# How to Work Exposure Assessment

## –Large Scale Birth Cohort and Exposomics–

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JECS
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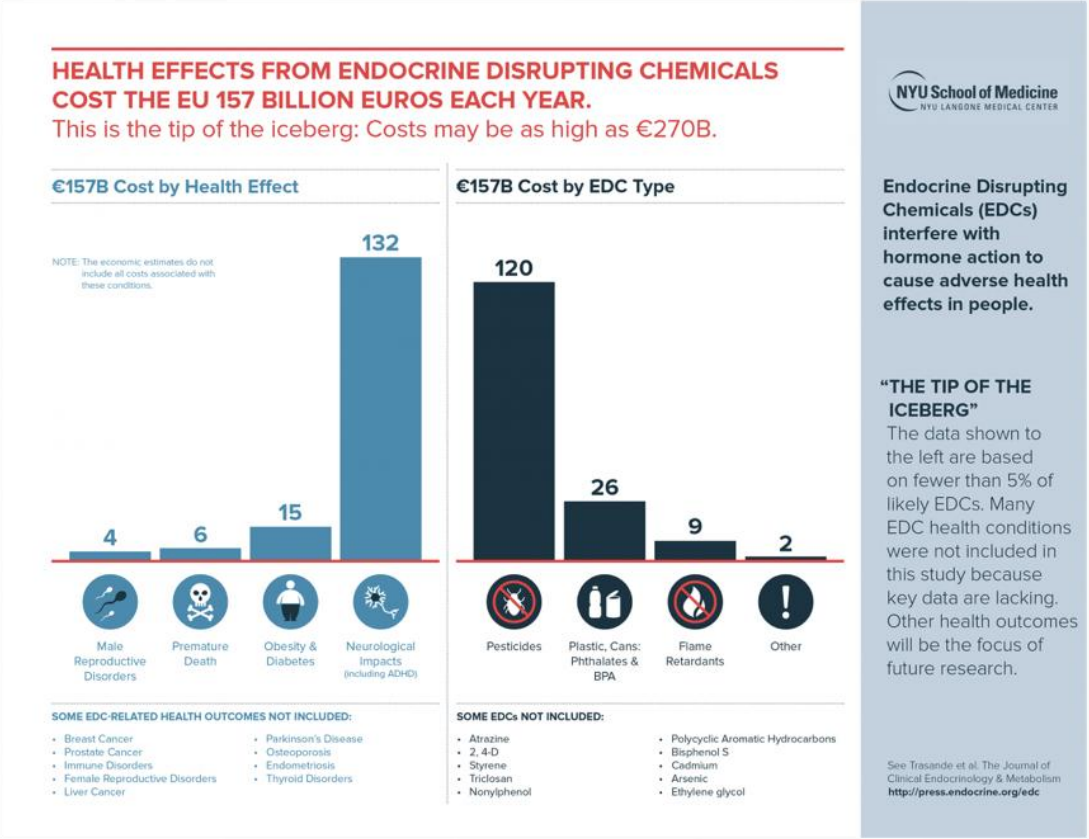
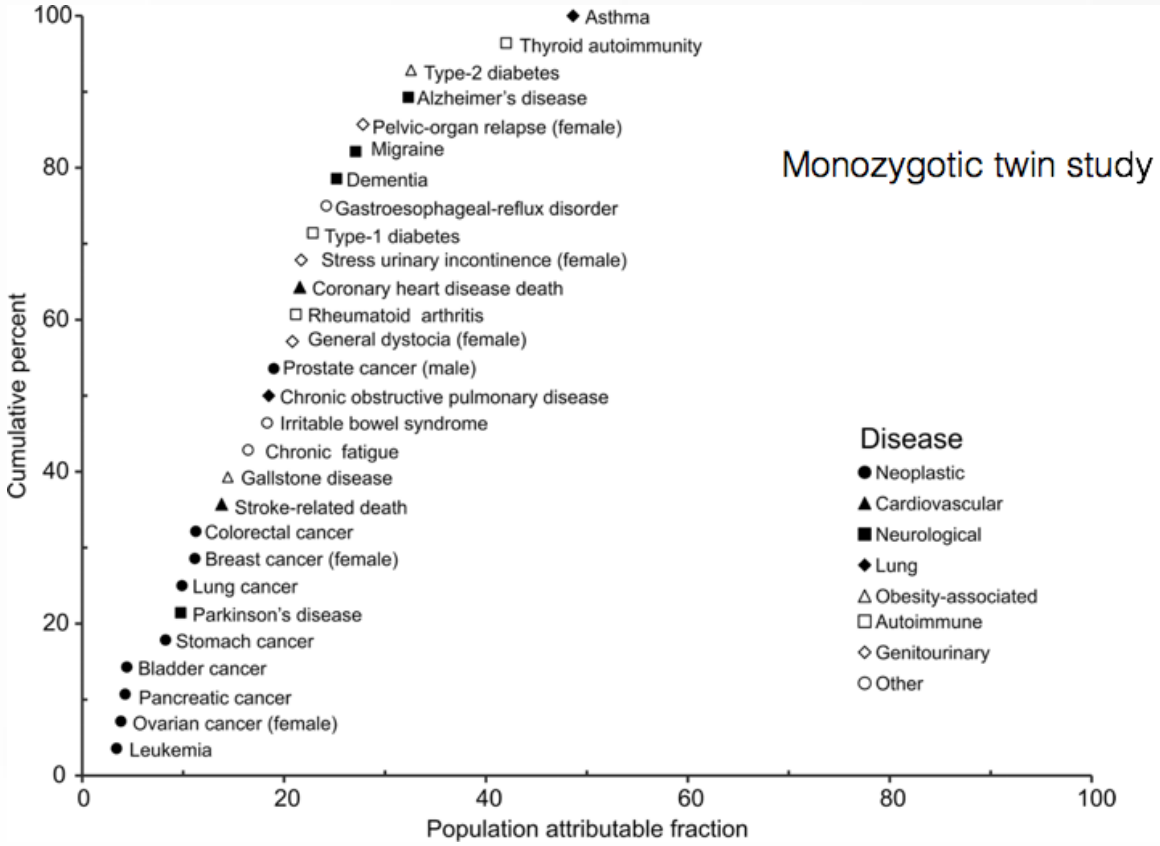
# The cost of inaction




