International Symposium of Environmental Medicine Program in Taiwan, October 24-25, 2015

Environmental Health Intervention and Preventive Medical Studies on Chemical Exposure Issues

Chisato Mori , M.D., Ph.D

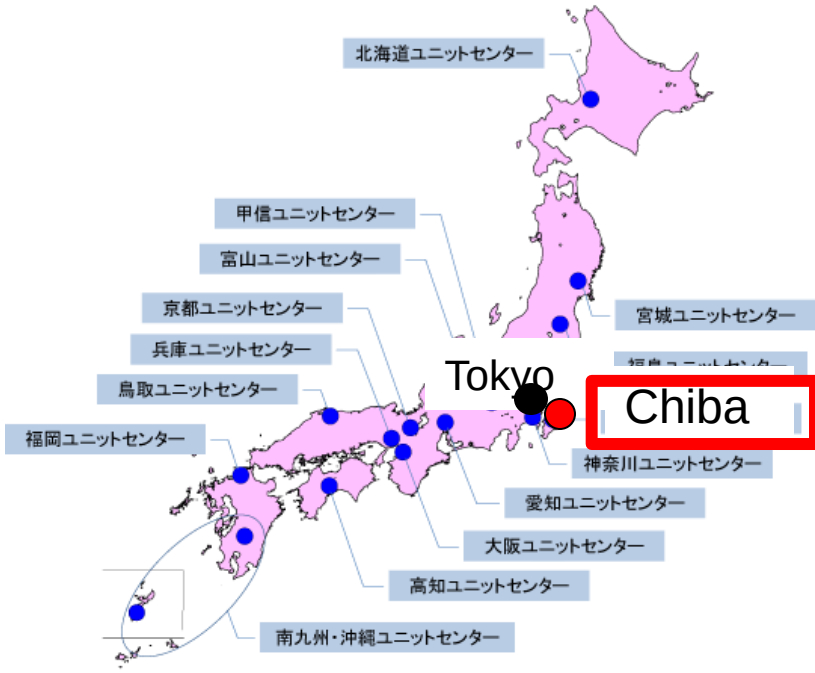
Center for Preventive Medical Sciences

&

Dept of Bioenvironmental Medicine,

Graduate School of Medicine,

Chiba University, Japan



Today's talk

1. Recent change of children's health and fetal contamination
2. Children's cohort study in Japan
3. How can we reduce the exposure?

3-1. Health examination approach on reducing internal exposure of POPs

3-2. Town planning trial to prevent sick building syndrome by indoor chemical exposure "Chemiless Town project"

- Chemi-less Town Project & TOP (Town of Public Health) project

Key Word: prevention, intervention, education of talented students

Three generations of my families were residents in Taipei, Taiwan (1895 – 1947)

Rintaro Mori
(My great grandfather: Ogai Mori)

(1862 – 1922) *1895*

- 1885年から3年間ドイツ留学
- 帰国後、西洋近代衛生学を日本に導入
- 軍医の道を進み、41歳の時に軍医総監
- 傍ら、小説・戯曲などを執筆。「舞姫」「最後の一句」「高瀬舟」 な

Otto Mori
(My grandfather)

(1890 ー 1967)

1935 - 1947

Hans Mori
(My father)

(1928 2007)

1935 - 1945

Today's talk

1. **Recent change of children's health and fetal contamination**

2. Children's cohort study in Japan

3. How can we reduce the exposure?

Chemicals and heavy metals reported to have adverse effects on human neurological development

- Lead
- Mercury
- Arsenic
- PCBs
- PBDEs and PFOS/PFOA

  Polybrominated diphenyl ethers (PBDE)

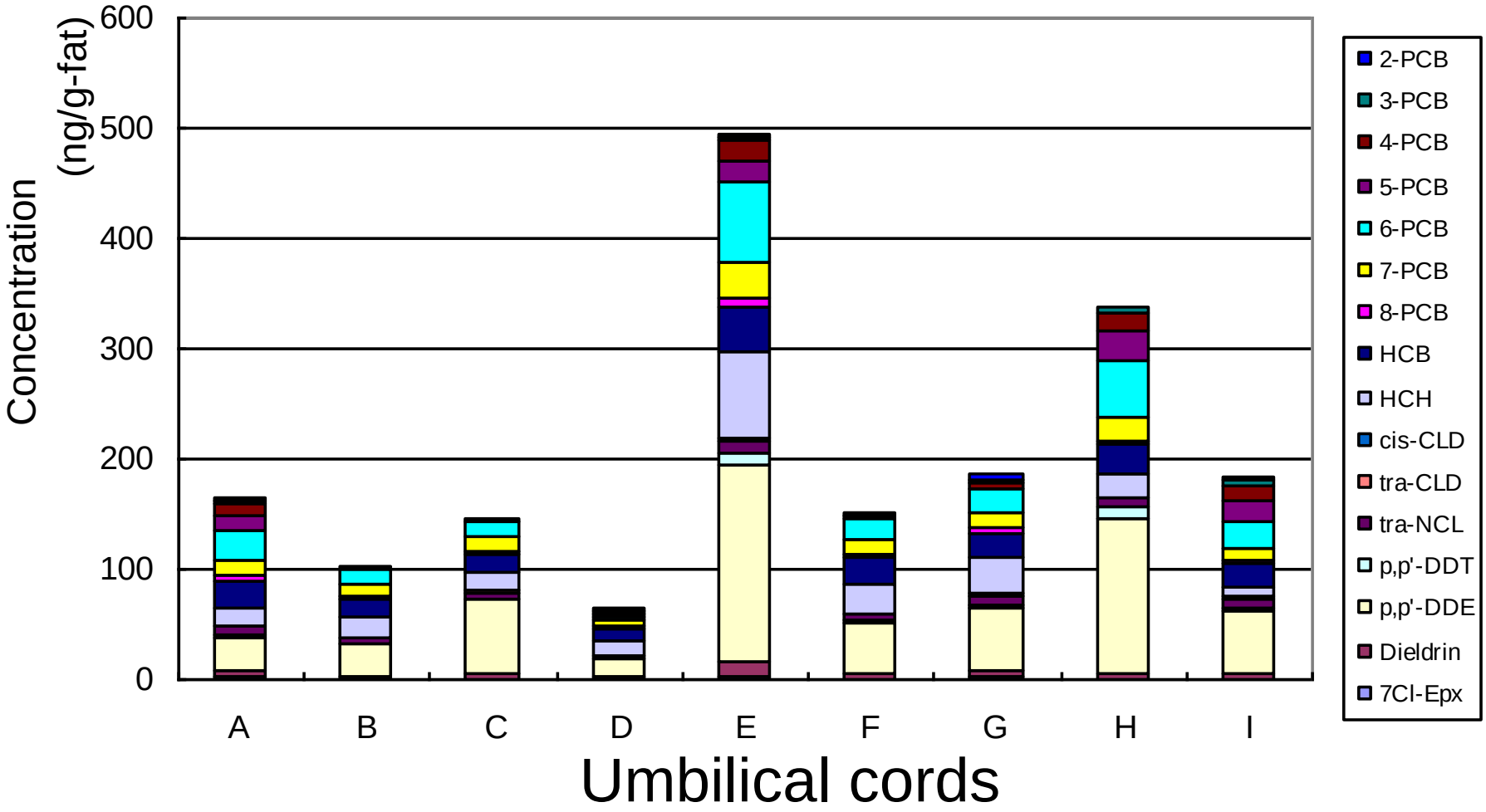
  Perfluorooctane sulfonate (PFOS)/ Perfluorooctanoic acid (PFOA)
- Tobacco smoke
- Alcohol

Prenatal exposure: analysis of human umbilical cords

Umbilical cord tells us about fetal contamination

Umbilical cord (UC) connects placenta and fetus, and is a part of fetus.
UC is easy to collect ethically and techinically after birth.
Human UCs were collected from over 1000 normal newborns at Chiba Univ Hospital.

Exposure Assessment:
Individual difference of exposure



Modified from Mori et al., Reprod Med Biol 3, 51-58, 2004.

The sum of the concentration of persistent chemicals in each umbilical cord

Endocrine Disrupting Chemicals (EDCs)

An exogenous agent that interferes with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body which are responsible for maintenance or homeostasis, reproduction, development and/or behavior.

EDCs are thought to have

- a variety of effects on the reproductive system,

  immune system, nervous system and metabolic system etc.

- a possibility to affect at low dose (exposure level)

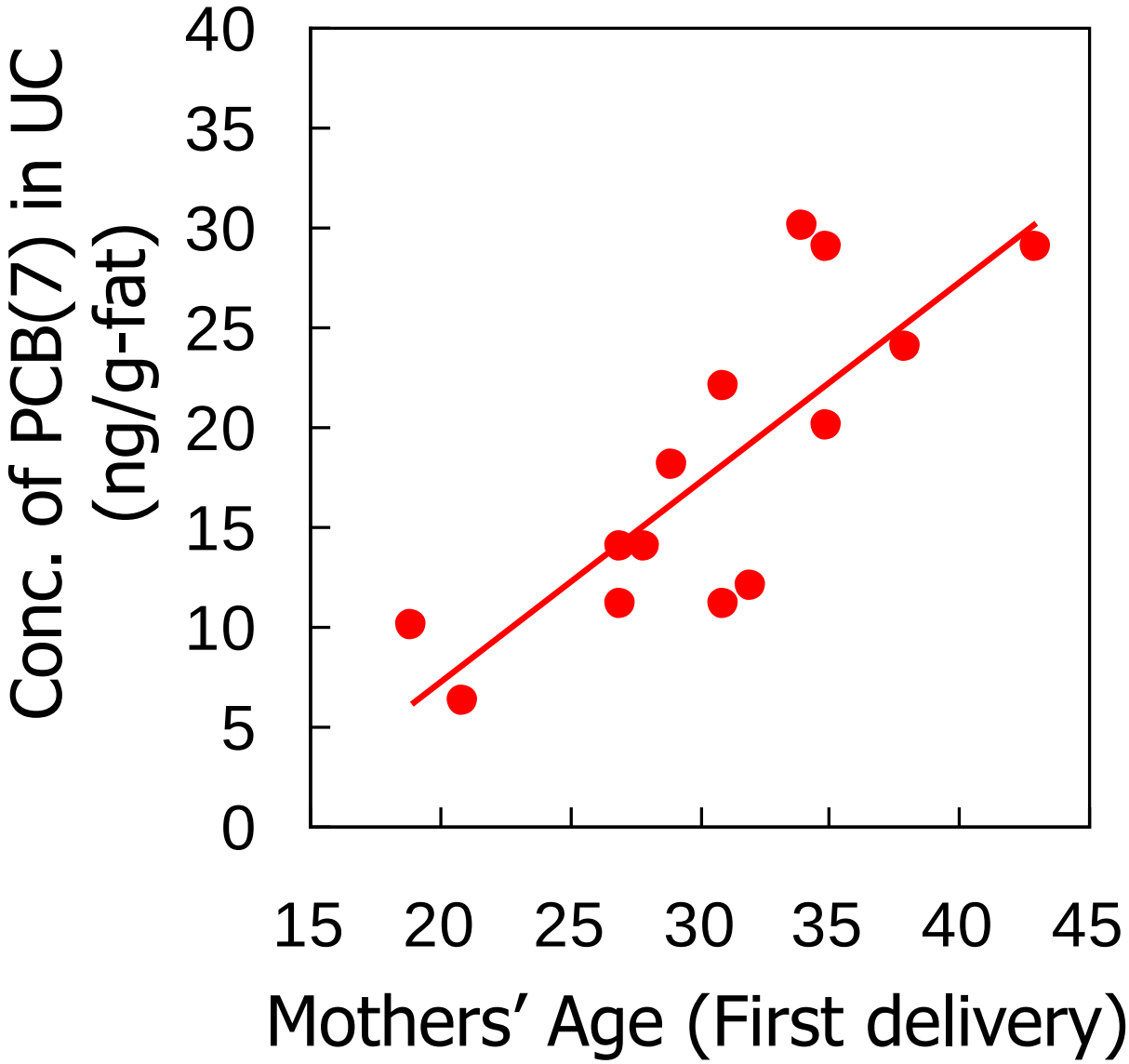
- a possibility to have additive or synergic effects

