

Children's Environments, Health and Wellbeing: Making the Links, November 28, 2013




The importance of healthy eating:
How early life exposures to contaminants in food can lead to obesity and related diseases later in life

Prof. Juliette Legler
Institute for Environmental Studies, VU University
Amsterdam, The Netherlands

Why Do Some People Become Obese?
When Does Obesity Start?



Overweight/Obese (20-40%) Normal Weight (60-80%)

WHY?
Genetics AND Environment


Slide courtesy of Jerry Heindel, NIEHS

Developmental Origins of Health and Disease (DOHaD)

- Adverse fetal environment leads to a **functional** change resulting in increased susceptibility to disease later in life
- Maternal risk factors for obesity:
 - Over/under nutrition
 - Disease, stress
 - Smoking
 - **Exposure to environmental chemicals?!**



DOHaD: Dutch Hunger Winter (1944)



Prenatal famine (low birth weight) associated with adult incidence of:


- CV disease
- Obesity
- Cognitive dysfunction

“Adverse fetal environment followed by plentiful food in adulthood may be a recipe for adult chronic disease”.

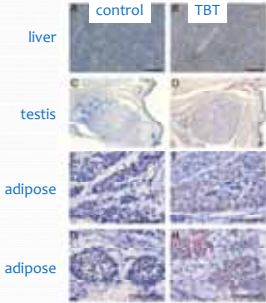
Schulz, 2010 PNAS

Evidence of obesogenic effects of chemicals

1. Animal studies



Synthetic estrogen (DES)
(Newbold et al., 2007, *Repro.Tox*)



control TBT

liver

testis

adipose

adipose

Pesticide (tributyltin TBT)
(Grun et al., 2006, *Mol.Endocrin.*)

Evidence of obesogenic effects of chemicals

2. Epidemiological studies



ACTA PEDIATRICA
Official Journal of the International Society for Pediatric Endocrinology

REGULAR ARTICLE

Exposure to hexachlorobenzene during pregnancy increases the risk of overweight in children aged 6 years

Agnes Smiå ¹ (e-smi@iuhm.uu.se), Maria Ribas-Far ², Roger Garcia ², Males Terres ³, Michelle A Mendes ⁴, Juan O Grimal ⁵, Jordi Sunyer ^{1,6}

Intrauterine Exposure to Environmental Pollutants and Body Mass Index during the First 3 Years of Life

Stijn L. Verhulst ¹, Vera Nelen ², Elly Den Hond ^{3,4}, Gudrun Koppen ^{5,6}, Caroline Beunckens ⁷, Carl Vael ⁸, Greet Schoeters ^{1,4} and Kristine Desager ¹

¹Department of Pediatrics, University of Antwerp, Antwerp, Belgium; ²Provincial Institute for Hygiene, Antwerp, Belgium; ³MIG (Flemish Institute of Technological Research), Melle, Belgium; ⁴Department of Biomedical Sciences, University of Antwerp, Antwerp, Belgium; ⁵Center for Statistics, Hasselt University, Hasselt, Belgium; ⁶Department of Microbiology, University of Antwerp, Antwerp, Belgium

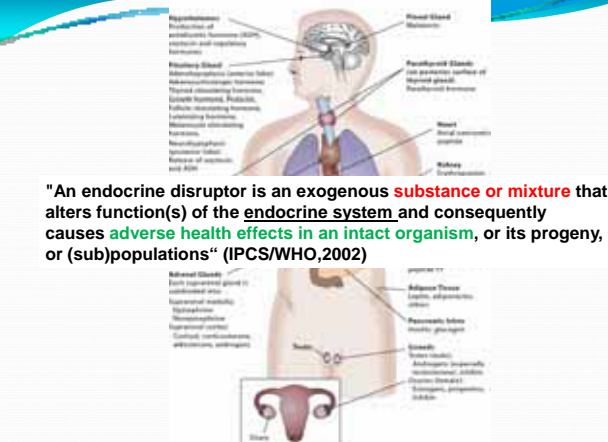
Environmental Health Perspectives • VOLUME 117 | NUMBER 1 | January 2009



BELIX

**OBesogenic Endocrine disrupting chemicals:
Linking prenatal exposure to the
development of obesity later in life**

- European Commission FP7 funded research project
- 7 laboratories throughout Europe
- Project duration: May 2009 – November 2013



"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" (IPCS/WHO,2002)

Hypothalamus: Production of antidiuretic hormone (ADH), prolactin and vasopressin hormones.

