Impact of environmental chemical exposure on childhood asthma and allergies, and infections.

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\textsuperscript{1}Hokkaido University Faculty of Health Sciences
\textsuperscript{2}Hokkaido University Center for Environmental and Health Sciences
\textsuperscript{3}WHO Collaborating Centre for Environmental Health and Prevention of Chemical Hazards
Outline

1. Background

2. Brief introduction of the Hokkaido Study and findings
   ① Persistent Organic Pollutants (dioxins and per and polyfluoroalkyl substances (PFAS))
   ② Short half-life chemicals (Phthalate esters)

3. Future directions
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3. Future directions
Dramatical increase of Chemicals

- Since WWII, more and more synthetic chemicals are produced.

- More than 160 Million chemical substances are registered in CAS (Chemical Abstract Service) (www.cas.org)

- Many of chemicals make our lives easy and convenient, as well as healthy, e.g. medicine and drugs, etc.

http://www.cas.org/content/chemical-substances/cas-registry-100-millionth-fun-facts
Chemicals may harm the environment

A crop-duster spreading DDT on a ranch in Oregon in 1948.

PCB pollution may alter marine mammals immune functions, e.g. Orcas.

Many of them have been released in the environment, and we are exposed to these chemicals.
What about for human?

• More than 5000 substances are registered in Hazardous Substances Data Bank (toxnet.nlm.nih.gov)
Timing of organ development (WHO 2012)

In utero and early life is important for child development.

Figure 1.4. Timing of organ development. Hormones affect each of these indicating that they are important, and in different ways, throughout life.
In 1986, Barker and Osmond suggested the relationship between poor nutrition in early life and later risk for ischemic heart disease, which had linked the importance of the intrauterine and early childhood nutritional environment and later disease risk.

Today, these concepts have been expanded from birth weight to the entire fetal and infantile development, which led to the establishment of the Developmental Origin of Health and Disease (DOHaD) hypothesis.

Prenatal exposure to environmental chemicals might damage children’s health outcomes such as growth, metabolism, immune system, etc.

**Motivation of the study**

- Early life exposure to the environmental chemicals might linger throughout one’s life.
- How relatively low levels of chemical exposure in our daily lives affect our health?
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Objectives

1. To find the effects of **perinatal environmental factors** on birth outcomes including congenital anomalies and growth retardation.

2. To evaluate the prevalence of **allergic diseases, developmental and neurobehavioral disorders**.

3. To identify a high-risk group classified by **genetic susceptibility (SNPs)** and investigate **trans-generational epigenetic effects** of environmental chemicals.

4. To provide scientific evidence for **health policies** based on human epidemiological data.

### Recruitment periods and number recruited

<table>
<thead>
<tr>
<th>Location</th>
<th>Recruitment periods</th>
<th>Number recruited</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sapporo</td>
<td>2002-2005</td>
<td>514 (1 hospital)</td>
</tr>
<tr>
<td>Hokkaido</td>
<td>2003-2012</td>
<td>20,926 (37 hospitals)</td>
</tr>
</tbody>
</table>
Long Follow-up of the participants

Risk for future diseases and health status?

Chemicals
Dioxins/PCBs
Organochlorines
PFAS
Phthalates etc.

Tobacco
Lifestyle
Socioeconomic Status
Stress

Blood (M)
Blood (M, C)
Urine
Urine, dust
Urine, blood

Epigenetics
SNPs (Single Nucleotide Polymorphisms)

Birth defect
Development
Puberty
Heart failure

Birth size
Obesity
Diabetes
Cancer

Birth defect, Development, Puberty, Heart failure
Allergies, infectious diseases
Cancer

tobacco
Long Follow-up of the participants (Morgenstern, et al., IJE 2011, EHPM 2013, EHPM 2017, EHPM 2021)

Kishi et al., IJE 2011, EHPM 2013, EHPM 2017, EHPM 2021
Targeted environmental chemicals

