How contaminants can affect brain development

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Outline of the presentation

• The sensitive fetal brain
• Contaminants in our environment
• History lesson
• Contaminants in NeuroTox (Metals and PFASs)
• Mechanism of developmental toxicity
  thyroid hormone disruption
  epigenetic changes

+ a sneak preview of some results.....
What happens in the womb stays with us for life

The new science of **fetal origins** links our health to our experience in the womb.

“Critical windows of vulnerability” during embryonic and fetal development.


And neurodevelopmental (and -degenerative) disorders?

Maternal (mal)nutrition, overweight, stress, disease and infections, smoking, alcohol, substance abuse, medicines & **toxicants**
The developing brain is extraordinary sensitive to neurotoxic contaminants

- Placenta is not a barrier for toxicants
- Undeveloped blood-brain barrier
- Lack detoxifying enzymes
- Chemicals cross the placenta and reaches the fetal brain
Our chemical world – pesticides, industry, waste, building materials, chemicals for our safety & convenience (cosmetics/consumer products)
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Environmental contaminants:
Persistent - Long-range transport –Bioaccumulation
Food-chain transfer
Maternal transfer (placenta, milk)

Toxic effects :
Immune system, Reproduction, Cancer, Genotoxic, Endocrine disruption, Neurotoxic (Developmental neurotoxic)
Many contaminants are known or suspected developmental neurotoxicants (red = NeuroTox)

Methyl-mercury (Hg), Lead (Pb), PCBs, Arsenic (As), Toluene

New: Manganese (Mn), Fluoride, PBDEs, DDE/DDT, Chlorpyrifos, Perchlorate, Solvents (tetrachloroethylene)

Suspected: Phthalates, Bisphenol A, Perfluoroalkyl substances (PFASs), various pesticides

and many unknown........


Many sources of contaminant exposures before and during pregnancy

- **Food**
- Drinking water
- Air/dust
- Cosmetics
- Consumer products
The paradoxical fish — on one side full of important nutrients beneficial for neurodevelopment and the other side an important source of contaminants that can negatively affect brain development.
What has history taught us?

Minamata Bay: methyl-Hg

Faroe Islands: POPs & methyl-Hg

Inuit populations: POPs & methyl-Hg

Lead – still a problem?
MIXTURE EFFECTS?

Mechanisms?
Contaminants in NeuroTox: Neurotoxic metals

**Metals** are naturally present, elevated levels due to human activity: coal burning, industry and products, mining and smelters

Mercury (Hg) - organic form **methyl mercury** most toxic
Arsenic (As) - metallic form most toxic (organic form is less toxic)
Lead (Pb) -
Cadmium (Cd) -
Manganese (Mn) – essential element (deficiency/toxicity)

**Sources of human exposure:** Fish, shellfish, game (Pb), drinking water, tobacco (Cd), vegetables/grain grown in contaminated soil + accidental poisoning episodes
Studies on prenatal metal exposure and cognitive functions

- **Mercury** associated with IQ, language, attention, memory and neurobehavioral function (Faroe Islands, South-Korea)

- Association between **mercury** and psychomotor development among girls, but not boys (Spain)

- **Manganese** and **lead** associated with cognitive and language functions (Taiwan)

- Prenatal **lead** concentrations related to infant attention (Inuit pop., Canada)

  - Debes et al., 2006. Neurotoxicology and Teratology.
  - Lin et al., 2013. Environmental Research.
  - Plusquellec et al., 2007. Neurotoxicology and teratology.
Studies on prenatal metal exposure and NDDs

- Cord blood lead levels associated with hyperactivity (Belgium)
- Mercury exposure associated with ADHD-related behaviors (stronger association for boys) (USA)
- Mercury and lead associated with ADHD symptoms (Inuit pop., Canada)

Postnatal (levels measured in the child):

- Lead and mercury exposure associated with ADHD (China, USA)
- Mercury exposure associated with Autism (USA)

- Sioen et al., 2013. Environment International.
- Sagiv et al., 2012. Archives of pediatrics & adolescent medicine.
- Kim et al., 2013. Environmental Research.
- Adams et al., 2013. Biological trace element research.
Metal levels in maternal samples/cord blood (prenatal exposure) compared to Norway

- **Median mercury (ug/L)**
  - Norway: 0.00
  - Inuit, Arctic Québec: 15.00
  - Taiwan: 10.00
  - Faroe Islands: 25.00
  - Spain: 5.00

