HUMIS

Environmental toxicants in Food & Breast milk & Adverse Health effects

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Faculty Disclosure

Commercial Interest	Nature of Relevant Financial Relationship (Include all those that apply)	
	What was received	**For what role**
• None	• N/A	N/A

Presentation Learning Objectives

After participating in this presentation, learners should be better able to:

- Identify toxicants in foods and the associated potential health effects
- Understand the adverse health risks of certain otherwise healthy foods for young girls and pregnant women.
- Understand the impact of food toxicity on the highly exposed fetus

Content

- History persistent toxicants
- Exposure to toxicants across the world
- Adverse health effects
- HUMIS/NoMIC study
  - Correct exposure assessment, pre-and postnatal effects
  - Mixtures
- Sources
- Recommendations

History is short….

- 1950
  - Birds dead
  - Analysis dead birds
    - High concentration
      - Mercury
      - DDT
        - Toxic to many more organisms than intended to kill.
  - Analyses food
    - Egg, meat and fish
      - DDT and mercury
        - Become far more widely distributed

One Earth

- Mid-1950s:
  - Pilots
    - Discolored haze on the horizon
    - Identified as pollutants industrialized areas Europe
  - Norway
    - Svalbard: clean undisturbed environment?
      - Toxic organic compounds in polar bears
        - Unexpectedly high levels.

Persistent environmental pollutants POPS

Bioaccumulate

- –Long half lives
- –Fat-solubility
- –Accumulate in fatty tissue

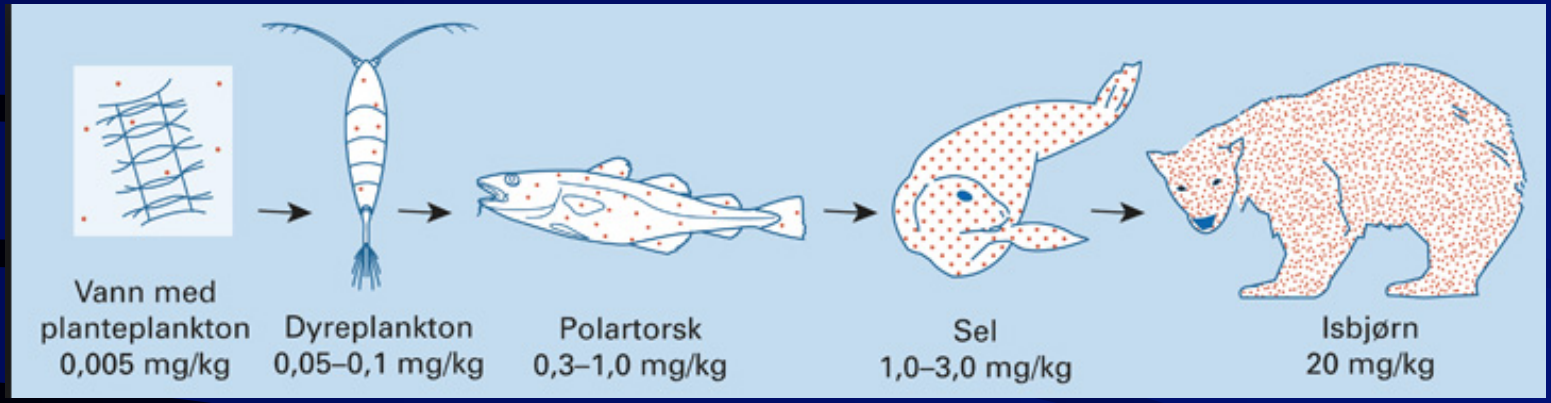
The baby,

before birth and when breast-fed,

consumes the most concentrated amount of POPs (PCBs, DDT, HCB and dioxins etc).