Persistent Organic Pollutants (POPs) (Stockholm Convention)
- Dioxins and PCBs (66 congeners)
- Organochlorine pesticides (OCP) e.g. DDT
- Per- and polyfluoroalkyl substances (PFAS) e.g. 6-13 carbon chain

Short half-lives
- Phthalate esters
- Bisphenols
- Phosphate flame retardants

- Pesticides
- PCBs
- Fluorinated products
- Polycarbonate goods
- Food containers
- Floor materials
- Floor wax
- Electronics
- Toys
- Personal care products
- Flammable textile
- Cans
### Biological measurements

<table>
<thead>
<tr>
<th>Variables</th>
<th>Specimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cotinine*</td>
<td>Maternal blood</td>
</tr>
<tr>
<td>Folic acid*</td>
<td>Maternal blood</td>
</tr>
<tr>
<td>Fatty Acids and triglyceride**</td>
<td>Maternal blood</td>
</tr>
<tr>
<td>IgE, IgA**</td>
<td>Cord blood</td>
</tr>
<tr>
<td>Thyroid hormones: TSH, fT4, fT3*</td>
<td>Maternal and cord blood</td>
</tr>
<tr>
<td>Reproductive hormones: steroid hormones, prolactin, LH, FSH, SHBG, Inhibin B, INSL3</td>
<td>Cord blood</td>
</tr>
<tr>
<td>Genes (SNPs, DNA methylation)</td>
<td>Maternal and cord blood</td>
</tr>
</tbody>
</table>

*Hokkaido Only, **Sapporo Only
Various outcomes and their risk factors

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Associated risk factors</th>
<th>(Journal name, year)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Dioxins</strong> (Environ Res, 2009), <strong>Perfluoroalkyl substances</strong> (EHP, 2009; JESEE, 2017, Env Int 2020), <strong>Me-Hg</strong> (STOTEN, 2015), <strong>Phthalates</strong> (STOTEN, 2017), <strong>Pregnancy Hypertensive Disorder</strong> (JERPH, 2021), <strong>Dioxins</strong> (EHP, 2011; STOTEN, 2018)</td>
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<td></td>
<td><strong>Hormones</strong> (Am J Human Biol, 2018)</td>
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<td></td>
<td><strong>Perfluoroalkyl substances</strong> (EHPM, 2016; Environ Int, 2019), <strong>Dioxins</strong> (STOTEN, 2018), <strong>OH-PCB</strong> (Environ Res 2018), <strong>Phthalates</strong> (Env Res 2020)</td>
<td></td>
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<tr>
<td></td>
<td><strong>Perfluoroalkyl substances</strong> (Environ Int, 2016; EHP, 2017; Environ Res, 2017), <strong>Phthalates</strong> (PLOS One, 2014; STOTEN, 2017), <strong>Bisphenol A</strong> (Epidemiology, 2017), <strong>Organochlorine pesticides</strong> (Environ Int, 2018), <strong>Dioxins</strong> (Environ Int, 2018), <strong>Reproductive Hormones</strong> (PLOS One 2015; Pediatr Int, 2019)</td>
<td></td>
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<tr>
<td></td>
<td><strong>Socioeconomic factors</strong> (IEA, 2014; Child Care Health Dev, 2017, Pediatr Int 2020), <strong>Dioxins</strong> (EHP, 2006; Environ Res, 2017; STOTEN, 2018), <strong>Organochlorine Pesticides</strong> (Neurotoxicology, 2018), <strong>Perfluoroalkyl substances</strong> (STOTEN, 2016), <strong>Bisphenol A</strong> (STOTEN, 2018), <strong>Adipokines</strong> (JERPH, 2019)</td>
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<td></td>
<td><strong>Gene-Environment Interaction</strong></td>
<td></td>
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<td></td>
<td><strong>Epigenetics</strong></td>
<td></td>
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<td></td>
<td><strong>Tobacco smoke</strong> (Sci Rep, 2018), <strong>Tobacco smoke and ADHD</strong> (Clin Epigenetics, 2021), <strong>Folate and allergies</strong> (Ped allerg Immunol, 2021), <strong>Perfluoroalkyl substances</strong> (IJHEE, 2018; Environ Int, 2018), <strong>Bisphenol A</strong> (Sci Rep, 2019), <strong>Phthalate</strong> (STOTEN, 2021)</td>
<td></td>
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<tr>
<td></td>
<td><strong>Exposure levels and trend</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Perfluoroalkyl substances</strong> (El 2014), <strong>Phthalates</strong> (IJHPH, 2021), <strong>Bisphenol A</strong> (Env Res 2020), <strong>Phosphate Flame retardants</strong> (IJHEH 2020)</td>
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<tr>
<td></td>
<td><strong>Indoor</strong></td>
<td></td>
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<tr>
<td></td>
<td><strong>Asthma and allergies</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Dampness, fuel use, ventilation</strong> (IAOEH 2013; JE, 2014), <strong>Phthalates</strong> (STOTEN 2014; Environ Int 2016 ), <strong>Phosphate Flame Retardants</strong> (Indoor Air, 2014; Environ Int, 2018; Environ Res 2019), <strong>Microbial VOCs</strong> (STOTEN 2012)</td>
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<td></td>
<td><strong>Sick Building Syndrome</strong></td>
<td></td>
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<tr>
<td></td>
<td><strong>Formaldehyde and VOCs</strong> (IAOEH 2009;2010; STOTEN 2012), <strong>Microbial VOCs</strong> (STOTEN, 2010), <strong>Phthalates and Phosphate Esters</strong> (Indoor Air 2010), <strong>Fungi and dust mite allergen</strong> (Indoor Air, 2012), <strong>Lifestyle</strong> (EHPM2020)</td>
<td></td>
</tr>
</tbody>
</table>
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Dioxins and POPs in the environment

