HOKKAIDO UNIVERSITY

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In Preparation for future WHOCC activities:
Thinking about the prevention of health disorders caused by environmental chemicals from a global perspective

WHOCCとしての活動に向けて：
グローバルな視点で
環境化学物質による健康障害の予防を考える

北海道大学環境健康科学研究教育センター
岸　玲子

Outline

1. A era of the advancement of globalization
2. Disease prevention of chemical exposures ：many examples
   ① MethyImercury （ Tragedy ⇒ The Minamata Convention on Mercury Control）
   ② Protection of workers exposed to organic solvents,
   ⇒new threshold Limit Value (TLV) in the occupational settings
   ③ POPs New challenge for scientific evidence
   ⇒focused on the most vulnerable population, fetus
   (perinatal window's period for toxic substances)
3. Mission as activities of WHO・CC in Hokkaido Univ. Env./ Health Center
4. Strengthen the cooperation of the people of Asia
   eg. BiCCA (birth cohort consortium in Asia)

A era of the advancement of globalization
(拡大するグローバリゼーション）
From “International Health”
to “Global Public Health”

A global perspectives is indispensable when discussing solutions for and the prevention of health hazards caused by environmental chemicals

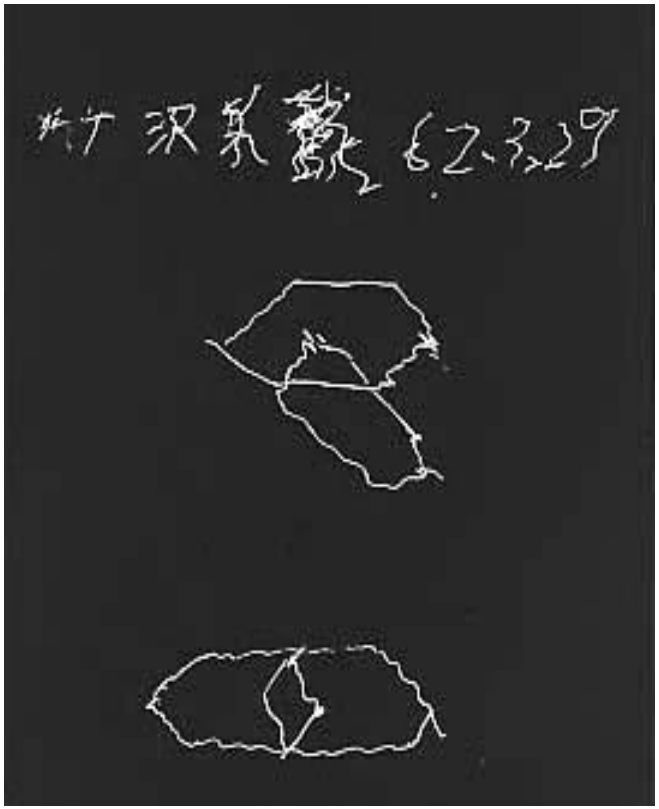
環境化学物質の健康ハザードへの対策や予防を考える際にもグローバルな視点が最重要である

Children born in Minama with fetal disorder

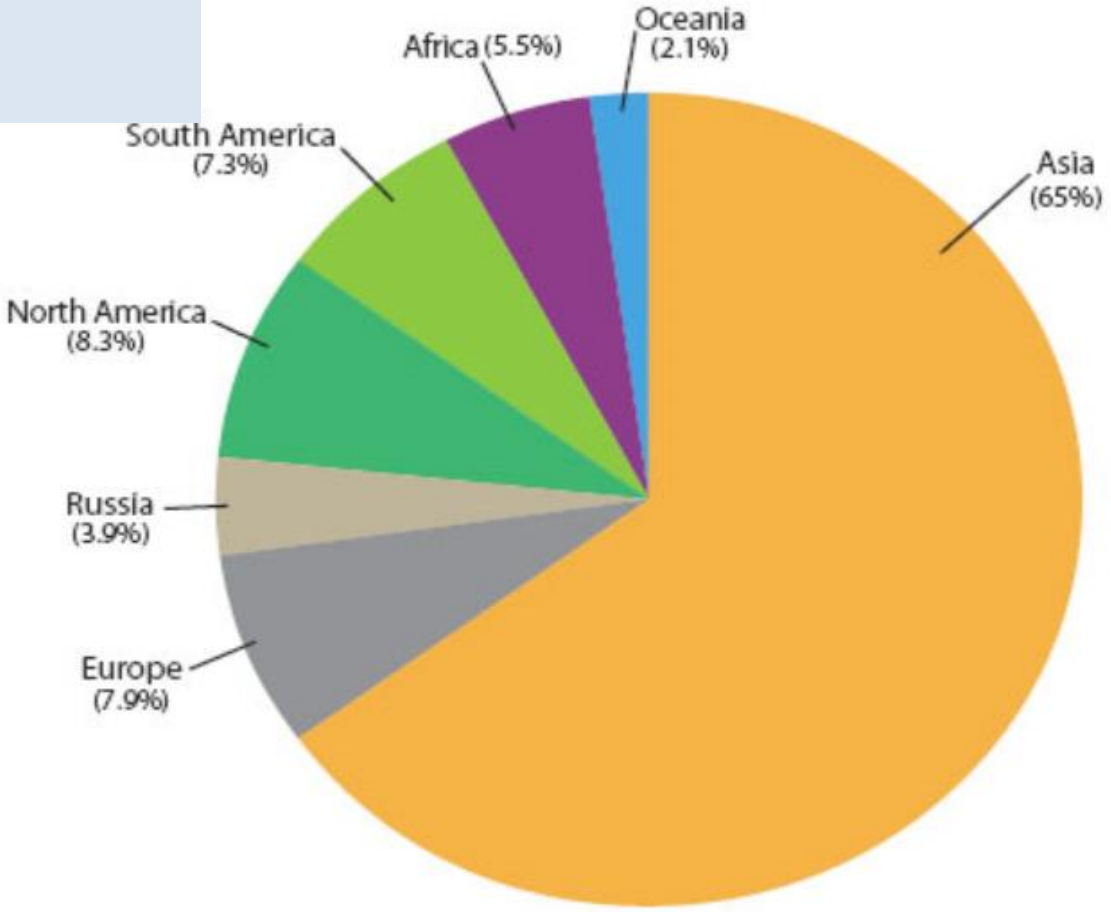
① 水俣の悲劇

Top emitter of human-caused mercury is Asia

水銀鉱山の元鉱夫、採掘　/精錬工など
200人を閉山後　18年目に追跡し
重篤な無機水銀後遺症
（震え、協調運動障害など）



アジアで世界の65%の水銀



E-waste and health risks

- **Electrical and electronic equipment contain different hazardous materials which are harmful to human health and the environment.**
- **Hazardous Substances in e-Waste:**

Halogenated compounds such as PCB, PVC(塩ビ), &heavy metals such as Mercury（水銀） and Lead（鉛）

As a result of Japan's painful past experiences, the Japanese government called for and facilitated the adoption of the international Minamata Convention on Mercury Control

on the possible effects on human health and the environment in Asia and the Pacific of the trade of products containing lead, cadmium and m

arded mercury-containing lamps are stored for recycling at a dumpsite area in Tondo, Manila, Phc

Source - UNEP

②. chemical risk assessment in the workplace to ensure the safety of workers for safer & acceptable concentration levels

より安全な職場の許容濃度：化学物質のリスク評価

I wondered if it would be possible to identify subclinical potential neurologic dysfunction before the emergence of critical pathological changes such as Minamata Disease

The Lanthony desaturated 15 hue test

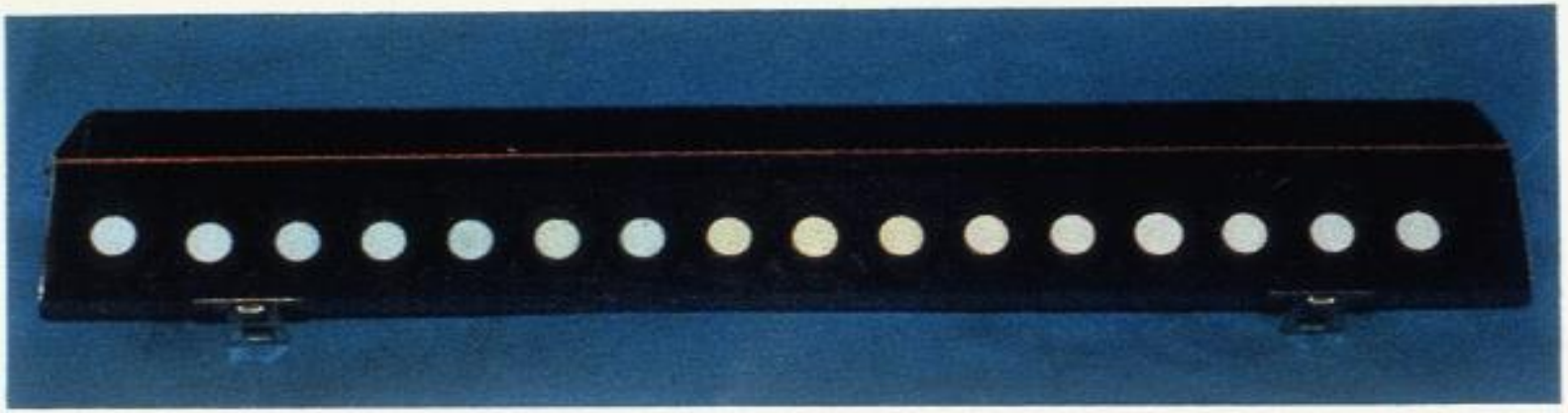


図 27-84 Lanthony desuturate panel D-15[96)97)]