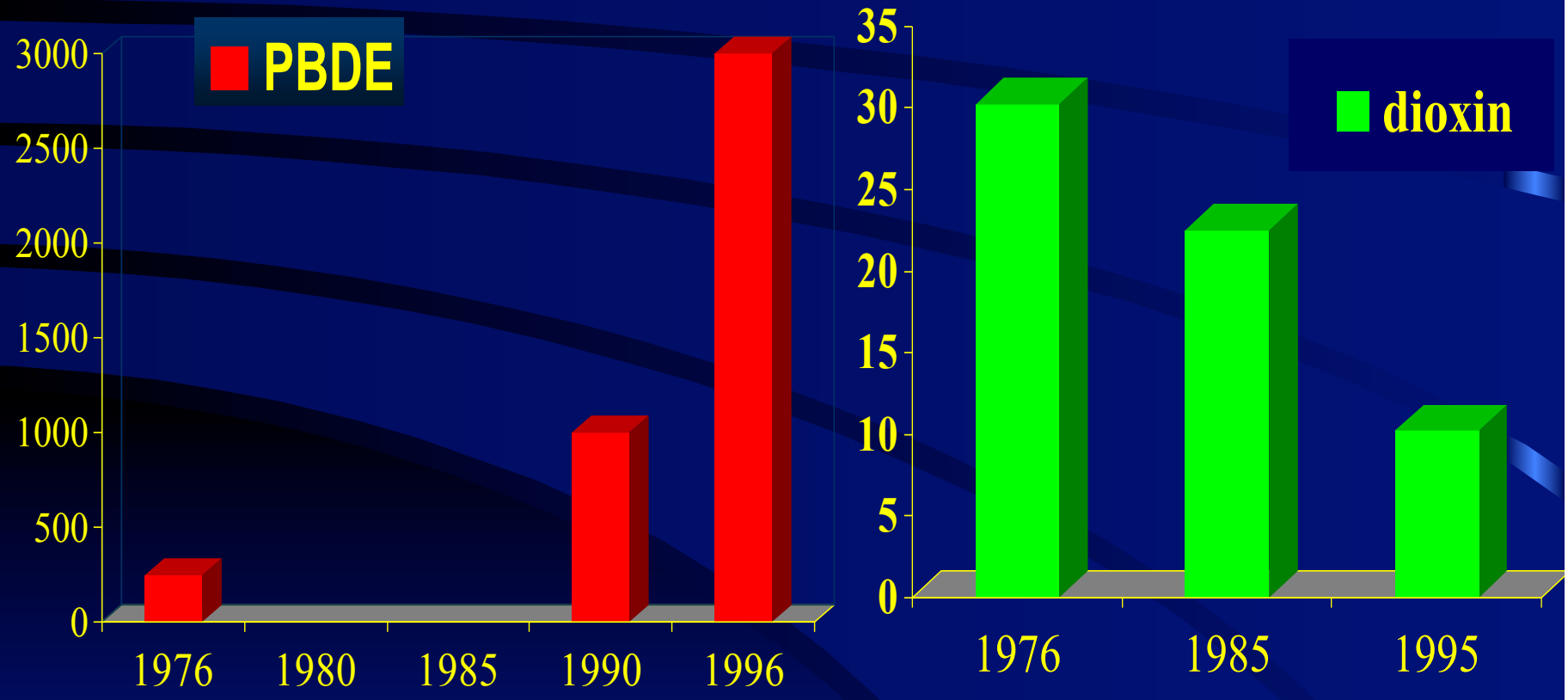
Biomagnifies in the food chain

– Highest concern humans and animals on the top of the food chain

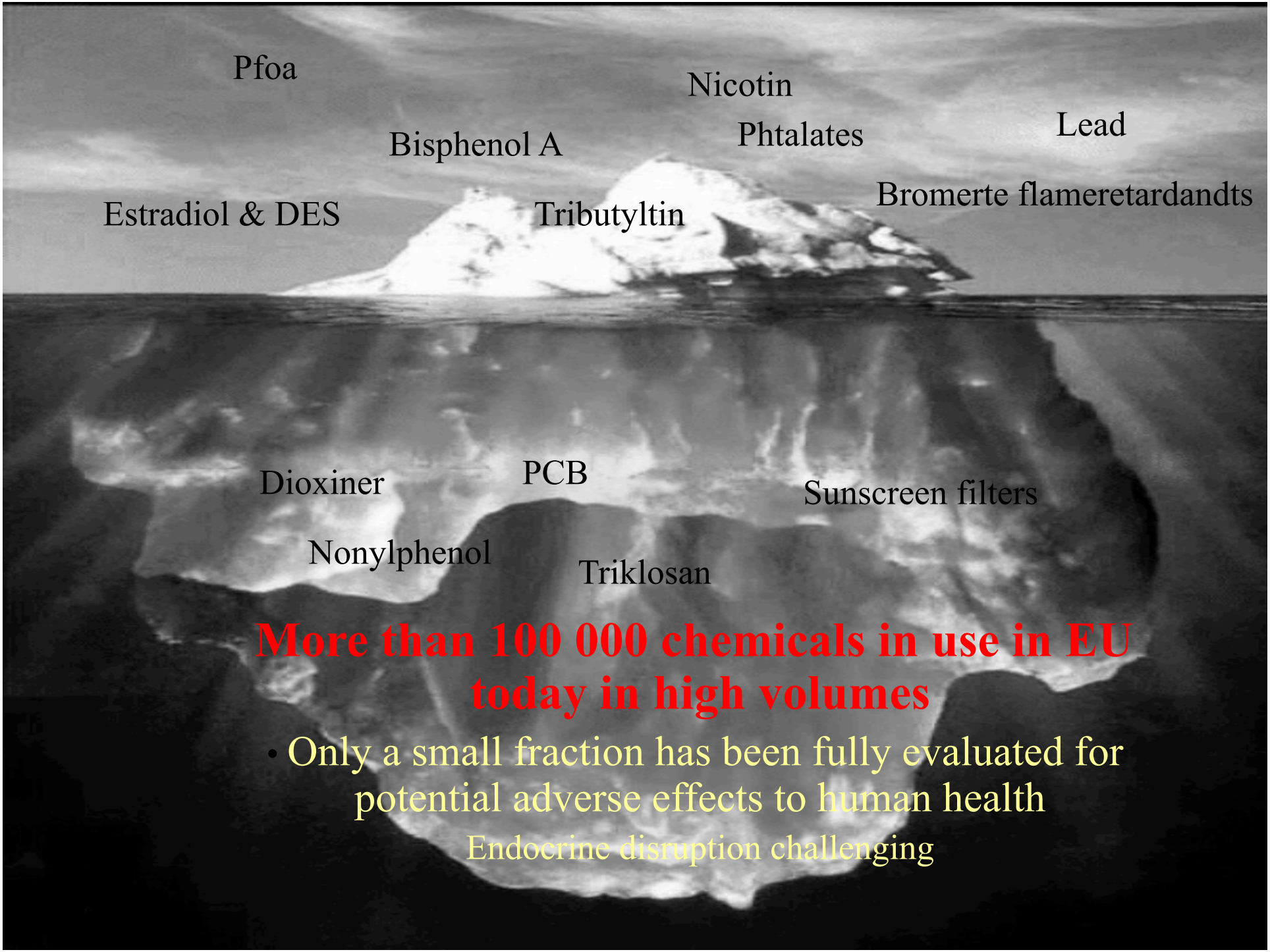


- High concentration in fish, seal and seabirds (seabirdseggs)
- High concentrations in human milk
  - Humans on top of food web
  - Accumulate throughout the life time of the mother
  - High fat content of milk
- Reflects current **AND** earlier exposure

Time-trends:
Dioxin and PBDE in human milk



Borrowed with the courtesy of Gunilla Lindstrøm


Pfoa
Nicotin
Bisphenol A
Phtalates
Lead
Bromerte flameretardandts
Estradiol & DES
Tributyltin
Dioxiner
PCB
Sunscreen filters
Nonylphenol
Triklosan
More than 100 000 chemicals in use in EU today in high volumes
• Only a small fraction has been fully evaluated for potential adverse effects to human health
Endocrine disruption challenging

WHO-UN report

- The vast majority of chemicals in current commercial use have not been tested at all.
  - 800 chemicals are known or suspected of interfering with hormone receptors, hormone synthesis or hormone conversion
  - Only a small fraction of these chemicals have been investigated in tests capable of identifying overt endocrine effects

UN, WHO panel calls hormone-disrupting chemicals a 'global threat'

An international team of experts reported today that evidence linking hormone-mimicking chemicals to human health problems has grown stronger over the past decade, becoming a "global threat" that should be addressed. The report is a joint effort by the World Health Organization and the United Nations Environment Programme to give policymakers the latest information on chemicals that seem to mess with the hormones of people and wildlife. Much has changed since 2002, when the organizations released a report that called the evidence "weak." The panel of 16 scientists from 10 nations found that endocrine-related diseases and disorders are on the rise. There is now "emerging evidence for adverse reproductive outcomes" and "mounting evidence" for effects on thyroids, brains and metabolism, the report summary says.

- Recent UN/WHO report concludes:
  - Synthetic chemicals have serious health implication and has become a "global threat"
  - Proven or suspected behind many of the diseases we see increasing in the western world
    - Diseases of the endocrine system (diabetes, thyroid disease, obesity, infertility, and breast and prostate cancers)

POPs

- Fetotoxic
- Neurotoxic
- Immunotoxic
- Cancer promoters
- Hormonal effects

- Basic mechanisms
  - molecular level
- Health effects
  - secondary effects
    - long chain of disturbances.
- Complicated research
  - Analysis require expertise
  - PCB: 209 congeners
    - Toxicity
  - Sensitivity vary between species
  - Occur in mixtures
    - additive, synergistic or even antagonistic effects

Persistent organic pollutants

- Dioxins and Furans
- PCB
- PBDE/ Flame retardant
- Organopesticides (DDT, HCB ++)
- Perfluorinated compounds
- Others

Adverse effects some specific toxicants

- DDT: suspected or proven
  - Spontaneous abortions, preterm delivery, obesity, delayed puberty, length-growth, behavioral effects, liver cancer, reproduction, neurodevelopmental, adrenal gland
- Mercury:
  - Exposure during pregnancy developmental delays and brain damage

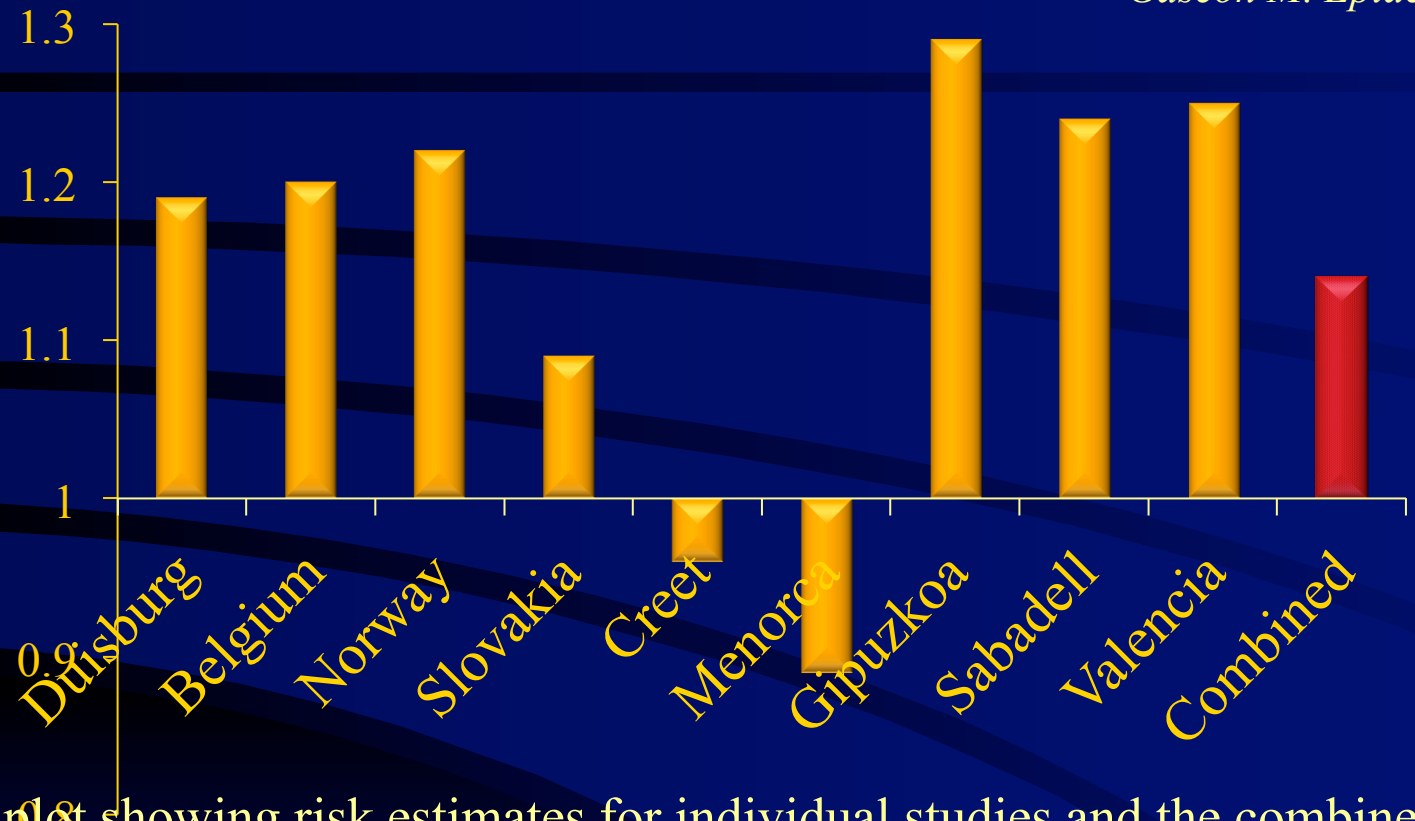
Priority

- Pooled analysis on data from multiple cohorts
  - Data files actually shared
- Power
- Standardized analysis
- Eliminates publication bias
- Improves control for unmeasured confounding