- Polychlorinated Biphenyls (PCBs) and Dioxins
- Organochlorine Pesticides (OCPs) ex. DDT
- Per- and polyfluorinated substances (PFAS)
- Polybrominated Diphenyl Ethers (BDEs)

long-range transport where they have never been used or produced, (Worldwide threats)

bio-accumulation of POPs from plankton to fish, whale and white bear in the north pole
Circulation of Dioxins in the environment

- Some of the most toxic chemicals known to science.
- Highly persistent in the environment.
- Mainly formed by burning chlorine-based chemical compounds, but also tobacco smoke and automobile exhaust gas.
- In Japan, main exposure source is fish.
Perfluorinated alkyl substances (PFAS)

- PFASs are an organofluorine compounds with all hydrogens replaced by fluorine on a carbon chain.
- They have unique properties to make materials stain, oil, and water resistant, and their industrial applications are including water-proofing, insulating agents, and in fire extinguishing foam, etc.
- Main exposure sources are drinking water, food, food packaging, house dust (Hölzer et al. 2008; Halldorsson et al. 2008; Begley et al. 2005; Björklund et al. 2009)
- Elimination half-life in humans are PFOS 5.4 years, PFOA 3.8 years (Olsen et al. 2007)
Chemical exposure levels

RESEARCH ARTICLE

The Hokkaido Birth Cohort Study on Environment and Children’s Health: cohort profile—updated 2017

Rieko Kishi1, Atsuko Asael2, Masahiro Minatoya,1 Tomoyoshi Kanazaki,1 Chihito Aihara,1,2 Sadako Itoh,1,2 Sumiko Kobayashi,1 Yuu Aita1, Reiko Yamauchi,1 Ryu Matsui,1 Kazumi Tamura2, Kazuaki Kyo1,3 Houman Goudadi1,4 and the members of The Hokkaido Study on Environment and Children’s Health