- "sensitive window"…(fetus, neonate, infant)

- delayed long-term effects on the next generation

Adverse effects of EDCs on human are not clear.

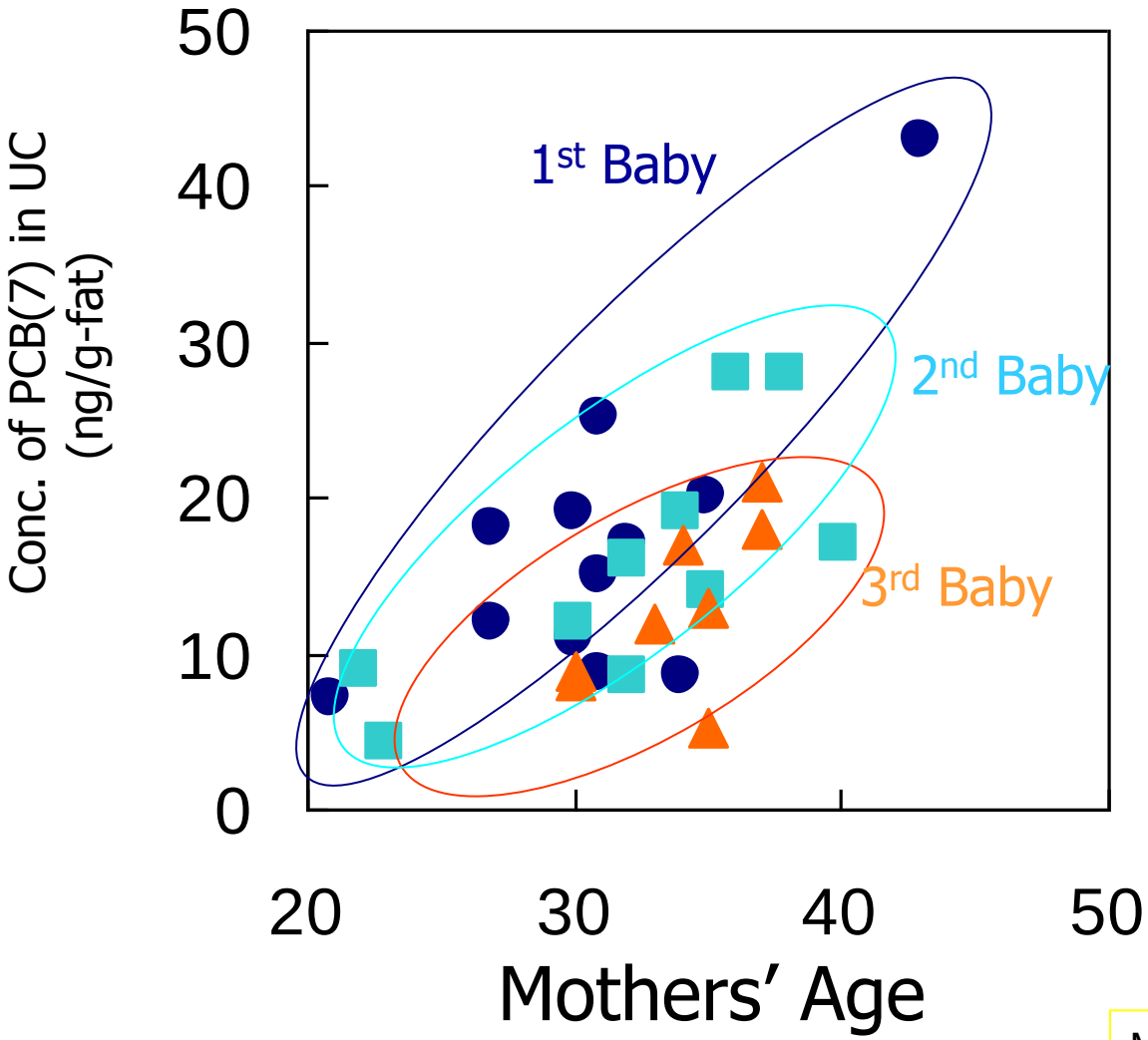
Correlations between PCB conc in UC & mothers' age at 1st delivery



Concentration level of PCBs increases with maternal age

Fukata et al.,
Environ Health Perspect
113, 297-303, 2005

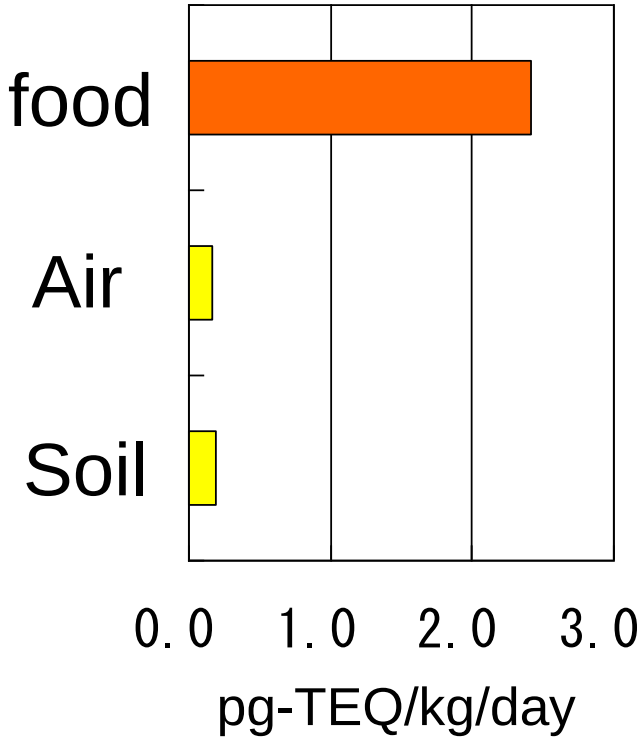
Correlations between mothers' age and 1st, 2nd & 3rd babies

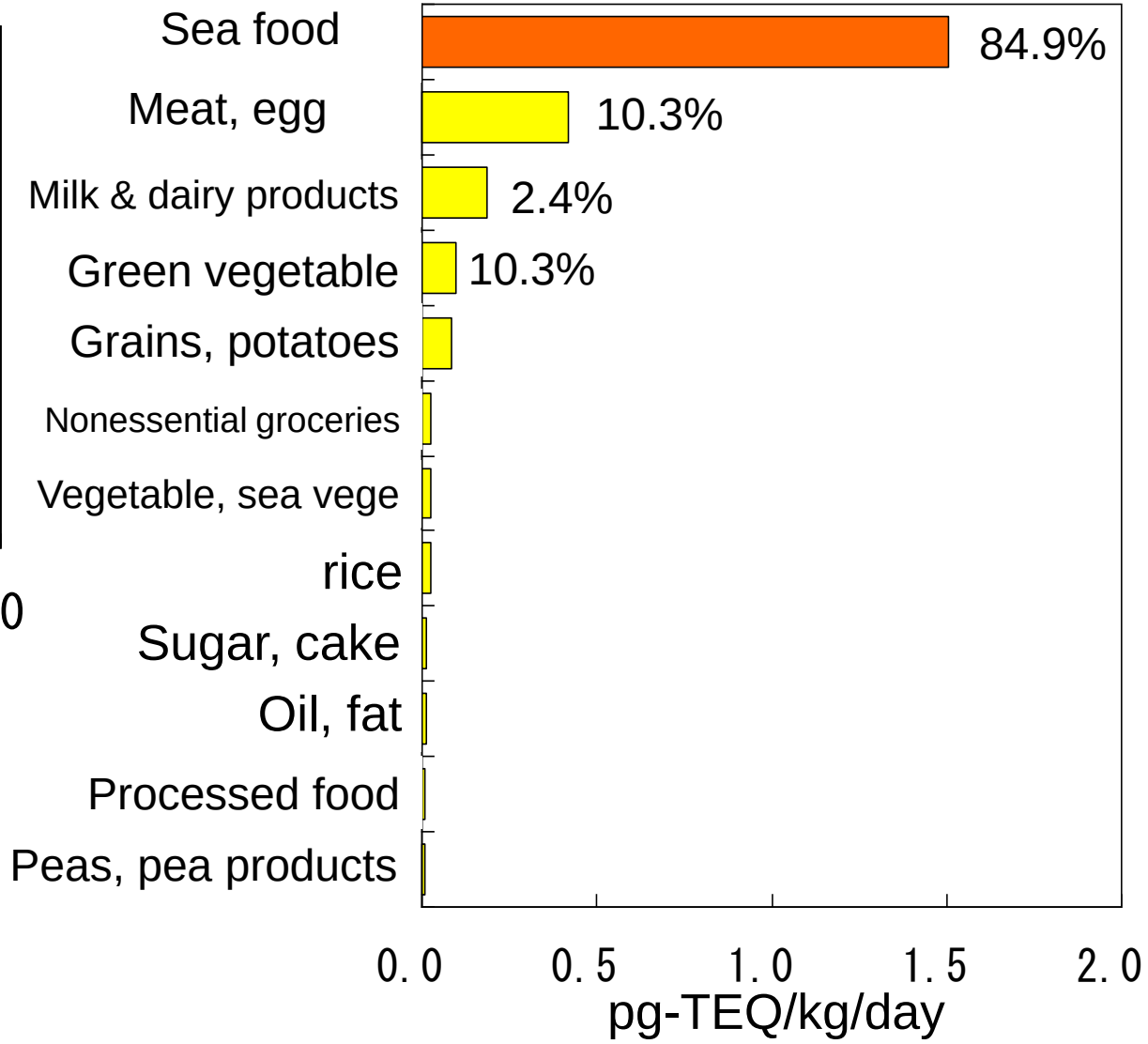


The first babies have the highest concentration of PCBs. It decreases in the second, third babies.