- Some selected POPs

Risk of wheeze or bronchitis in high DDE versus low exposed group

Gascon M. Epidemiology 2014



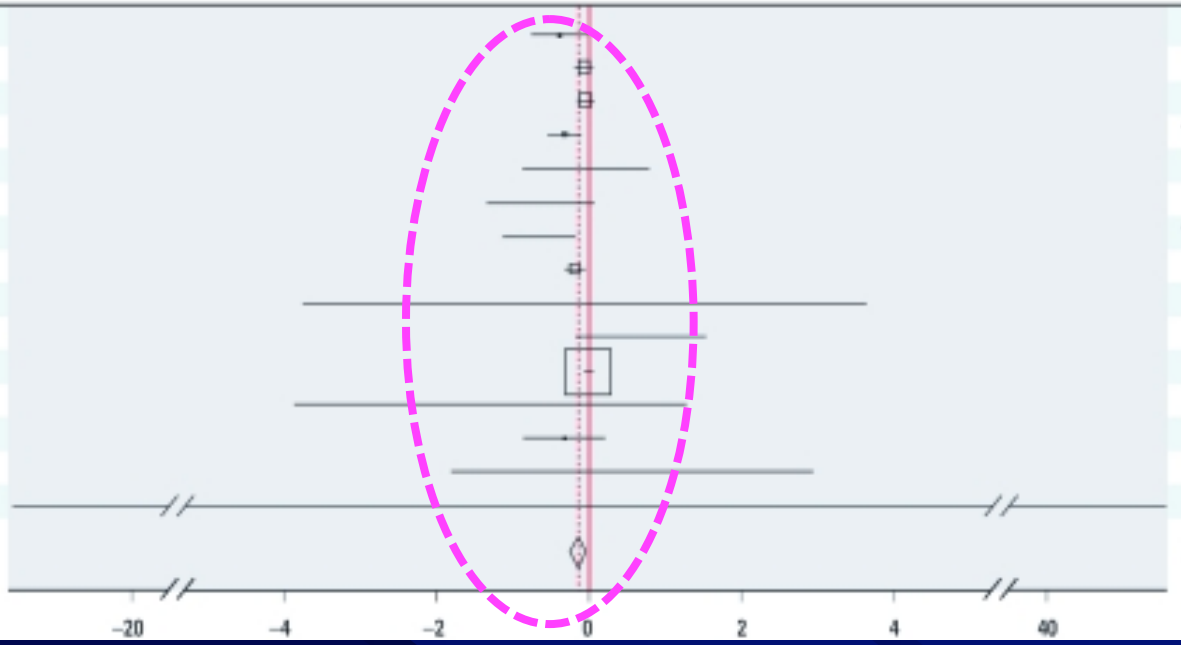
Forest plot showing risk estimates for individual studies and the combined meta-analysis results for the highest versus the lowest DDE exposure and the occurrence of bronchitis or wheeze. 14% increase

Adjusted for gender, age of the child at the time of outcome assessment, duration of breastfeeding, gestational age, number of siblings of the child at the time of birth, maternal age, maternal body mass index, maternal smoking during pregnancy and during postnatal life of the child, maternal education, maternal allergy or asthma, and time of sample collection for POPs analyse

PCB and birth weight

- 15 European cohorts, including 8000 children.

Study	β (95% CI)	No. of subjects
GRD	−0.386 (−0.758, −0.014)	523
FAROES2	−0.070 (−0.182, 0.042)	167
FAROES3	−0.054 (−0.158, 0.050)	549
INMA cord	−0.319 (−0.531, −0.107)	1,222
INMA mat	−0.037 (−0.868, 0.794)	854
DUISBURG	−0.630 (−1.332, 0.072)	189
FLEHSI	−0.659 (−1.133, −0.185)	1,000
Greenland	−0.190 (−0.313, −0.067)	545
Warsaw	−0.067 (−3.758, 3.624)	196
Kharkiv	0.675 (−0.168, 1.518)	573
Michalovce	−0.012 (−0.067, 0.043)	978
HUMIS	−1.294 (−3.867, 1.279)	409
PELAGIE	−0.322 (−0.857, 0.213)	393
ELFE pilot	0.569 (−1.797, 2.935)	43
RHEA	11.274 (−20.888, 43.436)	25
Combined effect (random)	−0.15 (−0.24, −0.05)	7,666



Although variation across cohorts, most show negative estimates
Total combined effect estimate: - 150 g in birth weight

Govarts et al. EHP

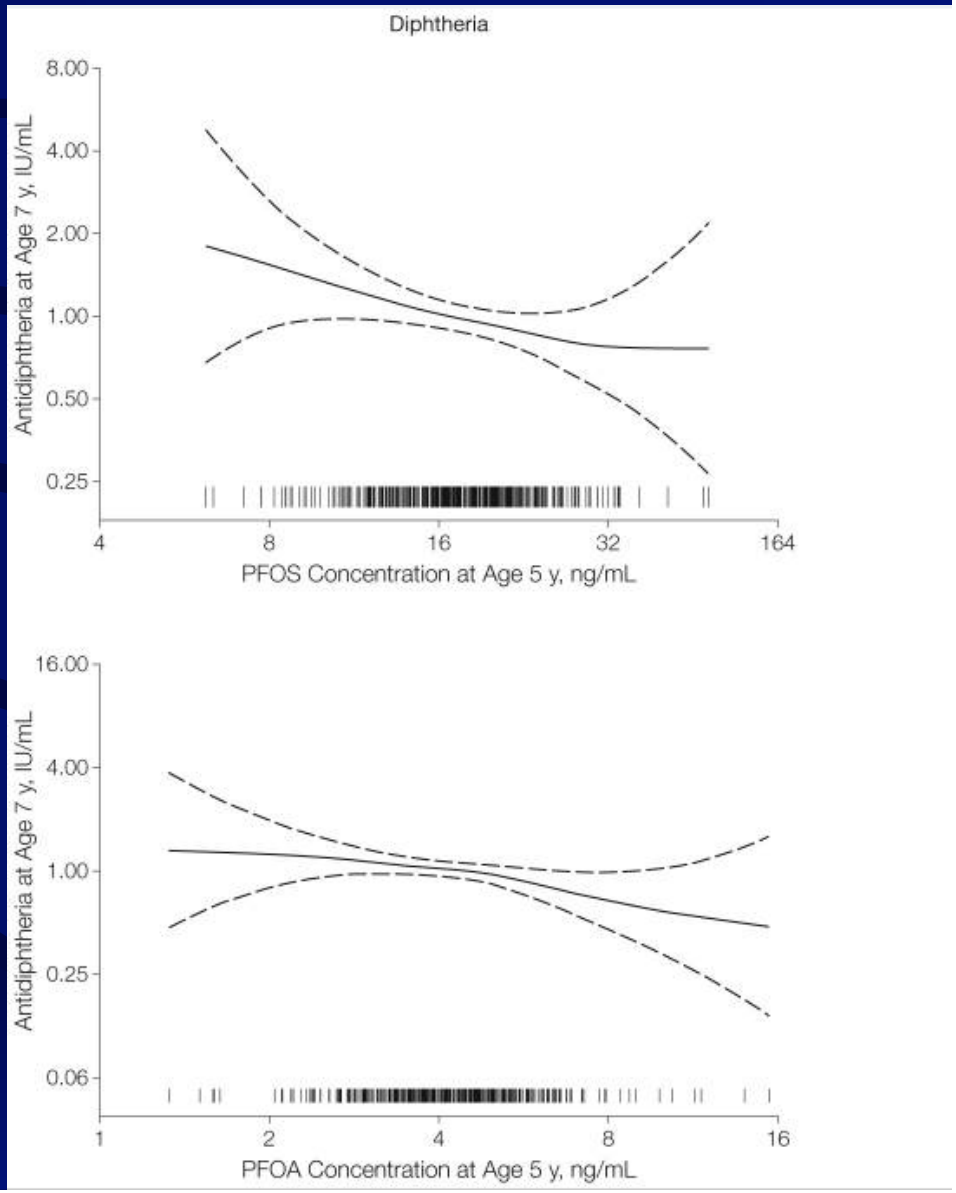
Perfluorinated compounds

- Single study from the Faroese
- 656 infants

- Prenatal effects
- For each doubling in prenatal exposure to PFOS 40% lower antibody responses at 5y

