NIMD Forum　2014

“Evaluation of methylmercury exposure and health effects in human”

Date　：October 18, 2014

Venue　：Minamata Disease Archives
National Institute for Minamata Disease
Minamata City, Kumamoto, Japan

Program

15:15 - 15:25	***Opening remarks:* Minoru Koga** (Prefectural University of Kumamoto, Japan / President)
Session	***Chair:* Laurie H.M Chan** (University of Ottawa, Canada / Professor) **Mineshi Sakamoto** (NIMD, Japan / Director, Department of Environmental Science and Epidemiology) ***Moderator of secretariat:* Megumi Yamamoto**(NIMD, Japan / Chief, Department of Basic Medical Science)
15:25 - 15:45	**Mineshi Sakamoto** (NIMD, Japan / Director, Department of Environmental Science and Epidemiology) Significance of fingernail and toenail mercury concentrations as biomarkers for prenatal methylmercury exposure
15:45 15:55	*Greeting messages :* **Shigeo Kitamura** (State Minister of the Environment, Japan)
15:55 - 16:15	**Hiroshi Satoh** (Food Safety Commission of Japan) Seafood for thought: fish-eating and methylmercury in fish
16:15 - 16:35	**Milena Horvat** (Jozef Stefan Institute, Ljubljana , Slovenia / Head, Department of Environmental Sciences) Evaluation of methylmercury exposure and health effects in the Mediterranean population
16:35 - 16:55	**Laurie H.M. Chan** (University of Ottawa , Canada / Professor) Relationship Between Paraoxonase-1 (PON1) and Metal Concentrations in the Whole Blood of Inuit in Canada
16:55 - 17:15	**Masaaki Nakamura** (NIMD, Japan / Chief , Department of Clinical Medicine) Methylmercury exposure and neurological outcomes by ingesting whale mea
17:15 - 17:35	**Anna Choi** (Harvard University , USA / Research Scientist) Negative Confounding by Essential Fatty Acids in Methylmercury Neurotoxicity Associations
17:35 - 17:45	***Summary:* Laurie H.M Chan** (University of Ottawa, Canada) **Mineshi Sakamoto** (NIMD, Japan)
17:45 - 17:55	***Closing Remarks:* Hiroshi Noda** (NIMD, Director General)

State Minister's Greetings

Shigeo Kitamura
State Minister for the Environment, JAPAN

Good afternoon. I'm Shigeo Kitamura, State Minister for the Environment. I've come today to Minamata, where the Minamata Convention was adopted, to offer a few words of encouragement to you, the researchers at the frontlines of research into mercury in Japan and the world.

The United Nations Environmental Programme, or UNEP, acts as the provisional secretariat for the Minamata Convention on Mercury. It warns that mercury continues to accumulate on the earth's surface as a result of human industrial activity and is reaching levels that will impact human health and the environment on a global scale. I believe that now is the time to advance global strategies to prevent this problem from being passed on as a negative legacy to future generations.

To eliminate the damage from mercury pollution worldwide, the Japanese Government and the Ministry of the Environment are determined to go beyond the minimum measures sought under the Convention. We are stepping up our efforts, for example through aid for developing countries that makes use of Japan's excellent mercury control technologies.

I am confident that the research results of all of you attending this NIMD Forum at the National Institute for Minamata Disease today will play a great role in the resolution of this worldwide problem.

Lastly, I hope that you will continue your tremendous efforts in this difficult struggle, for the future of Japan and the world.

Thank you very much.

Shigeo Kitamura
State Minister of the Environment, Japan

Significance of fingernail and toenail mercury concentrations as biomarkers for prenatal methylmercury exposure

Mineshi Sakamotoa*, Hing Man Chan, José L Domingo, Ricardo B Oliveira, Shoichi Kawakami, Katsuyuki Murata

Department of Environmental Sciences and Epidemiology, National Institute for Minamata Disease, Minamata, Japan

Objective: To investigate the appropriateness of mercury (Hg) concentrations in fingernails and toenails at parturition for detecting prenatal exposure to methylmercury (MeHg).

Methods: Total Hg concentrations were measured in 54 paired samples of fingernails, toenails, maternal blood, and maternal hair (1cm incremental segments from the scalp toward the tip) collected at 4th weeks of (early) pregnancy, and the same specimens and cord blood collected at parturition.

Results: Strong correlations were observed between Hg concentrations in fingernails and toenails at early pregnancy ($r=0.923$, $p<0.01$) and at parturition ($r=0.895$, $p<0.01$). At early pregnancy, Hg concentrations in fingernails and toenails showed the strongest correlations with those in hair 3–4 cm from the scalp. Mercury concentrations in fingernails and toenails at parturition represented strong correlations with those in cord blood ($r=0.803$, $p<0.01$ for fingernails and $r=0.792$, $p<0.01$ for toenails, respectively). At parturition, Hg concentrations in fingernails had the highest correlation with those in hair 0–1 cm from the scalp ($r=0.918$, $p<0.01$), and Hg concentrations in toenails showed the highest correlation with those in hair at 2–3 cm from the scalp ($r=0.872$, $p<0.01$). In addition, the correlation coefficients of Hg concentrations between nails and hair segments at parturition were equally high among hair at 0-1, 1-2, and 2-3 cm from the scalp.

Conclusion: This is the first comprehensive study investigating the appropriateness of using Hg concentrations in fingernails and toenails as biomarkers for maternal and fetal MeHg exposure at parturition, compared with those at early pregnancy. Mercury in fingernails and toenails at early pregnancy reflected the maternal Hg body burden level approximately 5 months retroactively. At parturition, Hg levels in fingernails and toenails also showed strong correlations with those in cord blood. In addition, Hg levels in fingernails and toenails at parturition reflected MeHg levels throughout third-trimester of gestation. These results suggest that fingernails and toenails at parturition are useful biomarkers for prenatal MeHg exposure for mothers and fetuses, especially during the third-trimester of gestation.

Significance of fingernail and toenail mercury concentrations at parturition as a biomarker of MeHg exposure to fetus

Mineshi Sakamoto*,
Hing Man Chan,
Jose L Domingo,
Ricardo B Oliveira,
Shoichi Kawakami and
Katsuyuki Murata

Minamata disease 1956
by Eugene Smith

Fetal-type patients

Iraq MeHg intoxication 1971

Background

- The target organ of MeHg exposure during gestation is the fetal brain, especially the developing brain at the 3rd trimester (Rice and Barone, 2000).
- For this reason, biomarkers reflecting the MeHg exposure level in the fetus during the 3rd trimester are very important to predict the effects of MeHg on child development.

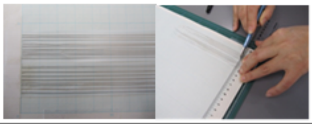
- A number of studies have employed Hg concentrations in toenails and/or fingernails as biomarkers for MeHg exposure.
- However, the time-lag of the nail growth from the nail matrix to the nail free edge is not well specified in the above mentioned studies.
- Also, the significance of the nails for the assessment of the maternal and fetal MeHg exposure at the parturition has never been studied so far.

Objective

- **To investigate the appropriateness of Hg concentrations in fingernails and toenails at parturition for detecting prenatal exposure to MeHg.**

Materials and methods

- Total Hg concentrations were measured in 54 paired samples of fingernails, toenails, maternal blood, and maternal hair collected at 4th weeks of (early) pregnancy, and the same specimens and cord blood collected at parturition.
- Hair strings were cut into 1 cm incremental segments from the scalp toward the tip.



