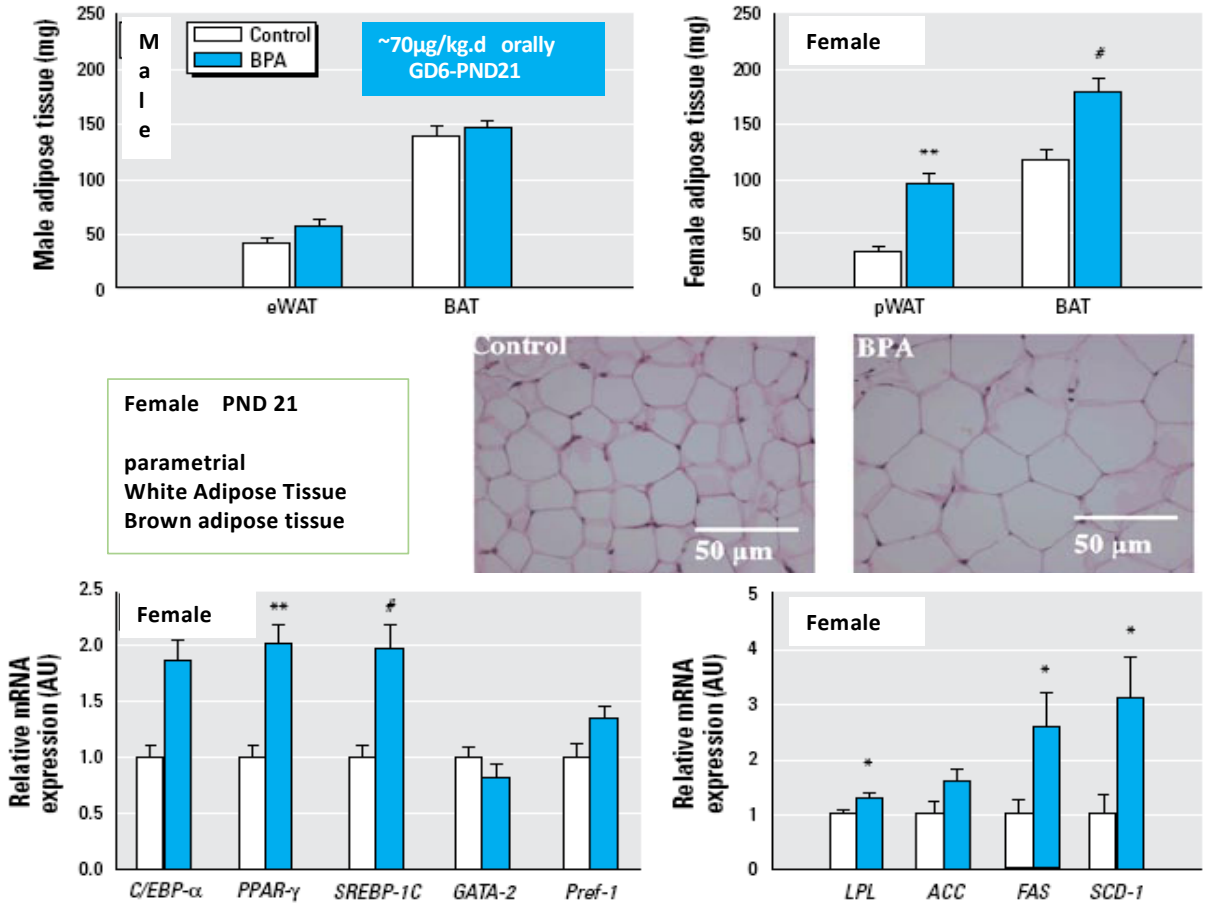


Somm E. et al Environ Health Perspect 117:1549–1555 (2009)



Rubin et al. Environ Health Perspect 109:675–680 (2001)

EDCs and energy balance



Gestational and neonatal exposure to BPA increases adipose tissue and expression of lipogenic genes in females

Somm E. et al Environ Health Perspect 117:1549–1555 (2009)