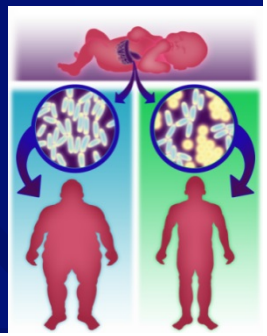
- Postnatal effects
- A 2-fold increase in PFOS and PFOA concentrations at age 5 years was associated with odds ratios between 2.4 and 4.2 for falling below a clinically protective level of 0.1 IU/mL for tetanus and diphtheria antibodies at age 7 y

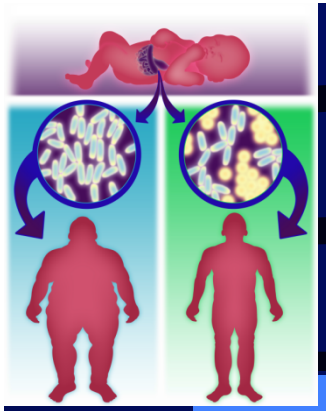
  - *Grandjean JAMA 2012*



HUMIS/ NoMic Study

- Cohort of 2600 mother-child pairs
  - Recruited 2002-2009
  - 200 ml milk in 2400
    - Pooled 8 samples
    - Approx. 1 month
  - Subset of 550
    - Infant fecal samples at 6 age-points up to 2
    - Recruited at hospital
    - Followed up at 10-12y





HUMIS-NoMIC

Pregnancy

1 & 4 days

1 & 4 months

6 months

1 year

2 years

10-12 years

Fecal samples

Child

Childs Hospital Journal

Hair, spit, skin swabs

Clinical examination

Medical Birth Registry

QI

QII

QIII

QIV

QV

Mother

Pregnancy journals

200 ml Milk

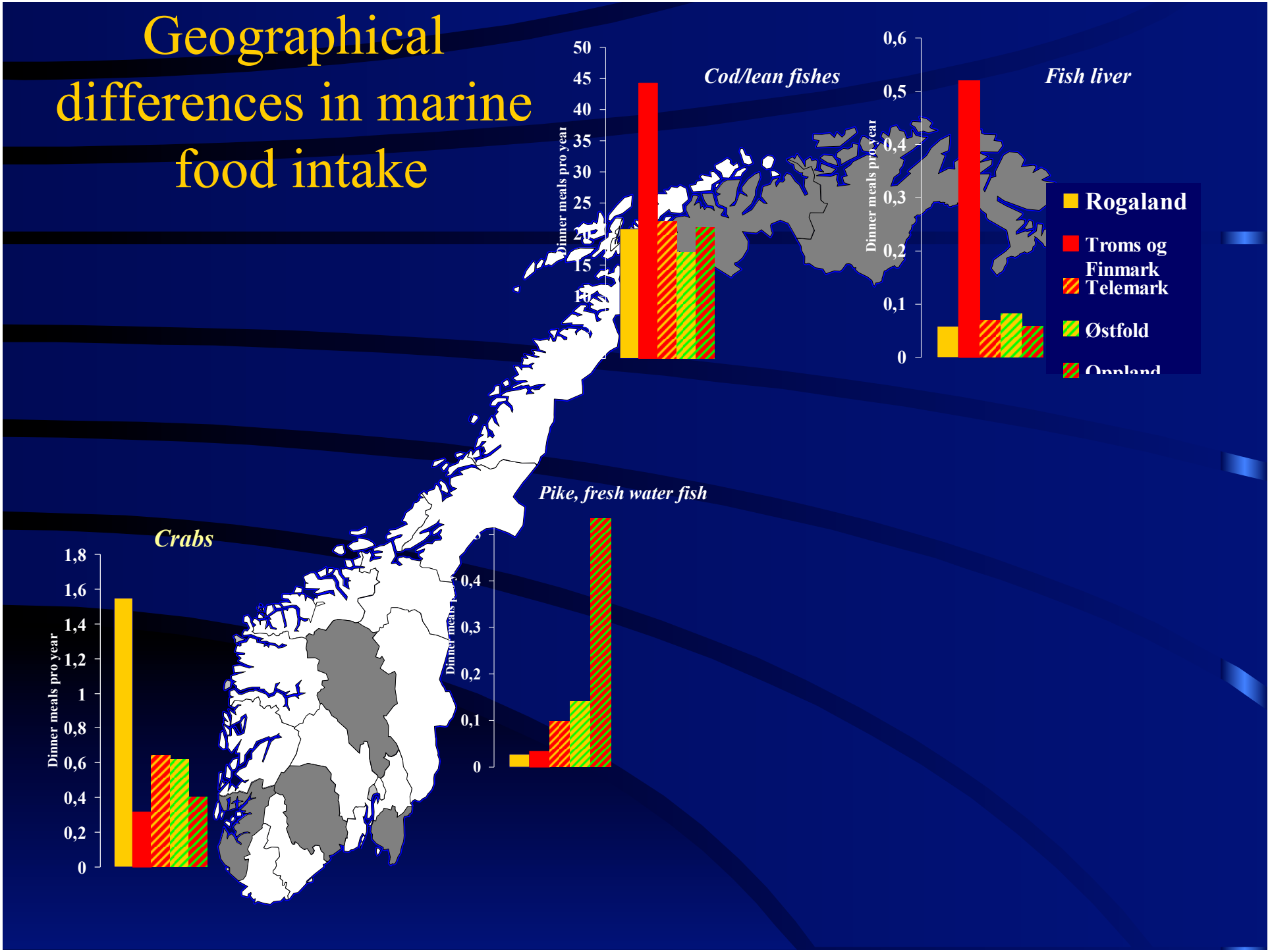
Norwegian Patient Register linked in

- **PCBs**:
- -28, 52, 74, 99, 101, 138, 153, 170, 180, 194, 8
- mono-*ortho* PCBs 105, 114, 118, 123, 156, 157, 167, 189
- **BFRs**:
- 28, 37, 47, 85, 99, 119, 153, 154, 181, 183
- 209 & HBCD
- **Organopesticides:**
- DDE, HCB, bHCH, oxychlordane
- **Perfluorated compounds**
- PFOS, PFOA, PFHxS
- Heavy metals: Mercury, Lead, Arsenic and other heavy metals

In subsets

- **In 70 (15) samples:**
  - PCBs 31, 47, 66, 56, 87, 136, 110, 151, 149, 141, 137, 187, 183, 128, 199, 196, 20 and 209, DDT, α-HCH, γ-HCH, cis-chlordane, trans-nonachlor, mirex, 17 dioxins and furans
- **Organotins**
- **Phtalates**