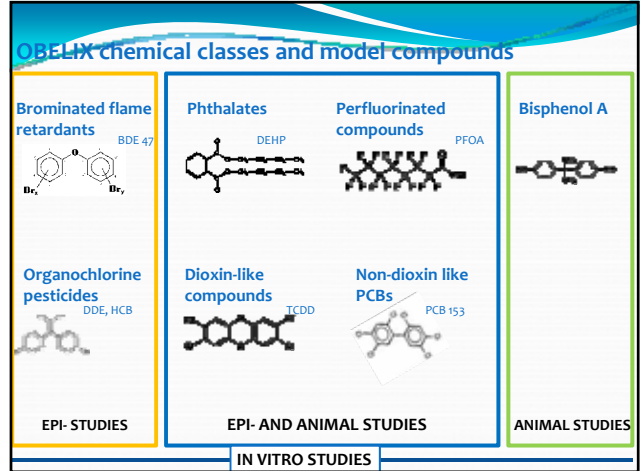
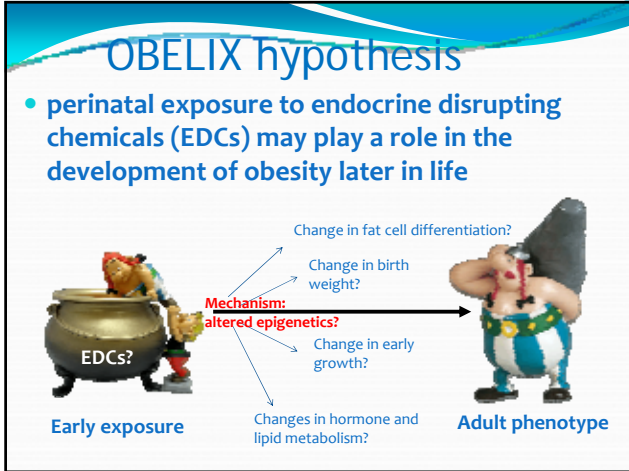
Pituitary Gland: Gonadotropin-releasing hormone (GnRH), somatotrophic hormone (GH), prolactin-releasing hormone (PRH), growth hormone-releasing hormone (GHRH), vasopressin-releasing hormone (VRH), neurohypophysial hormones (oxytocin and vasopressin).

Thyroid Gland: Thyroxine (T4), triiodothyronine (T3), calcitonin.

Parathyroid Gland: Calcitonin-receptor-related protein (CGRP), parathyroid hormone (PTH).

Adrenal Gland: Cortisol, corticosterone, and androgens.

Other glands shown: Hypothalamus, Pituitary Gland, Thyroid Gland, Parathyroid Gland, Adrenal Gland, Pancreas, Ovary, Testis.



Dioxin-like compounds

TCDD

Dioxins and furans
(By-products of waste incineration)
Selected PCBs (AhR agonists)

Non dioxin-like polychlorinated biphenyls (NDL-PCBs)

PCB 153

Industrial applications (dielectric fluids, transformers etc),
banned since 1980

Organochlorine pesticides

DDT

HCB

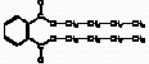
Insecticides or fungicides
DDT (ppDDE), HCB: no longer in use in Western countries

Brominated Flame Retardants (BFR)

BDE 47

Consumer products
Electrical appliances


Phthalates



DEHP

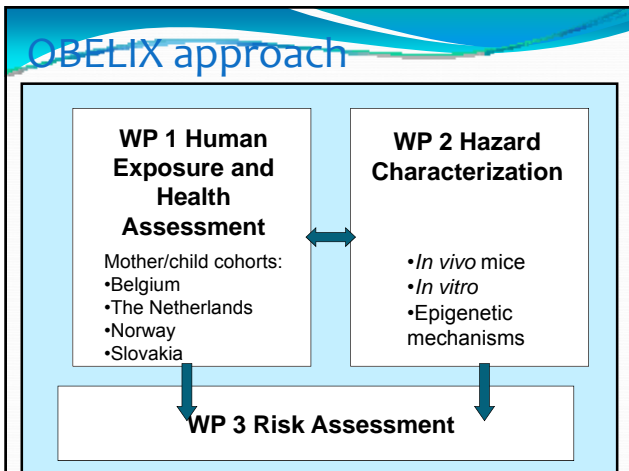
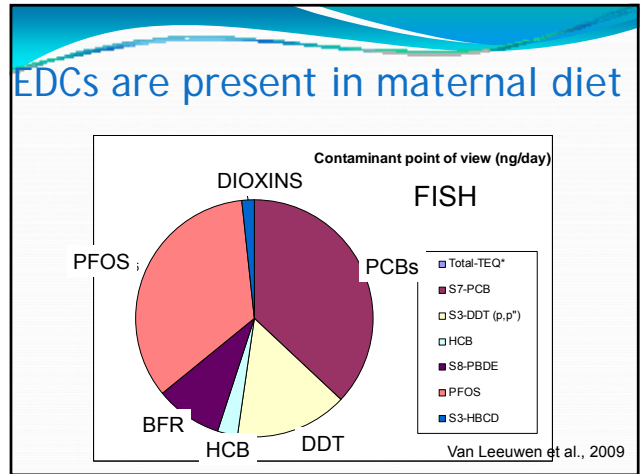
Plasticizers in various plastics
eg. food packaging, bottles