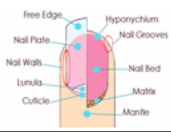
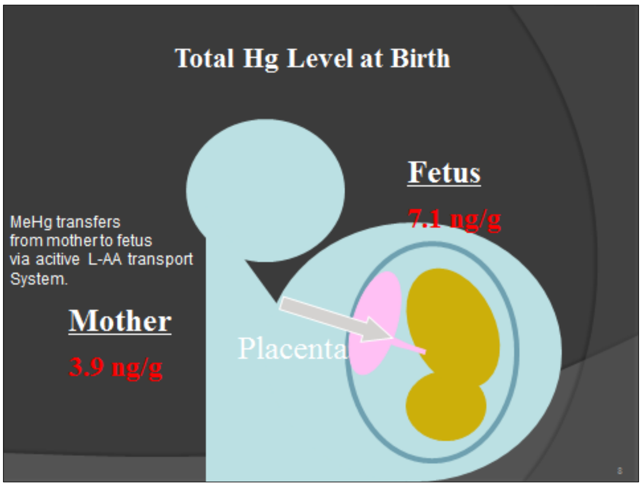


Table 1. Geomean (25-75 percentile) of Hg concentrations (ng/g) in maternal and cord blood, fingernail and toenails and in segmental hair at early gestation and parturition.

	At early gestation	At parturition
Maternal blood	4.40 (3.58 - 5.44)	3.89 (3.25 - 4.69)**
Cord blood		7.14 (6.02 - 9.38)**
Fingernail	547 (425 - 727)	504 (426 - 585)*
Toenail	465 (358 - 624)	427 (350 - 544)**
Hair length (cm)		
0-1	1268 (941-1798)	1314 (1090-1709)
1-2	1276 (928-1827)	1257 (1030-1540)
2-3	1261 (885-1850)	1243 (1019-1533)
3-4	1244 (892-1922)	1252 (1045-1573)
4-5	1234 (898-1844)	1234 (1018-1605)
5-6	1215 (851-1840)	1241 (1032-1535)
6-7	1194 (844-1686)	1238 (1109-1622)
7-8	1141 (844-1714)	1272 (1055-1622)
8-9	1159 (845-1648)	1273 (1042-1744)

The differences in Hg concentrations between paired samples were determined by paired t-test using logarithmically transferred Hg concentrations.
Hg concentrations in maternal blood, ringer- and toenails at parturition were significantly (* $p < 0.05$, ** $p < 0.01$) lower than those at early gestation.
Hg concentrations in cord blood was significantly (** $p < 0.01$) higher than those in maternal blood at parturition.



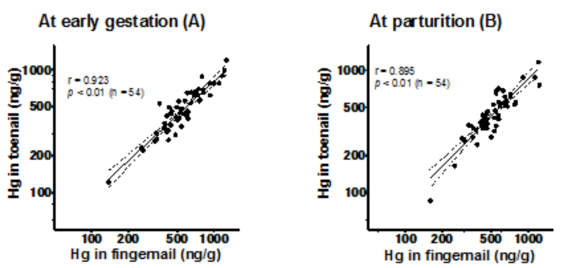


Fig. 1. Correlations between fingernail and toenail Hg concentrations in mothers at early gestation (A) and at parturition (B).
Dotted lines denote 95% confident intervals for the regression line.

Table 2. Correlations among Hg concentrations (ng/g) in maternal blood, fingernail and toe nails and segmental hair at early gestation.

	Correlation coefficients		
54 samples	Mother Blood	Fingernail	Toenail
Maternal blood	1		
Fingernail	0.735	1	
Toenail	0.707	0.923	1
Hair length (cm)			
0-1	0.661	0.787	0.711
1-2	0.669	0.784	0.714
2-3	0.630	0.780	0.706
3-4	0.633	0.818	0.744
4-5	0.599	0.813	0.733
5-6	0.576	0.806	0.734
6-7	0.545	0.779	0.718
7-8	0.438	0.616	0.588
8-9	0.468	0.692	0.643

Correlation coefficients were calculated using logarithmically transferred Hg concentrations.
All the correlation coefficients were statistically significant ($p < 0.01$).

Table 3. Correlations among Hg concentrations (ng/g) in maternal and cord blood, fingernail and toe nails, and segmental hair at parturition.

	Correlation coefficients			
54 samples	Maternal blood	Cord Blood	Fingernail	Toenail
Maternal blood	1			
Cord Blood	0.878	1		
Fingernail	0.697	0.803	1	
Toenail	0.689	0.792	0.895	1
Hair length (cm)				
0-1	0.842	0.918	0.878	0.868
1-2	0.772	0.870	0.875	0.871
2-3	0.749	0.846	0.873	0.872
3-4	0.737	0.792	0.825	0.835
4-5	0.722	0.779	0.749	0.794
5-6	0.688	0.739	0.716	0.791
6-7	0.617	0.680	0.662	0.730
7-8	0.612	0.638	0.631	0.737
8-9	0.471	0.492	0.513	0.595

Correlation coefficients were calculated using logarithmically transferred Hg concentrations.
All the correlation coefficients were statistically significant ($p < 0.01$).

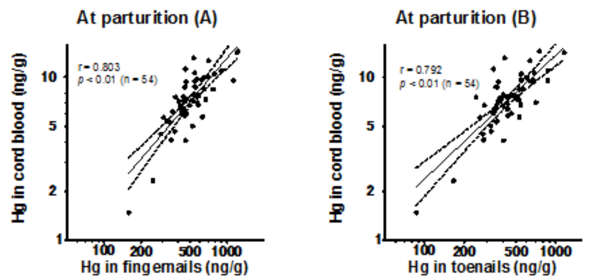


Fig. 2. Correlations between Hg concentrations in cord blood and those in fingernail (A) and toenails (B) and at parturition.
Dotted lines denote 95% confident intervals for the regression line.

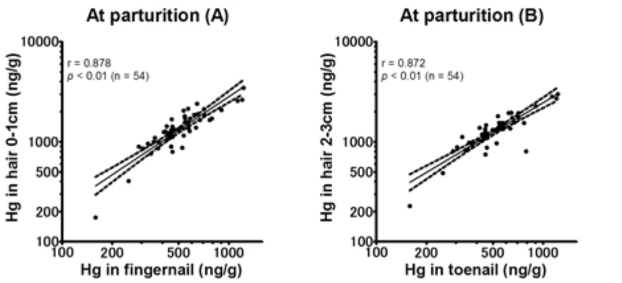


Fig. 3. Correlations between Hg concentrations in fingernail and maternal hair segment 0–1 cm from the scalp (A) and those between Hg concentrations between toenail and maternal hair segment 2–3 cm from the scalp (B) at parturition.
Dotted lines denote 95% confident intervals for the regression line.

Results

- Strong correlations were observed between Hg concentrations in fingernails and toenails at early pregnancy (r=0.923, p<0.01) and at parturition (r=0.895, p<0.01).

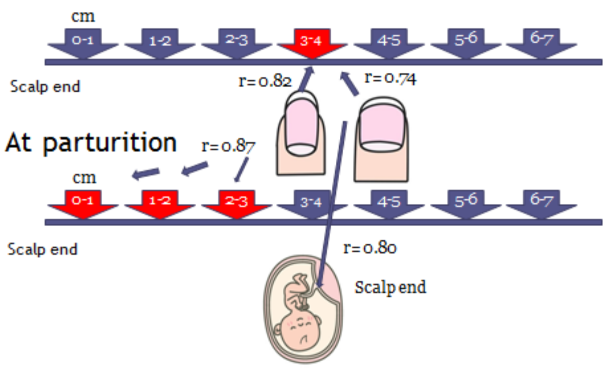
At early pregnancy

- Hg concentrations in fingernails and toenails showed the strongest correlations with those in hair segment 3–4 cm from the scalp (r=0.818 and r=0.747, p<0.01, respectively) among the 1 cm incremental hair segments.

At parturition

- Hg concentrations in fingernails (r=0.803, p<0.01) and toenails (r=0.792, <0.01) showed strong correlations with those in cord blood.
- Hg concentrations in fingernails had the highest correlation with those in hair 0-1 cm from the scalp (r=0.918, p<0.01), and Hg concentrations in toenails showed the highest correlation with those in hair at 2-3 cm from the scalp (r=0.872, p<0.01).
- In addition, the correlation coefficients of Hg concentrations between nails and hair segments at parturition were equally high among hair at 0–1, 1–2, and 2–3 cm from the scalp.