Modified from Fukata et al., EHP 2005, 113, 297-303.

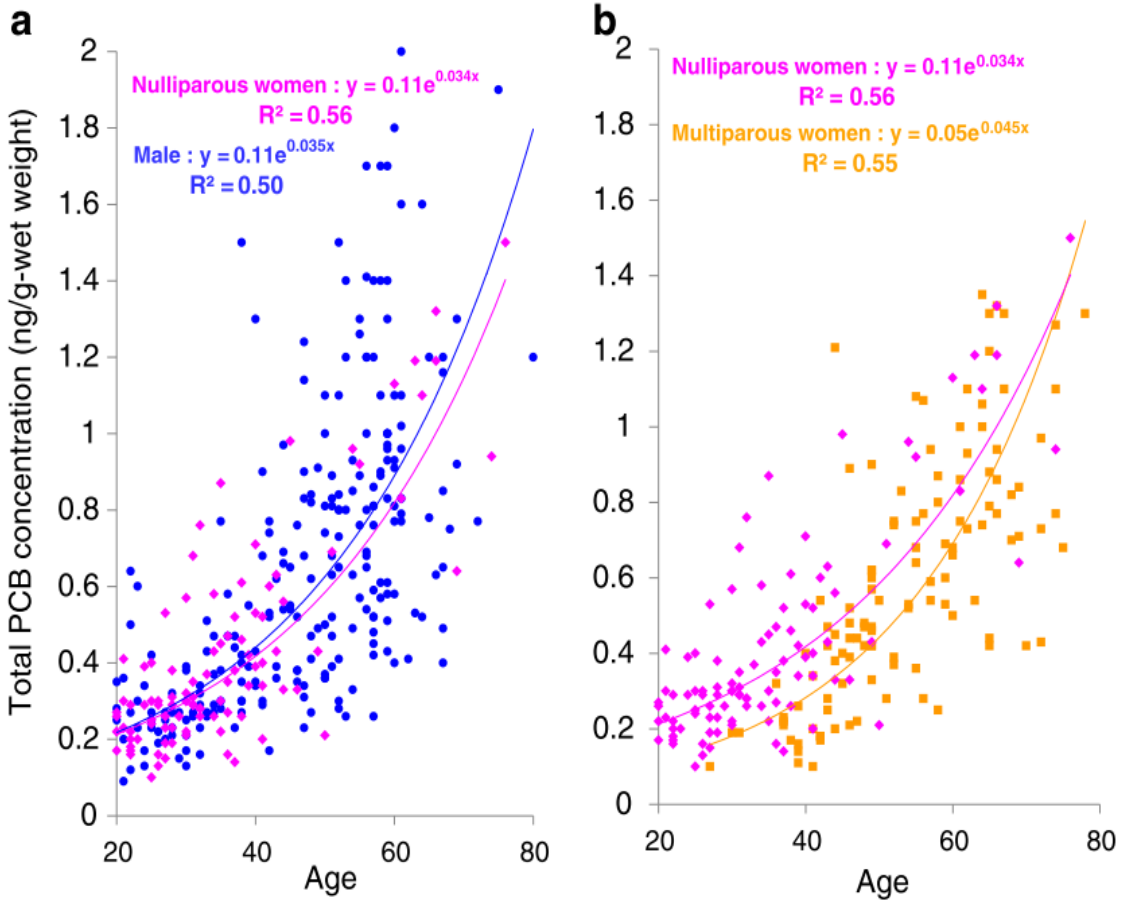
Exposure source of PCBs (dioxins) per day of Japanese people
(Ministry of Health and Welfare, Japan)





Association of blood PCB level and age, gender, experience of delivery

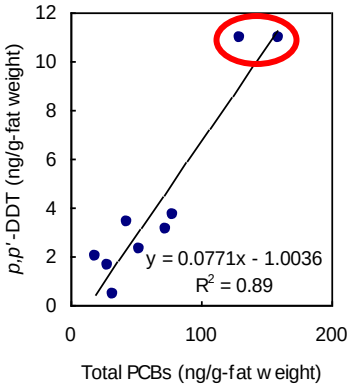
Fig. 1 Association of blood PCB concentration and age, gender, experience of delivery. **a** PCB concentration and age, males (n=242, *closed blue circle*), nulliparous women (n=99, *closed pink diamond*). **b** PCB concentration and age, nulliparous women (n=99, *closed pink diamond*), multiparous women (n=119, *closed orange square*)



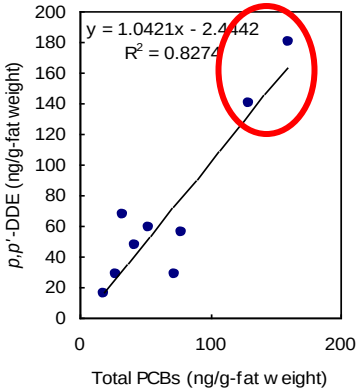
Mori C et al. Polychlorinated biphenyl levels in the blood of Japanese individuals ranging from infants to over 80 years of age. Environ Sci Pollut Res, 21:6434-6439, 2014

Correlations between PCB and other POPs

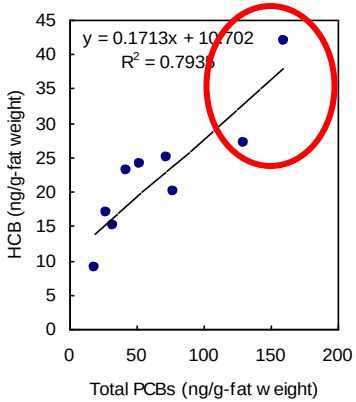
DDT



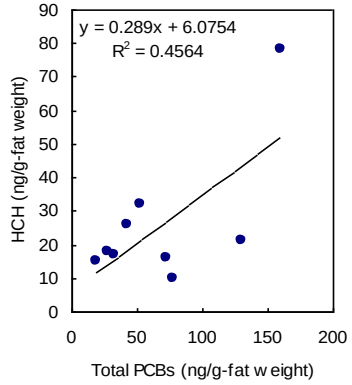
DDE



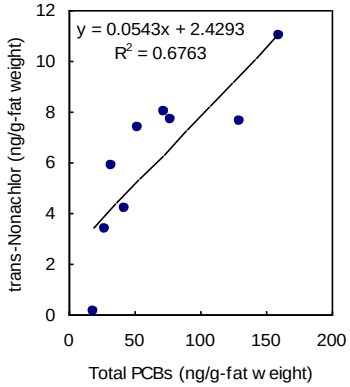
HCB



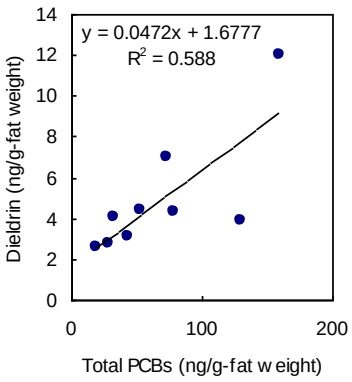
HCH



t-Nonachlor



Dieldrin



The babies who accumulate PCB at higher level also accumulate other POPs at higher levels.

Modified from Mori et al., Environ Herlth Perspect 111, 803-809, 2003.

Correlation between PCBs and other POPs in human umbilical cords

***r* (correlation coefficient)**	***PCBs***	*p,p'-DDT*	*p,p'-DDE*	*DDTs (DDTs+DDEs)*	*trans-Nonachlor*	*cis-Nonachlor*	*Oxychlordane*	*HCB*	*Mirex*	*β-HCH*
PCBs	***1.000***									
p,p'-DDT	***0.705***	1.000								
p,p'-DDE	***0.783***	0.700	1.000							
DDTs (DDTs+DDEs)	***0.787***	0.713	1.000	1.000						
trans-Nonachlor	***0.588***	0.464	0.409	0.414	1.000					
cis-Nonachlor	***0.741***	0.609	0.521	0.528	0.933	1.000				
Oxychlordane	***0.678***	0.512	0.486	0.491	0.968	0.914	1.000			
HCB	***0.698***	0.631	0.592	0.597	0.546	0.644	0.640	1.000		
Mirex	***0.747***	0.513	0.447	0.452	0.379	0.514	0.438	0.465	1.000	
β-HCH	***0.658***	0.476	0.739	0.738	0.502	0.567	0.565	0.607	0.327	1.000