https://med.nyu.edu/pediatrics/research/environmentalpediatrics/policy-research/disease-burden-and-costs-due-endocrine-disrupting-chemicals

Adopted: Trasande et al., J Clin Endocrinol Metab, 2015, 100(4):1245–1255

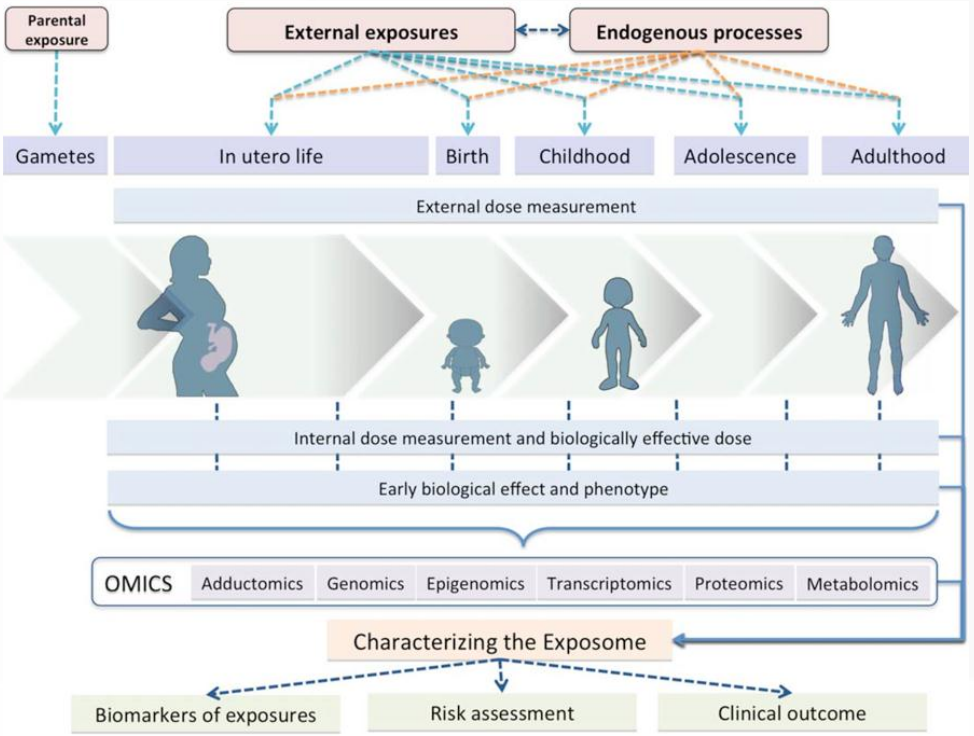
# Genome isn't everything




Stephen M. Rapparport, PLoS One, 2016

# Exposome: Life-course total exposure

- ✓ Exposome is composed of every exposure to which an individual is subjected from conception to death