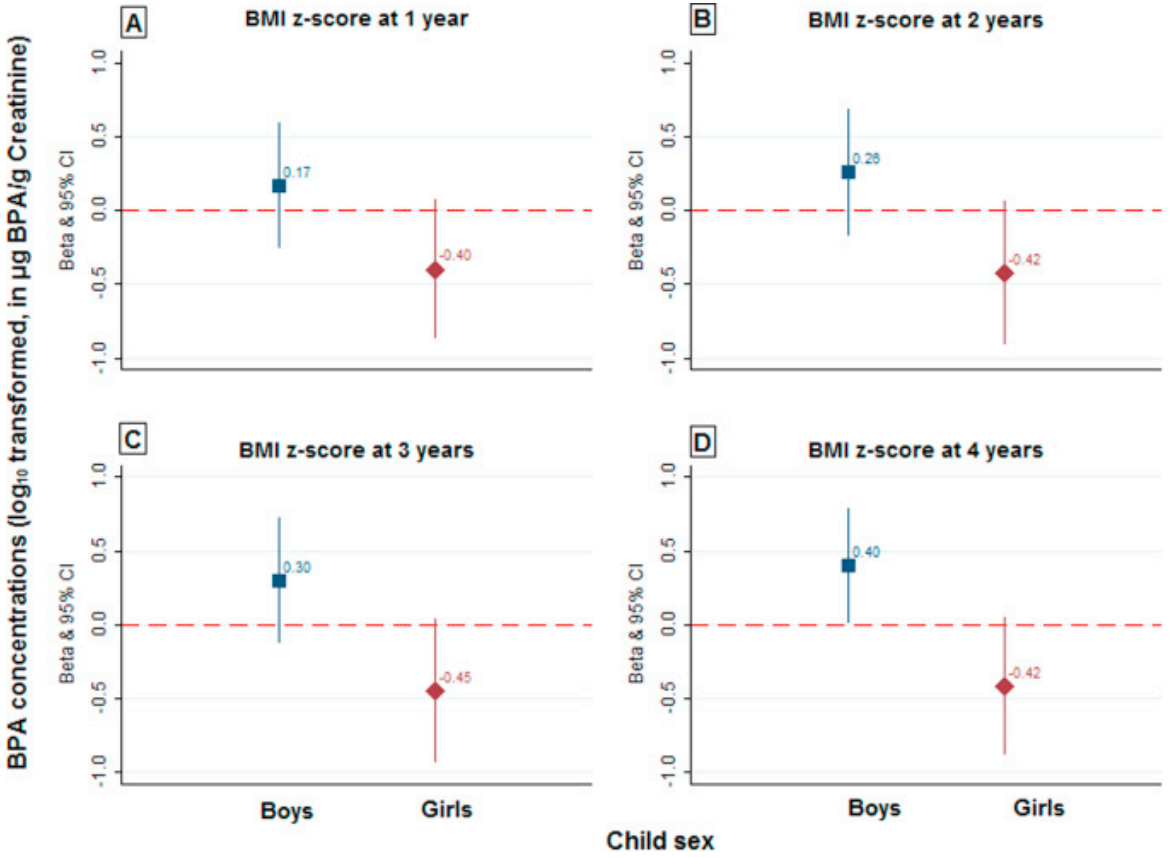
Association between urinary BPA and overweight and obesity in children

Quartile	Prevalence of overweight
1	28.5%
2	34.3%
3	36.6%
4	36.5%

Quartile	Prevalence of obesity
1	9.8%
2	19.9%
3	19.1%
4	22.5%

Trassande L et al, JAMA 2012

EDCs and energy balance



No significant association between prenatal BPA exposure and BMI Z Score at 1,2,3 and 4 years old

Vafeiadi et al, 2016
Environ Health Research

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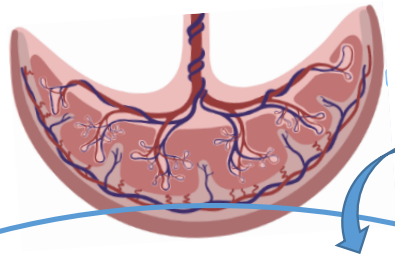
Role of placenta in DOHaD

Environmental factors
Endocrine disruption
nutrition

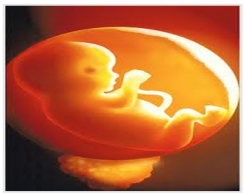
Maternal conditions
Gestational diabetes
Obésity
Stress



♀♂

epigenome ⟷ transcriptome

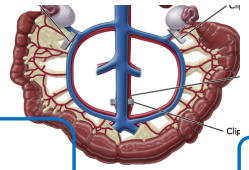
Placental development and function



Fetal programming

Pregnancy conditions (IUGR, HTA, PE)

Early exposure to BPA/BPS and placenta



BPA 4 µg/kg/j BPA 25 ng/kg/j
BPS 4 µg/kg/j BPS 25 ng/kg/j

♀♂

BPS 25 ng/kg/j

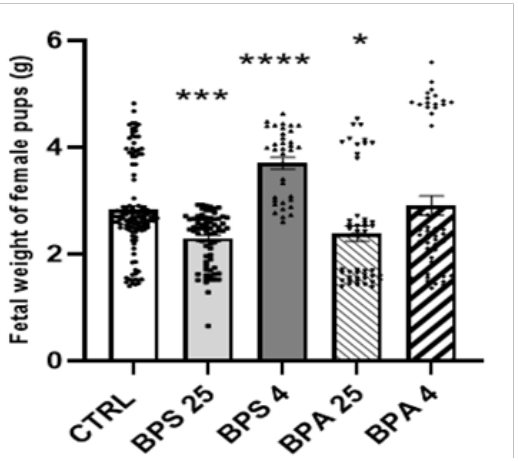
1 week before mating | GD1 | GD18 de gestation | GD21 | GD90