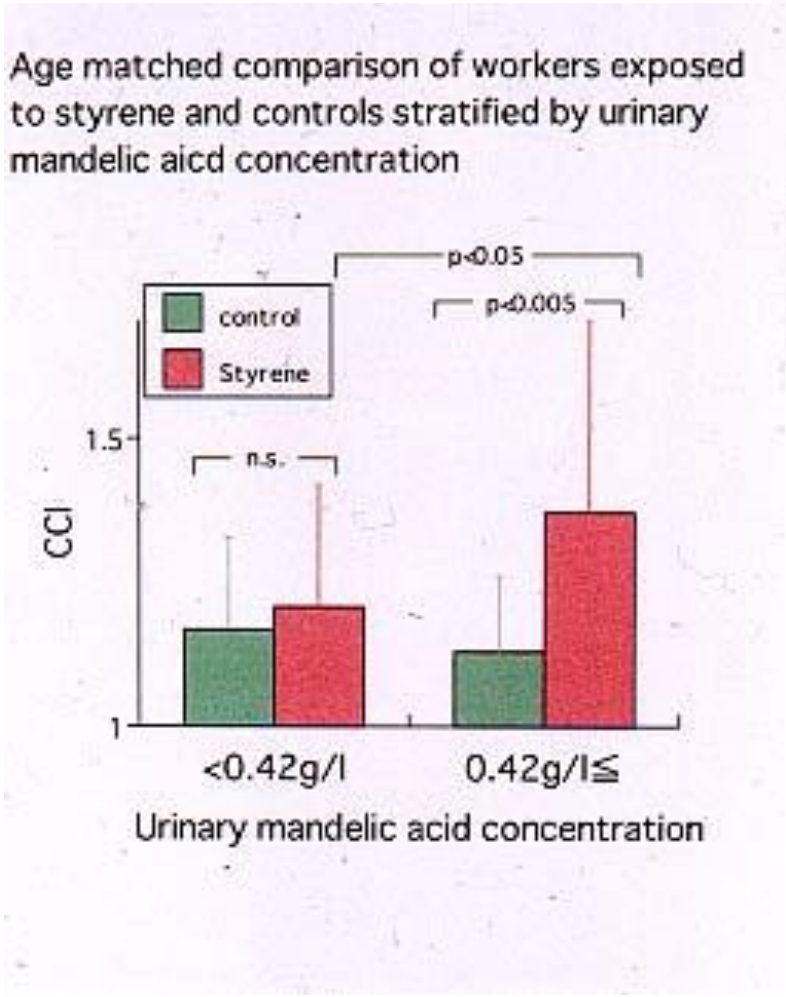
1．Ｐａｎｅｌ　Ｄ－１５と同じ色相で飽和度を低下させたテスト

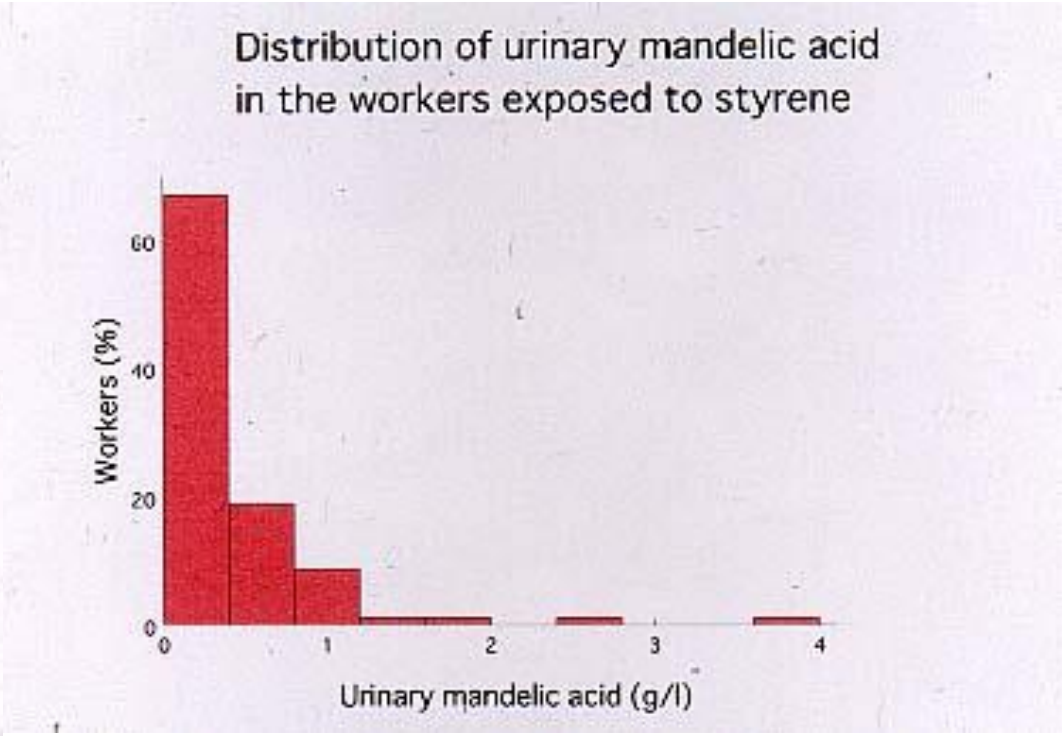
2．低彩度のため鋭敏であるが異常タイプの判別は不定確

3．簡単・短時間で検査できる

Acquired Color discrimination (blue-yellow type) by Color Confusion Index test

Color discrimination (confusion) of Styrene workers exposed to TLV level (urine manderic acids higher 0.42g/l)

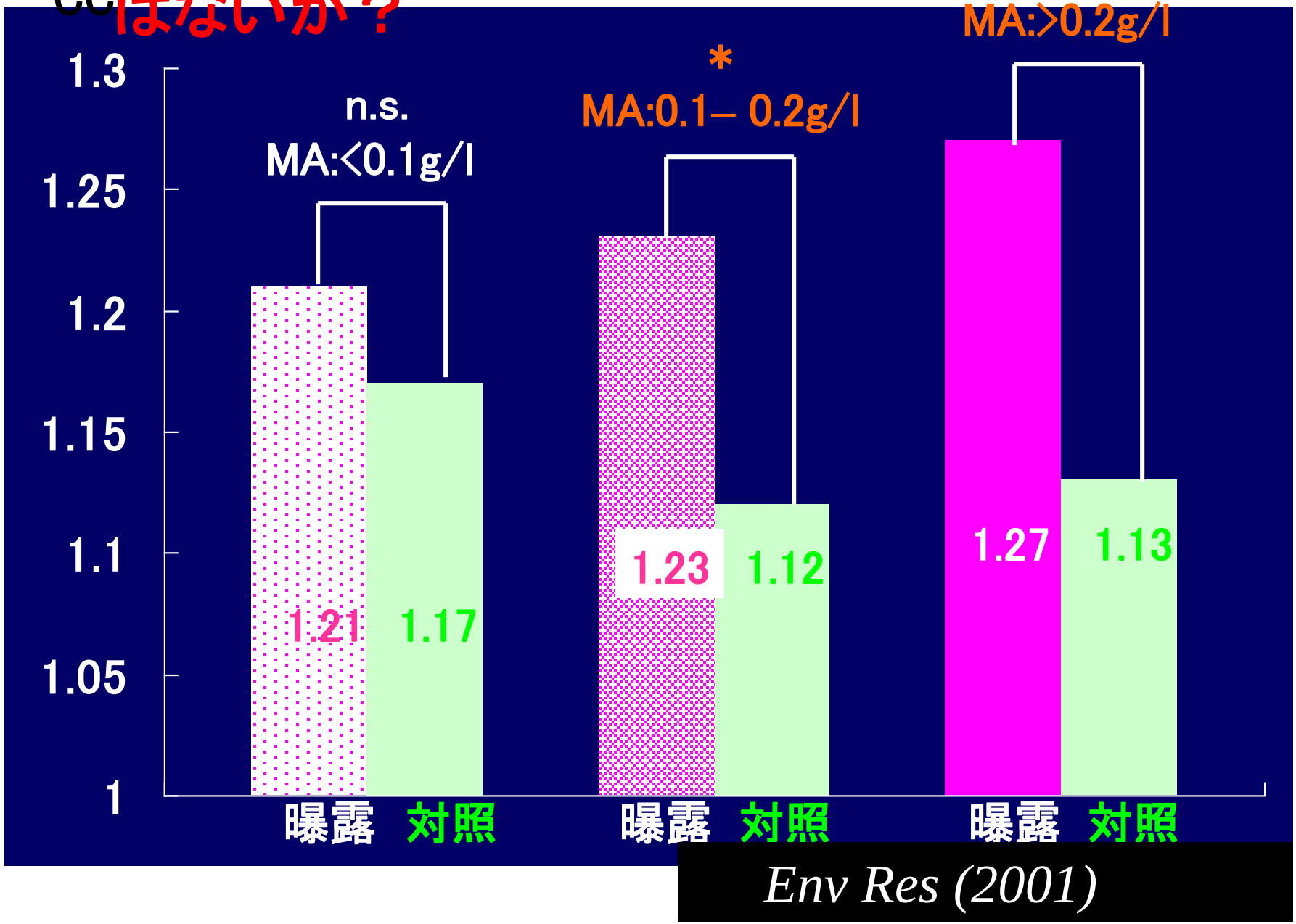




1996年 アメリカ ACGIH Styrene TLV (50 ⇒20ppm）へ下げた根拠になった

Occup Env Med（1994）

色覚低下の閾値はもっと低いのではないか？



Env Res (2001)

Neurobehavioral tests for workers exposed to chemicals

JICA technology transfer program in Malaysia, Philippine,,,,,,, in ”90 to early 2000.

Biological half-lives を考えてみよう

PCB, dioxins and chlorinated pesticides have long half-lives than mercury.