Wild CP. (2013) Environ. Molecular Mutagenesis

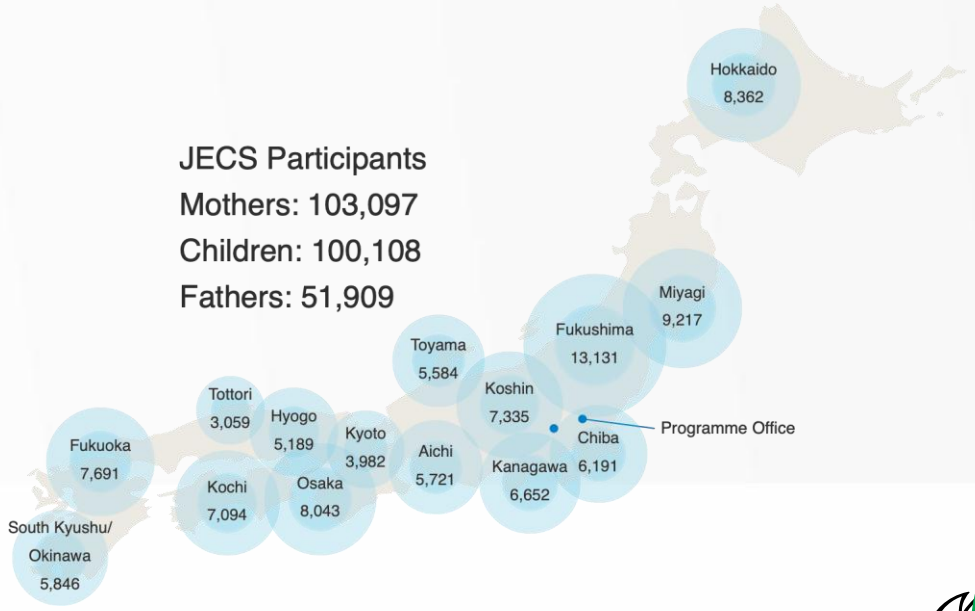
# Japan Environment and Children's Study (JECS)


**The Japan Environment and Children's Study**

**For the future crew of the Earth**

How can we keep the environment healthy and hand it over to the next generations? The Japan Environment and Children's Study (JECS) started in 2011 is to answer such a question by investigating a wide range of environmental factors that could affect children's health and development.

JECS Participants
Mothers: 103,097
Children: 100,108
Fathers: 51,909

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# Goals and vision of JECS

- The ultimate goal of JECS is to identify environmental factors that affect children's health and development and help the government design better risk management strategies, i.e. **prevention** and **intervention**
- The government may use the information to help plan health policy and services
- The government may share the study information with other countries and international organizations such as the World Health Organization (WHO)

# JECS study design

- **Main Study** = 100,000
  - ✓ Biological sample collection from mothers, children and fathers
  - ✓ Questionnaire administration during pregnancy, at birth, 1 month, 6 month, and every 6 month after that until children reach 13 yo
  - ✓ Medical record, resident registry and school record transcription
- **Sub-Cohort Study** = 5,000
  - ✓ Home visit—Indoor and outdoor air quality, particulate matter, house dust, noise, dwelling inspection… at 1.5 and 3 years
  - ✓ Psychological development test, physical examination, blood and urine collection at 2 and 4 years
- **Adjunct Studies** conducted with extramural funding
- **Pilot Study** to evaluate the feasibility, acceptability and cost of the proposed procedures and processes to be used in the Main Study

JECS Japan Environment and Children's Study

Kawamoto et al., BMC Public Health. 2014; 14: 25

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# Priority outcomes

| | |
|---|---|
| Reproduction and pregnancy complication | Stillbirth, preterm delivery, low birth weight |
| Congenital anomalies | Cleft lip and palate, ventricular septal defect, hypospadias, cryptorchidism, Down syndrome |
| Neuropsychiatric and developmental disorders | Autism spectrum disorders, learning disability, ADHD |
| Allergy and immune system disorders | Asthma, atopic dermatitis, food allergy, Kawasaki disease |
| Metabolism and endocrine system dysfunction | Glucose metabolism disorder, obesity |
| Cancers for international co-operation | Leukaemia, solid cancers |

JECS Japan Environment and Children's Study

Kawamoto et al., BMC Public Health. 2014; 14: 25

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# Exposures of interest

| | |
|---|---|
| Chemicals from environment/occupation | Metals, POPs, pesticides, organofluorine compounds, aroma compounds, phthalate metabolites, phenols, others |
| Physical environment | Noise, heat, ionising radiation, housing condition, neighbourhood |
| Lifestyle | Stress, nutrition, daily rhythm, smoking and alcohol, infections, medications |
| Socio-economic status | Education, house-hold income, social bonding, community support |
| Genetics/-omics (when new funding available) | Genomics, epigenetics, metabolomics, aductomics |

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Kawamoto et al., BMC Public Health. 2014; 14: 25