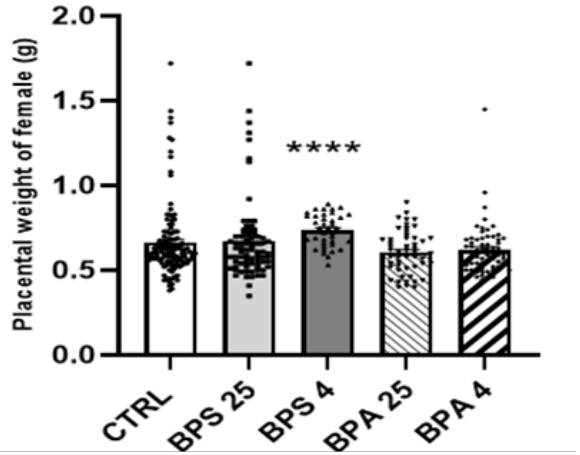
- Fetal and placental weight
- Sex determination
- Transcriptome in female placenta(séquençage ARNm)
- DNA methylation of specific genes(séquençage au bisulfite)

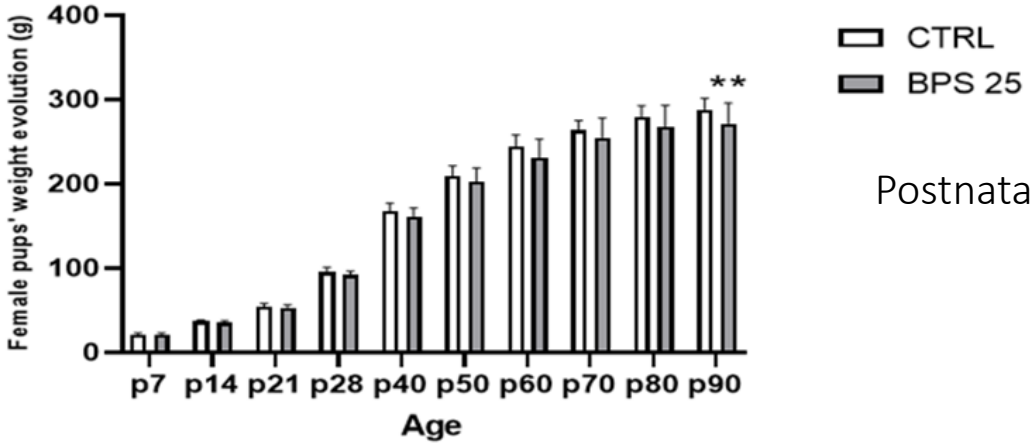
- Vaginal opening
- Cyclicity
- Balano-preputial separation
- Weight gain