At early gestation



Conclusion

- This is the first comprehensive study investigating the appropriateness of using Hg concentrations in fingernails and toenails as biomarkers for maternal and fetal MeHg exposure at parturition, compared with those at early pregnancy.
- Both fingernails and toenails collected at parturition can be used as biomarkers for maternal and fetal MeHg exposure, throughout the 3rd trimester of pregnancy.

Seafood for thought: fish-eating and methylmercury in fish

Hiroshi Satoh

Food Safety Commission of Japan

Mercury occurs ubiquitously in the environment. It has been used from the ancient age as well as lead and iron. Mercury and its compounds are classified into three chemical forms such as metallic (elemental) mercury, inorganic and organic mercury compounds. Metallic mercury is in liquid form at room temperature and generates mercury vapor, which exist in atmosphere. Mercury in the environment partially converted into methylmercury by micororganisms. Methylmercury is bio-concentrated and accumulated in large carnivore fish and sea mammals.

Major toxicity of methylmercury is manifested in the central nervous system (CNS) and the fetal CNS has been considered to be vulnerable from the observations in Minamata disease and Iraqi tragedy. Therefore, birth cohort studies have been conducted among the fish-eating populations with high methylmercury exposure.

Food Safety Commission (FSC) was established in 2003 as a risk assessment organization independent from risk management organizations. In 2005 FSC published "Food Safety Risk Assessment Related to Methylmercury in Seafood" and the tolerable weekly intake of 2 μg/kg bw/week (as Hg) was proposed for pregnant and potentially pregnant women, since fetuses are the high-risk group. The risk assessment report referred to the benefit of fish-eating. Following the risk assessment report, a risk management organization, Ministry of Health, Labour and Welfare, issued "Advice for Pregnant Women on Fish Consumption and Mercury" to avoid excessive methylmercury exposure during pregnancy. In the advice frequencies of consumption of high mercury content fish were shown to keep the methylmercury intake below the TWI.

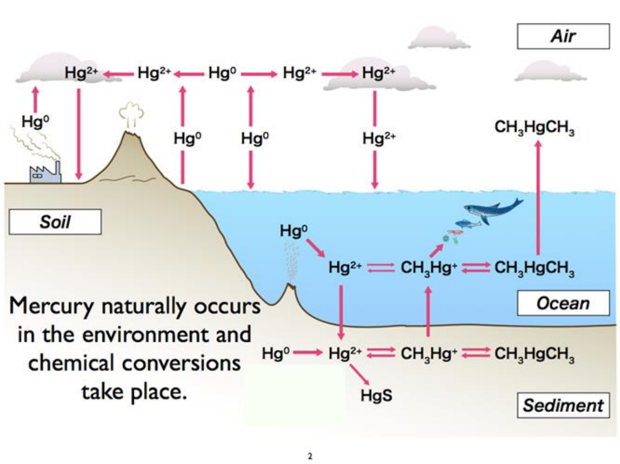
October 18, 2014

NIMD Forum

Seafood for thought:
fish-eating and methylmercury in fish

Hiroshi SATOH, M.D., Ph.D.

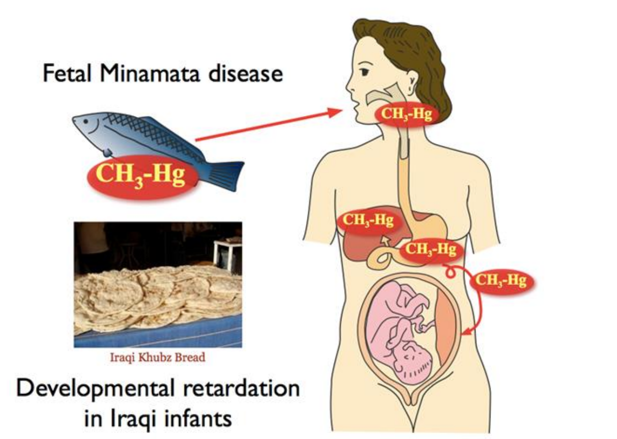
Food Safety Commission
Cabinet Office, Government of Japan



WHO

- **The general population does not face a significant health risk from methylmercury. .... The fetus is at particular risk. .... A prudent interpretation of the Iraqi data implies that a 5% risk may be associated with a peak mercury level of 10-20 μg/g in maternal hair (during pregnancy).**
- **胎児がリスクに曝されている集団**
- **妊娠中のピーク毛髪水銀濃度が10-20 μg/gで5%のリスクがあると考えるのが妥当**

(WHO/IPCS, 1990; Environmental Health Criteria 101 Methylmercury 1990)



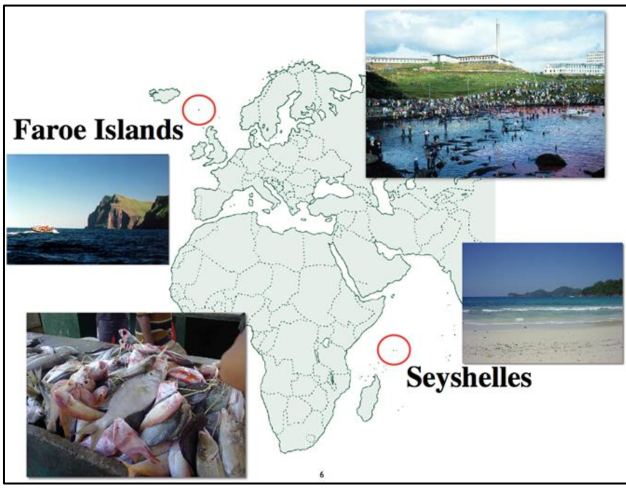
食品安全委員会

Establishment of
Food Safety Commission Japan
(FSCJ, July 1st, 2003)

- Food Safety Basic Act was enforced.
  →based on the simple recognition that the protection of health of our citizen is a top priority
- Introduction of Risk Analysis to food safety administration
- FSCJ was established as a part of Japanese Cabinet Office, independently from risk managing ministries such as MHLW* and MAFF.**

**Ministry of Agriculture, Forestry and Fisheries
*Ministry of Health, Labour and Welfare

- FSCJ's mission is to implement science-based risk assessments in an objective, neutral and impartial manner.



耐容摂取量の算定：Calculation of TWI

Maternal hair mercury during pregnancy not affecting development of children	Blood mercury calculated from the hair mercury (hair/blood)	Intake of mercury estimated by toxicokinetic model (biological half-life)
児に影響をおよぼさない母体の毛髪中水銀濃度	毛髪中濃度から算出した血中水銀濃度	代謝モデルから算出した摂取量