Geographical differences in marine food intake

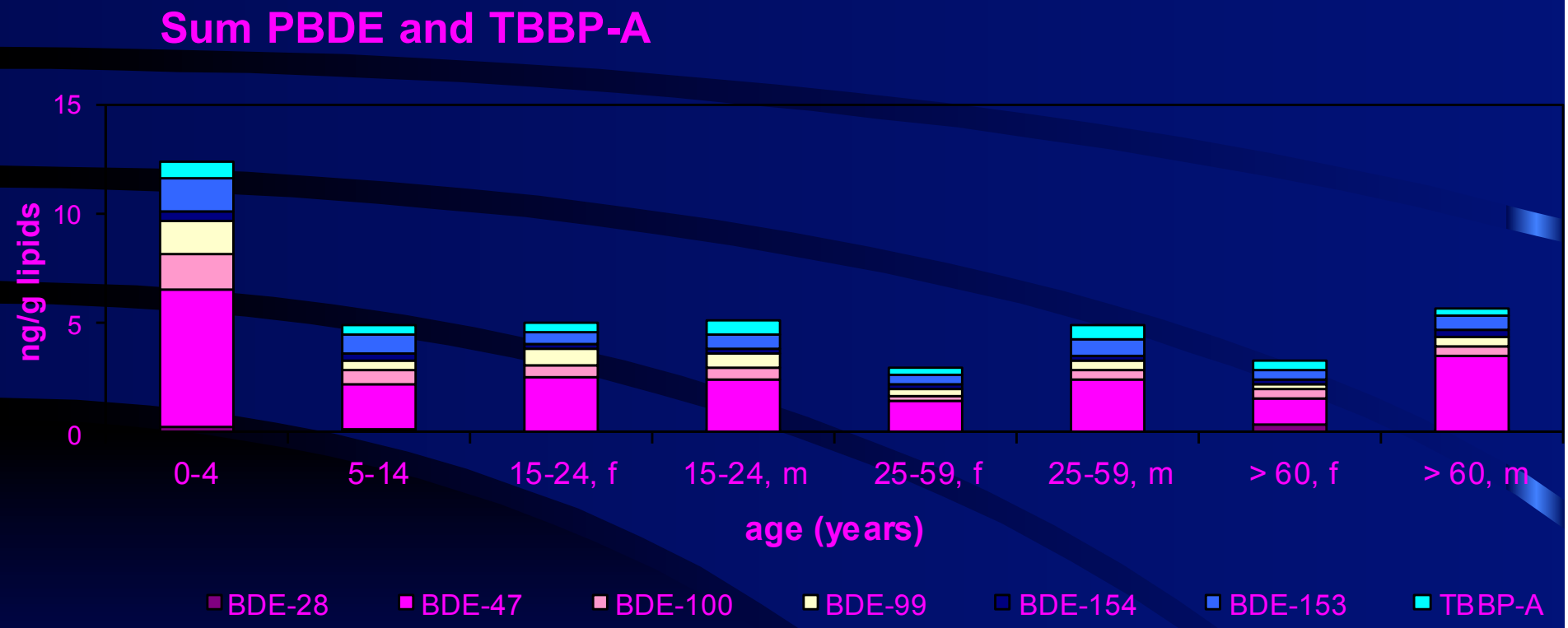


Challenges perinatal assessment POPs

- Exposure assessment
  - Due to long half-lives single exposure assessments have been assumed to be accurate
  - However, major limitations to this assumption in pregnancy and lactation
    - Marked changes in blood lipid composition, maternal weight, glomerular filtration rate during pregnancy
    - Elimination by transfer to the child during breastfeeding
- Concentrations POPs vary in the period of pregnancy breastfeeding and for the infant while being breastfed and growing

Brominated flameretardants

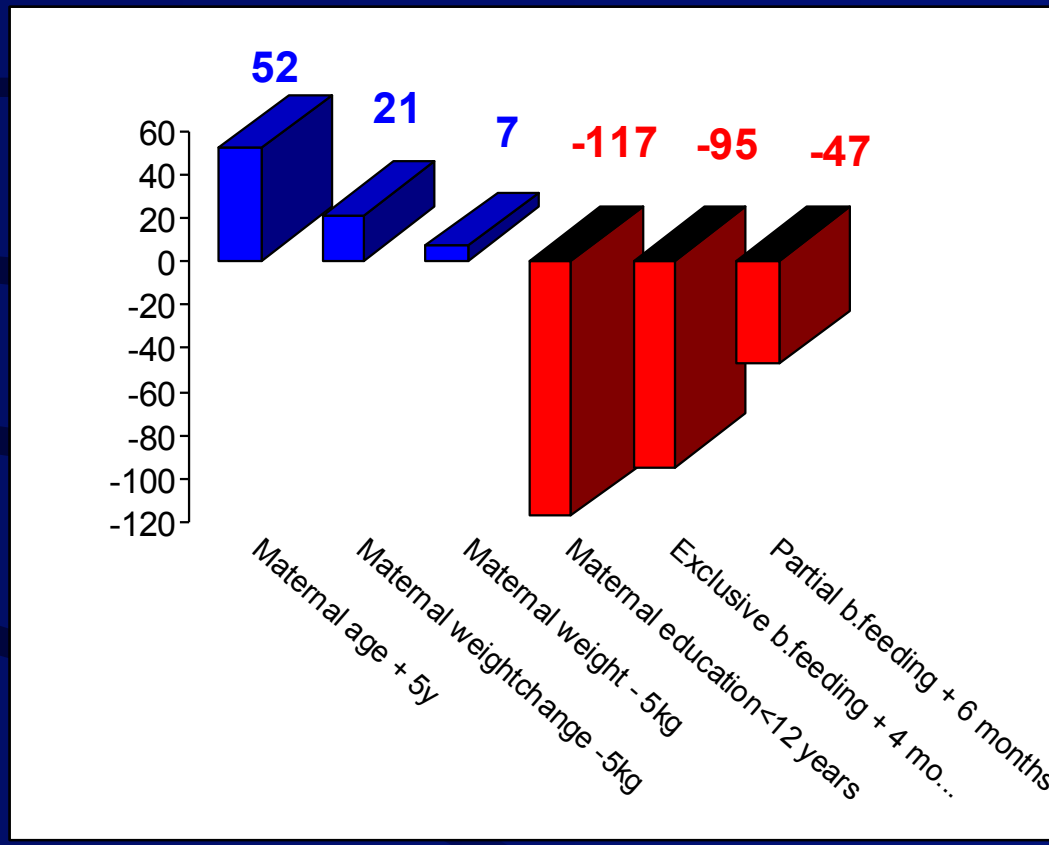
The youngest are the highest exposed within a population-Norway 1998



- *Cathrine Thomsen et al*

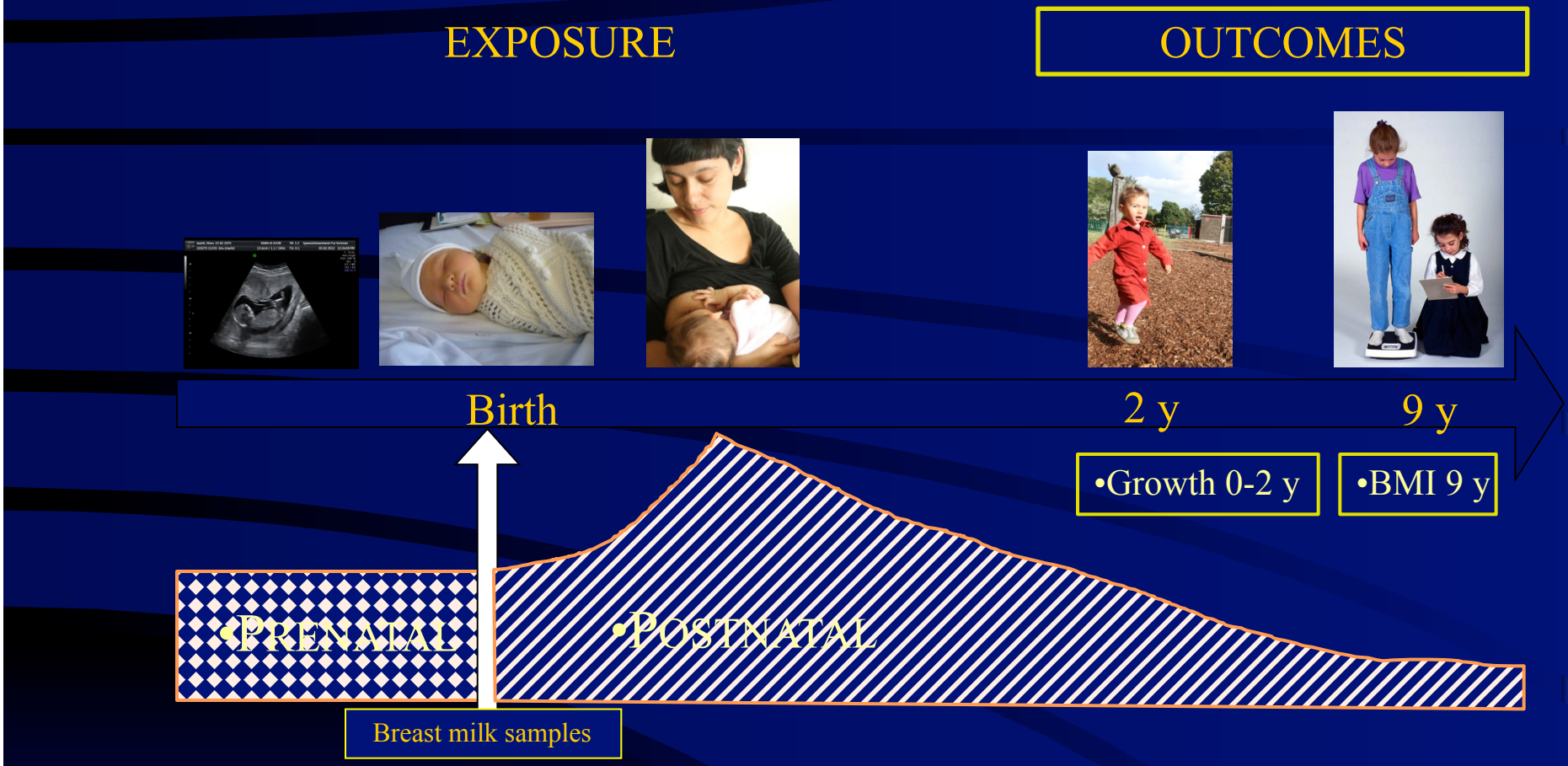
Factors influencing levels of DDE in human milk

- Statistical significant factors shown
  - Smoking significant in crude but not adjusted model.
  - Siblings, sex, maternal education, number of years between last and current child not significant
- 38% explained variance prior to input of dietary variables
- Largely the same variables that predicted other POPs