Early exposure to BPA/BPS and placenta

Female fetal growth is affected by gestational exposure to BPS 25





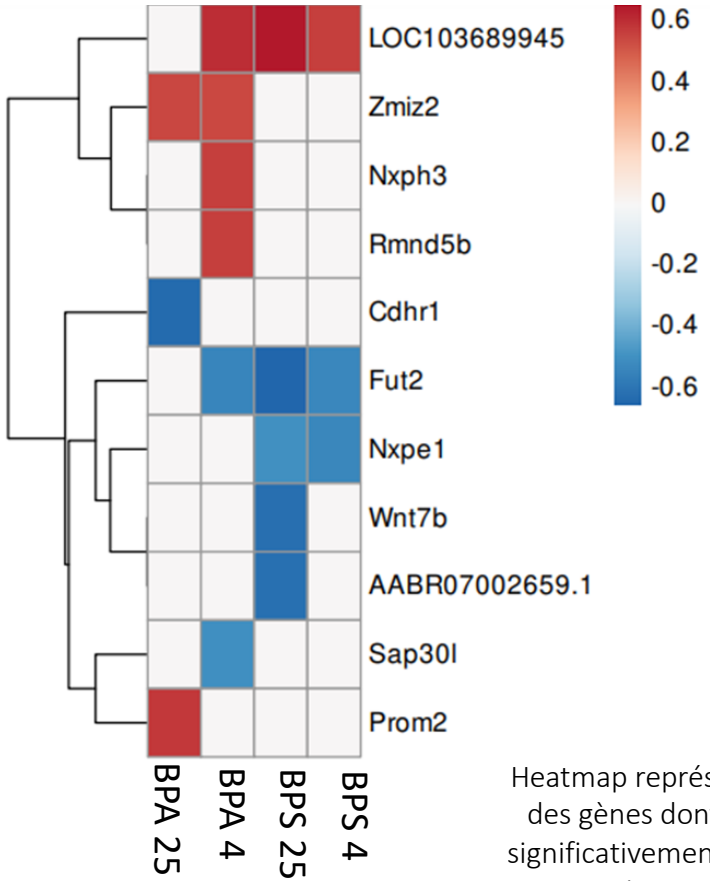


Postnatal female growth is affected by exposure to BPS 25

Fudvoye J et al, in revision

Early exposure to BPA/BPS and placenta

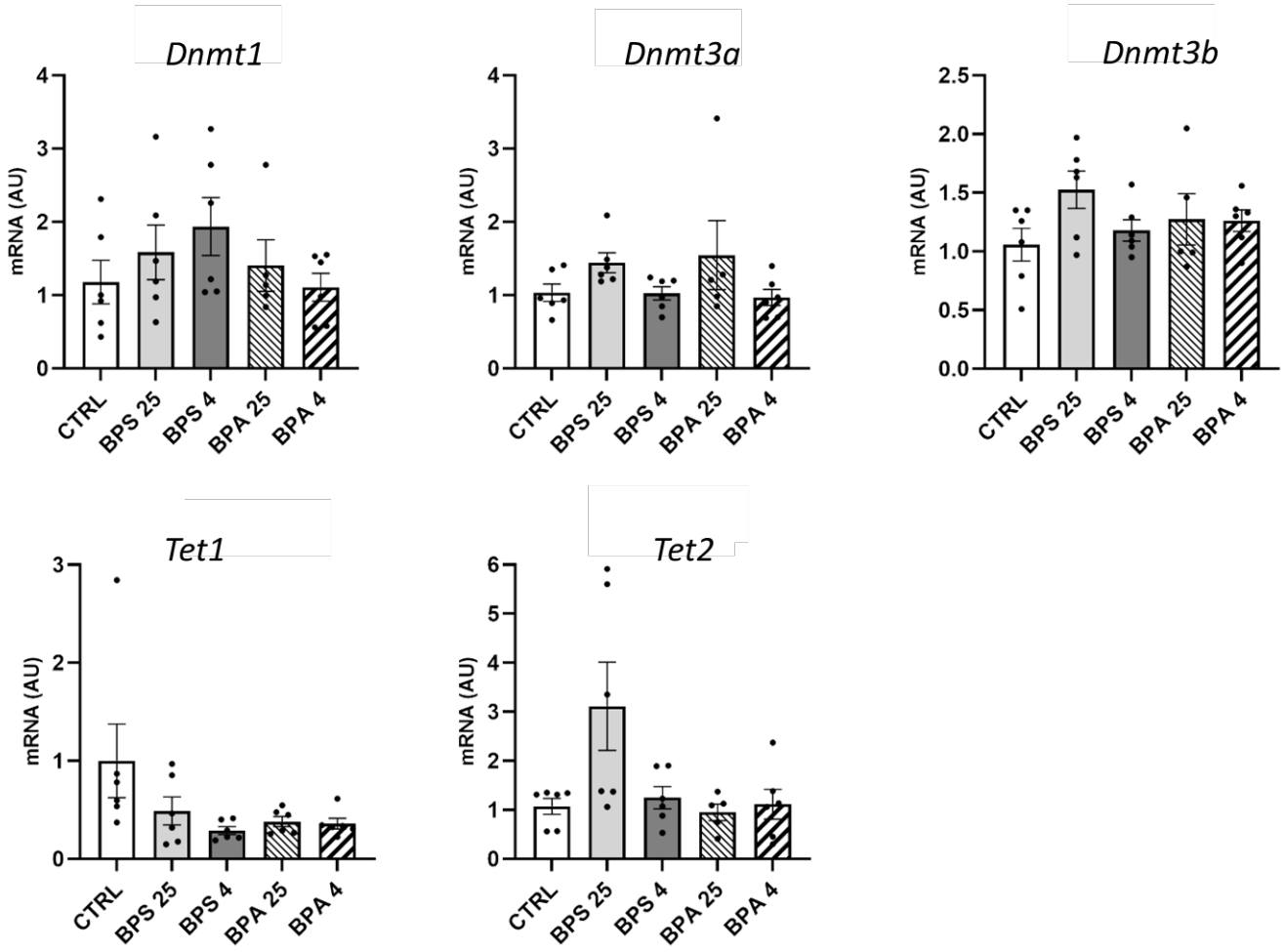
Exposure to BPA and BPS affects the expression of specific genes



Heatmap représentant le log 2 FC des gènes dont l'expression est significativement affectée dans au moins un des groupes