Estimated Intake = 1.167 µg/kg/day

Uncertainty factor = 4 → 0.292µg/kg/day

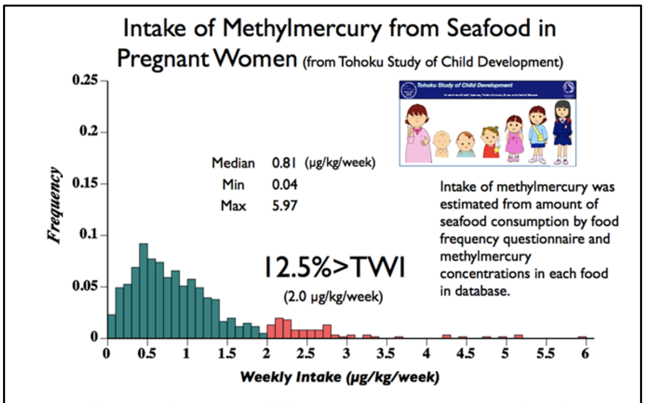
（不確実係数）

耐容週間摂取量（TWI）
Tolerable Weekly Intake   0.292×7 = **2.0µg/kg/week**

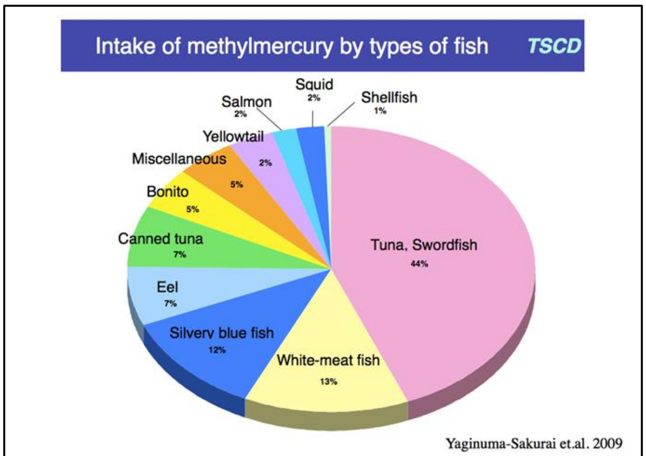
食品安全委員会 Food Safety Commission of Japan

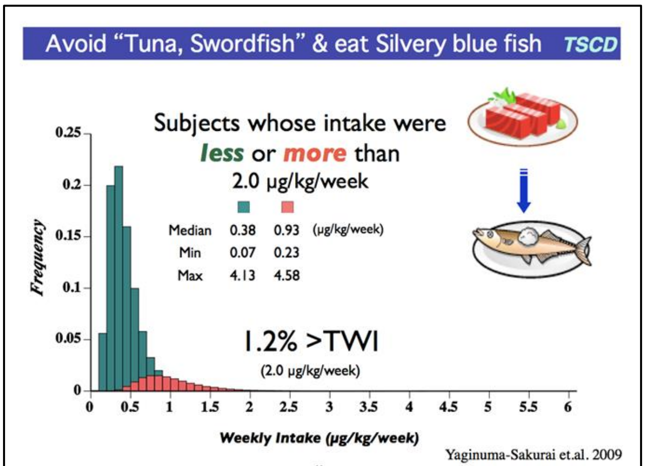
Recommendations for pregnant women to select and eat fish and shellfish
妊婦が注意すべき魚介類の種類とその摂食量の目安

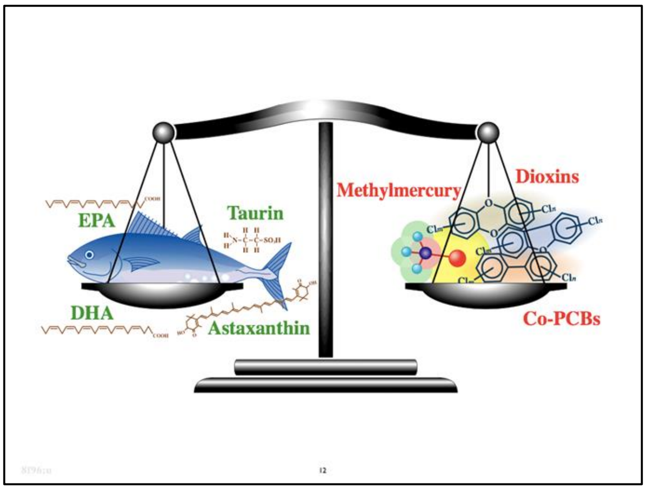
Recommended amount (muscle)	Kind of fish and shellfish	
Up to about 80 grams (average 1 meal) per 2 months (10 grams/week)	Bottlenose dolphin	バンドウイルカ
Up to about 80 grams (1 meal) per 2 weeks (40 grams/week)	Short-finned pilot whale	コビレゴンドウ
Up to 80 grams (1 meal) per week (80 grams/week)	Alfonsino Swordfish Bluefin tuna Bigeye tuna Finely-striate buccinum Baird' beaked whale Sperm whale	キンメダイ メカジキ クロマグロ メバチ(メバチマグロ) エッチュウバイガイ ツチクジラ マッコウクジラ
Up to 160 grams (average 2 meals) per week (160 grams/week)	Yellowback seabream Marlin Hilgendorf saucord Southern bluefin tuna Blue shark Dall's porpois	キダイ クロムツ マカジキ ユメカサゴ ミナミマグロ ヨシキリザメ(筋肉) イシイルカ



Assessment of exposure to methylmercury in pregnant Japanese women by FFQ. Yaginuma-Sakurai et.al. Public Health Nutrition / Volume 12 / Issue 12 / December 2009, 2352 - 2358 (DOI: 10.1017/S1368980009005011)





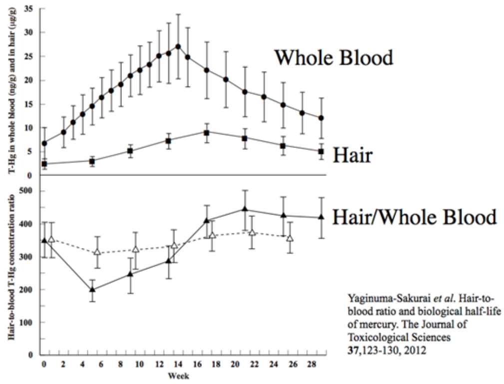


ワンコンパートメントモデルのパラメータに対する不確実性

- 毛髪と血液中水銀濃度の比
- 排泄係数（生物学的半減期）

Uncertainties for parameters of the one-compartment model

1. Ratio between mercury concentrations in hair and blood
2. Elimination constant (Biological half-life)



Yaginuma-Sakurai *et al.* Hair-to-blood ratio and biological half-life of mercury. The Journal of Toxicological Sciences **37**,123-130, 2012

Temporal changes of total mercury (T-Hg) concentrations in whole blood (●) and hair (■) and of hair-to-blood T-Hg concentration ratios in 27 subjects (mean and SD). The symbols of △ and ▲ represent the time lag-adjusted (3 weeks) and unadjusted hair-to-blood ratios, respectively.

Evaluation of methylmercury exposure and health effects in the Mediterranean population

Milena Horvat*, Janja Snoj Tratnik, Darja Mazej, Marta Jagodic, Ingrid Falnoga, Majda Pavlin, Anja Stajnko

***Department of Environmental Sciences, Jožef Stefan Institute, Ljubljana, Slovenia**

Objective: To investigate MeHg exposure, effects, and susceptibility in Mediterranean population in early life.

Methods: PHIME was the largest study ever conducted in the general European population on the impact of Hg through food consumption. It included 1700 mother – child pairs from Italy, Slovenia, Greece and Croatia. Children of the PHIME Mediterranean cohort were tested for neurodevelopment (Bayley III test) at 18 months of age. Mother hair, cord blood, cord tissue and meconium have been sampled at birth, breast milk and mother's hair 1 month after birth. Hair samples have been analysed for mercury, cord blood and breast milk for mercury (and MeHg), cadmium, lead and arsenic, as well as for essential elements (selenium, zinc, copper).

Results: The results of the PHIME Mediterranean cohort have been evaluated, particularly in relation to methyl mercury (MeHg) exposure though fish consumption. Mercury in mother´s hair and in cord blood did not predict Bayley scores but a moderate beneficial effect of fish consumption in pregnancy was observed. Other chemical elements were not associated with the outcome. It was also demonstrated that the ABC transporters appear to play a major role in transport of MeHg across the placenta and accumulation of MeHg during early development. It was shown (1) that in three large Mediterranean birth cohorts the association between maternal fish intake and Hg in cord blood has different magnitudes depending on the children's genotype ABCB1, ABCC1, and ABCC2. The findings strengthen the hypothesis that ABC transporters play a role in mercury transport across the placenta and accumulation of MeHg during early development. As these genes appear to influence MeHg internal dose they might offset MeHg neurotoxicity.

Conclusions: The studies performed so far showed that the environmental neuroepidemiology studies need to include a new focus on genetically susceptible groups in order to assess a more realistic potential risk of neurotoxicant exposures at low levels.