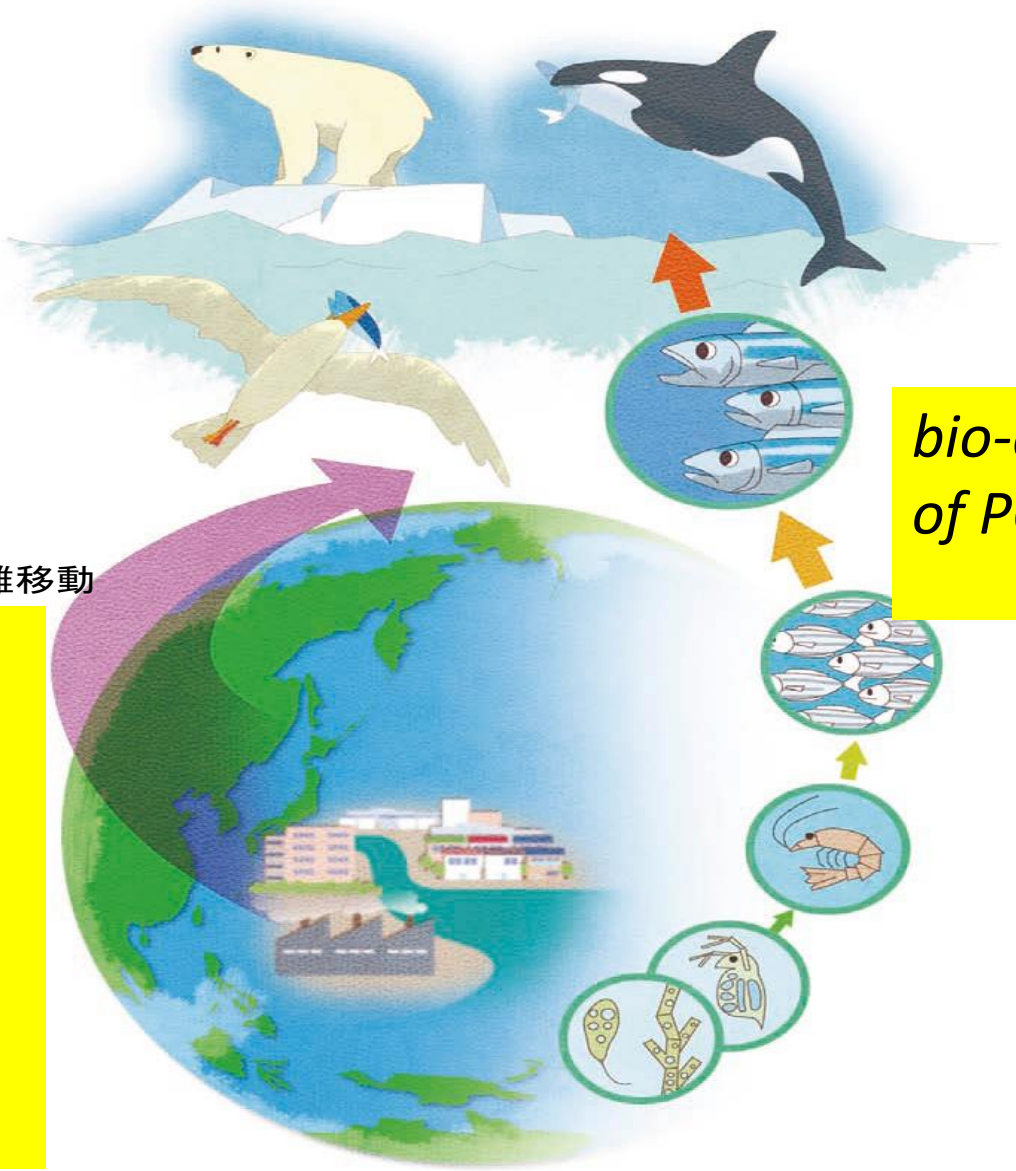
Substance	Half-life
PCBs 塩素系	7 years
2,3,7,8-TCDD (dioxins)	7 years
DDE (DDT metabolites)	10 years
PFOS/PFOA （PFCs）フッ素系	5 years
Lead 鉛	10 years
Methyl mercury	70 days
Mercury 水銀	40-60 days

③ POPs : Persistent Organic Pollutants 残留性有機汚染物質）

- **POPs are chemicals, which are persistent, bio-accumulate and pose a risk of causing adverse effects to human health and the environment.**
- **難分解性、高蓄積性、長距離移動性、有害性（人の健康・生態系）物質**
- ***Scientific evidence indicates that exposure to very low doses of certain POPs can lead to cancer, damage the central and peripheral nervous systems, cause diseases of the immune system, reproductive disorders, and interfere with normal infant and child development.***

ersistent rganic ollutants

transboundary movement of chemicals



POPs の長距離移動

bio-accumulation of POPs

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

The Stockholm Convention on Persistent Organic Pollutants adopted in 2001 (ストックホルム条約)

Countries must make determined efforts to identify, label and remove PCB-containing equipment from use by 2025.

The Convention also seeks the continuing minimization and, where feasible, elimination of the releases of unintentionally produced POPs such as the industrial byproducts dioxins and furans. ダイオキシン　フラン

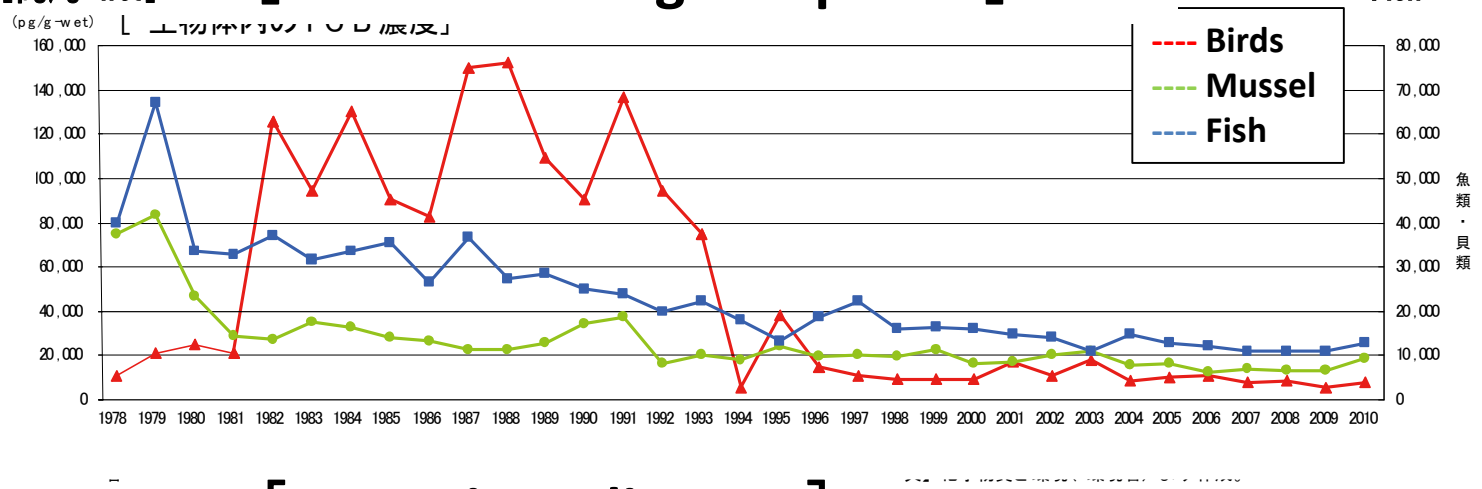
Stockpiles must be managed and disposed of in a safe, efficient and environmentally sound manner. The Convention imposes certain trade restrictions.　環境保全

. & . . . levels in .apan

Birds
[pg/g-wet]

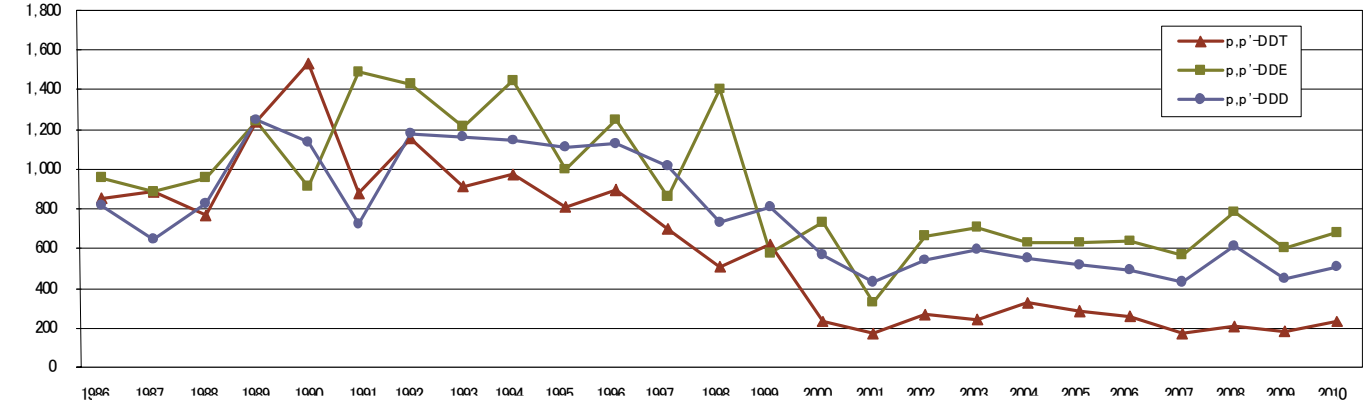
[PCBs in biological species]