Fudvoye J et al, in revision

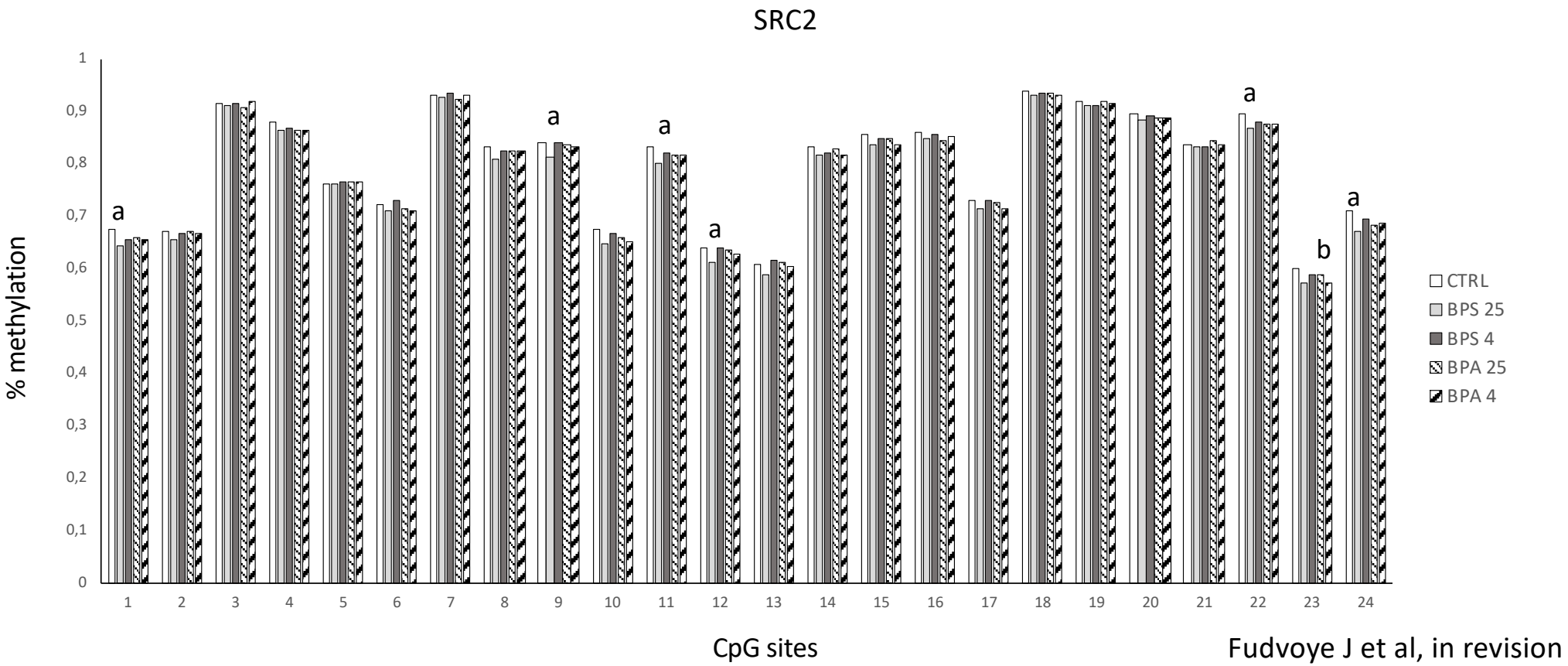
Early exposure to BPA/BPS and placenta



Fudvoye J et al, in revision

Early exposure to BPA/BPS and placenta

Prenatal exposure to BPS 25 decreases DNA methylation in SRC2 promoter in female placentas



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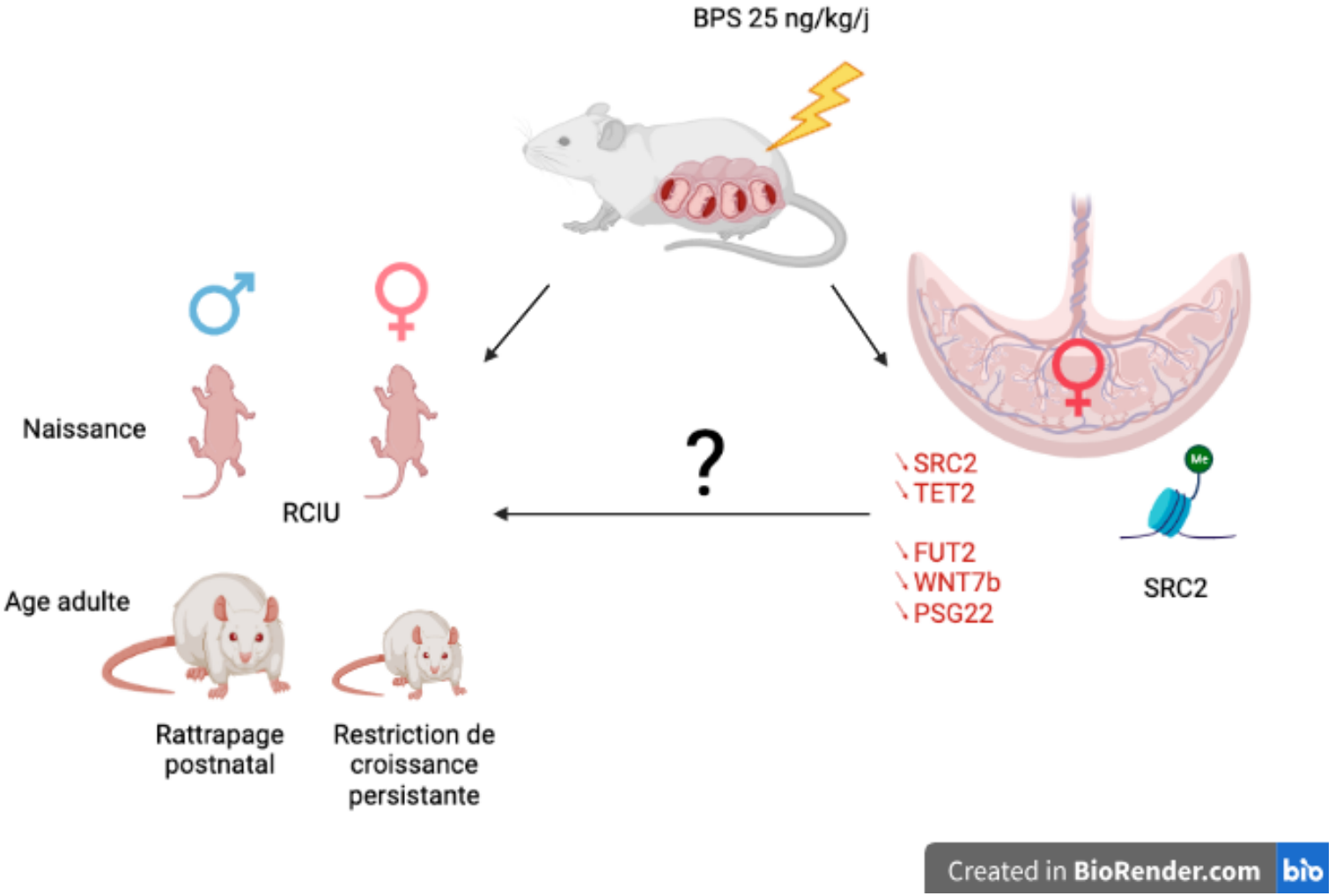