(1)LLOP, Sabrine, SNOJ TRATNIK, Janja, MAZEJ, Darja, HORVAT, Milena, et al. Polymorphisms in ABC transporter genes and concentrations of mercury in newborns - evidence from two Mediterranean birth cohorts. PloS one, 2014, vol. 9/5, e97172-1-e97172-9.

Institut "Jožef Stefan", Ljubljana, Slovenija

PHIME

Evaluation of methyl mercury exposure and health effects in the Mediterranean population

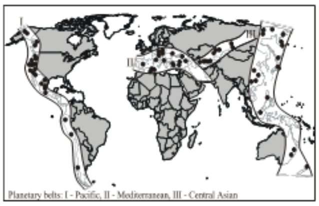
Milena Horvat, Janja Snoj Tratnik, Darja Mazej, Marta Jagodic, Ingrid Falnoga, Majda Pavlin, Anja Stajnko

Department of Environmental Sciences, Jožef Stefan Institute, Ljubljana, Slovenia

Mercury sources

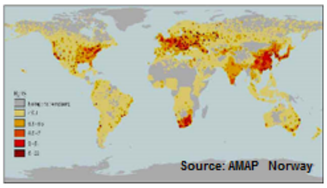
- Natural vs. antropogenic
- Significant increase of Hg globally due to anthropogenic activities
- Most significant releases to the atmosphere, also to waters and land
- Industrial and mining sites
- Land, water and resource management activities can make Hg more bioavailable
- Mercury waste

Natural mercury –planetary Hg belts



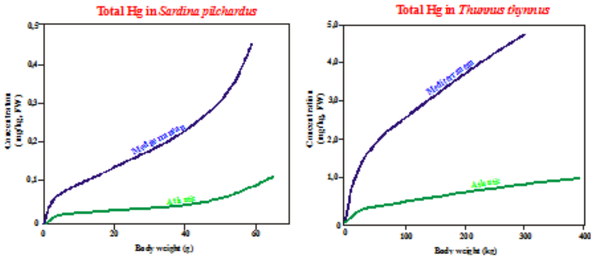
Planetary belts: I - Pacific, II - Mediterranean, III - Central Asian

Spatial global mercury emissions of Hg to air



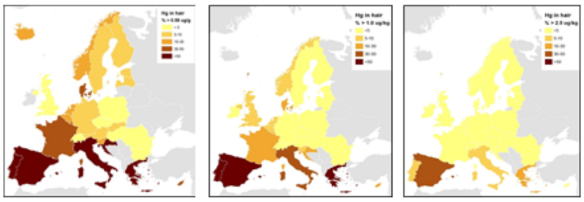
Source: AMAP Norway

MERCURY IN THE MEDITERRANEAN FISH

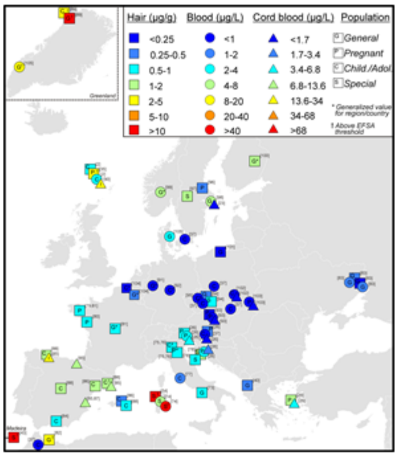


Bernhard et al., 1990

THg in hair – DEMOCOPHES study (based on data from Bellanger et al., 2013)



- Percent of population exceeding 0.58 µg/g, 1.0 µg/g and 2.5 µg/g THg levels in hair
- Exposure assessed on country level from harmonized study
- Only ~120 subjects (mother-children)/country
- Local variations blended



Hg levels in biomarkers (2000-2013)

- 50 studies
- 12.000 individuals included

Miklavčič et al, 2013

Longitudinal cohort study of prenatal exposure to mercury in the Mediterranean region

PHIME

WORK PACKAGE 3

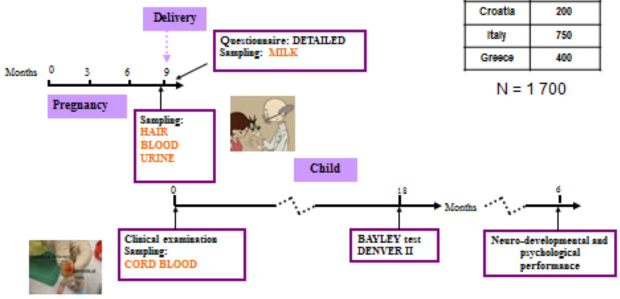
University of Udine, Italy
University Medical Centre Ljubljana, Slovenia
Institute "Jozef Stefan", Slovenia
OIKON Ltd, Croatia
Institute of Child Health, Athens, Greece

Study design

- GENERAL population, random recruitment
- Only healthy pregnant women, living in non-industrial enviornment and non professionaly exposed included

Country	Mother-child pairs
Slovenia	350
Croatia	200
Italy	750
Greece	400

N = 1 700



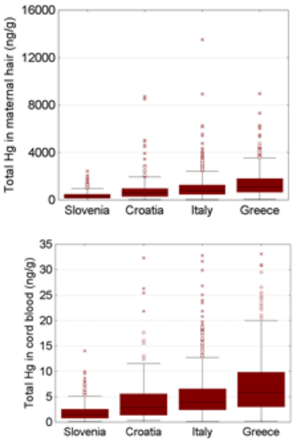
Biochemical analyses

Sample	Analyte
Hair	Total Hg, MeHg (samples above 1 mg/g)
Cord blood	
Whole blood	Total Hg, MeHg (samples above 1 mg/g of hair), Cd, Pb, As, Se, Mn, Cu, Zn, polymorphism
Plasma	Se, Zn
Serum	Fe, Mg, Ca
Milk	Total Hg, MeHg (samples above 1 mg/g of hair), Cd, Pb, As, Se, Mn, Cu, Zn
Cord tissue	Total Hg, MeHg (samples above 1 mg/g of hair)
Meconium	Total Hg, MeHg (samples above 1 mg/g of hair)

THg in maternal hair and umbilical cord blood

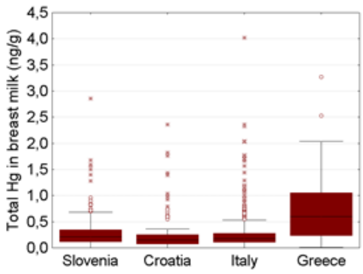
H-THg	*Slovenia*	*Croatia*	*Italy*	*Greece*
n	*574*	*234*	*591*	*454*
Mean	377	851	1032	1440
SD	332	1088	954	1187
Min	15	16	17	55
Median	**287**	**604**	**770**	**1122**
Max	2439	8710	13520	8973
P10	73	137	316	369
P90	780	1806	2016	2764

CB-THg	*Slovenia*	*Croatia*	*Italy*	*Greece*
n	*443*	*209*	*609*	*391*
Mean	1.98	4.29	5.37	7.33
SD	1.73	4.44	4.69	5.83
Min	0.16	0.33	0.12	0.21
Median	**1.62**	**2.84**	**3.88**	**5.81**
Max	14.1	32.3	32.8	33.1
P10	0.46	0.94	1.33	1.68
P90	4.20	9.05	10.7	14.8



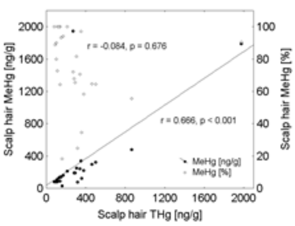
THg and MeHg in breast milk

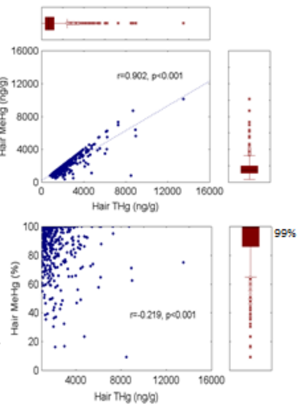
M-THg	*Slovenia*	*Croatia*	*Italy*	*Greece*
n	*272*	*124*	*603*	*33*
Mean	0.28	0.27	0.27	0.75
SD	0.30	0.38	0.33	0.77
Min	0.00	0.00	0.00	0.01
Median	**0.21**	**0.15**	**0.18**	**0.60**
Max	2.86	2.36	4.02	3.27
P10	0.06	0.03	0.07	0.06
P90	0.53	0.66	0.61	1.70