Perfluorinated compounds



PFOS

Surfactants in fire fighting foams,
aviation fluids, water and dirt
repellent, mist suppressant etc.



OBELIX cohorts

Country	Name cohort	Recruitment Period	No.	Age at Follow-up
Belgium	FLEHS-1	2002-2004	1196	3,6,12,18,24, 36 m, 3, 8 years
	FLEHS-2	2008-2009	250	6, 12 months
Norway	HUMIS	2003-2008	2000	1, 6, 12, 24 months, 8 years
Slovak Republic	Michalovce	2003-2005	1134	6,16,45 months, 7 years
Netherlands	Zwolle/LINC	2011-2013	200	1,6,9,12,24,36,48 months

Major research questions in human studies

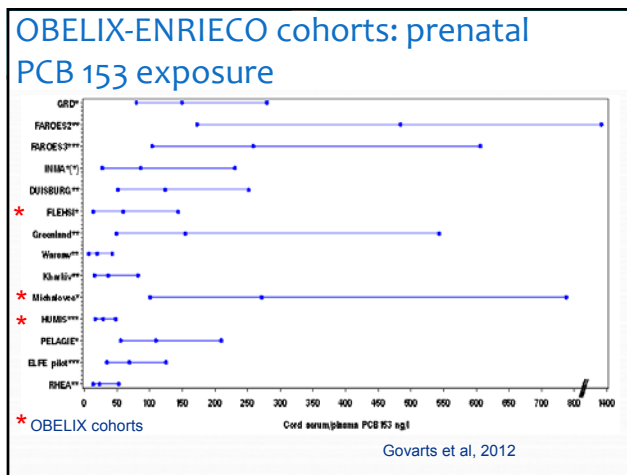
- Prenatal exposure to EDCs and
 - birth outcomes (birth weight, SGA/LGA)
 - thyroid hormones at birth
- Pre- and postnatal exposure to EDCs, early childhood growth and BMI at 2 and 7 years
- Pre- and postnatal exposure to EDCs and metabolic hormones (insulin, leptin, adiponectin) at birth and age 7 years

Prenatal exposure to EDCs and birth weight

Birth Weight and Prenatal Exposure to Polychlorinated Biphenyls (PCBs) and Dichlorodiphenyldichloroethylene (DDE): A Meta-analysis within 12 European Birth Cohorts

Eva Govarts,¹ Mark Nieuwenhuijzen,^{2,3,4} Greet Schoeters,^{1,5} Ferran Ballster,^{2,6,7} Kerstin Bloemen,¹ Michiel de Boer,⁸ Cecile Chevrier,^{9,10} Merete Eggesbø,¹¹ Mónica Guisasa,^{2,12} Ursula Krämer,¹³ Juliette Legler,¹⁴ David Martinez,^{2,7} Lubica Palkevicova,¹⁵ Esviki Patalary,¹⁶ Ulrich Ranft,¹⁷ Arja Rautio,¹⁸ Maria Skarlam-Petersen,¹⁹ Ilse Stang,^{10,19} Hain Stigum,²⁰ Gunnar Taru,²¹ Tomas Tizovac,¹⁴ Stephanie Vandentorren,²¹ Pal Weihe,¹⁷ Ajnska Weigula-Kasperus,²² Michael Wilhelm,²³ Jürgen Wittsiepe,²⁴ and Jens Peter Bonde,²⁵ and OBELIX/ENRIECO