Ochiai *et al* : Chemosphere 94; 48-52, 2014

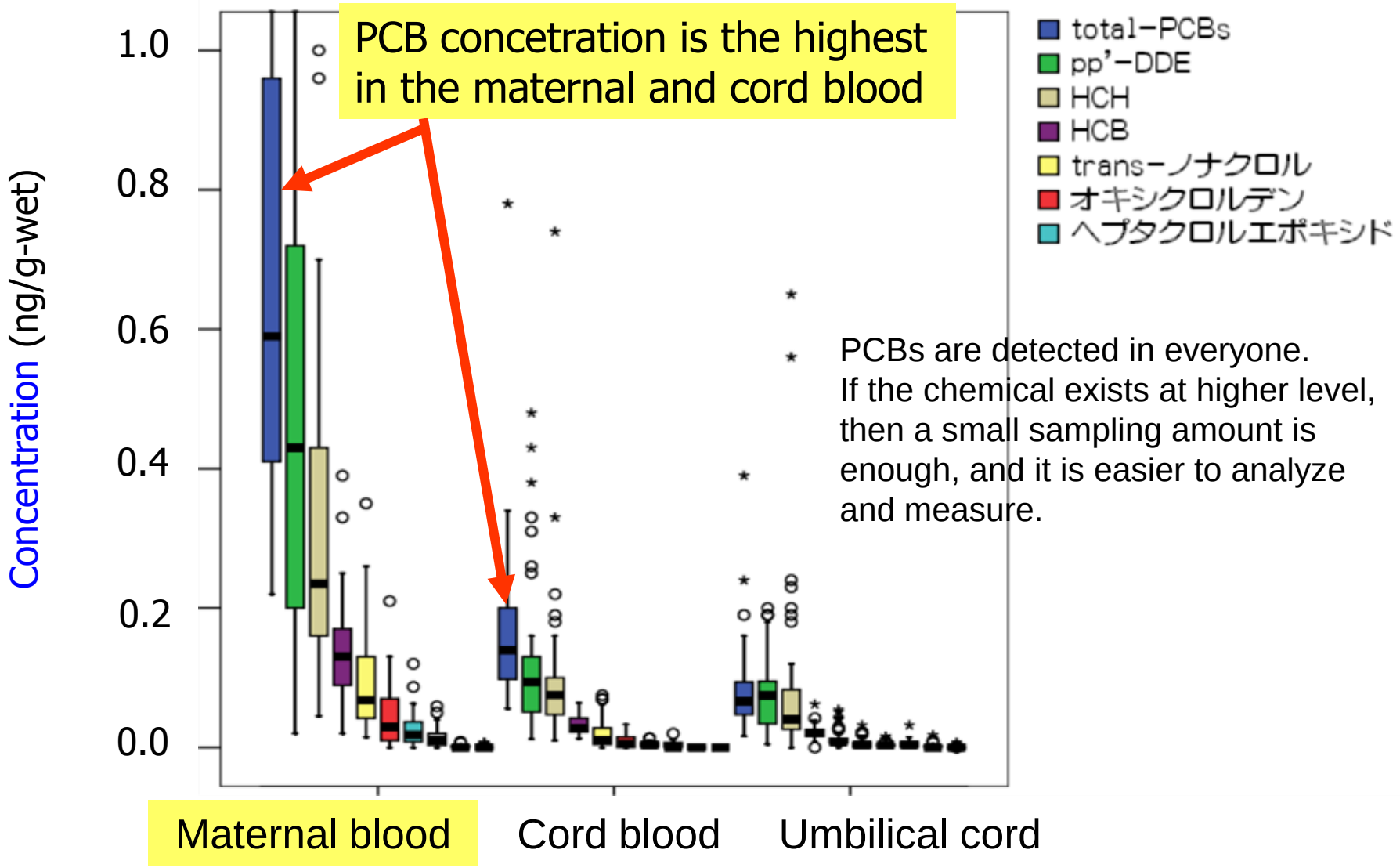
Maternal–Fetal Transfer Rates of PCBs, OCPs, PBDEs, and Dioxin-like Compounds Predicted through Quantitative Structure–Activity Relationship Modeling

Eguchi, Hanazato, Suzuki, Matsuno, Todaka, C Mori

Environ Sci Pollut Res, 2015 (in press)

The present study aims to predict the maternal–fetal transfer rates of the polychlorinated biphenyls (**PCBs**), organochlorine pesticides (**OCPs**), and polybrominated diphenyl ethers (**PBDEs**), and **dioxin like compounds** using a quantitative structure–activity relationship model. The relation between the maternal–fetal transfer rate and the contaminants' physico-chemical properties was investigated by multiple linear regression (MLR), partial least square regression (PLS), and random forest regression (RF). The 10-fold cross validation technique estimated low predictive performances for both MLR and PLS models (R^2_{CV} = 0.480 ± 0.134 for MLR and R^2_{CV} = 0.484 ± 0.132 for PLS), and is in agreement with an external test (R^2_{EXT} = 0.121 for MLR and R^2_{EXT} = 0.107 for PLS). In contrast, the RF model exhibits good predictive performance, estimated through 10-fold cross validation (R^2_{CV} = 0.520 ± 0.111) and an external test set (R^2_{EXT} = 0.490). **Molecular weight and polarity were selected in all models as important parameters that may predict the ability of a molecule to cross the placenta to the fetus.**

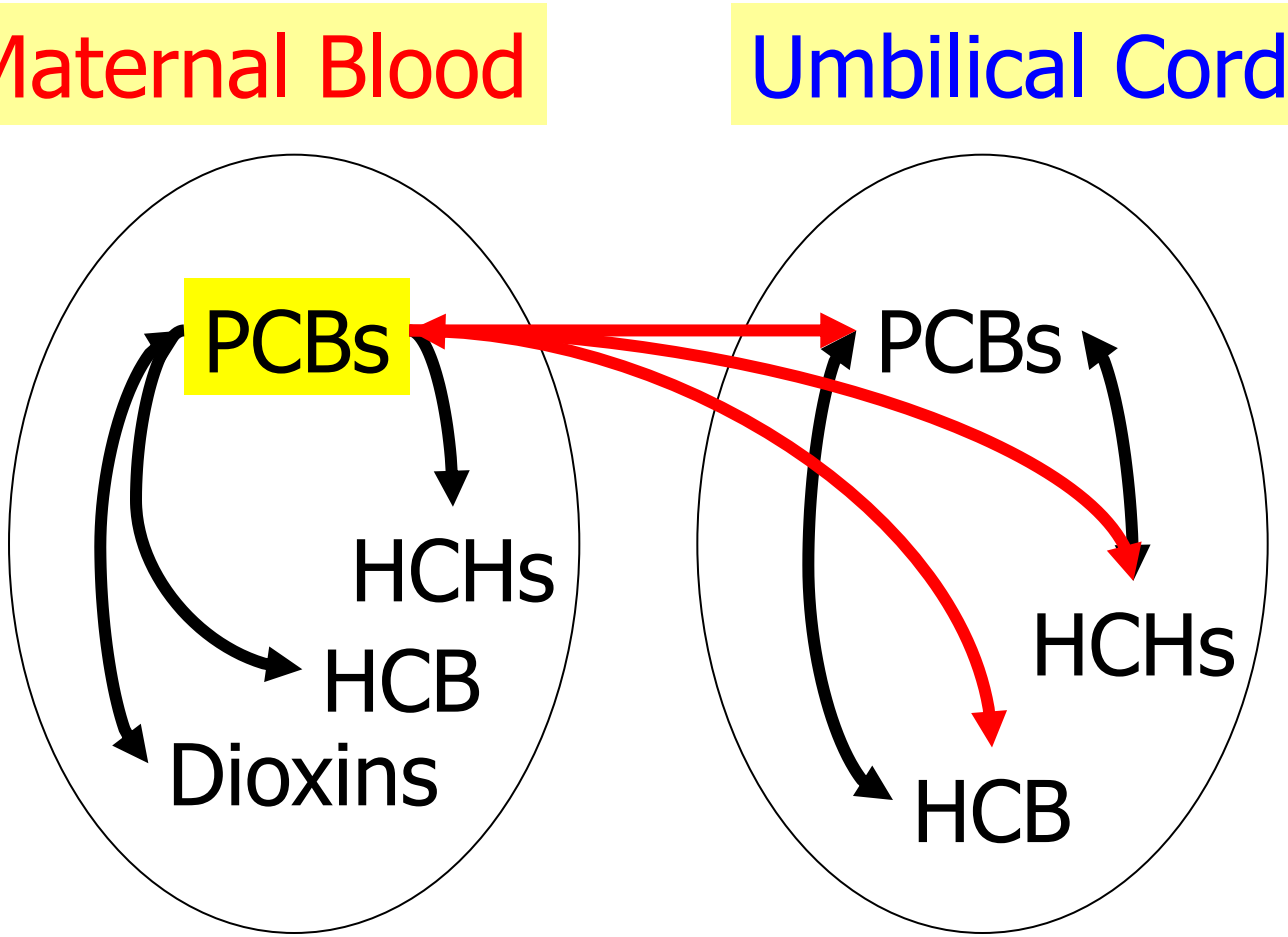
Why use PCB level as an indicator?



PCBs are detected in everyone.
If the chemical exists at higher level, then a small sampling amount is enough, and it is easier to analyze and measure.

Fukata H et al. Environ Health Perspect 113, 297-303, 2005.

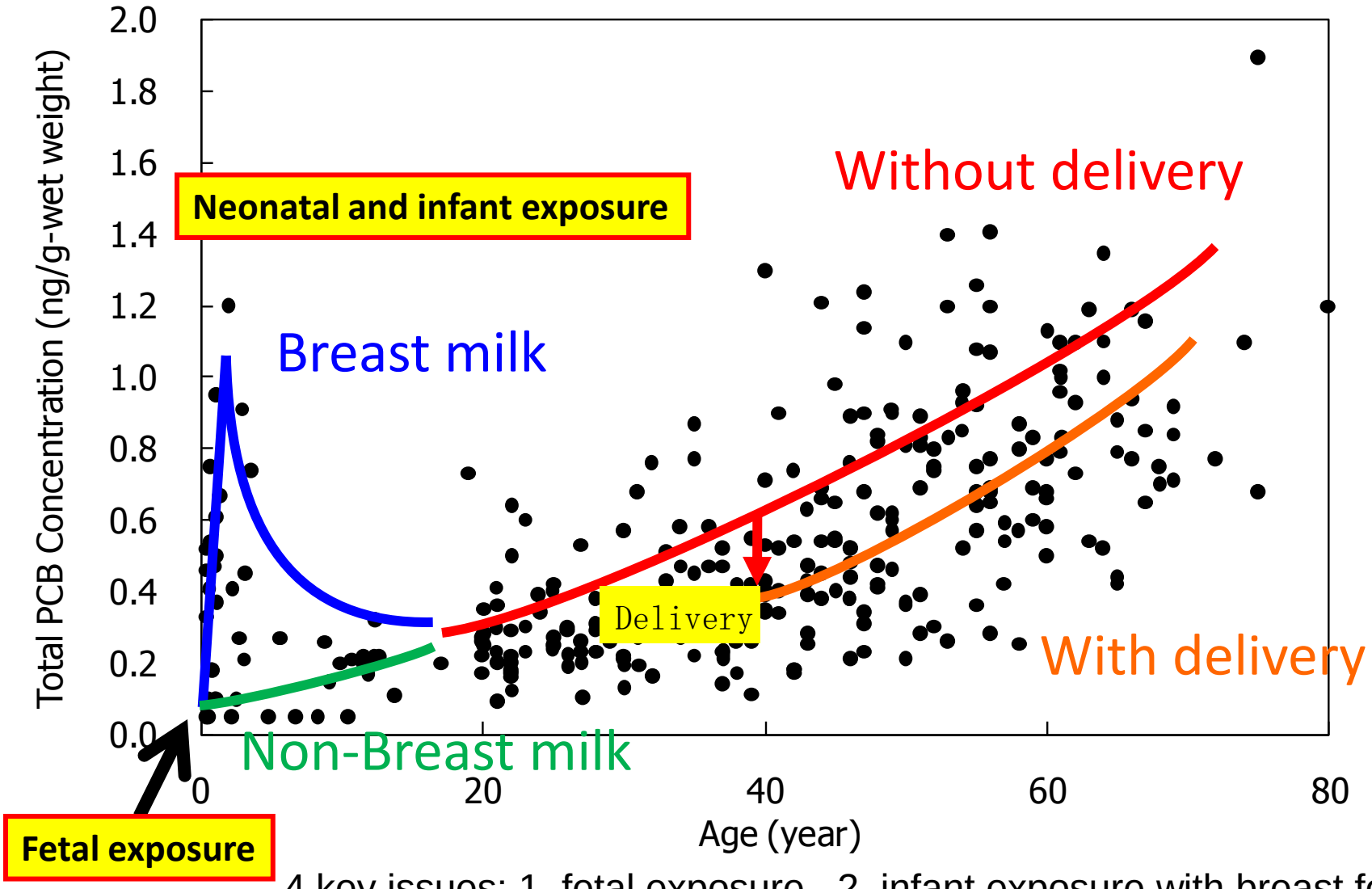
Correlation between maternal PCB level and other persistent chemicals