THg vs. MeHg in scalp hair

Pilot study: proportion of Hg as MeHg
20-100 %

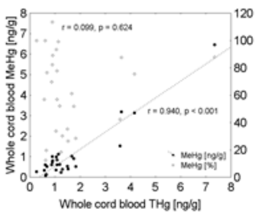


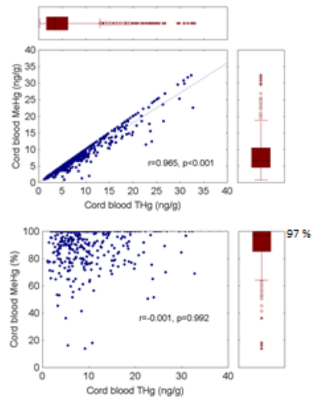


proportion of Hg as MeHg:
9-100 %

THg vs. MeHg in umbilical cord blood

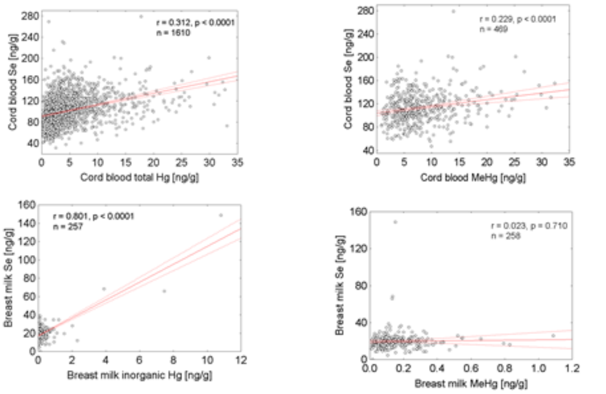
Pilot study: proportion of Hg as MeHg
12-100 %





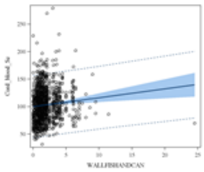
proportion of Hg as MeHg:
14-100 %

Correlation between Hg and Se



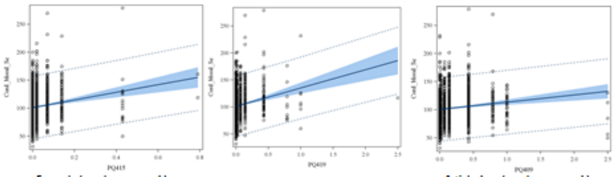
Se vs. dietary items

Fish (meals per week)
r_s = 0.130; p < 0.0001
n = 1355



	SLO	CRO	IT	GR
Fish vs. Hg	0.387	0.455	r=0.397	r=0.229
	p<0.001	p<0.001	p<0.001	p<0.001
Fish vs. Se	0.235	-0.0170	r=0.098	r=0.011
	p<0.001	p=0.817	p=0.020	p=0.850

Cord blood



Fennels (meals per week)
r_s = 0.249; p < 0.0001
n = 1376

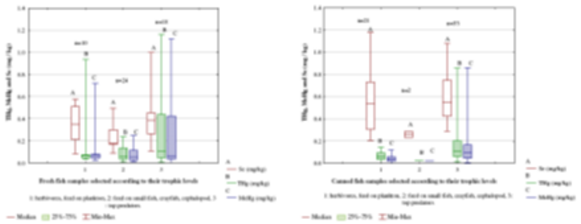
Cheese (meals per week)
r_s = 0.266; p < 0.0001
n = 1380

Artichokes (meals per week)
r_s = 0.214; p < 0.0001
n = 1370

Hg and Se in fish

Fresh fish

Canned fish



(Miklavčič et al, 2011; *Food Chemistry*)

-No significant correlation was found between Se and Hg levels in fish.
-However, an excess of Se in relation to mercury was observed.
-No significant correlation was found between trophic levels and selenium levels of the fresh and canned fish.

Association of THg, fish, and BSID composite cognitive score

	Unadjusted		Adjusted for each other		Adjusted for each other and country		Large model 1[1]		Large model 2[2]	
	beta	p	beta	p	beta	p	beta	p	beta	p
Ln THg hair	-1.6987	<0.0001	-1.8929	<0.0001	0.2152	0.5745	-0.0369	0.9325	0.0614	0.9034
All fish	0.0312	0.8916	0.4398	0.0651	0.3399	0.1325	0.3917	0.1423	0.5645	0.0701
Model R^2 (N)			0.02 (N=1127)		0.14 (N=1127)		0.17 (N=959)		0.21 (N=689)	
Ln cord blood THg	-1.8344	<0.0001	-2.1121	<0.0001	0.0080	0.9847	-0.2521	0.5947	-0.2524	0.6472
All fish	0.0312	0.8916	0.5685	0.0358	0.4675	0.0677	0.6667	0.0261	0.9312	0.0084
Model R^2 (N)			0.03 (N=945)		0.15 (N=945)		0.19 (N=806)		0.23 (N=571)	

[1]Adjusted for country, mother's age at delivery, pre-pregnancy B;I, weight gain, cigarettes smoked, alcohol intake, dental visits, dental work, marital status of mother, home area, home ownership, number of children in family, parental education, sex of child, birth weight.
[2]Adjusted for the same variable as above plus daycare attendance at 18 months, child's intake of fresh and homogenized fish at 18 months, breastfeeding, its length, and exclusiveness up to 4 months.
❑ Similar estimates were obtained using all seafood instead of all fish.
❑ Analyses stratified by sex showed no difference in the estimates of the effects of Hg (whereas a significant positive association with fish intake was only found among males).

Association of THg, fish, and BSID composite language score

	Unadjusted		Adjusted for each other		Adjusted for each other and country		Large model 1[1]		Large model 2[2]	
	beta	p	beta	p	beta	p	beta	p	beta	p
Ln THg hair	-0.9695	0.0113	-1.3497	0.0007	0.5882	0.1636	0.4505	0.3367	1.1992	0.0255
All fish	0.5740	0.0217	0.8608	0.0010	0.5248	0.0349	0.7879	0.0067	0.7752	0.0189
Model R^2 (N)			0.01 (N=1127)		0.12 (N=1127)		0.21 (N=959)		0.23 (N=689)	
Ln cord blood THg	-1.0442	0.0131	-1.4996	0.0007	0.2908	0.5322	0.1009	0.8450	0.3264	0.5809
All fish	0.5740	0.0217	0.9322	0.0018	0.6024	0.0344	0.9504	0.0036	1.0489	0.0056
Model R^2 (N)			0.02 (N=945)		0.12 (N=945)		0.21 (N=806)		0.24 (N=571)	

[1]Adjusted for country, mother's age at delivery, pre-pregnancy B;I, weight gain, cigarettes smoked, alcohol intake, dental visits, dental work, marital status of mother, home area, home ownership, number of children in family, parental education, sex of child, birth weight.
[2]Adjusted for the same variable as above plus daycare attendance at 18 months, child's intake of fresh and homogenized fish at 18 months, breastfeeding, its length, and exclusiveness up to 4 months.
❑ Similar estimates were obtained using all seafood instead of all fish.
❑ Analyses stratified by sex showed no difference in the estimates of the effects of Hg (whereas a significant positive association with fish intake was only found among males).