Mussel
Fish

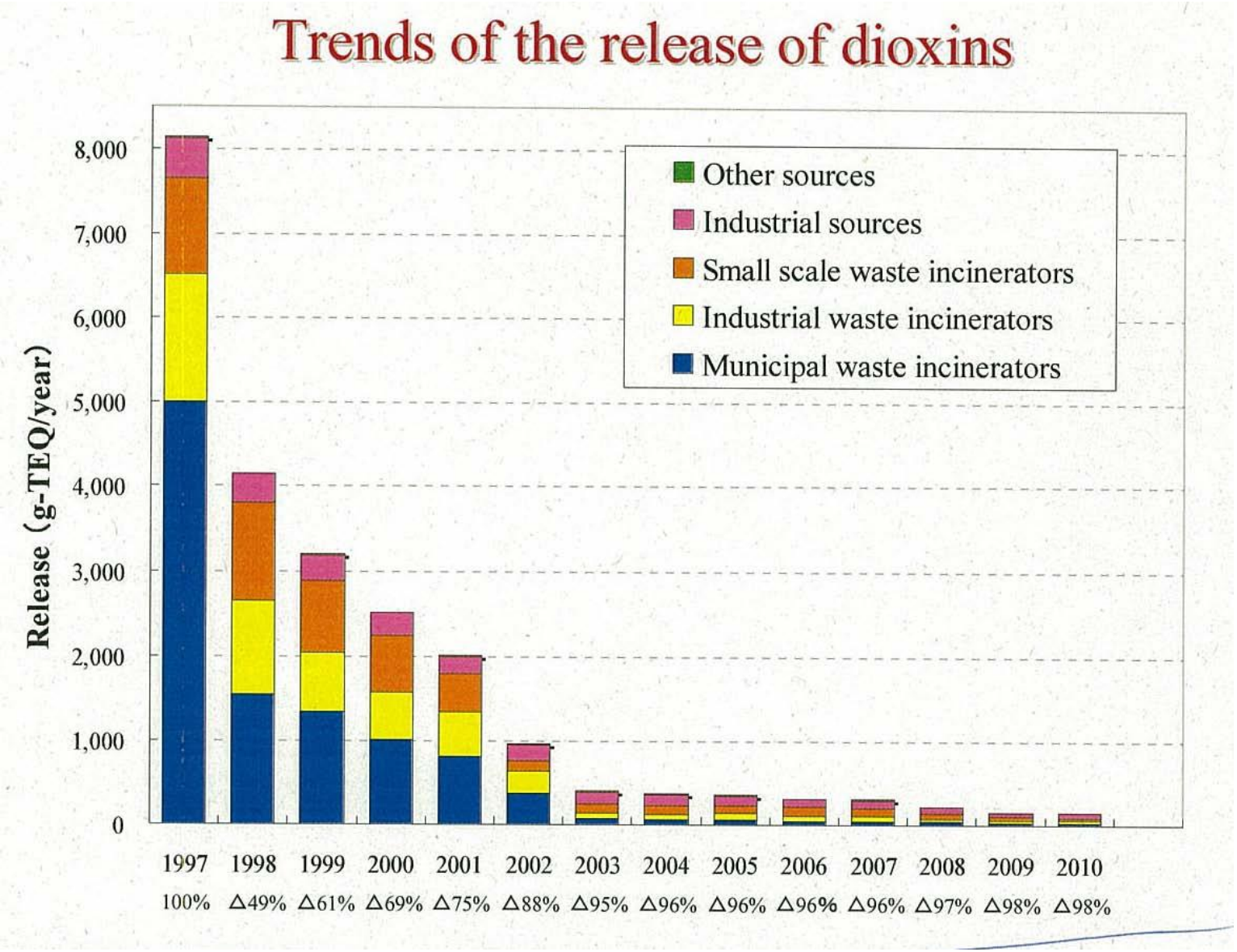


[pg/g-wet]

[DDTs in sediments]



JAPAN EPA



JAPAN Ministry of Environment

Location

Hokkaido Prefecture :

Two cohorts,

N=514 in Sapporo: (since 2002)

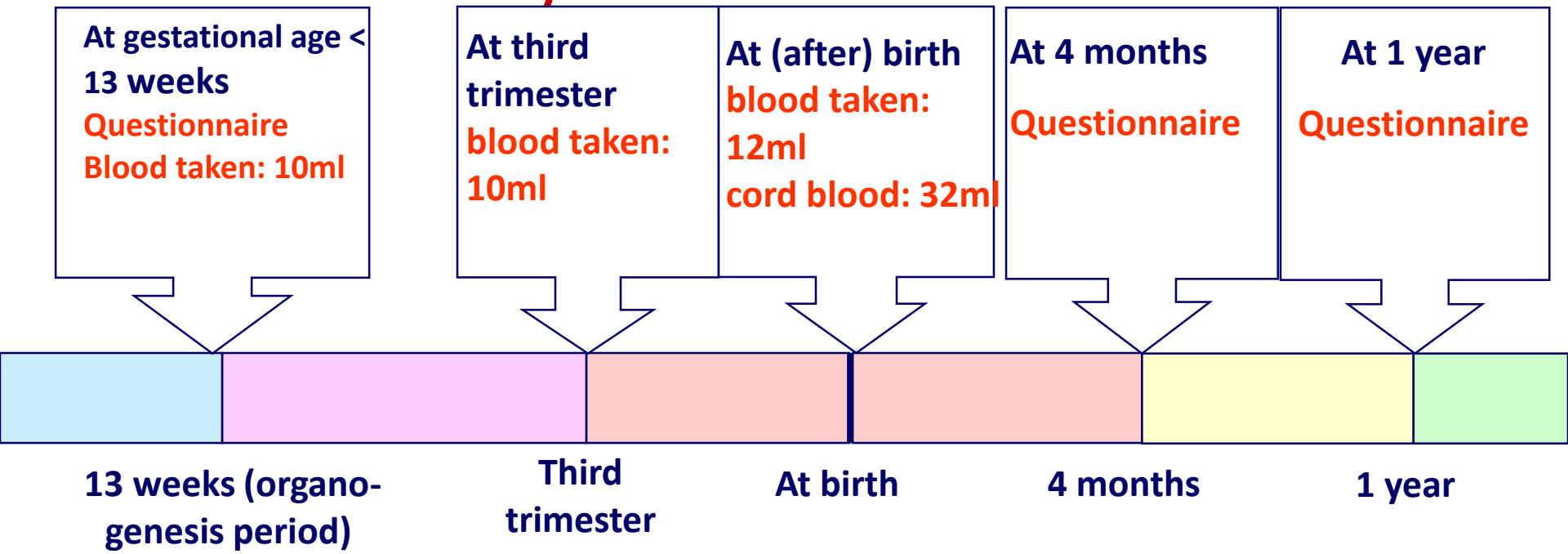
N=20,838 Hokkaido: (since 2003)

JAPAN

前向き出生コーホート研究

Birth Cohort ① from 2002

The Hokkaido Study on Environment and Children's Health



This study is specifically aimed to elucidate

1. Associations between maternal blood levels of chemicals in organogenesis period(1st) and 3rd trimester , and offspring's adverse outcomes such as congenital malformations, growth retardation, allergies, and impairments of development.

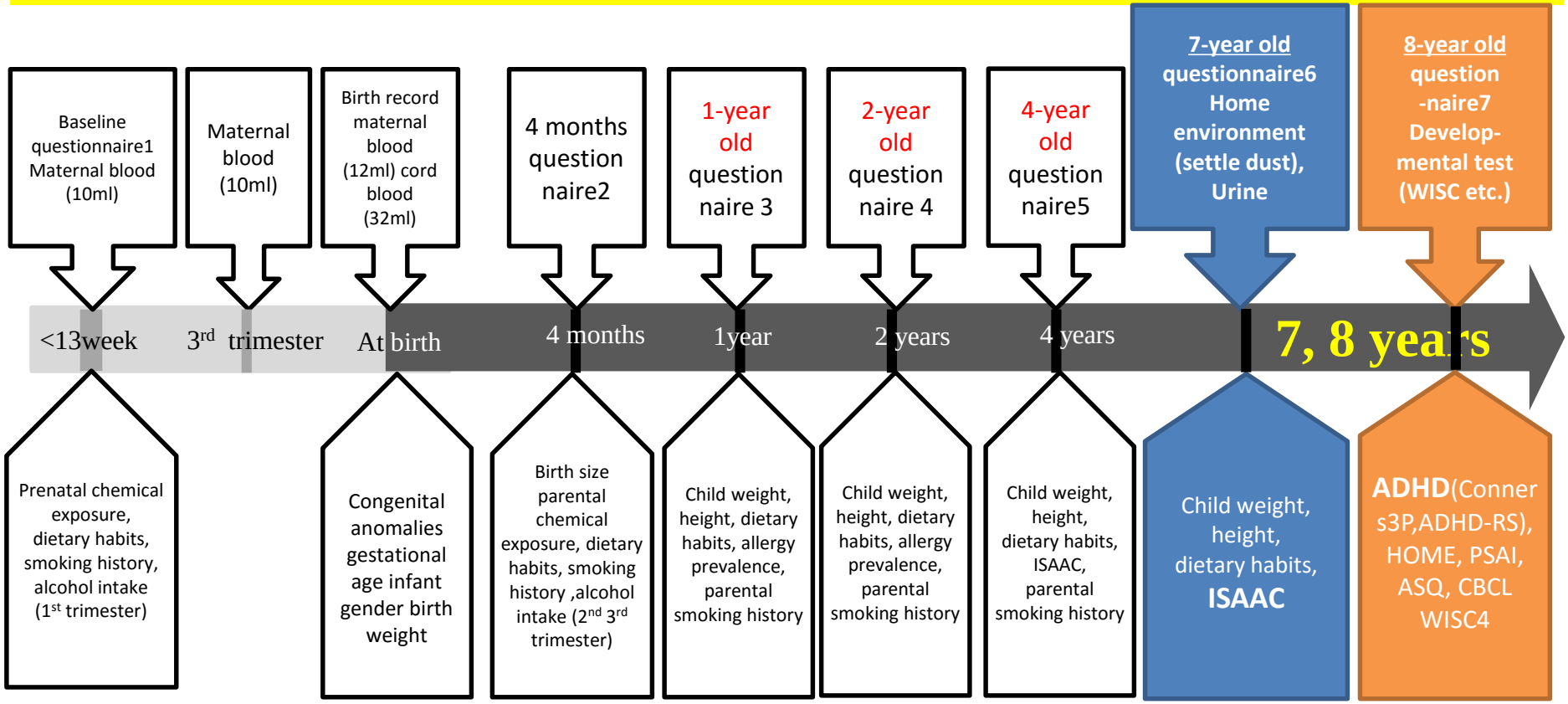
2. Associations between the sensitivity to offspring's adverse outcomes and genetic polymorphisms of biotransformation enzymes etc.