Conclusion

- Early fetal environment is crucial for the lifelong health

- There are accumulating evidence about the detrimental effects of early exposure to EDCs. However, demonstrating the endocrine disruption remains a challenge:

- Variable persistence in the organism and the environment (PCBs, DDE, ..)
- Long latency between effects and exposure
- Different effects regarding the period of exposure and the duration
- Effects of low dose mixtures
- Multiple mechanisms, epigenetic effects

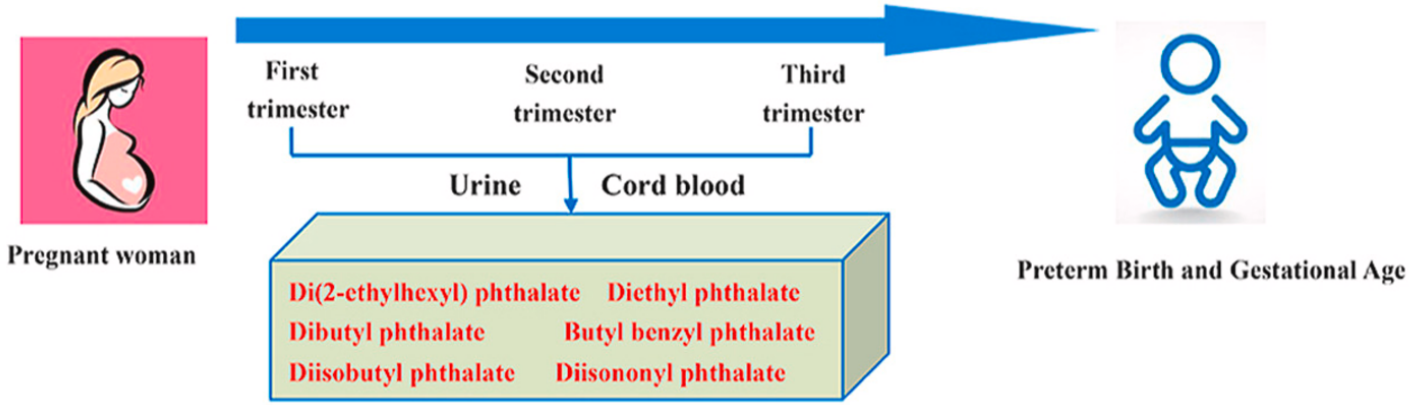
- Recommandations based on the precaution principle

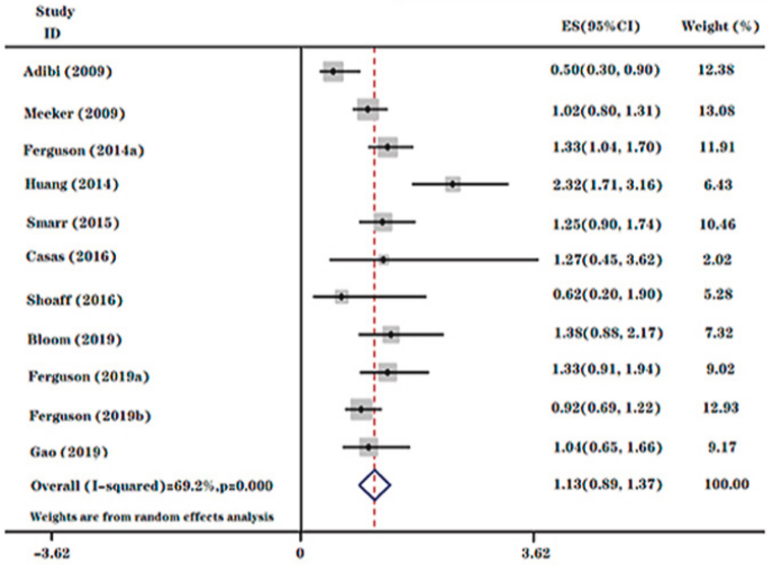
Examples of recommendations based on the precaution principle