Association of THg, fish, and BSID composite motor score

	Unadjusted		Adjusted for each other		Adjusted for each other and country		Large model 1[1]		Large model 2[2]	
	beta	p	beta	p	beta	p	beta	p	beta	p
Ln THg hair	-1.5641	<0.0001	-1.6444	<0.0001	-0.3548	0.2211	-0.2569	0.4337	0.0100	0.9783
All fish	-0.1516	0.3832	0.1820	0.3110	-0.0480	0.7786	0.0152	0.9396	0.1640	0.5205
Model R^2 (N)			0.03 (N=1127)		0.14 (N=1127)		0.16 (N=959)		0.19 (N=689)	
Ln cord blood THg	-1.4829	<0.0001	-1.6419	<0.0001	-0.3797	0.2316	-0.3336	0.3535	-0.3266	0.4141
All fish	-0.1516	0.3832	0.3254	0.1116	0.0825	0.6703	0.1888	0.4057	0.3555	0.1644
Model R^2 (N)			0.03 (N=945)		0.15 (N=945)		0.17 (N=806)		0.21 (N=571)	

[1]Adjusted for country, mother's age at delivery, pre-pregnancy B;I, weight gain, cigarettes smoked, alcohol intake, dental visits, dental work, marital status of mother, home area, home ownership, number of children in family, parental education, sex of child, birth weight.
[2]Adjusted for the same variable as above plus daycare attendance at 18 months, child's intake of fresh and homogenized fish at 18 months, breastfeeding, its length, and exclusiveness up to 4 months.
❑ Similar estimates were obtained using all seafood instead of all fish.
❑ Analyses stratified by sex showed no difference in the estimates of the effects of Hg.

Bayley III composite scores

BSID III composite score	N	Mean	STD	25th percentile	Median	75th percentile	Min	Max
Cognitive	1146	106.6	11.1	100	105	115	65	145
Language	1146	100.2	12.1	91	100	109	47	141
Motor	1146	102.3	8.4	97	103	107	61	139

BSID III composite score	Italy[1]		Slovenia		Croatia		Greece	
	Mean	Median	Mean	Median	Mean	Median	Mean	Median
Cognitive	106.3	105	114.1	115	107.6	105	101.5	100
Language	97.7	97	106.0	106	108.2	109	97.4	97
Motor	101.5	100	106.2	107	108.4	107	98.8	100

[1]Inter-rater reliability in Italy (2 testers): ICC=0.98 (0.97-0.99) for cognitive, 0.99 (0.99-1.00) for language, and 0.93 (0.90-0.97) for motor composite scores.

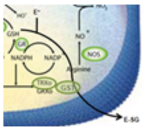
- p-value of Kruskal-Wallis test for BSID cognitive score across countries <0.0001
- p-value of Kruskal-Wallis test for BSID language score across countries <0.0001
- p-value of Kruskal-Wallis test for BSID motor score across countries <0.0001

Conclusions regarding Bayley testing and Hg from fish consumption (F. Valent; UNIUD)

- **In models adjusted for country and other potential confounders, Hg in hair and cord blood was NOT associated with BSID III composite scores.**
- **Nevertheless, a moderate but significant beneficial effect of fish consumption in pregnancy was observed for cognitive and language development.**
- Such effect may be due to PUFAs contained in fish. This hypothesis will be tested when the concentrations of PUFAs in the blood of the women is available (biochemical analyses are underway).

Glutathione S-transferase: GSTT1/GSTM1 gene deletion polymorphisms

- Glutathione (GSH) conjugation to electrophilic compounds **(inorganic Hg, MeHg)**
- ***GSTT1*** deletion and ***GSTM1*** deletion → lack of enzyme activity
- Ref: *Environmental Health Perspectives 2010****
- No GST-genetic studies have been done related to MeHg levels



Interaction between *GSTM1/GSTT1* Polymorphism and Blood Mercury on Birth Weight

Bo-Eun Lee,[1] Yun-Chul Hong,[2] Hyesook Park,[1] Mina Ha,[3] Bon Sang Koo,[4] Namsoo Chang,[5] Young-Man Roh,[6] Boong-Nyun Kim,[7] Young-Ju Kim,[8] Byung-Mi Kim,[1] Seong-Joon Jo,[9] and Eun-Hee Ha[1]

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Polymorphisms in ABC Transporter Genes and Concentrations of Mercury in Newborns – Evidence from Two Mediterranean Birth Cohorts

Sabrina Llop[1,2], Karin Engström[3], Ferran Ballester[1,2,4], Elisa Franforte[3], Ayman Alhamdow[3], Federica Pisa[5], Janja Snoj Tratnik[6], Datja Mazej[6], Mario Murcia[1,2], Marisa Rebagliato[2,7], Mariona Bustamante[2,8,9,10], Jordi Sunyer[2,8,9,11], Aikaterini Sofianou-Katsoulis[12], Alexia Prasouli[12], Eleni Antonopoulou[12], Ioanna Antoniadou[12], Sheena Nakou[12], Fabio Barbone[5], Milena Horvat[6], Karin Broberg[3,13]

- two birth cohort studies conducted in Spain (INMA), Italy and Greece (PHIME)
- ***ABCB1*** rs2032582, ***ABCC1*** rs11075290, and ***ABCC2*** rs2273697 modified the associations between maternal fish intake and cord blood mercury concentrations - *stronger association between maternal fish intake and cord blood mercury concentrations was shown*
- The **ABC transporters** appear to play a major role in transport of MeHg across the placenta and accumulation of MeHg during early development

Llop S, Engström K, Ballester F, Franforte E, Alhamdow A, et al. (2014) Polymorphisms in ABC Transporter Genes and Concentrations of Mercury in Newborns – Evidence from Two Mediterranean Birth Cohorts. PLoS ONE 9(5): e97172. doi:10.1371/journal.pone.0097172

CROME-LIFE

Protocol for the CROME **Cross-Mediterranean study**

BACKGROUND:

Epidemiological studies have demonstrated the developmental neurotoxicity is associated with prenatal MeHg exposure (Grandjean and Landrigan, 2006); however, susceptibility to MeHg toxicity may be modified by **genetic factors** (Julvez and Grandjean, 2013).

ORIGINAL ARTICLE

Prenatal Methylmercury Exposure and Genetic Predisposition to Cognitive Deficit at Age 8 Years

Jordi Julvez,[a,b] George Davey Smith,[c] Jean Golding,[d] Susan Ring,[e] Beate St. Pourcain,[c] Juan Ramon Gonzalez,[b] and Philippe Grandjean[a,f]

Epidemiology • Volume 24, Number 5, September 2013

- Avon Longitudinal Study of Parents and Children (Bristol, UK)
- 247 single-nucleotide polymorphisms (SNPs) within relevant genes
- Wechsler Intelligence Scale for Children Intelligence Quotient (IQ) scores at age 8 years

- Possible genetic predisposition to MeHg neurotoxicity in a substantial proportion of the population!
- Among 40 SNPs showing nominally significant main effects, MeHg interactions were detected for **paraoxonase 1** and **progesterone receptor** ($P < 0.05$) and for **transferrin** and **brain-derived neurotrophic factor** ($P < 0.10$)

Gene mutations affecting absorption-distribution-metabolism-elimination

Gene	Role	Reference
GCL (glutamyl-cystein ligase) - catalytic subunit **GCLC** - modifier subunit **GCLM**	rate-limiting enzyme for GSH synthesis	GCLC and GCLM polymorphism affecting retention of MeHg (Schlawicke et al., 2008; Barcelos et al., 2013); GCLS rs1555903 – Hg retention in umbilical cord (Julvez et al., 2013)
GST (glutathione-S-transferase)	catalyse conjugation of GSH	GSTP1 and GSTM1 polymorphism (Schlawicke et al., 2008; Barcelos et al., 2013)
Other **glutathione related genes…**		
MT (metallothionein)	metal-binding (regulation of metal homeostasis), protection against oxidative stress)	*MT2A* rs10636 - main effect on general cognitive functioning (Julvez et al., 2013).
ABC transporters (ABCC1, ABCC2, ABCB1)	Responsible for active transport of various compounds across biological membranes incl. therapeutical drugs and xenobiotics	Llop et al, 2014 (submitted): ABC transporters play a role in mercury transport across the placenta and accumulation of MeHg during early development