Table 6 Exposure levels of environmental chemicals in the Sapporo cohort

<table>
<thead>
<tr>
<th>Maternal blood</th>
<th>Number</th>
<th>DL</th>
<th>&gt;DL (%)</th>
<th>Min</th>
<th>25th</th>
<th>50th</th>
<th>75th</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total dioxins (TEQ pg/g lipid)</td>
<td>425</td>
<td>n/a</td>
<td>n/a</td>
<td>3.17</td>
<td>9.95</td>
<td>13.9</td>
<td>18.2</td>
<td>43.4</td>
</tr>
<tr>
<td>Total PCBs (ng/g lipid)</td>
<td>425</td>
<td>n/a</td>
<td>n/a</td>
<td>17.8</td>
<td>73.0</td>
<td>117.0</td>
<td>146</td>
<td>41,450</td>
</tr>
<tr>
<td>p,p’-DDE</td>
<td>379</td>
<td>0.60</td>
<td>100</td>
<td>49.52</td>
<td>401.53</td>
<td>650.99</td>
<td>1,011.48</td>
<td>4,575.67</td>
</tr>
<tr>
<td>PFOA (ng/mL)</td>
<td>447</td>
<td>0.50</td>
<td>100</td>
<td>1.30</td>
<td>3.40</td>
<td>5.20</td>
<td>7.00</td>
<td>16.2</td>
</tr>
<tr>
<td>PFOS (ng/mL)</td>
<td>447</td>
<td>0.50</td>
<td>92.0</td>
<td>0.25</td>
<td>0.80</td>
<td>1.30</td>
<td>1.80</td>
<td>5.30</td>
</tr>
<tr>
<td>MEOH (ng/mL)</td>
<td>493</td>
<td>0.278</td>
<td>100</td>
<td>1.94</td>
<td>5.82</td>
<td>9.95</td>
<td>7.00</td>
<td>16.2</td>
</tr>
<tr>
<td>Bisphenol A (ng/mL)</td>
<td>59</td>
<td>0.04</td>
<td>76.3</td>
<td>&lt;DL</td>
<td>0.040</td>
<td>0.057</td>
<td>0.072</td>
<td>0.419</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cord blood</th>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphenol A (ng/mL)</td>
<td>285</td>
<td>0.04</td>
<td>68.8</td>
<td>&lt;DL</td>
<td>&lt;DL</td>
<td>0.051</td>
<td>0.076</td>
<td>0.217</td>
</tr>
<tr>
<td>Maternal hair</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Me-Hg (µg/g)</td>
<td>420</td>
<td>n/a</td>
<td>100</td>
<td>0.24</td>
<td>0.96</td>
<td>1.40</td>
<td>1.89</td>
<td>7.59</td>
</tr>
</tbody>
</table>

*p,p’-DDE: p,p’-dichlorodiphenyldichloroethylene, DL: detection limit, Me-Hg: methylmercury, ARHP: mono-o-ethylphenyldihydrosulfate, n/a: not applicable, PCBs: polychlorinated biphenyls, PFOS: perfluorooctanoic acid, PFOA: perfluorooctanoic acid fluoride, TEQ: toxicity equivalency quantity

![Dioxins](image)

**Fig. 1.** Concentrations (median ± interquartile range) of dioxins in the 2006-2007 TGQ (µg/L) and 2008-2009 TGQ (µg/L). The bars show the mean ± standard deviation of concentrations of PCDDs + PCDFs and Dioxins (teflon-polypropylene, TGQ; pg/L) for the corresponding TGQ samples. The TGQs are country, sampling period, and reference.

**PFOS/PFOA**

![PFOS/PFOA](image)

**Fig. 2.** Maternal Cord Blood levels of PFOS and PFOA (adult study, n=616). The box plots show either maternal or cord blood levels of PFOS (µg/L) and PFOA (µg/L), respectively. The data are from samples for cord blood and maternal blood, respectively. The data are from samples for cord blood and maternal blood, respectively. The data are from samples for cord blood and maternal blood, respectively. The data are from samples for cord blood and maternal blood, respectively. The data are from samples for cord blood and maternal blood, respectively. The data are from samples for cord blood and maternal blood, respectively.