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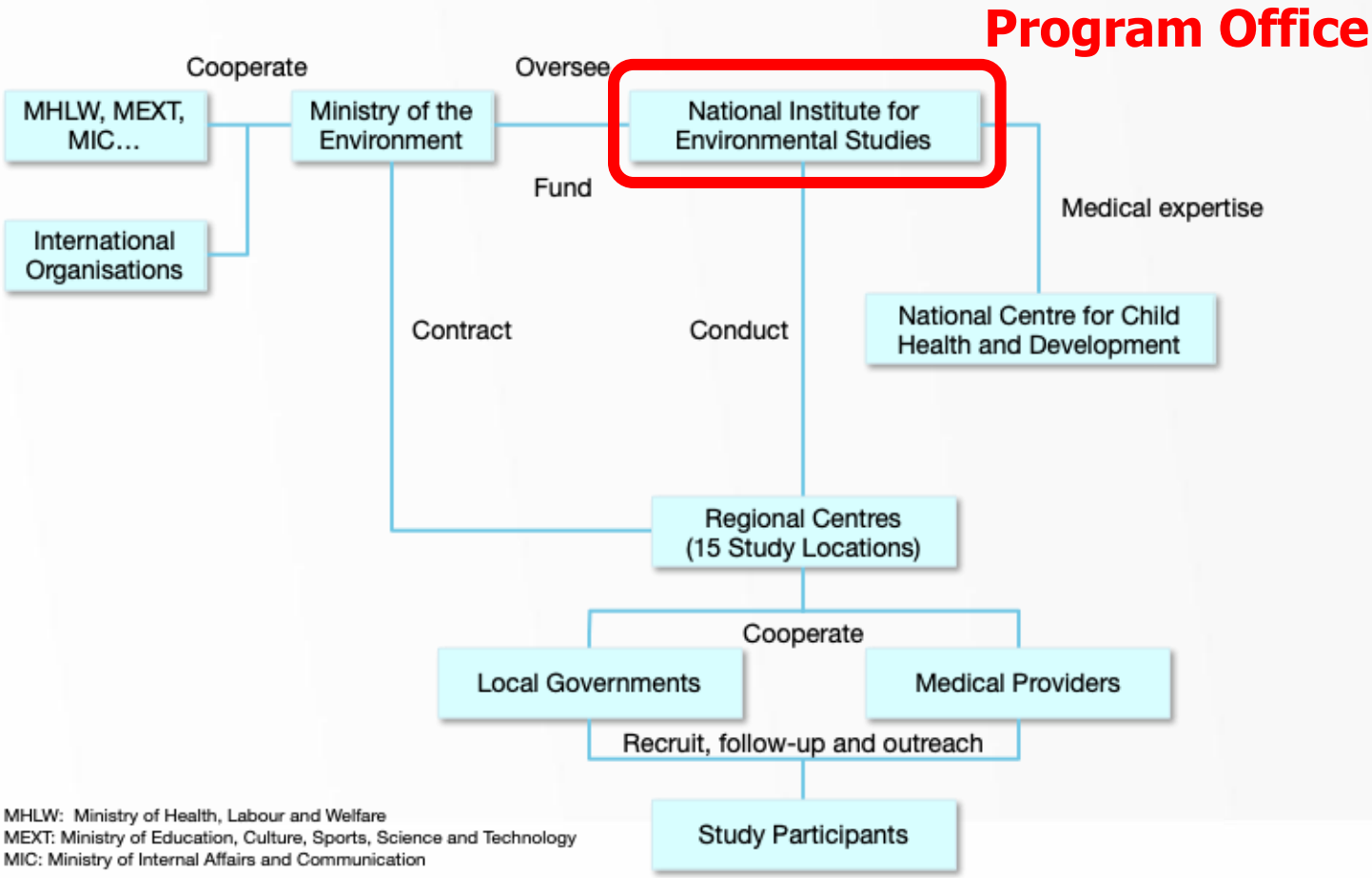
# Closer look at the target chemicals

| Group | Target compounds |
|---|---|
| Metals | Lead, cadmium, total mercury, methyl mercury, arsenics and its compounds including, arsenobetaine, metylarsonic acid, dimethylarsinic acid, trimethylarsine oxide, etc. |
| Inorganic substances | Iodine, perchlorate, nitrate nitrogen, etc |
| Chlorinated POPs (Persistent organic pollutants) | Polychlorinated biphenysl (PCBs), hydroxylated polychlorinated biphenyl (OH-PCB), dioxins (PCDDs, PCDFs, Co-PCBs), pexachlorobenzene (HCB), pentachlorobennzene (PeCB), etc. |
| Pesticides (including pesticide-POPs) | Chlordanes, DDT and its metabolites (DDE, etc.), drin compounds for agriculture (dieldrin, etc.), heptachlor, hexachlorocyclohexaxne (HCH), mirex, chlordecone, toxaphene, organophophorus pesticide metabolites (DMP, DEP, DMTP, DETP, etc.), fenitrothion metabolite (methylnitrophenol), acephate metabolite (methamidophos), pyrethroid metabolites (PBA, DCCA, etc.), dithiocarbamate fungicide metabolites (ethylene thiourea, etc.), neonicotinoid metabolites, pentachlorophenol (PCP), atrazine, dymron, glyphosate, flutolanil, iprodione, flusulfamide, etc. |
| Brominated POPs | Polybromodiphenylethers (PBDEs), polybromobiphenyls (PBBs), hexabromocyclododecan (HBCD), etc. |
| Organofluorine compounds | Perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), perfluorononanoic acid (PFNA), etc. |
| Aroma compounds | Nitromusks, cyclic musks, etc. |
| Phthalate metabolites | Mono (2-ethylhexyl) phthalates, etc. |
| Phenols | Bisphenol A, Nonyphenols, Parabens, etc. |
| Others | Triclosan, benzophenone, N, N-diethyl-meta-toluamide (DEET), polyaromatic hydrocarbons (PAHs) and their metabolites (1-hydroxypyrene, 3-hydroxyphenanthrebe, etc.), cotinine, thiocyanate, dichlorobenzene, phytoestrogen, caffeine, pyridine, acrylamide, tributyl phosphate, tributoxyethl phosphate, 8-hydroxydeoxyguanosine (8-OHdG), etc. |