VOLUME 120 | NUMBER 2 | February 2012 • Environmental Health Perspectives



Statistical analysis prenatal PCB 153 and birth weight

- Multiple linear regression in separate cohorts
- Meta-analysis: random-effects model for individual estimates
- Selected covariates
 - Gestational age
 - Region
 - Ethnicity
 - Maternal age
 - Parity
 - Gender
 - Prepregnancy weight
 - Maternal BMI
 - Socio-economic status

Statistical analysis prenatal PCB 153 and birth weight

Study	β (95% CI)	No. of subjects
ABCD	-0.286 (-0.758, 0.186)	1023
BRUNNEN	-0.038 (-0.762, 0.687)	187
BRUNNEN	-0.084 (-0.768, 0.600)	769
INMA cord	-0.191 (-0.327, -0.107)	1,222
INMA neon	-0.027 (-0.068, 0.794)	954
WISCONSIN	-0.028 (-0.222, 0.167)	109
PEHSI	-0.090 (-0.322, 0.142)	196
Greenland	-0.180 (-0.323, -0.037)	545
Wisconsin	-0.082 (-0.768, 0.604)	196
Alaska	0.075 (-0.168, 1.310)	571
Michigan	-0.012 (-0.087, 0.063)	976
WISCONSIN	-0.294 (-0.082, 1.278)	499
PELAGOS	-0.027 (-0.087, 0.033)	383
ELIZ	0.269 (-1.792, 1.255)	42
Combined effect (random)	-0.10 (-0.24, 0.05)	1,888

Birth weight declined by 150g (95% CI 50-250 g) per 1µg/L increase in PCB 153 cord serum concentration

Govarts et al, EHP, 2012

Meta-analysis prenatal DDE and birth weight

Study	β (95% CI)	No. of subjects
BRUNNEN	-0.017 (-0.262, 0.228)	187
BRUNNEN	-0.027 (-0.092, 0.037)	546
INMA cord	-0.005 (-0.019, 0.009)	1,222
INMA neon	0.012 (-0.013, 0.037)	954
WISCONSIN	-0.009 (-0.260, 0.242)	109
PEHSI	0.024 (-0.021, 0.148)	196
Greenland	-0.011 (-0.122, 0.099)	545
Wisconsin	-0.107 (-0.229, 0.016)	196
Alaska	0.014 (-0.082, 0.109)	571
Michigan	-0.010 (-0.040, 0.020)	976
WISCONSIN	-0.189 (-0.048, 0.269)	499
PELAGOS	0.022 (-0.108, 0.152)	383
ELIZ	0.019 (-0.221, 0.261)	42
Combined effect (random)	-0.007 (-0.016, 0.002)	1,821

NO effect of DDE on birth weight

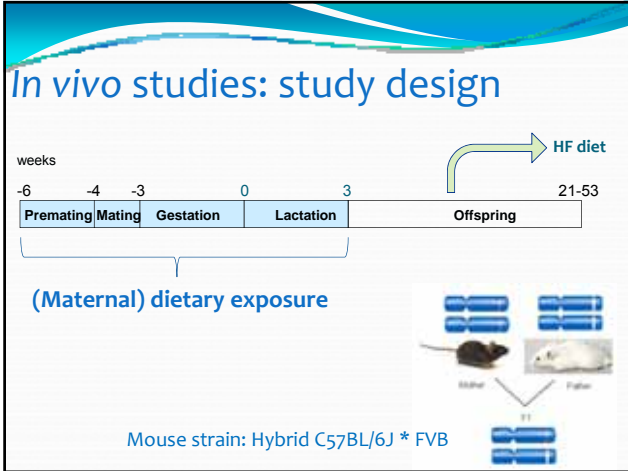
Govarts et al, EHP, 2012

Prenatal exposure to DDE related to increased growth and BMI in children -results not yet published, similar findings as Valvi et al, 2013:

Original Article
PEDIATRIC OBESITY

Prenatal Exposure to Persistent Organic Pollutants and Rapid Weight Gain and Overweight in Infancy

Dimitrios Valvi^{1,2,3,4}, Michelle Ann Mendez⁵, Raquel Garcia-Esteban^{1,2}, Ferran Ballaz^{1,2}, Aris Daskalou^{2,6}, Fernando Giner^{1,2}, Juan O. Ordoñez⁷, Sotiria Llagas⁸, Levent Saka Meryem^{2,6}, Esther Vignati^{1,2}, Joshi Sugan^{1,2,3,4,9}