Kishi et al., STOTEN2017
PFOS and PFOA concentrations declined, whereas PFNA and PFDA levels increased between 2003-2011. PFUnDA, PFDoDA, and PFTrDA were detected in the vast majority of maternal samples, but no significant temporal trend was apparent.
Maternal to child transfer of PFCs

• There was a high correlation of PFC concentrations between maternal and cord serum samples, implying *trans-placental transport*. (Inoue et al. EHP, 2004)
Higher dioxin levels in maternal blood, lower IgE levels in cord blood among **boys**

<table>
<thead>
<tr>
<th></th>
<th>IgE levels at birth</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Both</strong></td>
<td>β = -0.14</td>
<td>(95% CI)</td>
<td>-0.63, 0.35</td>
</tr>
<tr>
<td><strong>Boys</strong></td>
<td>β = -0.87</td>
<td>(95% CI)</td>
<td>-1.68, -0.06</td>
</tr>
<tr>
<td><strong>Girls</strong></td>
<td>0.27</td>
<td>(95% CI)</td>
<td>-0.38, 0.91</td>
</tr>
</tbody>
</table>

Adjusteda (ALL): adjusted for maternal factors (age, parity, smoking during pregnancy, pelagic fish intake during pregnancy, allergic history), and paternal allergic history, annual household income, blood sampling period, and infant gender.

Adjustedb (boy and girl): adjusted for potential confounding factors excluding infant gender from adjusteda (ALL) in stratified analysis by infant gender.
Effects of prenatal exposure to dioxin-like compounds on allergies and infections during infancy.

Chihiro Miyashita, Seiko Sasaki, Yasuaki Saijo, Noriaki Washino, Emiko Okada, Sumitaka Kobayashi, Kanae Konishi, Jumeku Kajiwara, Takashi Todaka, Reiko Kishi.

Higher dioxin levels increase risk of otitis media among 18 months boys

Adjusted Odds ratios

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Adjusted Odds Ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st quartile</td>
<td>1</td>
</tr>
<tr>
<td>2nd quartile</td>
<td>1.6</td>
</tr>
<tr>
<td>3rd quartile</td>
<td>2.2</td>
</tr>
<tr>
<td>4th quartile</td>
<td>2.5*</td>
</tr>
</tbody>
</table>

P for trend = 0.027

OR (95%CI) versus the first quartile (reference) in the logistic regression model adjusted for maternal educational level, parity, infant gender, duration of breast-feeding, environmental tobacco exposure, day care attendance and blood sampling period. *P < 0.05
Higher dioxin levels increase risk of wheeze at 7 years old

<table>
<thead>
<tr>
<th></th>
<th>3.5 years old</th>
<th>7 years old</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Any allergies</td>
<td>0.61 (0.16, 2.30)</td>
<td>2.17 (0.49, 9.59)</td>
</tr>
<tr>
<td>Food allergies</td>
<td>0.99 (0.21, 4.79)</td>
<td>1.39 (0.24, 8.05)</td>
</tr>
<tr>
<td>Eczema</td>
<td>0.82 (0.17, 3.96)</td>
<td>1.02 (0.21, 4.88)</td>
</tr>
<tr>
<td>Wheeze</td>
<td>0.44 (0.05, 3.59)</td>
<td>7.81 (1.42, 42.94)</td>
</tr>
<tr>
<td>Any infections</td>
<td>0.85 (0.21, 3.43)</td>
<td>3.80 (0.70, 20.61)</td>
</tr>
<tr>
<td>Otitis media</td>
<td>0.51 (0.14, 1.93)</td>
<td>0.78 (0.17, 3.46)</td>
</tr>
<tr>
<td>Respiratory infections</td>
<td>1.03 (0.21, 5.13)</td>
<td>0.51 (0.09, 3.11)</td>
</tr>
</tbody>
</table>

OR (95%CI) versus the first quartile (reference) in the logistic regression model adjusted for maternal educational level, parity, infant gender, duration of breast-feeding, environmental tobacco exposure, day care attendance and blood sampling period. *P< 0.05

Miyashita et al., STOTEN 2018
Prenatal exposure to perfluorinated chemicals and relationship with allergies and infectious diseases in infants.