- Data from a linear regression model, the estimated change shown as percentage change of median levels. Unpublished data

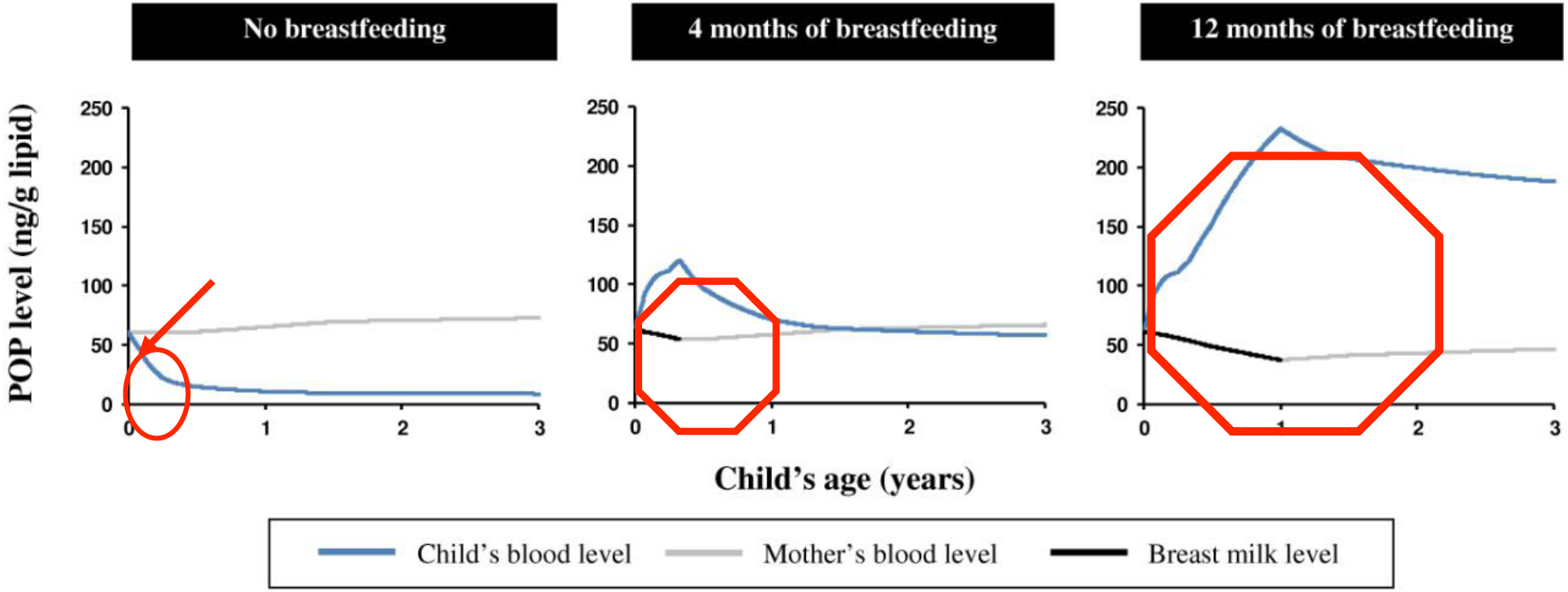
Challenge: exposure assessment in pre- and postnatal period



- Exposure in postnatal period not constant (BB)
  - One single estimate at any time point will misclassify
  - Critical windows within this period

•http://www.exrx.net/FatLoss/ChildObesityEvaluation.html

Exposure in early childhood



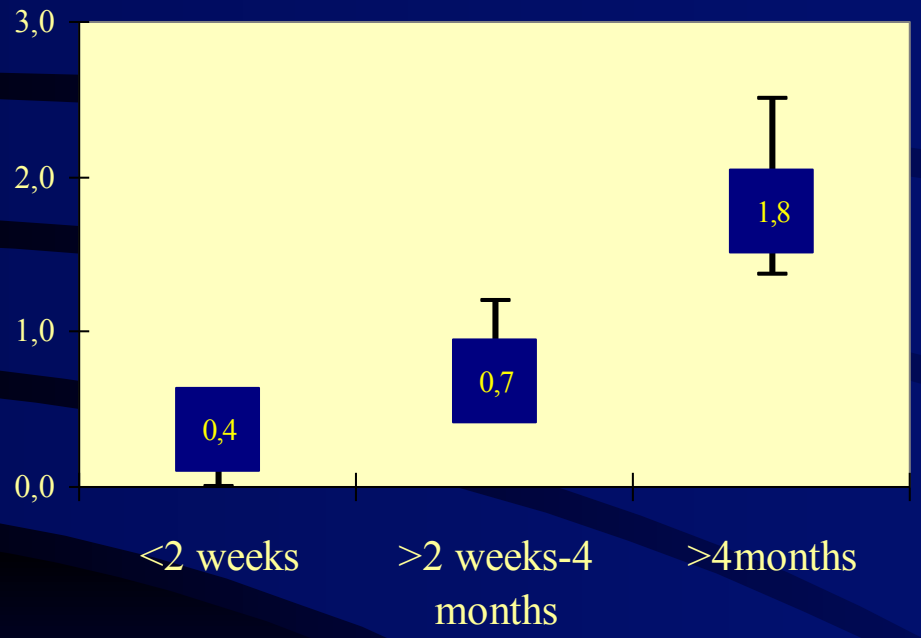
- Simulated toxicokinetic profiles in children breastfed for 4 months.
- Duration of breastfeeding determines postnatal exposure
  - In babies not breastfed: total exposure during infancy small
- Misclassification of exposure

Verner MA et al. EHP 2013

Child's PCB-load at 4 years

According to length of breastfeeding

Walkowiak Lancet 2001



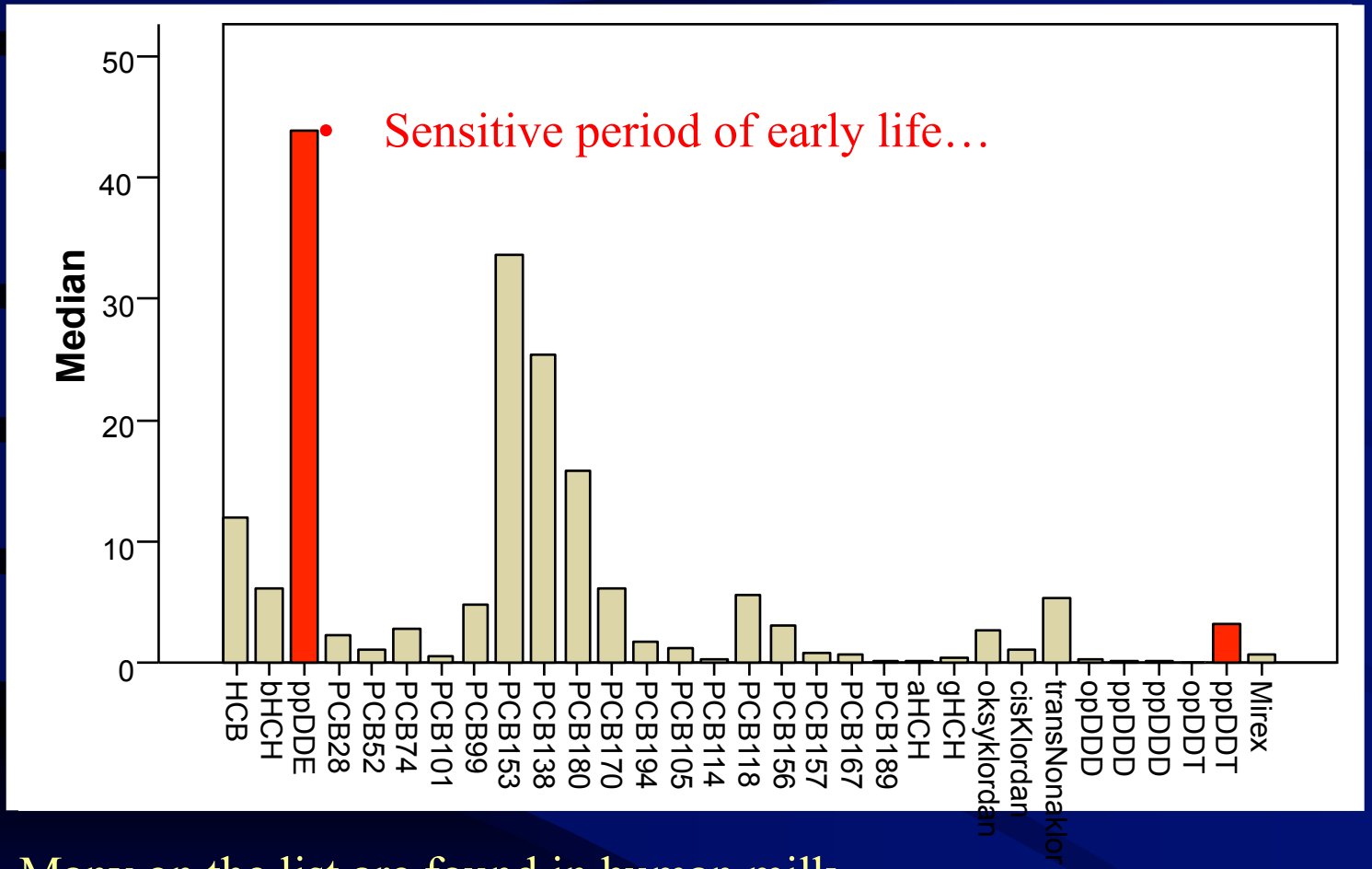
- Levels 5 x higher breastfed for more than 4 months
- Median breastfeeding 4 months

Table 2.6. List of known and suspected environmental obesogens (A=Animal study, C=Cell culture study, H=Human study). Janesick & Blumberg (2011) provide more detailed information about obesogens.