: KISHI et al., (Int J Epidimiol 2010, EHPM 2013)

Now on going studies at 7, 8 years old

① Hokkaido large cohort (n=20,940)

- 7-year old study: focused on allergy
- 8-year old study: focused on developmental disability



Exposure measurement 北海道

PCB & Dioxin, PCDD, PCDF (congener)	maternal blood
OH-PCB (congener level)	maternal blood
PFOS, PFOA and other PFAAs	maternal blood
Phthalate metabolite	maternal blood
Chlorinated pesticides	maternal blood
Bisphenol A	cord blood
Methyl mercury	Hair
Phthalate & Phosphate esters and their urine metabolites	house dust & child urine at 7 years
Other Biochemical Measurements	
Cotinine, Folic Acid, TSH, freeT4 & T3	maternal blood
IgE, TSH, freeT4 & T3, Steroid Hormones	cord blood
Cotinine	child urine at 7 years

Kishi et.al （Int Epi 2011、 EHPM 2013）

Birth size is important outcome, because it reflect fetal growth in utero, and may increase risks of disease later in life (cardiovascular diseases, Diabetes Mellitus, cancer,,)

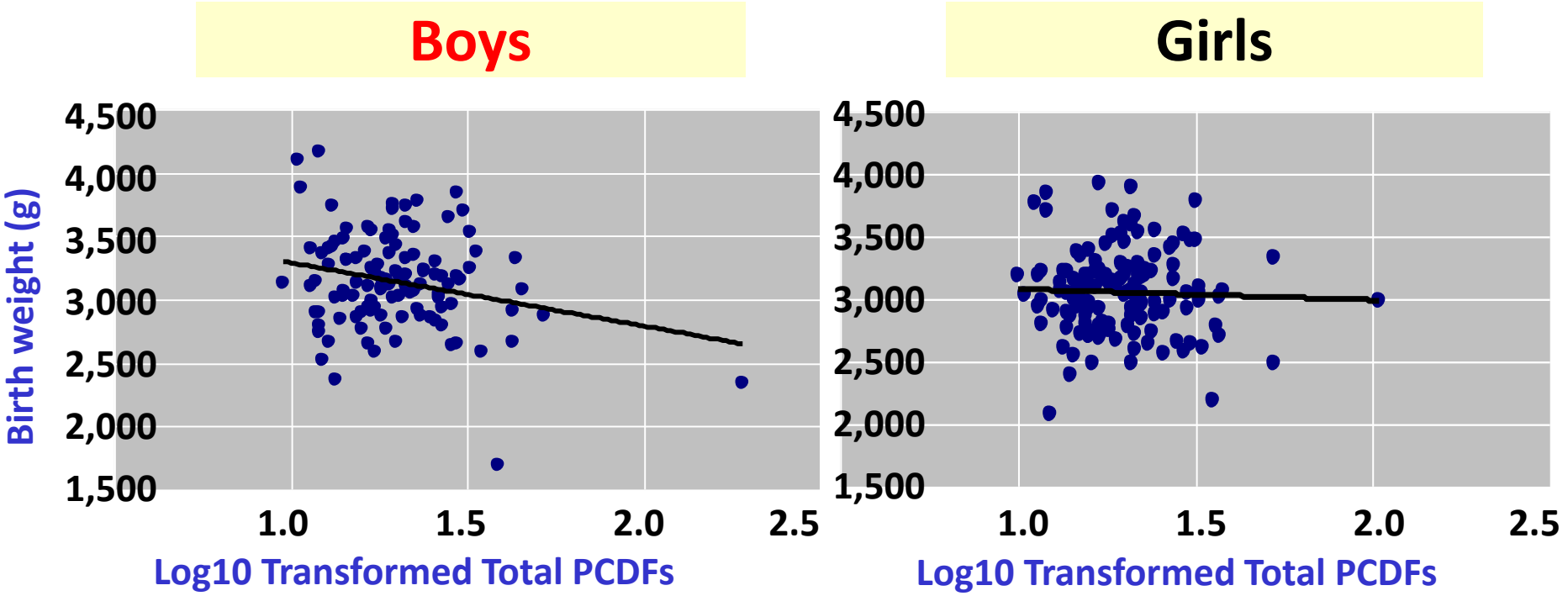
" Barker's Hypothesis"

or

DOHaD

(developmental origin of health and disease)

Correlation of *birth weight* with Log10 transformed *Total PCDFs* levels of maternal blood
– *Among boys and girls* –



r = -0.241
***P* < 0.03**

r = -0.04
***P* = 0.65**

Konishi et. al. (Dioxin 2007)

Multiple linear regressions for birth weight in relation to PCDDs/PCDFs and DL-PCBs by infant's gender

log_{10} scale	Male			Female	
	Beta [a]	*p* -values		Beta [a]	*p* -values
<Total> (pg/g lipid)					
Total PCDDs	-125.7	0.371		-19.3	0.890
Total PCDFs	-237.6	0.191		-304.9	0.058
Total PCDDs/PCDFs	-136.6	0.340		-28.7	0.839
Total non-*ortho* PCBs	-90.7	0.491		-122.4	0.286
Total mono-*ortho* PCBs	-138.6	0.244		-104.3	0.315
Total DL-PCBs	-138.7	0.245		-105.3	0.311
Total PCDDs/PCDFs and DL-PCBs	-148.5	0.229		-106.8	0.319
<WHO-2006> (TEQ pg/g lipid)					
Total PCDDs TEQ	-331.4	0.019	*	-126.3	0.336
Total PCDFs TEQ	-269.8	0.070		-241.7	0.058
Total PCDDs/PCDFs TEQ	-338.7	0.022	*	-173.9	0.195
Total non-*ortho* PCBs TEQ	-107.3	0.288		-114.8	0.196
Total mono-*ortho* PCBs TEQ	-138.6	0.244		-104.3	0.315
Total DL-PCBs TEQ	-112.1	0.278		-117.5	0.195
Total TEQ	-289.5	0.037	*	-144.2	0.243

[a] Beta coefficients represent the change in birth weight (g) for a 10-fold increase in the

*p <0.05

Among male infants, significant inverse associations with birth weight were found for total PCDDs TEQ level, total PCDDs/PCDFs TEQ level, and total TEQ level. However, among the female infants, these significant associations were not found. , ***Konishi et al., Env Res. 2009***

Neurobehavioural development in childhood (6m and 18months)

BSID--Ⅱ
（ベイリー乳幼児発達検査・第2版）

Prenatal Exposure to Dioxins in Relation to IgE level of Newborn and Allergic and Infectious Diseases of Infants at 18 months old.

(Miyashita et al., Env Res 2011)

Adjusted OR between Otitis media and dioxin levels

	Total		Male		Female	
	OR	P	OR	P	OR	P
<Total> (pg/g lipid)						
Total PCDD	1.01	＜0.05	1.02	N.S.	1.01	N.S.
Total PCDF	1.81	＜0.01	2.42	＜0.01	1.51	N.S.
Total PCDD/PCDF	1.01	＜0.05	1.02	N.S.	1.01	N.S.
Total Non-ortho PCBs	1.07	N.S.	1.12	＜0.05	1.04	N.S.
Total Mono-ortho PCBs	1.00	N.S.	1.00	N.S.	1.00	N.S.
Total Coplanar PCB	1.00	N.S.	1.00	N.S.	1.00	N.S.
Total Dioxin	1.00	N.S.	1.00	N.S.	1.00	N.S.
<WHO-05> (TEQ pg/g lipid)						
Total PCDD-TEQ	1.04	N.S.	1.16	N.S.	1.01	N.S.
Total PCDF-TEQ	1.36	＜0.05	1.56	＜0.05	1.30	N.S.
Total PCDD/PCDF-TEQ	1.05	N.S.	1.12	＜0.05	1.02	N.S.
Total Non-ortho PCBs-TEQ	1.05	N.S.	1.12	N.S.	1.00	N.S.
Total Mono-ortho PCBs-TEQ	1.14	N.S.	6.03	N.S.	0.24	N.S.
Total Coplanar PCB-TEQ	1.04	N.S.	1.11	N.S.	0.99	N.S.
Total Dioxin-TEQ	1.03	N.S.	1.07	＜0.05	1.01	N.S.