Emiko Okada, Seiko Sasaki, Yasuaki Sajo, Noritsuki Washino, Chihiro Miyashita, Sumitaka Kobayashi, Kanako Konishi, Yoichi M. Ito, Ric Ito, Ayako Nakata, Yukako Iwao and Koichi Saito, Hirofumi Nakazawa, Reiko Kishi

- Cord blood IgE levels decreased significantly with high maternal PFOA concentration among female infants.
- There were no significant association among maternal PFOA and PFOS levels and food allergy, eczema, wheezing or otitis media in the 18 month-old infants.
Prenatal PFAS on immune functions

Effects of prenatal exposure to perfluoroalkyl acids on prevalence of allergic diseases among 4-year-old children

Houman Goudarzi a, Chihiro Miyashita a, Emiko Okada b, Ikuko Kashino a,c, Sumitaka Kobayashi a, Chi-Jen Chen a,d, Sachiko Ito a, Atsuko Araki a, Hideyuki Matsuura a, Yoichi M. Ito e, Reiko Kishi a,f

Allergy

Adjusted ORs in the highest quartile vs lowest quartile for total allergic diseases were significantly decreased for PFDoDA (C12) and PFTrDA (C13). Associations were prominent among boys. Q: quartile. Logistic models were adjusted for maternal age, maternal educational level, parental allergic history, parity, children gender, day care attendance and ETS exposure in at 4-year-old, and breast feeding.

Infectious diseases

Prenatal exposure to perfluoroalkyl acids and prevalence of infectious diseases up to 4 years of age

Houman Goudarzi a, Chihiro Miyashita a, Emiko Okada b, Ikuko Kashino a,c, Chi-Jen Chen a,d, Sachiko Ito a, Atsuko Araki a, Sumitaka Kobayashi a, Hideyuki Matsuura a, Reiko Kishi a,f
Prenatal PFAS exposure reduced asthma and allergies, whereas increase infectious diseases

- Immunotoxic effects?
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3. Future directions
First produced during the 1920s, and have been produced in large quantities since the 1950s

- Used as plasticizers

The main source of phthalate exposure is caused by food ingestion (food contaminated during production, processing, packaging, or storage), cosmetics and consumer products, Indoor air and dust

- Banned the usage for mouthing toys, and toys for <6yrs old (DBP, DEHP, BBzP, DIDP, DINP), and food containers and cooking equipment which may contact with food contains oil (DEHP)
Cf. Populations (millions)
Japan, 120; USA, 320; EU; 740; Australia, 23; China, 1357; Other Asia (exclude China and Japan), 3000

**Phthalate consumption**

**In the world**

China
1218 (2005) to 1670 (2017)

**In Japan**

**TOTAL**

**DEHP**

**DINP**

**Others**

Cf. **Plasticizers, Malveda et al., HIS Market, 2018**

**The Chemical Daily, Japan**
胎児期フタル酸エステルDEHP曝露は、7歳までの食物アレルギーや感染症罹患リスクを増加。

Effects of prenatal di(2-ethylhexyl) phthalate exposure on childhood allergies and infectious diseases: The Hokkaido Study on Environment and Children's Health
Yu Ait Bami, Chihiro Miyashita, Atsuko Araki, Tamie Nakajima, Seiko Sasaki, Reiko Kishi
Biomonitoring of organophosphate flame retardants and plasticizers in children: Associations with house dust and housing characteristics in Japan