Maternal PCB level has strong correlation with dioxin, HCB, HCH in maternal blood, and also has PCB, HCB and HCH in umbilical cord .

The reason for why the level of PCBs correlates with other POPs is that both share a common source, food, which in Japan's case would be fish.

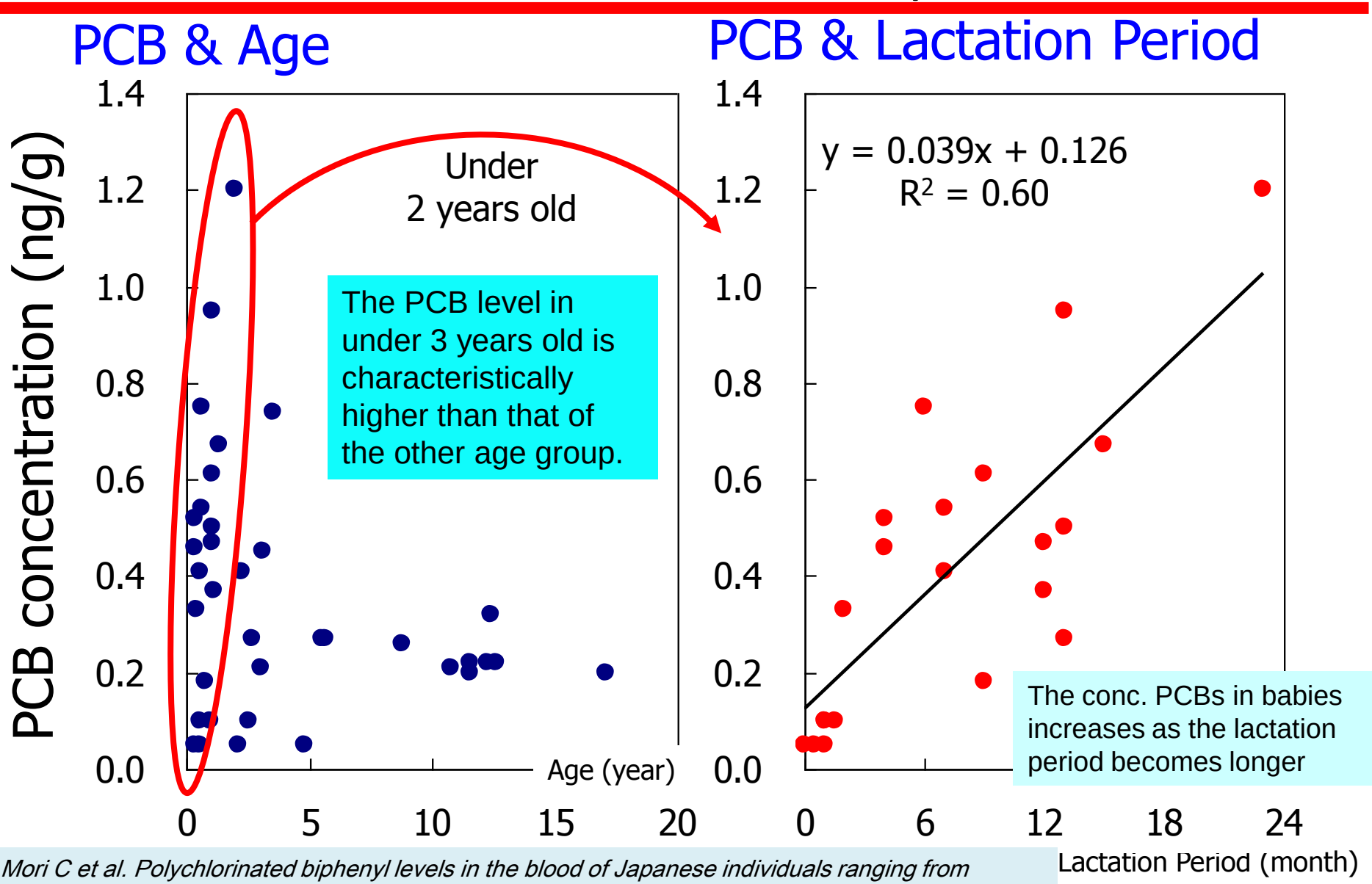
Summary of current exposure level of total PCBs in Japanese



4 key issues: 1. fetal exposure, 2. infant exposure with breast feeding
3. delivery experience, 4. aging

Mori C et al. Polychlorinated biphenyl levels in the blood of Japanese individuals ranging from infants to over 80 years of age. Environ Sci Pollut Res, 21:6434-6439, 2014

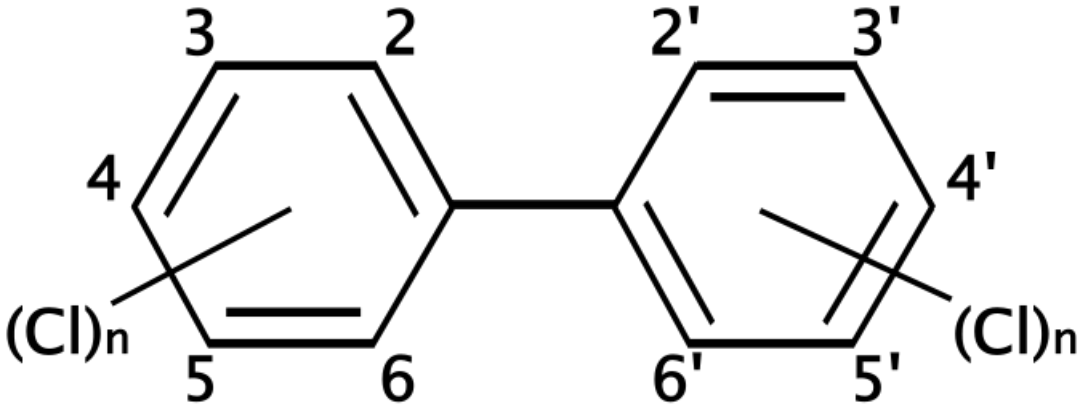
Relationship between PCB & age (0-19 years old), and between PCB & lactation period



Mori C et al. Polychlorinated biphenyl levels in the blood of Japanese individuals ranging from infants to over 80 years of age. Environ Sci Pollut Res, 21:6434-6439, 2014

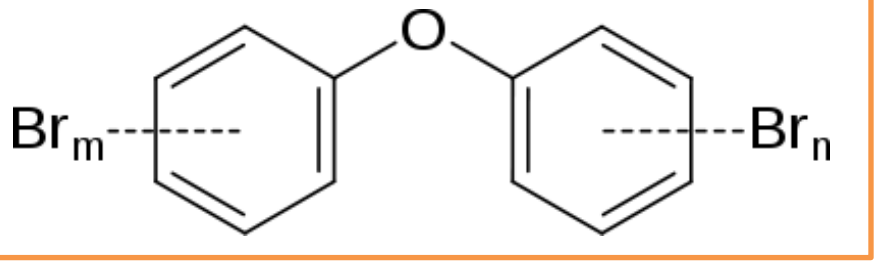
PCBs (Polychlorinated Biphenyls)

- Used to be used widely as dielectric oil
- Pale yellow, oil like liquid
- Fat, oil soluble
- Source of human exposure is mainly food
- Caused PCB poisoning in rice oil in 1968 in north of Kyushu Island in Japan (Kanemi Yusho)

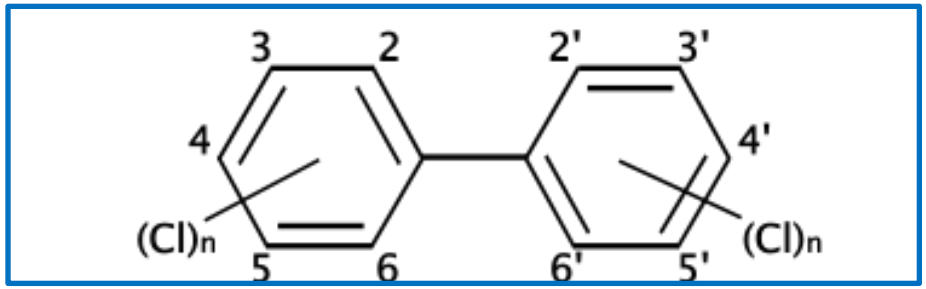


Brominated flame retardants (BFRs):
Polybrominated diphenyl ethers（PBDEs）

- Chemical structure resembles to PCBs
- Source of human exposure is food and indoor air dust