Adjusted for maternal educational level, parity, infant gender, breast-feeding duration, environmental tobacco exposure, day care attendance and blood sampling period

<Total> OR; Per each 10 increase in dioxins concentration　*p＜0.05; **p＜0.01

Public Health Implications北海道スタデイ

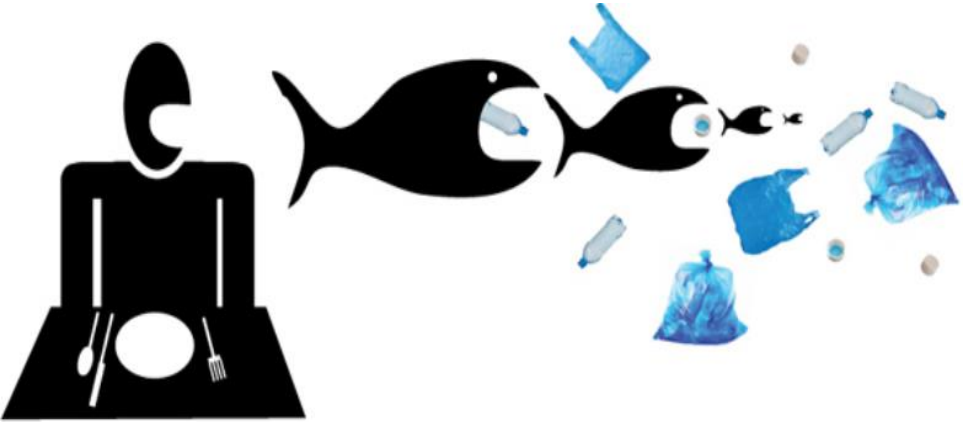
1. Even at low exposure levels, 低い曝露レベル PCBs, Dioxins, Perfluorinated chemicals have adverse health effects on outcomes of fetus and children.
2. Effects are statistically significant even after adjusting confounders. 交絡要因調整後も有意
3. We are currently following children up at the adolescent to detect ASD 自閉症、ADHD to confirm whether these health effects continue or not ?.
4. Social economical and social supporting factors recognized as an important roles in preventing adverse health effects of infant.
   （社会経済要因が影響を緩和）

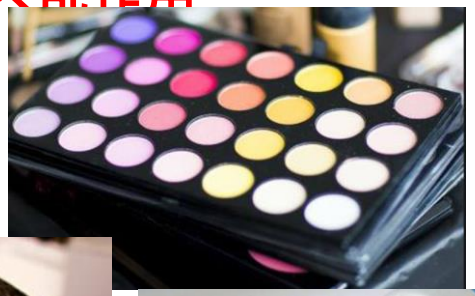
MICRO PLASTICS

◆Microplastics are tiny fragments, pellets or fibres of plastic,
◆with a size of ≤ 5 mm, マイクロプラステイクス
◆generated from industrial products household items, and decomposition　分解　of larger plastics.
◆ Due to their small size, the majority of microplastics are invisible to the naked human eye.　肉眼では見えづらい

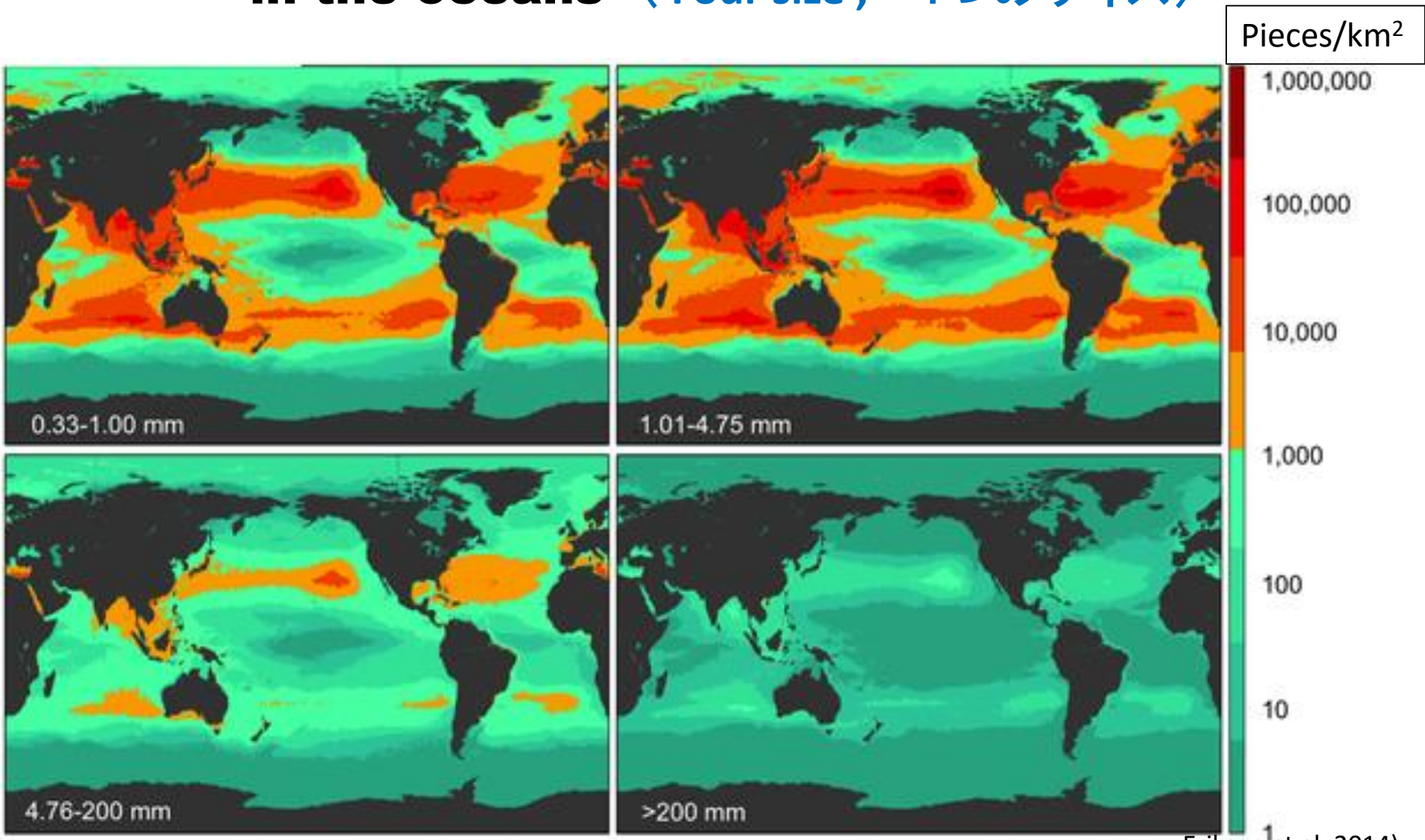
Human exposure to microplastics: Increasing scrutiny regarding potential effects of microplastics on human health

- **Plastic particles may highly concentrate and transport placticizers and persistent organic pollutants (POPs) such as PCBs, dioxins, DDT, flame retardants.**
- Microplastics can act as agents for the POPs を運ぶtransfer of POPs from the environment to organisms in this way, but evidence suggest this to be a potential portal for entering food webs 食品網に入る
- Endocrine disruption by plastic additives may affect the reproductive health of humans and wildlife alike. 可塑剤の内分泌かく乱作用





Microplastic particles as a vector in transporting persistent, bioaccumulating and toxic substances in the oceans （Four size , 4つのサイズ）

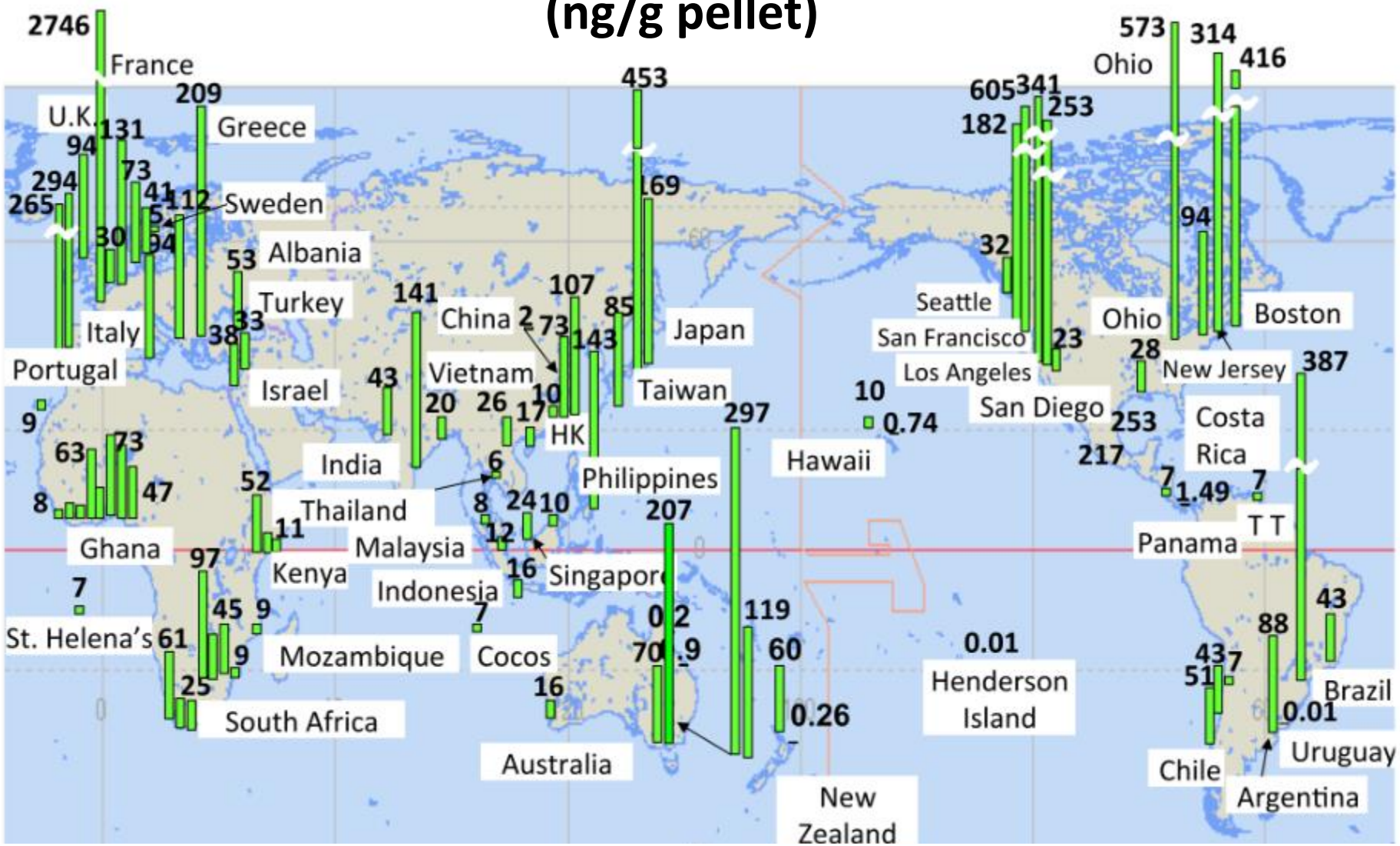


Eriksen et al. 2014)