CONDITION		MEASURE	*FEASIBILITY*
Nutrition & management	**Baby bottles**	Prioritize glass ; using plastics, exclude polycarbonate (7) and prefer polyethylene or polypropylene	Evidence-basing? Informing? Labelling? Reading? Banning? Distressing?
	Food heating	Glass receptables; no plastic in microwaves	
	Food/liquid containers	Prefer glass to plastics or metal cans; Avoid canned food	
	Fruits/ vegetables	Wash thoroughly; prioritize unprocessed products & raised without pesticides	
	Soy products	Breast feed infants whenever possible and minimize use of soy formula till long-term safety is clarified	
	Fish	Refrain from consuming top predator wild fish more than once a week	
Others	**No smoking**	Prevent fetal toxicity of tobacco and associated EDCs	
	Cosmetics	Avoid unnecessary skin cream or lotion; when necessary, prioritize products without parabens	
	In-house environment	Avoid or limit the use of air freshener and paint; do not use insect repellents (sprays or 'hang-up bars');	
	Furniture	Do not use new furniture/carpets (flame retardants)	
	Gardening	Avoid use of insecticides, fungicides	
	Patient care	Avoid or limit perfusion material containing phthalates	

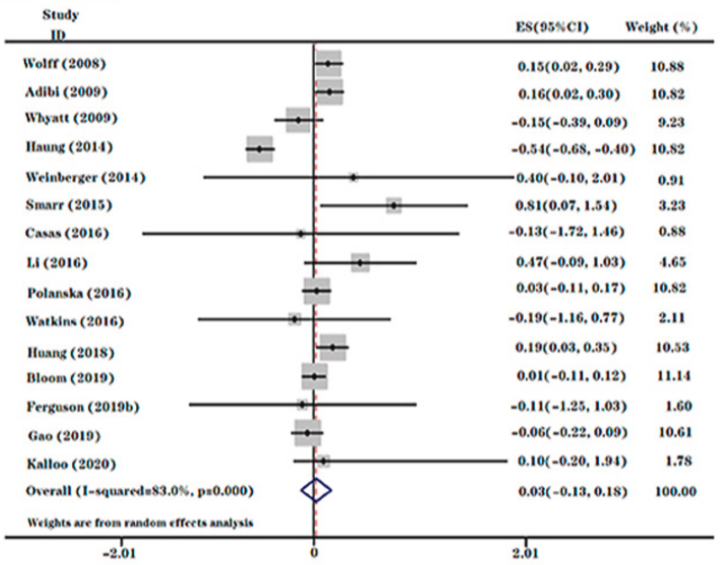
Thank you for your attention

What about neonatology ?