Spearman's ρ; *p<0.05; **p<0.01

<table>
<thead>
<tr>
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<th>尿中</th>
<th>床</th>
<th>棚上</th>
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<tbody>
<tr>
<td>MBzP (μg/kg/day)</td>
<td>0.27**</td>
<td>0.19**</td>
<td></td>
</tr>
<tr>
<td>DEHP (μg/kg/day)</td>
<td>0.24**</td>
<td>0.11</td>
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<tr>
<td>TBOEP (ng/mL)</td>
<td>0.34**</td>
<td>0.26**</td>
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<tr>
<td>TCIPP (ng/mL)</td>
<td>0.29*</td>
<td>0.12</td>
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</table>

子どもたちは、床ダスト中の化学物質を体内に取り込んでいる。
Outline

1. Background

2. Brief introduction of the Hokkaido Study and findings
   ① Persistent Organic Pollutants (dioxins and per and polyfluoroalkyl substances (PFAS))
   ② Short half-life chemicals (Phthalate esters)

3. Future directions
Q1: How long the effect continue?

Exposure to PFAS

DNA methylation (Naum 2016, Kobayashi 2017)

At birth
- Birthweight ↓
- Ponderal Index ↓

At birth
- Adiponectin ↑
  (Minatoya 2017)

At birth
- Thyroid hormone and antibody disruption ↑
  (Itoh 2019, Ito 2016)

6 months
- Neurodevelopment score ↓
  (Goudarzi 2016)

At birth
- Sex and steroid hormone disruption ↑
  (Goudarzi 2017, Ito 2016)

At birth
- IgE level ↓
  (Okada 2012)

2 years old
- Allergy ↓
  (Okada 2012)

4 years old
- Allergy ↓
- Infectious disease ↑
  (Goudarzi 2016, 2017)

7 years old
- Allergy ↓
- Infectious disease ↑
  (Alt Borsai 2020)

Affect obesity? or abnormal physique?

Increase of neurodevelopmental disorders?

Increase of lifestyle related diseases?

Affect puberty onset?

Affect reproduction?

Immunomodulation?
Q2: Is the environmental chemical exposure matter COVID-19 infection?

### Summary of previous findings

<table>
<thead>
<tr>
<th>Population</th>
<th>Outcomes</th>
<th>Exposures</th>
<th>PFOA</th>
<th>PFOS</th>
<th>PFNA</th>
<th>PFHxS</th>
<th>PFDA</th>
<th>Ref.</th>
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<tbody>
<tr>
<td>Faroe Island, n=587,</td>
<td>5, 7y</td>
<td>Prenatal</td>
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<td>↓</td>
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<td>Grandjean, 2012</td>
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<tr>
<td>Faroe Island, n=516,</td>
<td>7y and 13y</td>
<td>prenatal</td>
<td>↓@13y</td>
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<td>↓</td>
<td>Grandjean, 2017</td>
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<td>Faroe Island, n=399</td>
<td>7y, 14y, 21y, and 28y.</td>
<td>At birth</td>
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<td>Shin, 2021</td>
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<td>n=12</td>
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<td>Kielsen, 2016</td>
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<tr>
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<td>7-12y</td>
<td>Postnatal</td>
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<td>↑</td>
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</tbody>
</table>
Further studies

1. Long term follow-up
2. Examination of antibodies

Children's face-to-face examination (9-11y)
- Informed consent/assent
- Anthropometry measures
- FeNO (respiratory inflammations)
- Blood and urine sampling

Adolescents' face-to-face examination (14-17y)
- Informed consent/assent
- Anthropometry measures
- Tanner stage, blood pressure
- Blood and urine sampling

Now we are at this stage
Activities

1. Providing scientific evidence of chemical hazards and their health effects in the Western Pacific Region

2. Support updating and summarizing of WHO materials related to chemical hazards and health effects

3. Training and education on chemical hazards and their health impacts in countries of the Western Pacific Region
Thank you very much for your kind attention!!