Four size classes of plastics in oceans

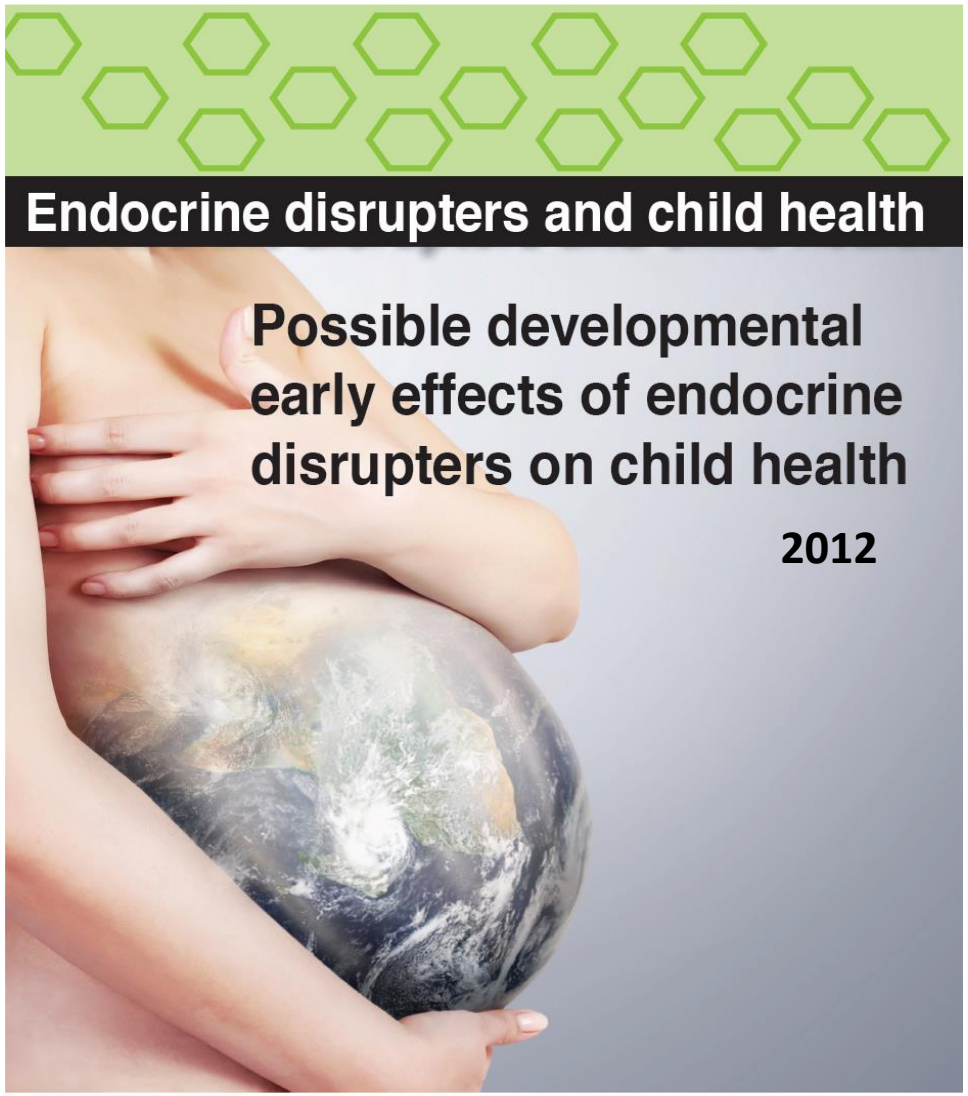
Concentration of PCBs in beached plastic resin pellet

(ng/g pellet)



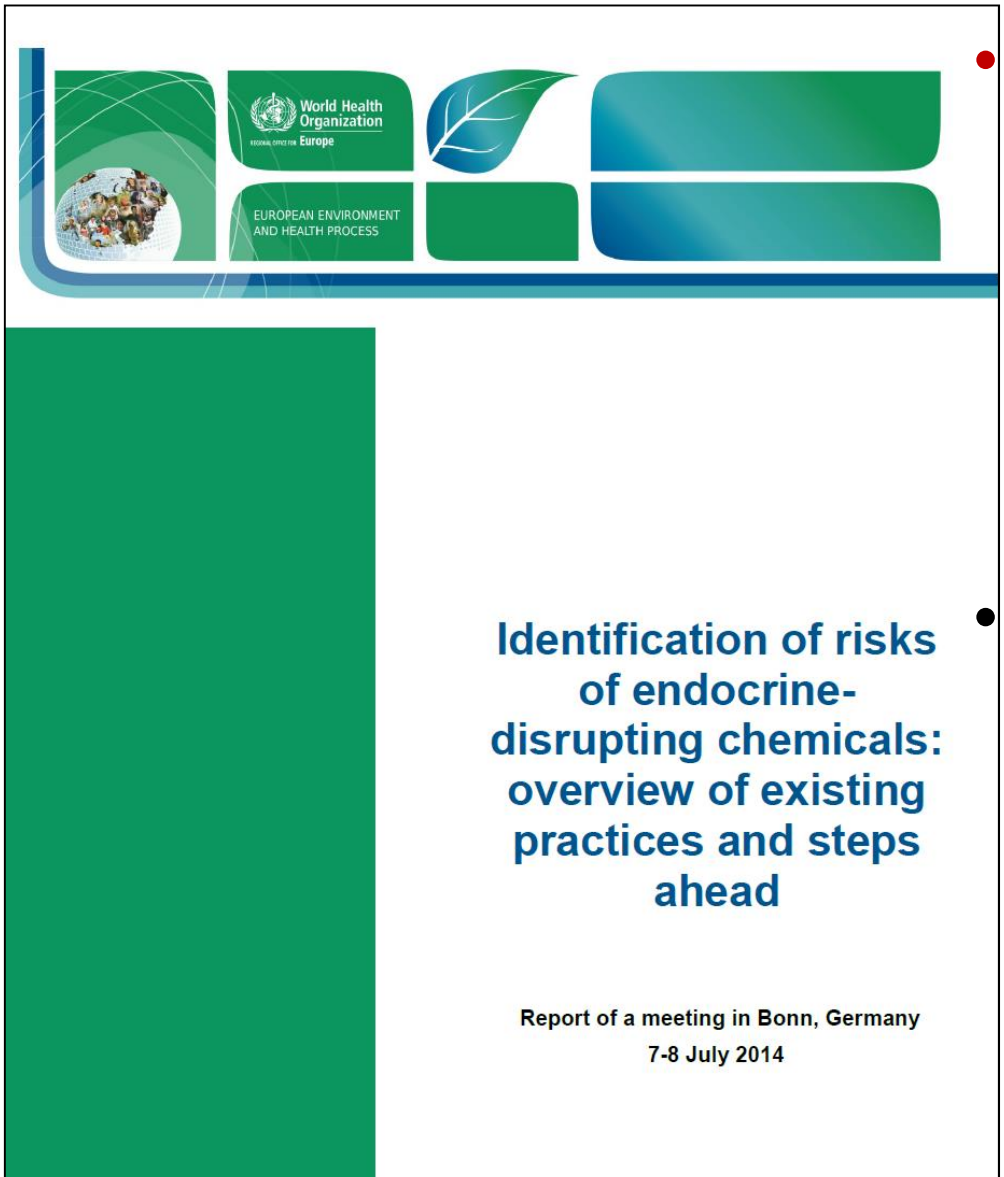
*sum of concentrations of CB#66, 101, 110, 149, 118, 105, 153, 138, 128, 187, 180, 170, 206

Measured by Polaris Q (Thermo Fisher Scientific)