Di(2-ethylhexyl) phthalate and preterm birth



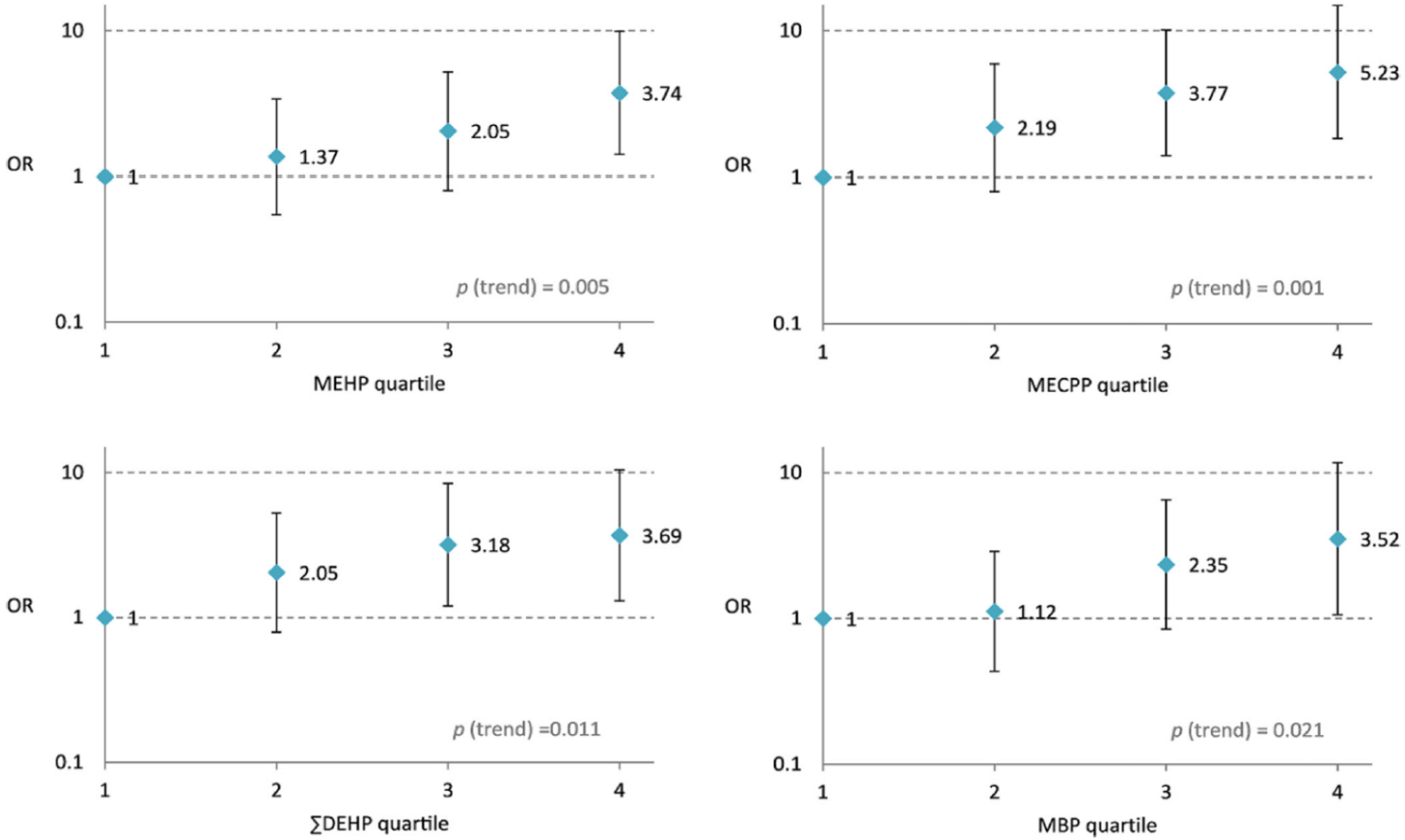
Di(2-ethylhexyl) phthalate and gestational age

EDCs and premature birth ?

JAMA Pediatr. 2014 Jan;168(1):61-7. doi: 10.1001/jamapediatrics.2013.3699.

Environmental phthalate exposure and preterm birth.

Ferguson KK[1], McElrath TF[2], Meeker JD[1].



EDCs and premature birth ?

Endocrine disruptors	Naissance prématurée	Age gestationnel		
	OR ↗	↘	↔	↗
Bisphenol A • production of epoxy resins and polycarbonate plastics • High levels in amniotic fluid and umbilical cord	Cantonwine et al. 2015 (BPA urinaire T3)		Wolff et al. 2008 (BPA urinaire T3)	
	Huang et al. 2019 (BPA urin T1 T2 T3)	Huang et al; 2019 (BPA urin T1 T2 T3)	Padmanabhan et al. 2008 (BPA sang maternel)	
	Padmanabhan et al, 2015			
		Weinberger et al. 2013 (BPA urinaire grossesse)		
Phtalates • Present in many consumer products • found in lotions, perfumes, and deodorants • platiscizers • Present in medical devices	Meeker et al, 2009 (Phtal urin T3)			
	Zhang et al 2020 (Phtal urin preconception)	Whyatt et al. 2009 (Phtal urin T3)		
	Walsh et ak 2022			Wolff et al, 2008 (u PthT3)
			Suzuki et al, 2010 (phtal urin)	
	Fergusson et al. 2014 (Pht urinaires, 4 spots)			
		Latini et al, 2003 (MEHP sg cordon)		

remature neonates are born before 37 weeks of pregnancy due to low birth weight (<2500 g) or a health condition requiring specialized medical care. Of all phthalates, DEHP is the most widely used plasticizer in medical devices (Den Braver-Sewradj et al., 2020). Few studies have reported elevated urinary levels of phthalate metabolites in preterm infants with low birth weight during the first weeks of intensive care or undergoing invasive procedures (Demirel et al., 2016; Frederiksen et al., 2014; Strommen et al., 2016). Another significant source of phthalate exposure, particularly for children and neonates, comes from total parenteral nutrition (TPN) (Demirel et al., 2016; Kambia et al., 2003; Loff et al., 2008). Exposure to DEHP in the neonatal intensive care unit (NICU) can significantly exceed the safe limit, and this might contribute to common short- and long-term complications of prematurity (Mallow and Fox, 2014). As preterm neonates have a small body size and pre-existing health conditions, the CRA of phthalate source of exposure in the NICU may be underestimated and should be of concern. Studies are lacking, and assessing the exposure of preterm neonates to anti-androgenic phthalates is crucial in evaluating their effects on fetal development and child health as they mature.