- **Median lead (ug/L)**
  - Norway: 0.00
  - Inuit, Arctic Québec: 10.00
  - Taiwan: 10.00
  - Belgium: 15.00
  - USA: 5.00

- **red column**: MoBa – unpublished NeuroTox data (n=875)
- Lin et al., 2013. Environmental research.
- Debes et al., 2006. Neurotoxicology and teratology.
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Maternal metal levels in blood and child IQ score (3.5 years)

Preliminary data analyses from NeuroTox and the ADHD sub-study population – not published

ADHD sub-study population

3.5 year old child: IQ (Stanford-Binet 5th revision)

Mercury (and Arsenic): ↓ IQ score

Confounders: Child age (days), gender, maternal age, parity and education, and maternal smoking, alcohol and fish intake during pregnancy. N= 700
Maternal metal levels in blood and child ADHD symptoms (3.5 years)

Preliminary data analyses from NeuroTox and the ADHD sub-study population— not published

Confounders: Child age (days), gender, maternal age, parity and education, and maternal smoking, alcohol and fish intake during pregnancy. N= 700
Contaminants in NeuroTox: PFASs

Perfluoroalkyl substances

• **Large** group of man-made fluorinated chemicals

• **Uses**: fire-fighting foam, food packaging, paper and textile coating, non-stick frying pans and more

• **Sources of exposure**: food (mostly fish and shellfish), food packaging and dust

• Most **prominent contaminant group** in human blood (PFOS and PFOA dominant)

• **Toxic**: endocrine disruption and neurotoxic

  **Developmental neurotoxic ?**

• **NeuroTox**: analyze 19 PFASs in maternal blood samples
Previous studies on prenatal PFAS exposure and NDDs and cognitive functions

- PFASs associated with Cerebral Palsy, not with ADHD and autism (Denmark)
- PFOA associated with mental development indices (Japan)
- PFOS associated with gross-motor development and executive functions (Taiwan and USA)
- PFNA associated with IQ test scores and attention (Taiwan)

- Chen et al., 2013. Epidemiology.
- Vuong et al., 2016. Environmental Research.
PFAS levels in maternal samples/cord blood (prenatal exposure) compared to Norway

- **red column**: MoBa – unpublished NeuroTox data (n=2334)
- Chen et al., 2013. Epidemiology.
- Vuong et al., 2016. Environmental Research.
Mechanisms: effects of neurotoxicants

- 1st TRIMESTER
  - Neurons develop
  - Neurons multiply
  - Neurons migrate

- 2nd TRIMESTER
  - Neurons branch, form synapses
  - Pruning (apoptosis)
  - Synapses reorganize

- 3rd TRIMESTER
  - Myelination
Mechanisms: effects of neurotoxicants

Neurotransmitter systems  
e.g. Dopamine, Serotonin, Noradrenaline, Glutamate

Phospholipid/lipid metabolism

Oxidative stress and cell death

Calcium-homeostasis

Neuroinflammation

Thyroid hormone balance

Epigenetic and genetic changes

Structural changes

Reduced volume and myelination

Reduced neural connectivity & plasticity

Deficits: Learning/cognition, motor function, behavior

Neurodevelopmental disorders: ADHD and Autism?

Neurological disorders (CP, Epilepsy) ??
Mechanism: thyroid hormone disruption

Hypothyroidism (↓T4 and ↑TSH)
Hyperthyroidism (↑T4 or ↓TSH)

T4=thyroxine    T3=triiodothyronine    TSH=Thyroid stimulating hormone
Newborn thyroid stimulating hormone (TSH) used in routine newborn screening

- Routine measurements of TSH in all newborns in Norway—screen for congenital hypothyroidism
- Measured 48-72 hours after birth
- Data stored in a database at the Newborn Screening Unit, Oslo University hospital
  (link TSH data to the populations in NeuroTox)
- Reflects fetal (and maternal) thyroid hormone status
Mechanism: Epigenetic - DNA methylation

- Epigenetics is the study of heritable changes (cell-cell or parent-offspring) in gene function that cannot be explained by changes in DNA sequence.

- DNA methylation – «turns DNA on-and-off»

Gene/epigene-environment interaction
Maternal metal levels during pregnancy and global (total) DNA methylation in newborn

MoBa ADHD sub-study population

Covariates: child age in days at clinical testing, gender, pregnancy, parity, maternal age, maternal education, maternal Se levels, maternal smoking, and intake of alcohol, folate and fish during pregnancy. (n=630)

Preliminary data analyses from NeuroTox and the ADHD sub-study population— not published
Thank you for your sustained attention 😊

Questions?