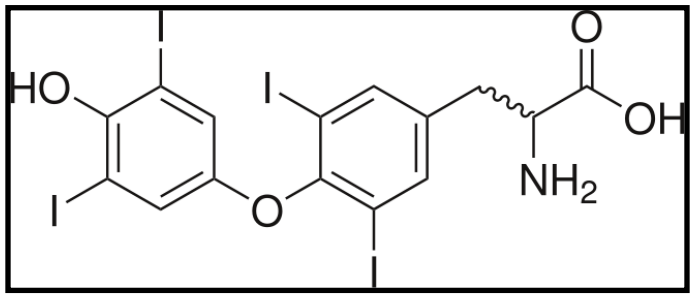


Structural formula of PBDEs

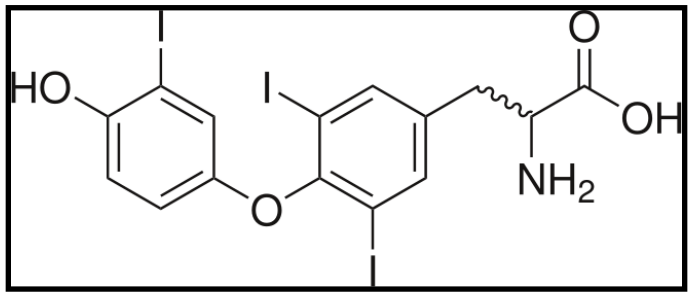


Structural formula of PCBs

- PBDEs resemble to thyroid hormones, and reported to disturb its function (endocrine disruptor)



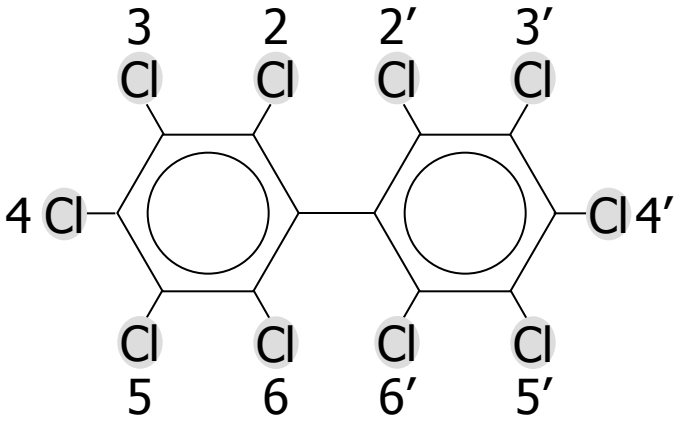
Thyroxin (T4)



Triiodothyronin (T3)

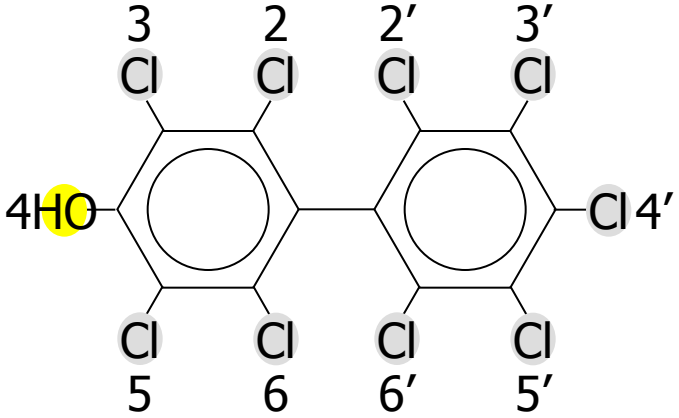
Thyroid hormone and OH-PCBs

PCB



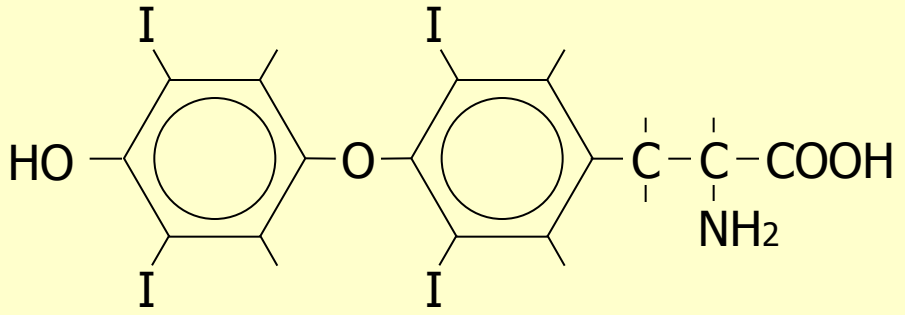
In human body

OH-PCB

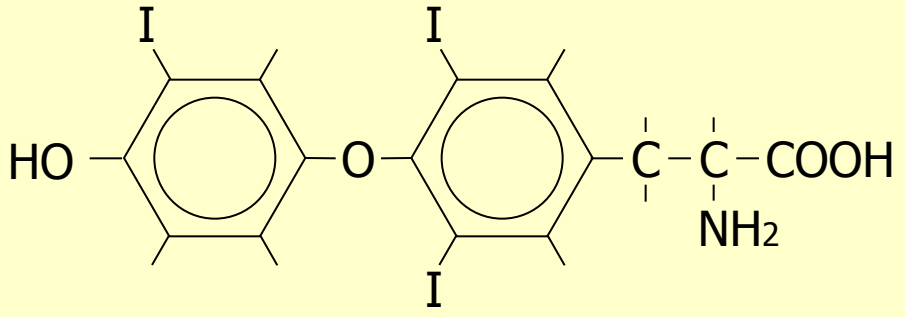


Thyroid hormones

T4: Thyroxine



T3: Triiodothyronine



Today's talk

1. Recent change of children's health and fetal contamination
2. **Children's cohort study in Japan**
3. How can we reduce the exposure?

- **If exposure is prevented also effects and disease are prevented.**
- **Toxicology at best is prevention:**

By J. Liesivuori, University of Turku, Finland

Well designed, large scale birth cohort study will lead us the core of the issue and will prevent possible adverse effects

Center for Preventive Medical Sciences, Chiba University

STUDY PROTOCOL Open Access

Rationale and study design of the Japan environment and children's study (JECS)

Toshihiro Kawamoto[1,2*], Hiroshi Nitta[1], Katsuyuki Murata[3], Eisaku Toda[4], Naoya Tsukamoto[4], Manabu Hasegawa[4], Zentaro Yamagata[5], Fujio Kayama[6], Reiko Kishi[7], Yukihiro Ohya[8], Hirohisa Saito[8], Haruhiko Sago[8], Makiko Okuyama[8], Tsutomu Ogata[8], Susumu Yokoya[8], Yuji Koresawa[1], Yasuyuki Shibata[1], Shoji Nakayama[1], Takehiro Michikawa[1], Ayano Takeuchi[1], Hiroshi Satoh[1] and Working Group of the Epidemiological Research for Children's Environmental Health

Abstract

Background: There is global concern over significant threats from a wide variety of environmental hazards to which children face. Large-scale and long-term birth cohort studies are needed for better environmental management based on sound science. The primary objective of the Japan Environment and Children's Study (JECS), a nation-wide birth cohort study that started its recruitment in January 2011, is to elucidate environmental factors that affect children's health and development.

Methods/Design: Approximately 100,000 expecting mothers who live in designated study areas will be recruited over a 3-year period from January 2011. Participating children will be followed until they reach 13 years of age. Exposure to environmental factors will be assessed by chemical analyses of bio-specimens (blood, cord blood, urine, breast milk, and hair), household environment measurements, and computational simulations using monitoring data (e.g. ambient air quality monitoring) as well as questionnaires. JECS' priority outcomes include reproduction/pregnancy complications, congenital anomalies, neuropsychiatric disorders, immune system disorders, and metabolic/endocrine system disorders. Genetic factors, socioeconomic status, and lifestyle factors will also be examined as covariates and potential confounders. To maximize representativeness, we adopted provider-mediated community-based recruitment.

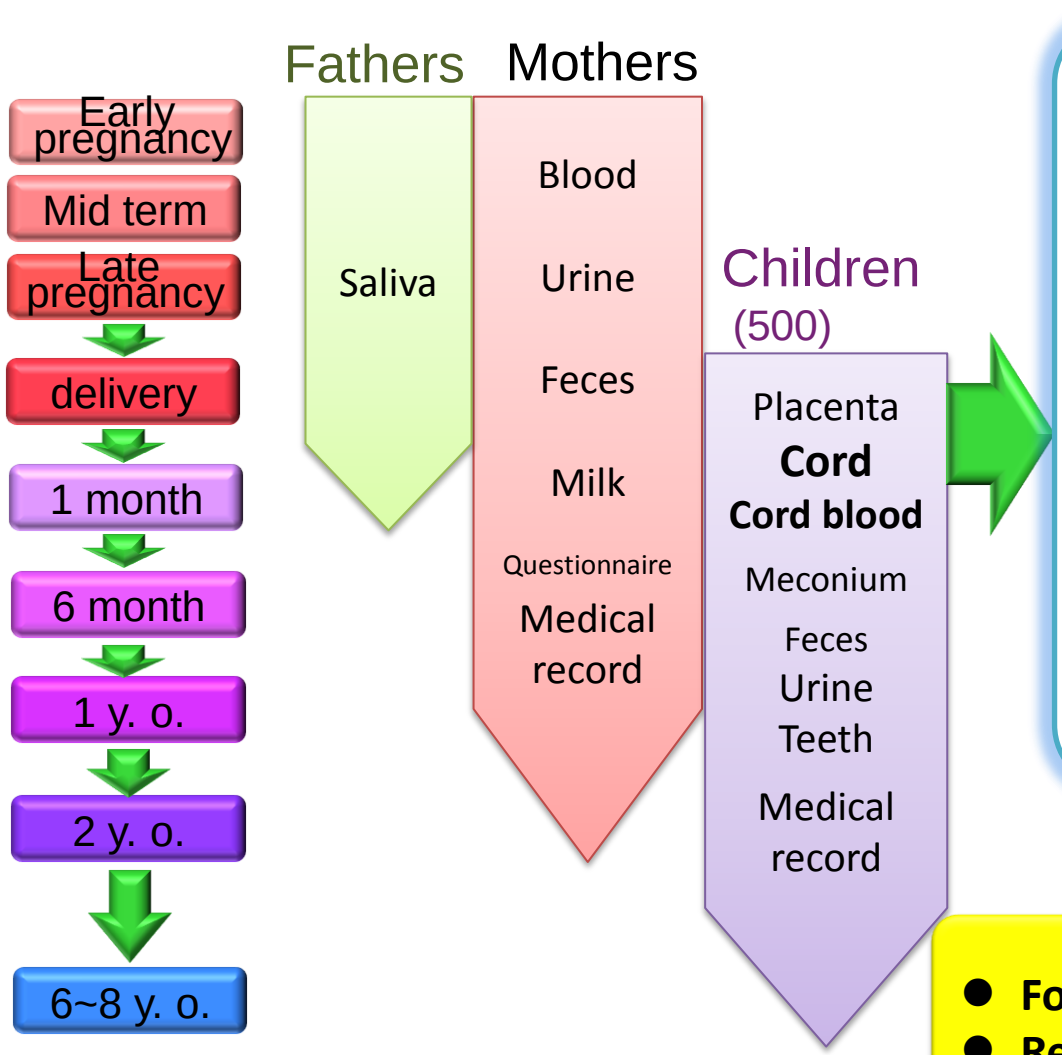
Discussion: Through JECS, chemical substances to which children are exposed during the fetal stage or early childhood will be identified. The JECS results will be translated to better risk assessment and management to provide healthy environment for next generations.