Chemical	Commercial use	Relevant EDC action	Obesogenic activity
Tributyltin	Pesticide, wood preservation	Binds PPARγ	Changes identity of adipose precursors, increases triglycerides in adipose tissue (A)
Phthalates	Plasticizer	Binds PPARγ	Induce adipocyte differentiation (C), men's waist size (H)
PFOA	Non-stick coatings	Weakly activates PPARγ	Induce adipocyte differentiation (C))
Flavanone	Natural plant products used as flavourings	Binds PPARγ	Induce adipocyte differentiation (C))
PCBs	Electronics	Binds AhR in adipocytes	CB-77 promotes adipocyte differentiation, obesity (C,A)
Bisphenol A	Plastics	Binds ER, ERRγ	Induces adipogenesis (C), obesity (A)
Hexachlorobenzene	Fungicide	Alters TH signaling	Gestational exposure levels influence BMI (H)
Bisphenol A diglycid ether	Epoxy resins	Unknown	Induces adipogenesis (C)
PBDEs	Fire retardants	Reduces thyroid function	Stimulate fat production (C)
Diethylstilbestrol	Pharmaceutical estrogen	Binds ER	Perinatal exposures cause obesity (A). BMI in young children (H)
Genistein	Natural component in soy	Binds ER	Perinatal exposures cause obesity (A).
Perfluoroalkyl sulfonate	Non-stick coatings	Binds ER	Perinatal exposures cause obesity, alter insulin & leptin levels (A).
Nicotine	Found in tobacco products		Alters development of pancreas & adipose tissue, increases adipose cell size (A)
DDE	DDT metabolite	Binds ER	Concentrations in mothers associated with weight and BMI in female offspring (H)

The mechanisms by which most of these chemicals affect weight gain are largely unclear. Tributyltin, one of the few chemicals studied in detail, activates the combined peroxisome proliferator -activated receptor gamma (PPAR-γ)/ retinoid-X-receptor (RXR) pathway, the main pathway for fat cell differentiation (Janesick & Blumberg, 2011) and thereby stimulates fat cell differentiation in vitro and increases adipose tissue in vivo in mice. Similarly, chemicals with estrogenic activity like DES, genistein and BPA appear to act via estrogen receptors on fat cells, and cells of the brain and other tissues to regulate adipose tissue and food intake (Janesick & Blumberg, 2011).

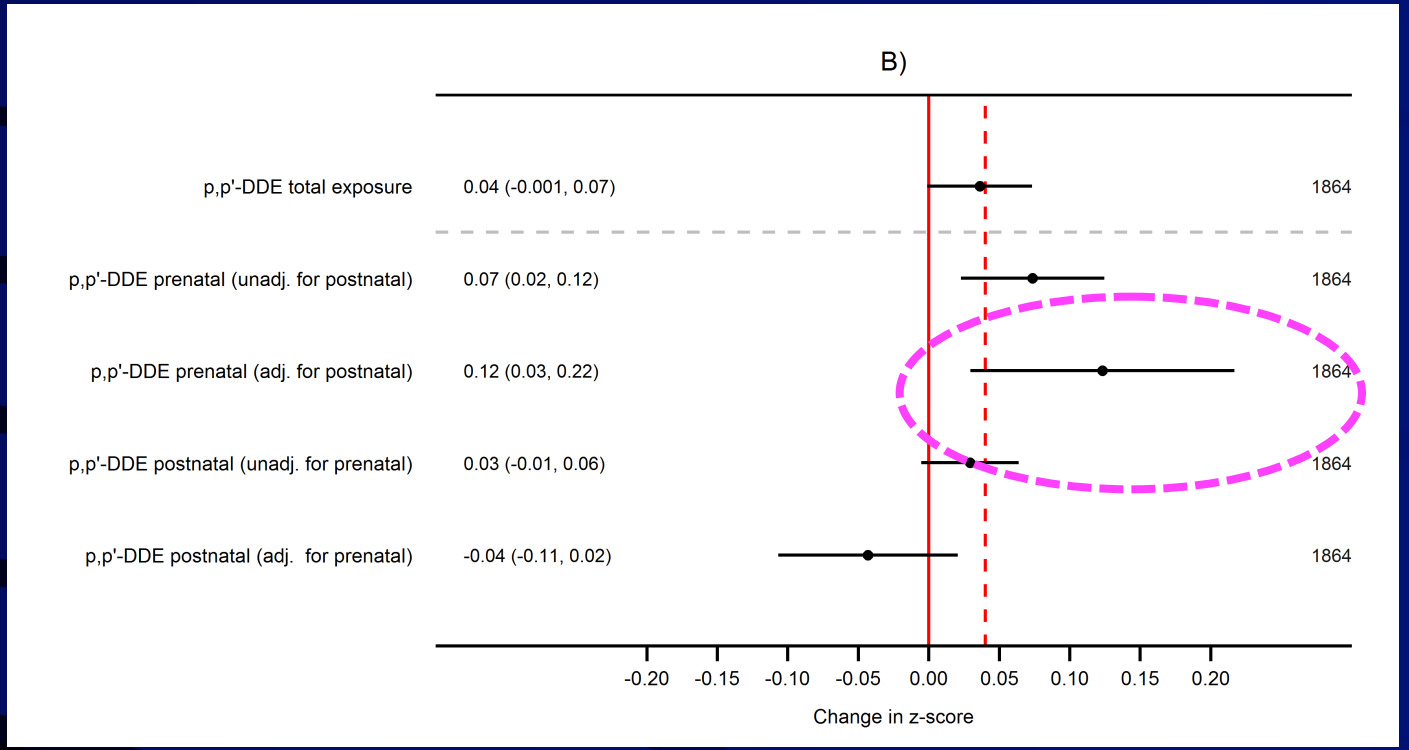
POPs in human milk. HUMIS study



- Many on the list are found in human milk
  - Organotins the exception on the list
  - Nicotin only if exposed to environmental smoking

Pre and postnatal effects of DDE on early growth
7 European cohorts n=1864

- DDE



The positive effect of DDE on rapid growth is tied to the prenatal period

Important to distinguish between pre- and postnatal exposure

Results shown for IQR, and corresponds to weighting 250g more (50th percentile)

Nina Iszatt EHP 2014

Environmental Research

Volume 151, November 2016, Pages 91–100

Novel application of statistical methods for analysis of multiple toxicants identifies DDT as a risk factor for early child behavioral problems

Joan Forns[a], Siddhartha Mandal[a], Nina Iszatt[a], Anuschka Polder[b], Cathrine Thomsen[c], Jan Ludvig Lyche[d], Hein Stigum[e], Roel Vermeulen[f], Merete Eggesbø[a]

- 24 different toxicants: PCBs, BDEs, HCB, DDT, DDE +
- Infant toddler check list
- Only DDT identified out of all studied
- A significant worsening in behavior at 12 months in offspring of mothers with high levels

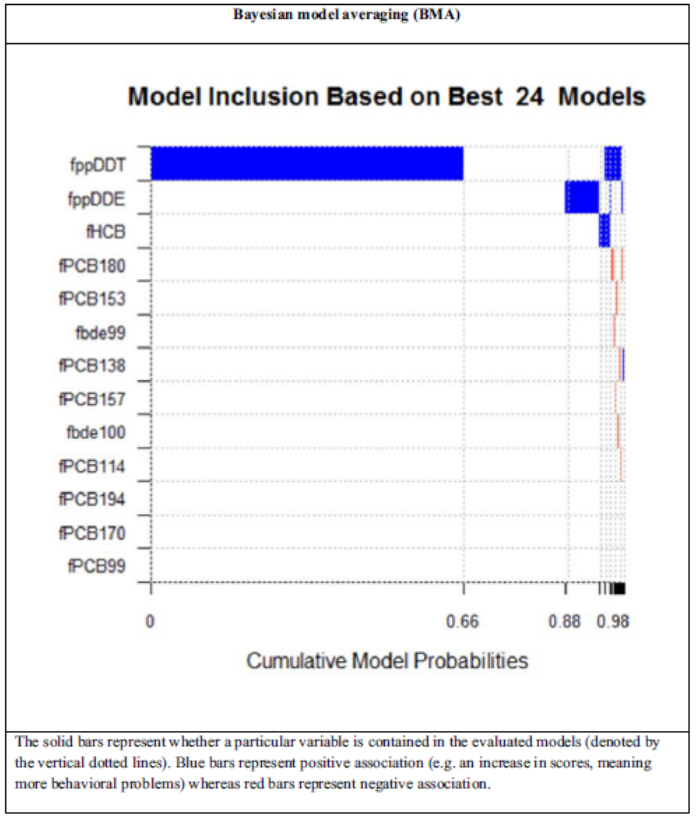


Fig. 3. Main results from selection methods BMA of toxicants associated with behavioral problems at 12 months assessed by the Infant Toddler Symptom Checklist (ITSC).