Kawamoto et al., BMC Public Health. 2014; 14: 25

# Organization




http://www.env.go.jp/chemi/ceh/en/index.html

# JECS current status: Overview

- **Recruitment completed in March 2014**
  - ✓ Mother: 103,097 (~80% consent rate)
  - ✓ Father: 51,909
  - ✓ Birth: 100,108
- **Questionnaire**
  - ✓ Through pregnancy to 6 years old (every 6 months)
- **Biological samples > 5,000,000 tubes**
  - ✓ Maternal blood, urine, breast milk, cord blood, hair, blood spots, paternal blood, …
- **Sub-Cohort Study (n = 5,000) started in November 2014**
  - ✓ Home visit (1.5 and 3 y/o): VOCs, aldehyde, PM, house dust, dwelling observation
  - ✓ Developmental test, physician's exam, blood (2 and 4 y/o) and urine (4 y/o) collection

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# JECS current status: Biospecimen

| Sample type | Collected from | | Number |
|---|---|---|---|
| **Blood/urine** | Mother | Early pregnancy | 91,935 |
| | | Mid–late pregnancy | 97,979 |
| | | At birth | 98,818 |
| | Father | Ad libitum | 49,796 |
| **Cord blood** | | At birth | 87,802 |
| **Blood spot** | Child | 1 month old | 94,841 |
| **Brest milk** | Mother | 1 month | 89,364 |
| **Hair** | Mother | At birth | 78,719 |
| | Child | 1 month old | 94,990 |
| **Blood** | Child | 2 y/o | 4,727 |
| **Blood/urine** | Child | 4 y/o | on going |

# JECS current status: Exposure

| Sample type | Analyte | Number |
|---|---|---|
| **Maternal blood (mid–late term)** | Metallic elements (Hg, Pb, Cd, Mn, Se) | 95,811 |
| **Cord blood** | Metallic elements (Hg, Pb, Cd, Mn, Se) | 3,897 (sub-cohort) |
| **Maternal urine (early term)** | Cotinine, 8-OHdG | 96,490 |
| **Maternal blood (mid–late term)** | Perfluoroalkyl substances | on-going (25,000) |
| **Home visit (1.5 y)** | VOCs<br>Aldehydes<br>NOx, SOx, O3<br>PM2.5 | Indoor (outdoor)<br>5,006 (4,990)<br>5,005 (4,993)<br>5,006 (4,992)<br>5,006 (4,993) |
| **Home visit (3 y)** | VOCs<br>Aldehydes<br>NOx, SOx, O3<br>PM2.5 | Indoor (outdoor)<br>4,712 (4,712)<br>4,712 (4,712)<br>4,712 (4,712)<br>4,712 (4,712) |
| **House dust (1.5 y)** | Mite allergen/endotoxin | 5,009 |
| **Vacuum dust** | Sieved | 4,920 |

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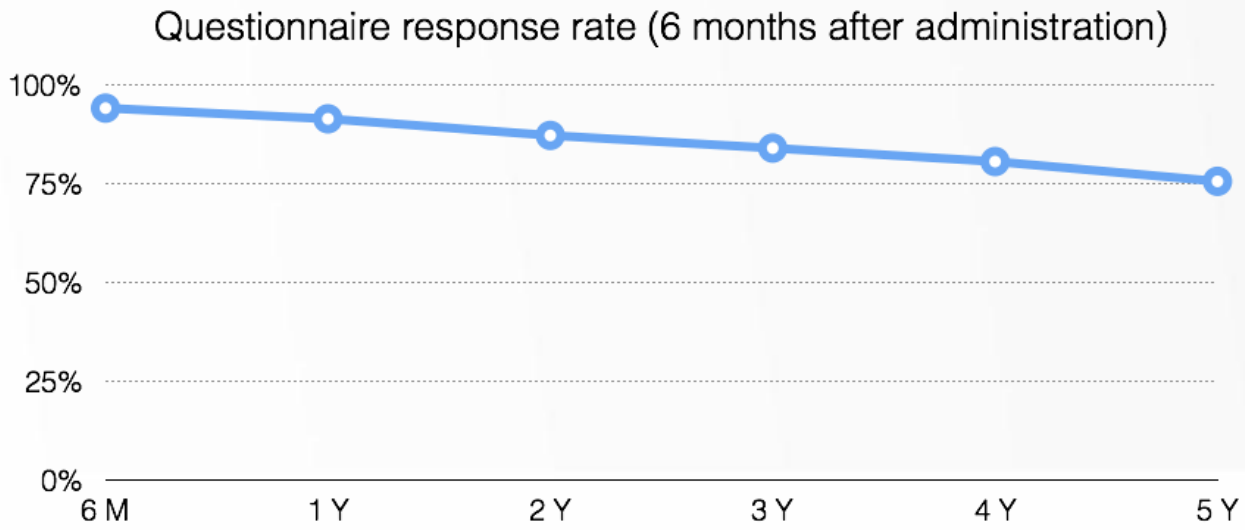
# JECS current status: Retention

| | Registered participants | Current number | Retention |
|---|---|---|---|
| **Mothers** | 103,099 | 96,043 | 93.2% |
| **Children** | 100,108 | 97,051 | 96.9% |
| **Fathers** | 51,909 | 49,549 | 95.6% |