- ### Animal studies: mimic human exposure
- Exposure route: via the feed, during gestation and lactation
 - dose-response design: control + 6 equidistant doses
 - dose range generally below “no observed adverse effect level!” (NOAEL) for developmental toxicity
 - BPA 0-3000 µg/kg/day
 - PFOA 0-3000 µg/kg/day
 - TCDD 0-10 ng/kg/day
 - DEHP 0-10 mg/kg/day
 - PCB 153 0-1400 µg/kg/day

OBELIX hypothesis

- perinatal exposure to endocrine disrupting chemicals (EDCs) may play a role in the development of obesity later in life

EDCs affect endocrine signalling pathways that may lead to changes in body weight

OBELIX summary

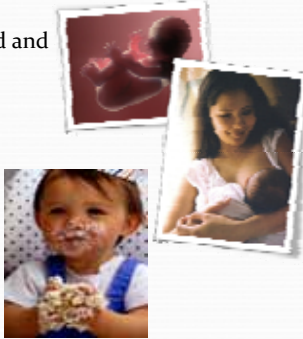
- Evidence for effects on hormone metabolism and weight related to maternal exposure of DDE, dioxins, PFOA in children up to 7 years

Longer term consequences?

We have looked at individual compounds for “proof of principle”: what are effects of mixtures?

We All Carry A Chemical Body Burden

- 287 chemicals in cord blood and breast milk
- Of people tested by CDC:
 - BPA (urine) in 93%
 - Phthalates (urine) 50-97%
 - PFCs in 91-99%
 - PBDEs in 100%
 - Triclosan in 80%
 - PCBs in 100%



Slide courtesy of Jerry Heindel, NIEHS

We All Carry A Chemical Body Burden

- 287 chemicals in breast milk
- Of people tested by CDC:
 - BPA (urine) in 93%
 - Phthalates (urine) 50-97%
 - PFCs in 91-99%
 - PBDEs in 100%
 - Triclosan in 80%
 - PCBs in 100%

The presence of chemicals in the womb does not mean that they are causing harm.

However, it does mean that we have accepted a strategy whereby every pregnant woman is contaminated with chemicals and the public pays the price of impaired health as well as health care costs and research.

It also opens the door to the possibility of harm.

Slide courtesy of Jerry Heindel, NIEHS

It is not all bad news...

Focus on prevention, intervention, awareness raising

Emphasis: pregnant & breastfeeding women

- **Improve nutrition**
 - Organic food
 - Limit fatty fish consumption
 - Fresh fruit and vegetables
- **Reduce exposures to environmental chemicals**
 - High quality drinking water
 - Organic cleaners, cosmetics, textiles, pesticides
 - Reduce plastics/canned food
 - Cosmetics/sunscreens
 - Ventilate houses and remove dust



<http://www.mst.dk/NR/rdonlyres/68EAF0D0-37BF-4E50-8405-27E5F8C3FCA9/0/Expectingababy.pdf>

EDCs are on the political agenda...

European Commissioner for the Environment Janez Potočnik 2012:
 "... Our policies must deliver a high level of protection for man and the environment, these policies must be objective and science-based, and the precautionary principle must be applied."




**EU CONFERENCE ON
ENDOCRINE DISRUPTORS**
 CURRENT CHALLENGES IN SCIENCE AND POLICY
 BRUSSELS, 11 & 12 JUNE 2012

VU University Amsterdam
 Timo Hamers
 Thijs van Boxtel
 Liana Bastos Sales
 Jorke Kamstra
 Peter Cenijn
 Marja Lamoree
 Marijke de Cock
 Margot van de Bor

RIVM Netherlands
 Leo van der Ven
 Martijn Dollé
 Joantine van Esterik

Slovak Medical University
 Tomas Trnovec
 Lubica Palkovicova
 Dana Jureckova

Norwegian Inst for Public Health
 Merete Eggesbo
 Nina Iszatt

Scientific Advisors
 Matt Longnecker
 Rebecca Simmons
 Reinhard Stoger
 Marc-André Verner

VITO Belgium
 Greet Schoeters
 Karolien Bloemen
 Eva Govarts
 Patrick de Boever
 Britt Wens
 Sylvie Remy

INRA – Met@Risk
 Philippe Verger
 Max Feinberg

Ecobaby
 Janna Koppe

www.theobelixproject.org



European Commission

THANKS TO THE  TEAM