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GettyImages
Christina Winther

www.fhi.no/prosjekter/neurotox/

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References

• Adams et al., 2013. Toxicological status of children with autism vs. neurotypical children and the association with autism severity.

• Boucher et al., 2012. Prenatal Methylmercury, Postnatal Lead Exposure, and Evidence of Attention Deficit/Hyperactivity Disorder among Inuit Children in Arctic Québec.

• Chen et al., 2013. Perfluorinated Compound Levels in Cord Blood and Neurodevelopment at 2 Years of Age.

• Cheuk & Wong, 2006. Attention-deficit hyperactivity disorder and blood mercury level: a case-control study in Chinese children.

• Davidson et al., 2010. Fish consumption, mercury exposure, and their associations with scholastic achievement in the Seychelles Child Development Study.

• Debes et al., 2006. Impact of prenatal methylmercury exposure on neurobehavioral function at age 14 years.

• Eubig et al., 2010. Lead and PCBs as Risk Factors for Attention Deficit/Hyperactivity Disorder.

• Forns et al., 2014. Exposure to metals during pregnancy and neuropsychological development at the age of 4 years.

• Goudarzi et al., 2016. Prenatal exposure to perfluorinated chemicals and neurodevelopment in early infancy: The Hokkaido Study.


• Gump et al., 2011. Perfluorochemical (PFC) Exposure in Children: Associations with Impaired Response Inhibition.

• Ha et al., 2009. Low blood levels of lead and mercury and symptoms of attention deficit hyperactivity in children: A report of the children’s health and environment research (CHEER).

• Hoffman et al., 2010. Exposure to Polyfluoroalkyl Chemicals and Attention Deficit/Hyperactivity Disorder in U.S. Children 12–15 Years of Age.


• Kern et al., 2016. The relationship between mercury and autism: A comprehensive review and discussion.

• Kim et al., 2013. Lead, mercury, and cadmium exposure and attention deficit hyperactivity disorder in children.

• Lien et al., 2016. Perfluoroalkyl substances in cord blood and attention deficit/hyperactivity disorder symptoms in seven-year-old children.
Liew et al., 2014. Prenatal Exposure to Perfluoroalkyl Substances and the Risk of Congenital Cerebral Palsy in Children

Liew et al., 2015. Attention Deficit/Hyperactivity Disorder and Childhood Autism in Association with Prenatal Exposure to Perfluoroalkyl Substances: A Nested Case–Control Study in the Danish National Birth Cohort.

Lin et al., 2013. In utero exposure to environmental lead and manganese and neurodevelopment at 2 years of age.

Llop et al., 2012. Prenatal Exposure to Mercury and Infant Neurodevelopment in a Multicenter Cohort in Spain: Study of Potential Modifiers. (only girls)

Myers et al., 2003. Prenatal methylmercury exposure from ocean fish consumption in the Seychelles child development study.

Nigg et al., 2008. Low Blood Lead Levels Associated with Clinically Diagnosed Attention-Deficit/Hyperactivity Disorder and Mediated by Weak Cognitive Control.

Plusquellec et al., 2007. The relation of low-level prenatal lead exposure to behavioral indicators of attention in Inuit infants in Arctic Quebec.

Sagiv et al., 2012. Prenatal Exposure to Mercury and Fish Consumption During Pregnancy and Attention-Deficit/Hyperactivity Disorder–Related Behavior in Children. (primarily boys)

Scassellati et al., 2012. Biomarkers and attention-deficit/hyperactivity disorder: a systematic review and meta-analyses.

Sioen et al., 2013. Prenatal exposure to environmental contaminants and behavioural problems at age 7-8 years.

Strøm et al., 2014. Persistent organic pollutants measured in maternal serum and offspring neurodevelopmental outcomes — A prospective study with long-term follow-up.


Vuong et al., 2016. Prenatal polybrominated diphenyl ether and perfluoroalkyl substance exposures and executive function in school-age children.

Wang et al., 2008. Case–Control Study of Blood Lead Levels and Attention Deficit Hyperactivity Disorder in Chinese Children.

Wang et al., 2015. Prenatal exposure to perfluoroalkyl substances and children's IQ: The Taiwan maternal and infant cohort study.

Yau et al., 2014. Prenatal and neonatal peripheral blood mercury levels and autism spectrum disorders.