Michikawa et al. Journal of Epidemiology (2017)

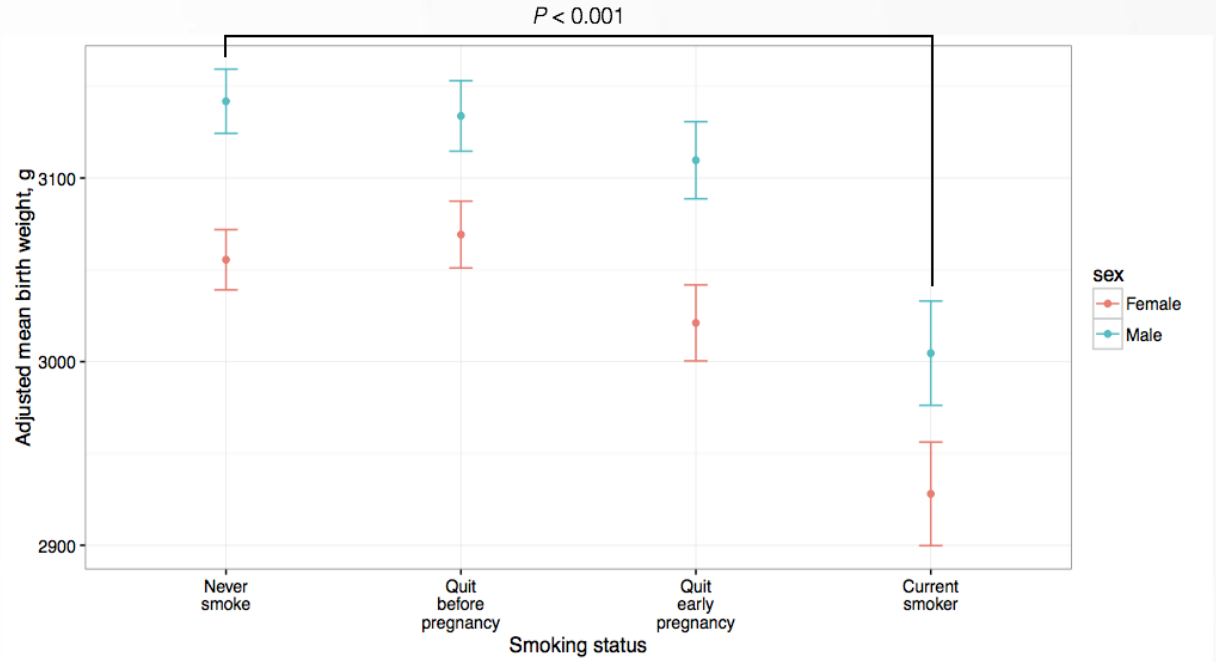
# JECS current status: Profile

| | | JECS (%) | National Statistics (%) | |
|---|---|---|---|---|
| **Maternal characteristics** | | | | |
| Age at delivery | 20-29 | **36.6** | 38.5 | Vital Statistics, 2011 |
| | 30-39 | **57.8** | 56.6 | |
| Parity | 0 | **40.9** | *a* | |
| **Infant characteristics** | | | | |
| Live births | | **98.1** | 98.0 | Birth Statistics, 2010 |
| Term birth[b] | (37–41 wks) | **94.2** | 94.9 | Birth Statistics, 2010 |
| Sex[c] | Female | **48.8** | 48.8 | Vital Statistics, 2011 |
| | Male | **51.2** | 51.2 | |
| Type of delivery | Cesarean | **20.1** | 19.2 | Surveys of Medical Institutions, 2011 |
| Birth weight[b] (g) | | | | |
| | < 2,500 | **8.1** | 8.3 | Birth Statistics, 2010 |
| | 2,500 – 3,000 | **38.7** | 39.0 | |
| | 3,000 – 3,500 | **42.1** | 41.8 | |
| | 3,500 ≤ | **11.1** | 10.9 | |

a. In Vital Statistics, birth order has been reported. The proportion of first child among the number of the total births was 47.1% in 2011. b. Singleton births only. c. Excluding missing.

Michikawa et al. Journal of Epidemiology (2017)