Breastfeeding

- Breastmilk:
  - Optimal nutrition for the baby
  - Immunological crosstalk mother-child
  - Oligosaccharides important for gut microbiota composition
- Benefits of breast-feeding is believed to outweigh risks from POPs in mother's milk

- Exceptions:
  - Women unusually high POPs
  - For long duration of breastfeeding there is a tradeoff between benefits and exposure to POPs

- Most important: reduce levels in girls/women in reproductive age!

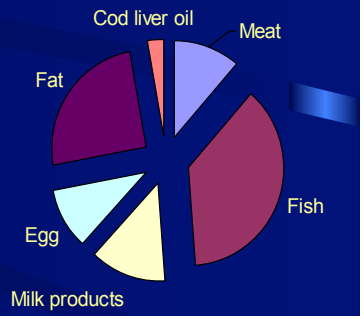
Sources

Sources

- POPs such as PCBs, DDT, HCB and Dioxins:
  - PCB: Electrical circuits/tarnsformers, isolated window, building materiale, airborn if proximity to contaminated sites
  - HCB: unintended biproduct chlorinated pesticide processes
  - Dioxins: unintended combustion products, fires
- Brominated flame retardants
  - Electronical equipment, furniture
- Perfluorinated compounds
  - Teflon, waterproof clothing (gortex), wax
  - Non-stick food packing

Sources

- POPs such as PCBs, DDT, HCB and Dioxins:
  - Fatty food, especially marine products
- Brominated flame retardants
  - Marine products, but also dust
- Perfluorinated compounds
  - Marine products, dust, water
  - Food choices (wrapping, teflon)



Contaminant pattern varies across marine products

- Lean fish: Mercury
- Fatty fish: POPs
- Shift in feed: farmed salmon fed more soy beans and less marine fats and the content of PCBs and other POPs have decreased while pesticides has increased
- Large and old fish
- Locally fished

Fish intake during pregnancy

- Omega-3 fatty acids promote brain development
- Source of Iodine
- Healthy proteins

- The 2010 Dietary Guidelines for Americans recommend 8 to 12 ounces — two average meals of seafood a week for pregnant women
- Avoid locally fished marine products
- Avoid fish known high content mercury

Original Investigation

Fish Intake in Pregnancy and Child Growth

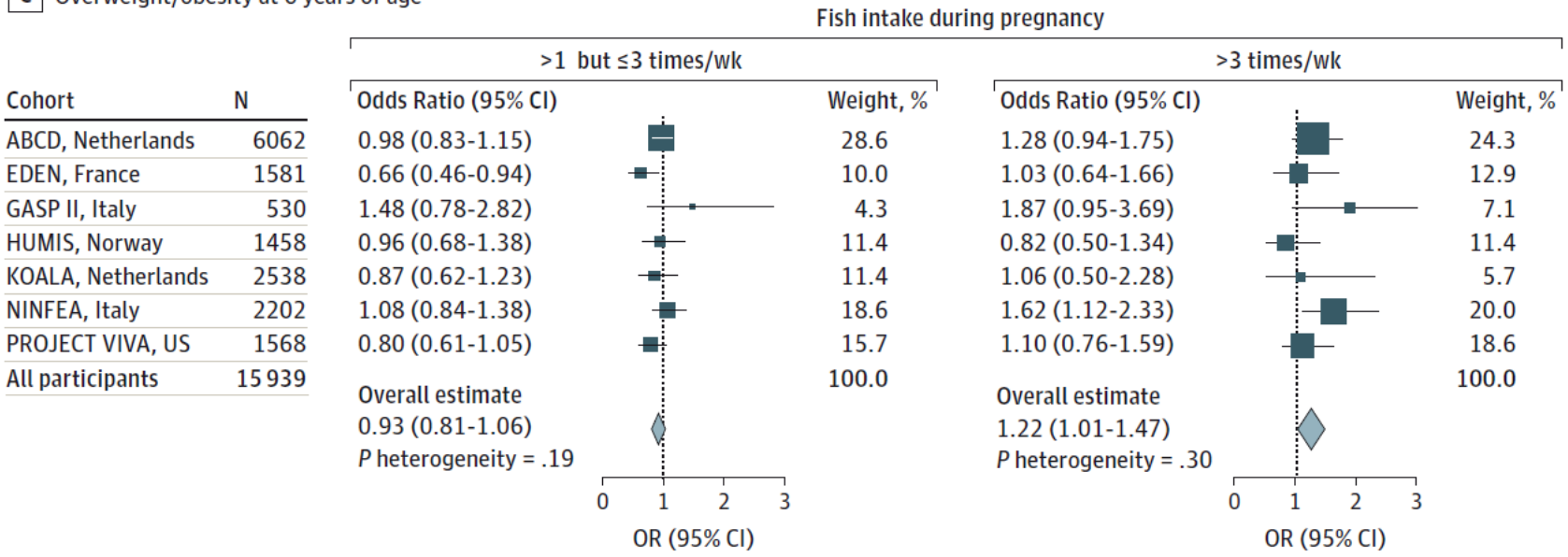
A Pooled Analysis of 15 European and US Birth Cohorts

Nikos Stratakis, MSc; Theano Roumeliotaki, MPH; Emily Oken, MD; Henrique Barros, PhD; Mikel Basterrechea; Marie-Aline Charles, MD; Merete Eggesbø, PhD; Francesco Forastiere, PhD; Romy Gaillard, PhD; Ulrike Gehring, PhD; Eva Govarts, MSc; Wojciech Hanke, PhD; Barbara Heude, PhD; Nina Iszatt, PhD; Vincent W. Jaddoe, PhD; Cecily Kelleher, DMed; Monique Mommers, PhD; Mario Murcia, MSc; Andreia Oliveira, PhD; Costanza Pizzi, PhD; Kinga Polańska, PhD; Daniela Porta, MSc; Lorenzo Richiardi, PhD; Sheryl L. Rifas-Shiman, MPH; Greet Schoeters, PhD; Jordi Sunyer, PhD; Carel Thijs, PhD; Karien Viljoen, PhD; Martine Vrijheid, PhD; Tanja G. M. Vrijkotte, PhD; Alet H. Wijga, PhD; Maurice P. Zeegers, PhD; Manolis Kogevinas, PhD; Leda Chatzi, PhD

IMPORTANCE Maternal fish intake in pregnancy has been shown to influence fetal growth.

Supplemental content at jamapediatrics.com

C Overweight/obesity at 6 years of age



- Pregnant women who ate fish >3 times /week
  - Offspring higher BMI values at 2, 4 and 6 years of age
- Fish consumption of >1 &< 3 not associated with increased risk of childhood overweight or obesity

When pregnant

- Avoid fish with high levels of mercury
  - Shark, swordfish, king mackerel, tuna and tilefish (sushi).
- Avoid old and large fish (large trouts, halibut, pike)
- Avoid locally fished products
  - Follow local fish and wildlife advisories strictly

Fish intake before pregnancy

In general

- Cooking reduces POPs in fish
- Avoid food-items from countries with less strict regulations, before childbearing and while pregnant
- Wash fruits and vegetables
- Follow fish and wildlife advisories
- The bigger and older the fish the worse (pike, halibut versus cod from open sea)
- Wild salmon will have more omega 3

Presentation Clinical Actions

After participating in this presentation, clinicians should be better able to:

- Apply specific concepts regarding the adverse health impact of environmental toxicants in food and breast milk when making dietary recommendations for young girls and pregnant women.

Acknowledgements

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