Keywords: Birth cohort, Children, Growth and development, Environmental chemicals, Pregnant women

Kawamoto, T. et al.; Working Group of the Epidemiological Research for Children's Environmental, H. Rationale and study design of the Japan environment and children's study (JECS). BMC Public Health. 14:25; 2014

Birth Cohort in Chiba: Hospital-based cohort study with omics analyses

Chiba study of Mother and Children's Health (C-MACH)



- Research on environment from fetal to infant period (Exposure to chemicals, lifestyle, food, psychological and social factors)
- Epigenomic analysis
- Biomarker/indicator analysis
- Intestinal microflora analysis

- **Follow the low birth weight babies**
- **Research on allergy, neurodevelopmental disorders, obesity, etc.**
- **Research on the causes of the above**

Today's talk

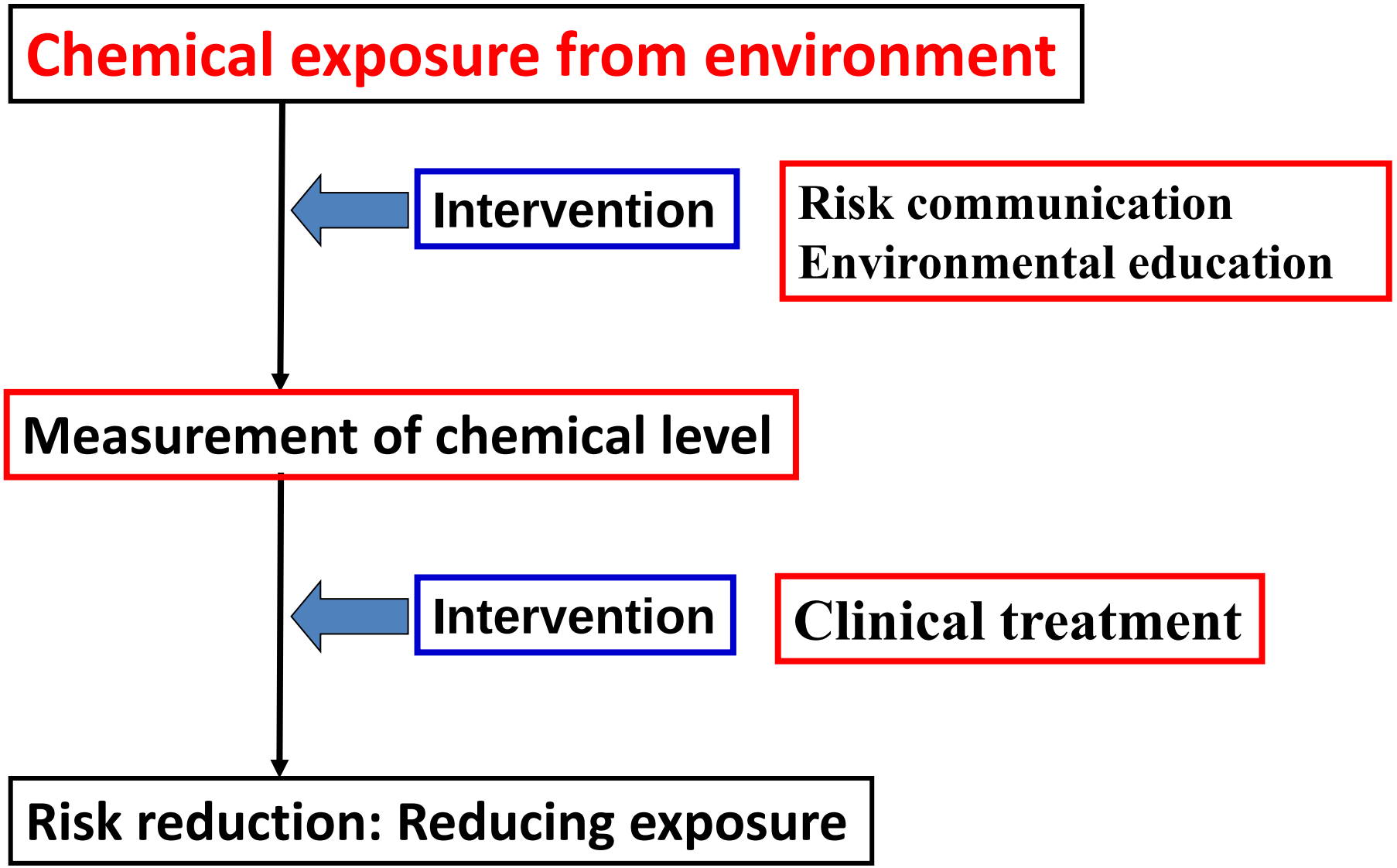
1. Recent change of children's health and fetal contamination
2. Children's cohort study in Japan
3. **How can we reduce the exposure?**

3-1. Health examination approach on reducing internal exposure of POPs

3-2. Town planning trial to prevent sick building syndrome by indoor chemical exposure "Chemiless Town project"

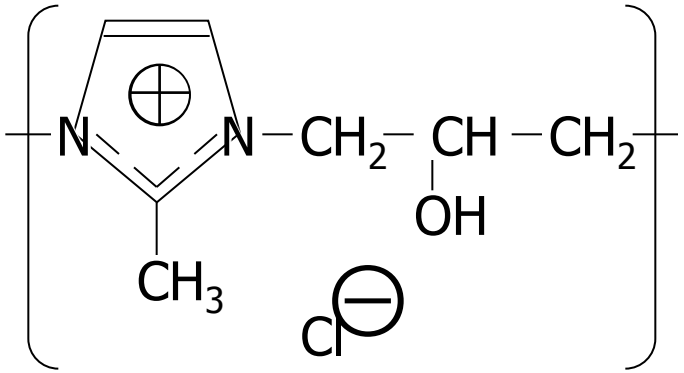
- Chemi-less Town Project & TOP (Town of Public Health) project