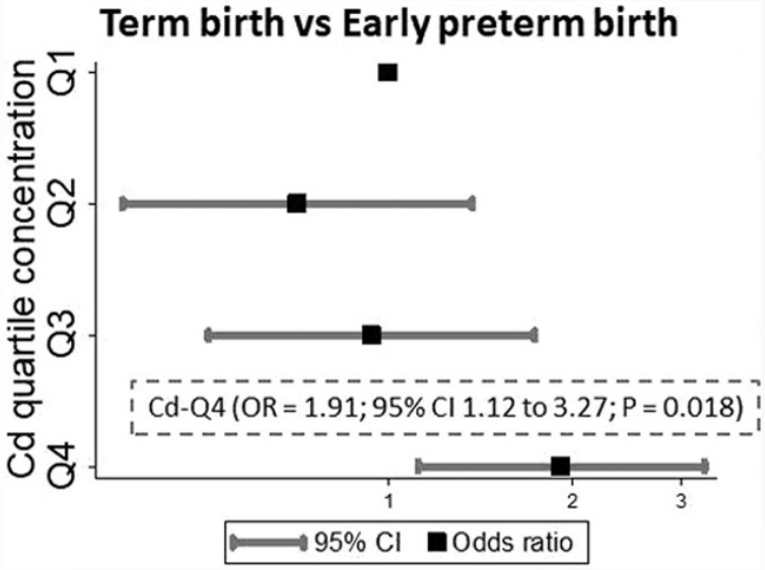
# JECS current status: Smoking and BW




Adjusted for partners' smoking status, annual household income, birth order of children, pregnancy-induced hypertension, diabetes mellitus/gestational diabetes mellitus, maternal weight before pregnancy, maternal weight gain during pregnancy, maternal age group at delivery, and gestational duration; calculated by least squares mean adjustment
P-value was calculated using Dunnett's test by least squares mean adjustment

Adjusted: Suzuki K et al (2016) J Epidemiology

# JECS current status: Association between blood metal level and premature birth




- Association between Cd, Pb, Hg, Se and Mn in maternal blood and early and late preterm birth was examined
- Maternal Cd level could increase the risk of early preterm birth
- Other metals and late preterm birth didn't show significant trend

Tsuji M. et al. (2018) Environ Res

# Human Biomonitoring in Asian Countries – Human breast milk as a bioindicator –

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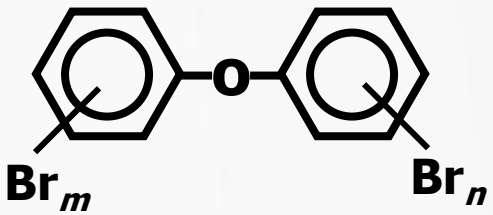
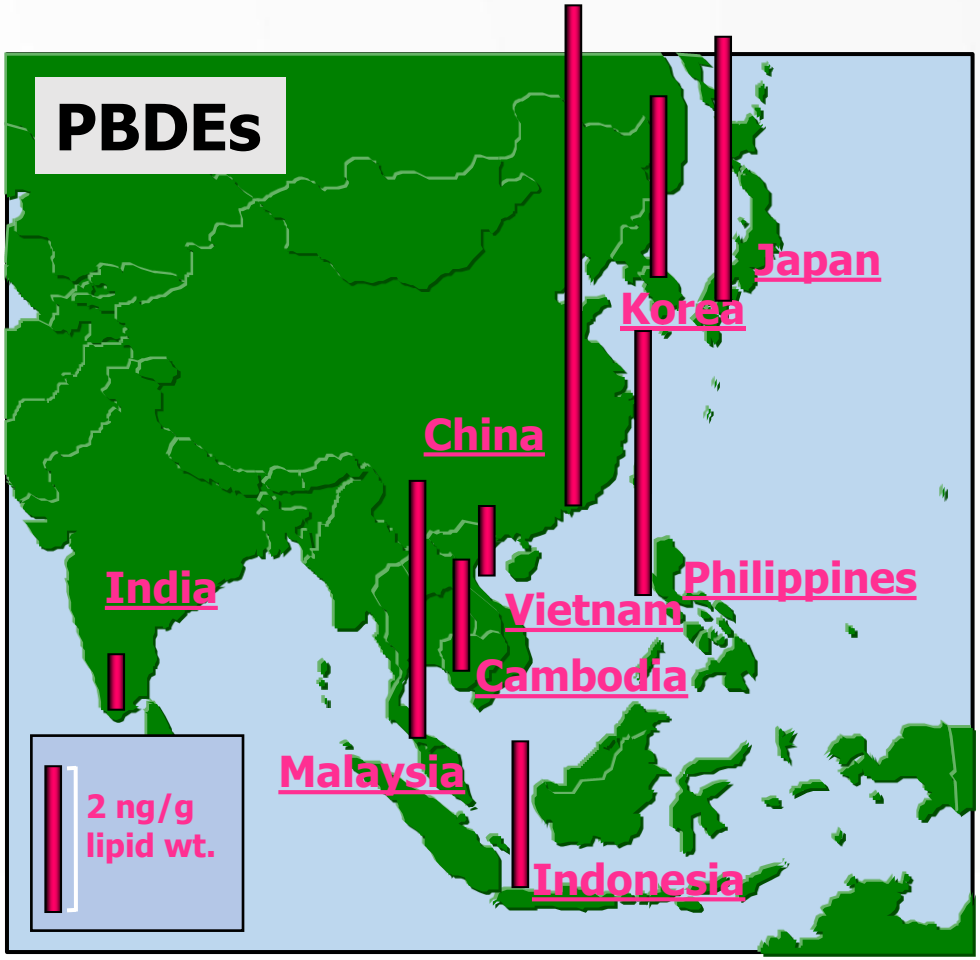
# Polybrominated Diphenyl Ethers (PBDEs)