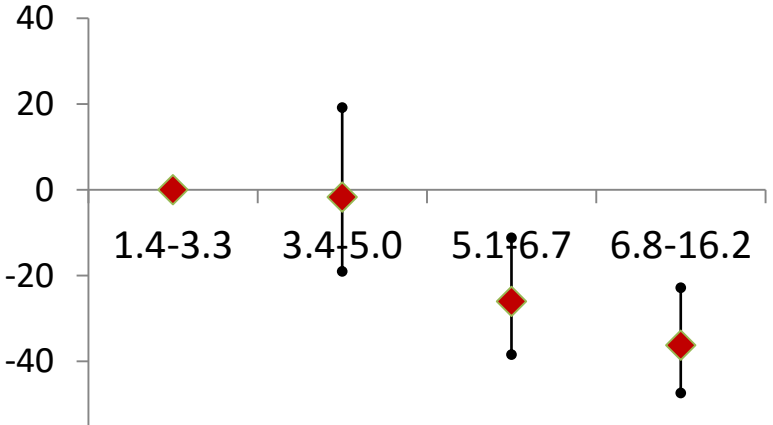


World Health Organization

WHO Europe（Bonn)（昨年7月）

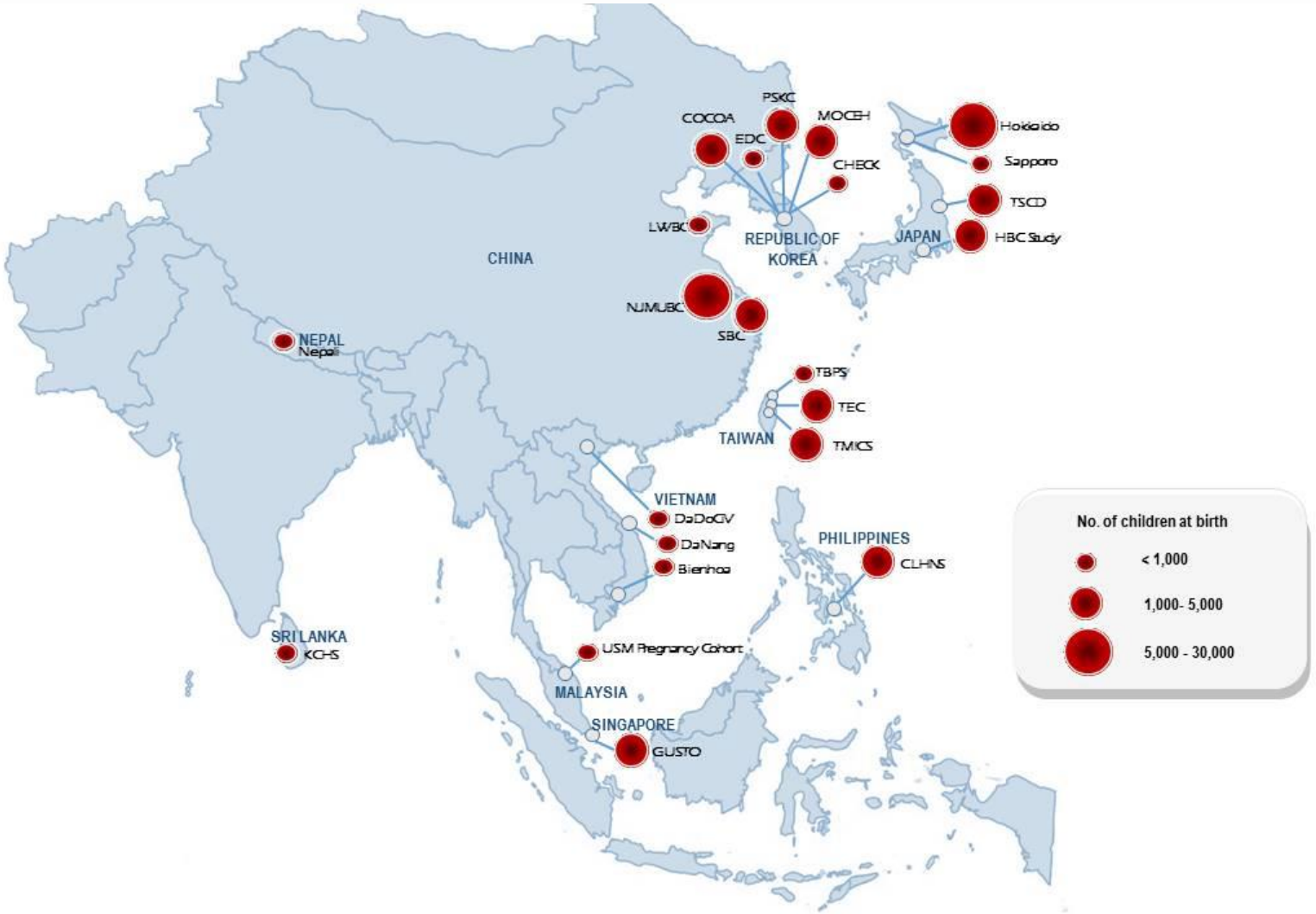


- ***Early Life Exposure Assessment: Challenges and Methodologies -- Based on the Hokkaido Birth Cohort Study-***
- Endcrine Disrupting 男の子のInhibin B



BiCCA

Birth Cohort Consortium of Asia



BiCCA

Birth Cohort Consortium of Asia

2011年に設立しました　Current statusは

- 23 cohorts in 10 countries are joining BiCCA
  - China (3 cohorts), Japan (3), Korea (5), Malaysia (1), Nepal (1), Philippine (1), Singapore (1), Sri Lanka (1), Taiwan (3) and. Vietnam (3)
  - Around 70,000 children
- Aims
  - to facilitate the exchange of knowledge and collaboration between cohorts and researchers; and
  - to explore the future need for children's environmental health research.

BiCCA

Birth Cohort Consortium of Asia

Health Outcomes （& Exposure measurements）

Prematurity, low birth weight

- Asthma, allergy
- Neurodevelopmental disorders
- Birth defects
- Reproductive function, Obesity, diabetes, cardiovascular disease
- Injuries, trauma
- Acute pediatric poisoning
- ….

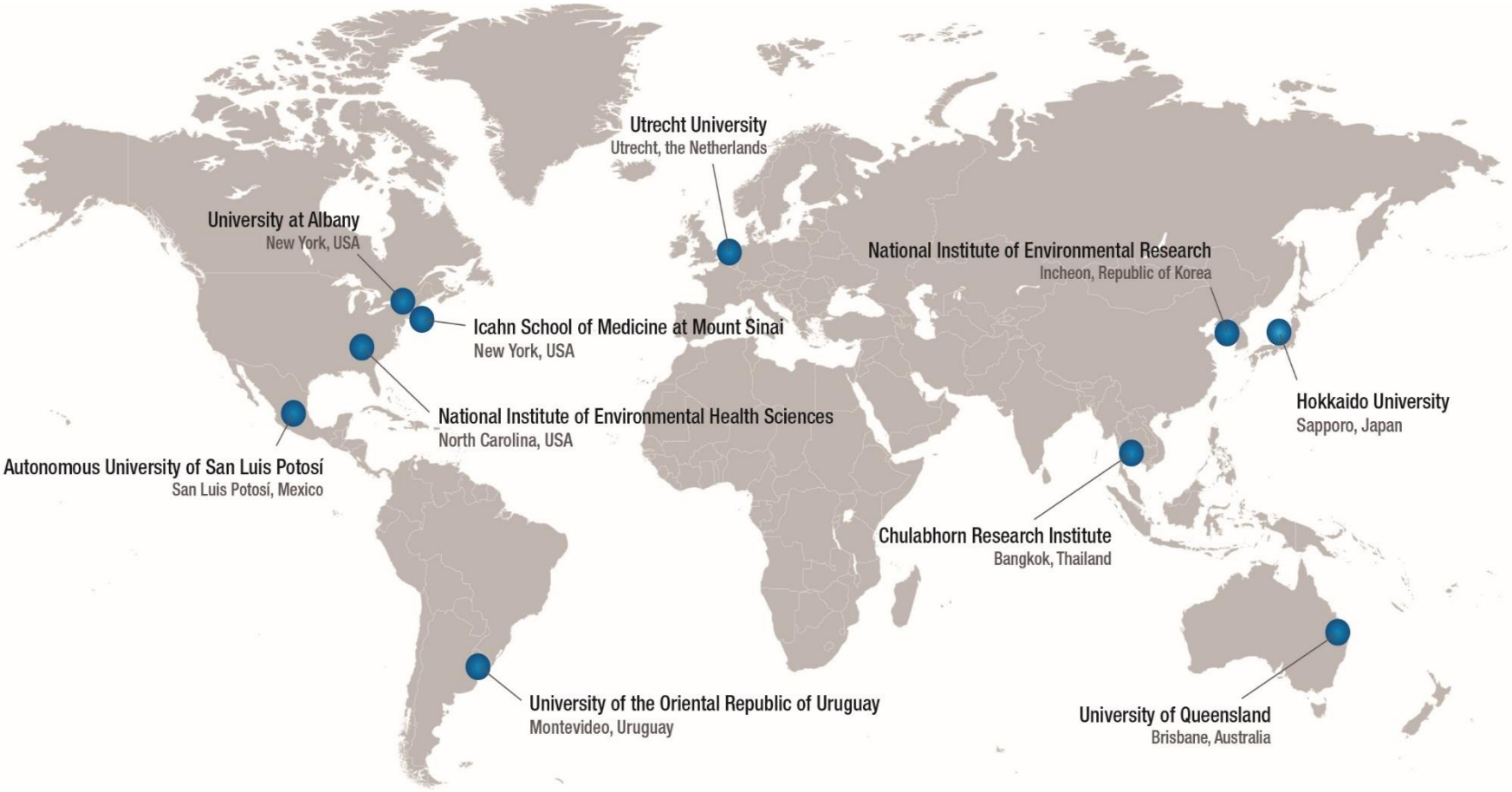
BiCCA

Birth Cohort Consortium of Asia

Environmental Hazards

- Outdoor air pollution
- Household air pollution
- Tobacco smoke: active and passive smoking
- Water pollution
- Sanitation and hygiene
- Hazardous waste and toxic hotspots
- Lead, mercury, arsenic, other metals
- Pesticides
- Polychlorinated biphenyls, dioxins, furans, DDT, polyfluorinated compounds, and other halogenated hydrocarbons
- Volatile organic compounds
- Endocrine disruptors
- Chemical obesogens
- Environmental carcinogens
- Mold
- Physical hazards
- Ionizing radiation
- Electromaganetic fields

WHO Collaborating Centre on Children's Environmental Health:広がる Networking



http://www.niehs.nih.gov/research/programs/geh/partnerships/network/index.cfm

3. 今後4年間 / WHO CC centre for Environmental Health and Prevention of Chemical Hazard (北海道大学)

TOR1 Assist WHO in developing capacity of selected countries on survey and research methods of chemical exposures on population to prevent chemical hazards and diseases

TOR2 Contribute to WHO's work to translate research findings and evidence of chemical exposures and health into guidelines, manuals and training modules.

TOR 3 Support WHO in training courses and raising awareness about disease prevention of chemical exposures for vulnerable population k

期待される重要な活動
（4 activities）

1. Capacity building of selected countries in this region on survey and research methods on the health effects and outcomes caused by chemicals and exposure measurements

2.Develop/coordinate the network group for chemical exposures and health

3.Translate research findings related to the impacts of exposure on vulnerable population

4. Provide training and capacity building about diseases prevention of chemical exposures on vulnerable population

ISEE-ISES AC2016

Joint Conference of International Society for Environmental Epidemiology and International Society of Exposure Science – Asia Chapter 2016

"Environment, Health, and Sustainable Society"

Date : Sunday 26th - Wednesday 29th, June, 2016

Venue : Hokkaido University Conference Hall

Place: Sapporo, Japan

Conference Chair : Reiko Kishi

* **Travel grants for students and new researchers Asian countries will be available.**
* **Activities for students, new researchers, and/or young health professionals (workshop, lecture, social event, etc.) are under planning.**

Thank you very much !

Going forward and working together,
for solution of issues related to
people's health and the environment
in Asia and in the world.