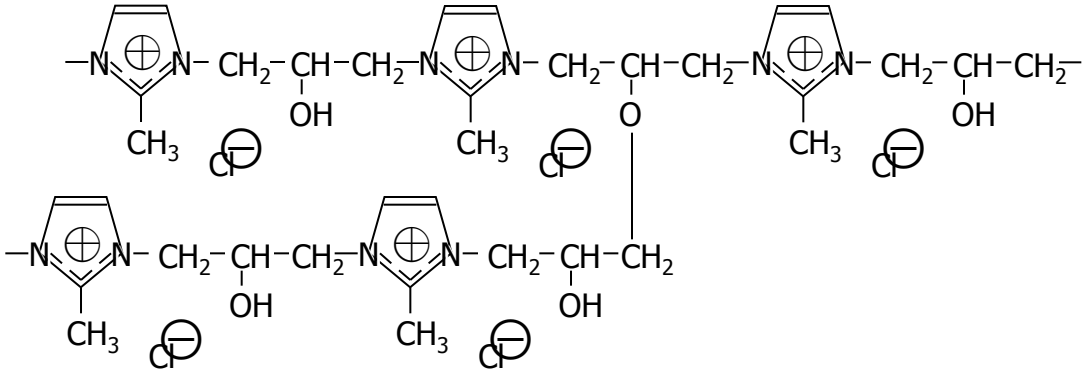
Strategy to reduce exposure of POPs



Reduction of Dioxins and PCBs by medical treatment

Colestimide

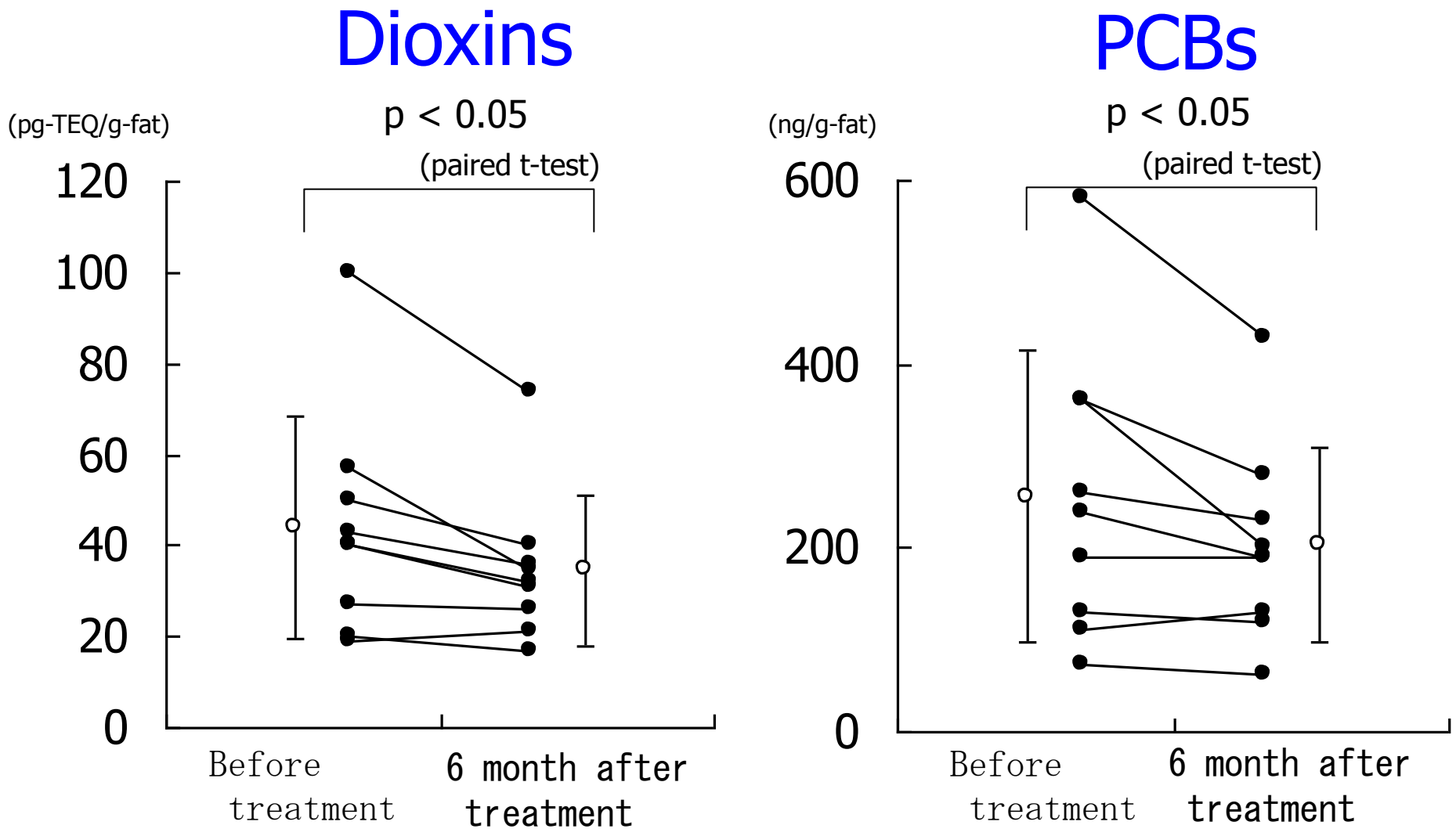




- An anion-exchange resin with an imidazolium salt on an epoxide polymer skeleton
- Used for hyperlipoproteinemia
- Reported to absorb bile acids and other lipophilic compounds

Modified from Sakurai et al., Internal Medicines 2004(Dioxin), 2006(PCBs)

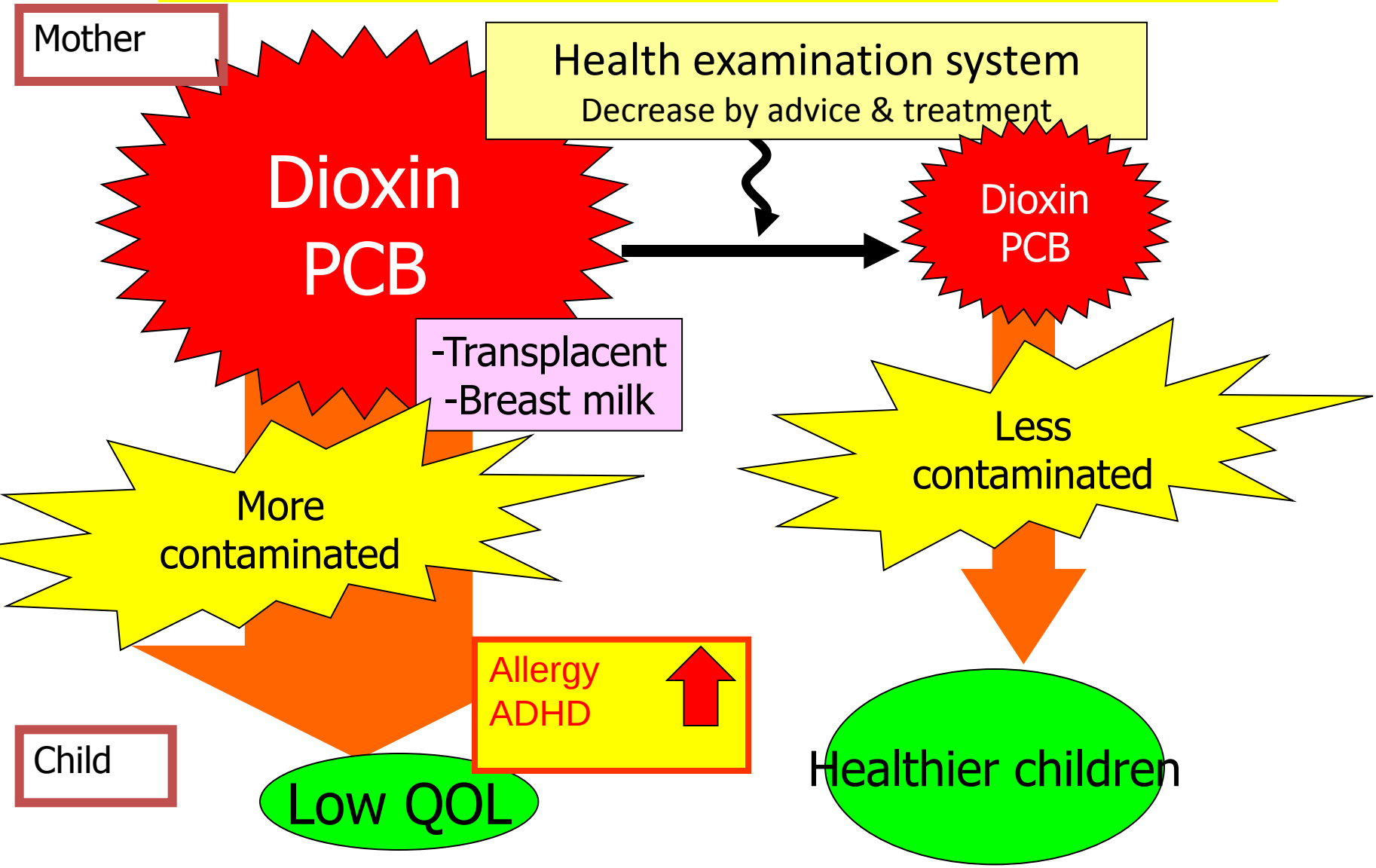
Reduction of Dioxins and PCBs by Colestimide



Modified from Sakurai et al., Internal Medicines 2004(Dioxin), 2006(PCBs)

For healthier future generations

Mori C and Todaka E, Environ. Health Prev. Med., 14: 1-6, 2009.



Today's talk

1. Recent change of children's health and fetal contamination
2. Children's cohort study in Japan
3. **How can we reduce the exposure?**

3-1. Health examination approach on reducing internal exposure of POPs

3-2. Town planning trial to prevent sick building syndrome by indoor chemical exposure "Chemiless Town project"

- Chemi-less Town Project & TOP (Town of Public Health) project

Environmental Preventive Medicine (EPM)

- Prevention preferable to cure
- Prevention strategies are more economical than cures.

In order to solve environmental problems and related sickness

EPM is necessary

In order to solve the problem of indoor air quality, we proposed to improve chemical exposure in Indoor Air by EPM

Background 1: Sick-building Syndrome(SBS)

- 2 ~ 20% of Japanese population is suspected to have sensitivities to chemicals or actually showing some symptoms induced by chemicals in house or building (Ministry of Health, Labor and Welfare)
- Indoor Formaldehyde has been regulated by the national law to be below 0.08ppm in 2003

However,

- The number of patients suffering from the syndrome is increasing

There are uncountable number of chemicals indoor air
So, it is extremely difficult to identify the causing chemicals

How can it be prevented?

Background 2

We conducted a research on SBS and found the followings;

- Indoor air chemicals vary depending on building materials, interior materials, furniture, etc.
- Total VOCs (TVOC) values are significantly correlated with SBS symptoms especially among sensitive people.
- When TVOC is low, sensitive people showed less symptoms.
- Causing chemicals are different in each individual.

Mori C, Todaka E. Environ Health Prev Med 2009
Mori C, Todaka E. Maruzen Planet Co., Ltd. 2011
Nakaoka H. et al. Indoor and Built Environment, 2014

What is “Chemiless”?

“Chemi” → “Chemicals”

“Less” → “Fewer”

It is not enough to regulate a few chemicals to prevent possible adverse health effect. It is necessary to construct a whole town caring about sensitive people. So, we constructed a model town in our university campus
It is the project to create a model town in a university campus.

ΣVOCs & SBS symptoms

SBS symptoms according to ΣVOCs quartile

① ΣVOCs was categorized into four groups in quartiles

category (μg/m³)
1 (37-110)
2 (220-270)
3 (430-840)
4 (980-12000)

②The correlation were examined separately for sensitive and insensitive groups of participants

	OR (95% CI)			
ΣVOCs category	1	2	3	4
ΣVOCs value (μg/m³)	**37-110**	**220-270**	**430-840**	**980-12000**
All	1	2.14 (0.87-5.27)	2.60 (1.13-6.02)*	3.12 (1.25-7.81) *
QEESI+	1	3.02 (0.75-12.2)	3.90 (1.06-14.3)*	7.33 (1.58-34.0) *
QEESI-	1	1.64 (0.49-5.47)	1.93 (0.64-5.78)	1.71 (0.51-5.75)

- A correlation was found between ΣVOCs and SBS symptoms when ΣVOCs was in category 3 and category 4.
- Sensitive people showed a strong correlation in category 3 and 4.
- However, the correlation was not significant in the insensitive group

Nakaoka H. et al. Indoor and Built Environment, 2014

Findings from Chemiless Town Project

- Natural materials are not always healthy
- If carefully chosen, indoor air TVOC can be lowered below 400 μg/m^3 from the beginning.
- If the indoor air TVOC is below 250 μg/m^3, even sensitive people don't show the sick building syndrome symptoms

Nakaoka H, et al：Correlating the symptoms of sick-building syndrome to indoor VOCs concentration levels and odour. Indoor and Built Environment, 2014, 23(6), 804-813

Proposed guidelines for indoor air quality to the public

- We successfully resulted in house and classroom prototypes that reduced VOCs in indoor air for the prevention of SBS.
- We proposed ΣVOCs (Sum of VOCs) as an evaluation index for indoor air quality
- "Chemiless standard for assessment" to ensure air in which people can stay comfortably,

"S": the standard value for sensitive people

⇒ 250 μg/m^3 of ΣVOCs

"A": the standard for non-sensitive people

⇒ 400 μg/m^3 of ΣVOCs.

Remarks from Chemiless Town Project

- **ΣVOC is important to evaluate indoor air quality, because there are countless VOCs in indoor air.**
- **Smell is also useful for indicator to prevent SBS.**
- **It is very difficult to determine cause-and-effect relationships between these substances and human health.**

Thank you for your attention!

Environmental Health Intervention and Preventive Medical Studies on Chemical Exposure Issues

If exposure is prevented by scientific efforts, adverse effects and disease are prevented for future generation's health.

"In Our Every Deliberation, We Must Consider the Impact of Our Decisions on the next Seven Generations" From: "Great Law of the Iroquois Nation"

Coming soon; March 1, 2016
Taiwan version in Taiwan