- ✓ Common additive flame retardants, used in industrial/household products
- ✓ Increasing environmental levels
- ✓ Similar structures and physico-chemical properties to PCBs and DDTs
- ✓ Persistent, bioaccumulative, toxic and high production volume substances
- ✓ Listed in Stockholm Convention
- ✓ Reported toxicity
  - *Alteration of thyroid homeostasis*
  - *Neurobehavioral effects*
  - *Hepatic EROD and PROD activities*




$m + n = 1 \sim 10$

# PBDEs in breast milk from several Asian countries

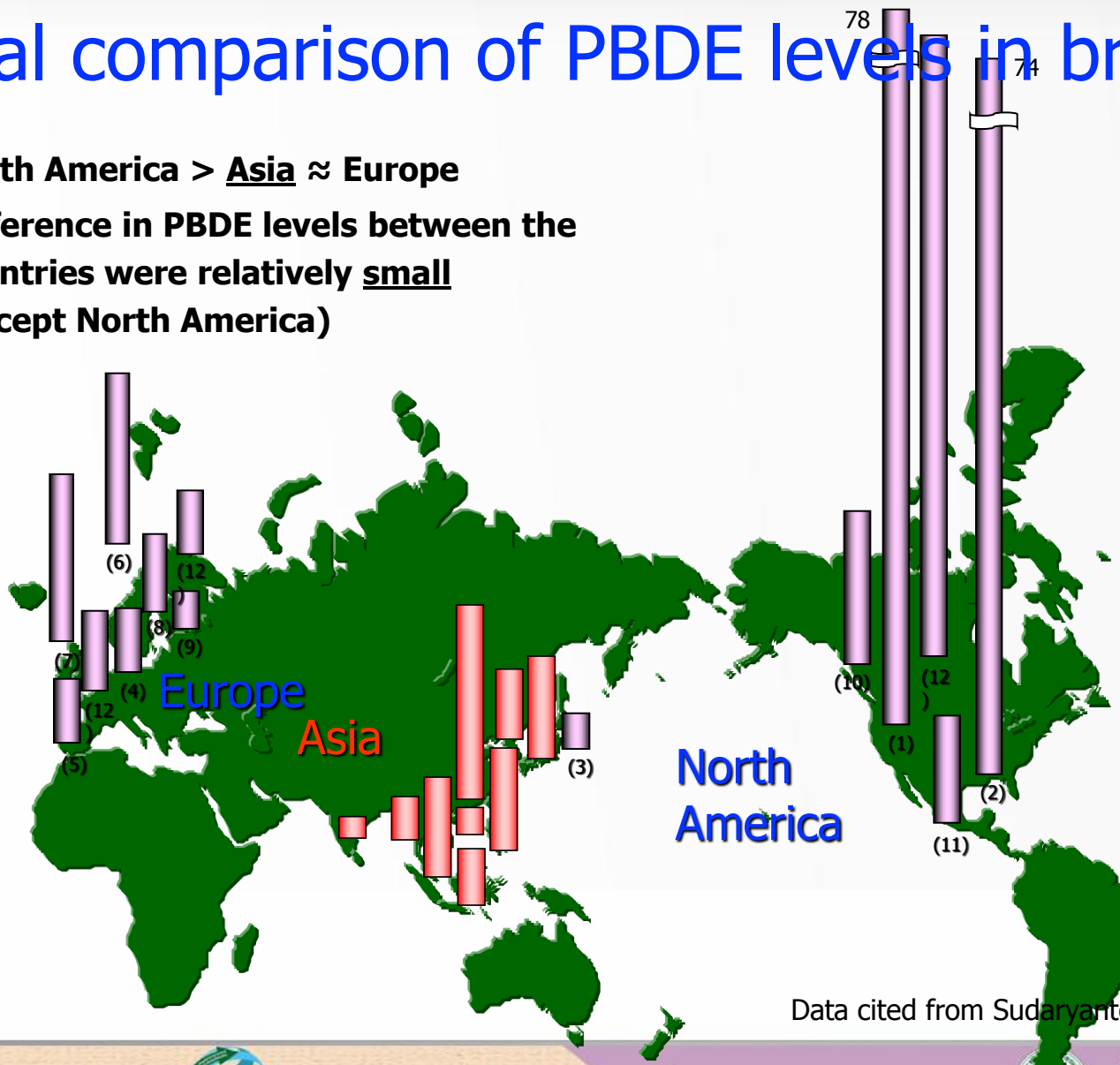



Data cited from Sudaryanto et al. (2005)

# Global comparison of PBDE levels in breast milk

**North America > Asia ≈ Europe**

**Difference in PBDE levels between the countries were relatively small (except North America)**




Data cited from Sudaryanto et al. (2005)

# Take home message: Future generation epidemiology

- Exposome: Life-course total exposure
  - ✓ Takes all covariates as exposure
- Personal exposure measurements
  - ✓ New exposure measurement tools to be developed including sensor technologies
- Multiple exposure effects
  - ✓ New statistical models are warranted
- International harmonization
  - ✓ Your collaborations are welcome

# Acknowledgement


- Participating families
- Regional Centre staff
- Program Office staff
- International partners
- Funding source
- Taxpayers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Authors declare no conflicts of interest associated with this presentation