Gene mutations affecting neuropsychological performance:

Gene	Role	Reference
CPOX4 *(coproporphyrinogen oxidase)*	related to brain development and neurotransmitter metabolism (MeHg could interact to their receptors) (Echeverria et al., 2006;)	deficits in neuropsychological performance (Echeverria et al., 2006); modifying general cognitive function (Julvez et al., 2013); *CPOX4* rs1131857 – Hg in urine and child neurodevelopment
APOE (apolipoprotein)	a protein transporter expressed in the brain; Epsilon4 allele associated with poor neural repair function (a risk factor for AD)	APOE variants modified the adverse effects of cord blood Hg on neurodevelopment (Ng et al., 2013).
BDNF (brain-derived Neurotrophic Factor)	related to brain development and neurotransmitter metabolism (methylmercury could interact to their receptors) (Echeverria et al., 2006;)	modifying the MeHg-outcome associations with cognitive deficits in children with the minor alleles (mutations).
PGR (progesterone receptor)	*same*	
PON1 (Paraoxonase 1)	enzyme that inhibits oxidation of lipoproteins through hydrolysis of lipid peroxides. Such oxidative damage can be induced by MeHg (Ayotte et al, 2011; Hernández et al., 2009).	
TF (transferrin)	Iron uptake (Woods et al., 2013)	

The way forward …

- Existing birth cohorts: **Slovenia, Croatia, Italy, Greece (PHIME) and Spain (INMA)**
- **Follow-up** at 6-7 years of age:
  Hair and urine sampling & saliva sampling
- Analyses of **trace elements**
- **Neuropsychological testing**
  (*Wechsler Intelligence Scale for Children*)
- **Genotyping**: GSTT1/GSTM, GSTM3, GSR, GPX1, SOD1, SOD2, CAT, **PON1, BDNF, PGR, TF… ?**

Key publications

- Valent F, Horvat M, Sofianou-Katsoulis A, Spiric Z, Mazej D, Little D, Prasouli A, Mariuz M, Tamburlini G, Nakou S, Barbone F, 2013. **Neurodevelopmental effects of low-level prenatal mercury exposure from maternal fish consumption in a Mediterranean cohort: study rationale and design.** J Epidemiol. 23(2): 146-52.
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Technical Report:

- Project no. FOOD-CT-2006-016253. PHIME **Public health impact of long-term, low-level mixed element exposure in susceptible population strata.** Instrument: Integrated Project. Thematic Priority: Priority 5, Food Quality and Safety.

Thank you for your attention

ありがとうございます

Relationship Between Paraoxonase-1 (PON1) and Metal Concentrations in the Whole Blood of Inuit in Canada

Brian D. Lairda, Alexey B. Goncharovb, Pierre Ayottec, Laurie Hing Man Chana*

*** *University of Ottawa, Canada***

Objective: This cross-sectional study aimed to determine whether environmental exposure to various metals is associated with paraoxonase-1 (PON1) activity in Inuit people routinely exposed to mercury (Hg), cadmium (Cd), lead (Pb), and (Se) selenium.

Methods: PON1 activity and metal concentrations were measured in blood collected from 2172 healthy participants. Sociodemographic, anthropometric and lifestyle variables were also assessed. The associations between PON1 activity and blood metal concentrations, HDL, omega-3 fatty acid blood levels, age, sex, body mass index (BMI), and lifestyle habits (eg. smoking and alcohol consumption) were explored via multiple linear regression.

Results: PON1 activity was positively associated with Se blood concentration ($\beta = 0.056$, $P = 0.001$) but was negatively associated with Cd blood concentration ($\beta = -0.025$, $P < 0.001$). No association was observed between PON1 activity and Hg or Pb blood concentrations.

Conclusions: Our results suggest that PON1 activity is modulated by metal exposure, and Inuit traditional foods may confer health benefit by increasing PON1 activity via higher Se intakes. These findings underline that current environmental metal exposures among Inuit living in the Canadian Arctic are associated with paraoxonase activity, a toxicologically-relevant biochemical parameter.

Relationship between PON1 and metal concentrations in the whole blood of Inuit in Canada

Laurie Hing Man Chan, Ph.D.

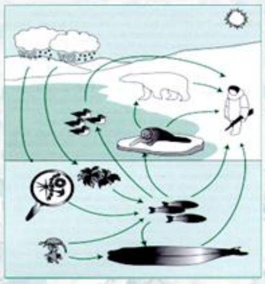
Professor and Canada Research Chair in Toxicology and Environmental Health

University of Ottawa

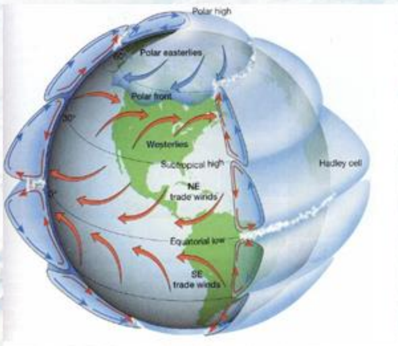
Inuit or Eskimos

Cultural Groups	Country	Populations
Yupik	Alaska	25,000
	Russia	45,000
Inupiat	Alaska	50,000
	Russia	2,000
Inuit	Canada	50,000
	Greenland	55,000
Total		227,000

Fish and Marine mammals are very important part of the Inuit diet



Long Range Transport of Global Pollutants



Mercury from Asia reaching Canada and the Arctic by air currents

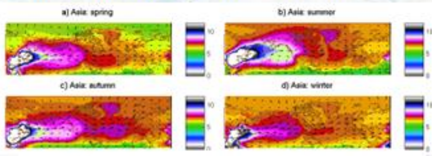


Table 4. Statistics pertaining to the number of long range transport events recorded over all verification stations over a year.

Source region	Median	75th percentile	Maximum
Asia	38	52	61
North America	11	14	25
Russia	20	24	33
Europe	1	5	27

Durnford et al. Atmos Chem Phys 10:6063-6086, 2010

Increasing Contaminant Burdens in an Arctic Fish, Burbot (*Lota lota*), in a Warming Climate

J. CARRIE, F. WANG, H. SANEI, R. W. MACDONALD, P. M. OUTRIDGE, AND G. A. STERN

Environ. Sci. Technol. **2010**, 44, 316–322

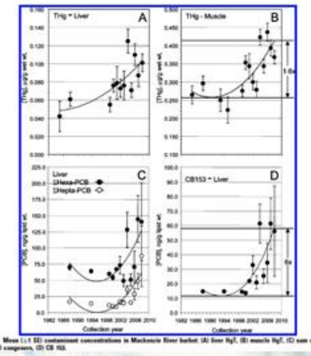
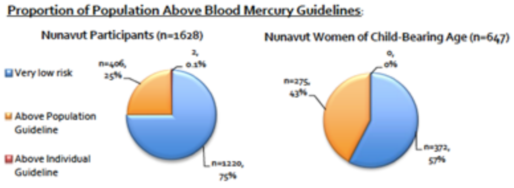


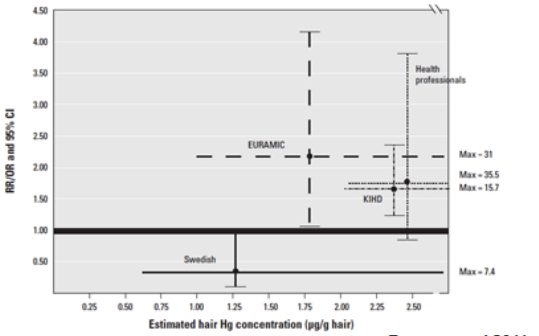
FIGURE 2. Mean (±1 SE) contaminant concentrations in Mackenzie River burbot: (A) liver HgT, (B) muscle HgT, (C) sum of hexa- hepta-PCB congeners, (D) CB 153.

Elevated levels of mercury were found especially among women of child bearing age



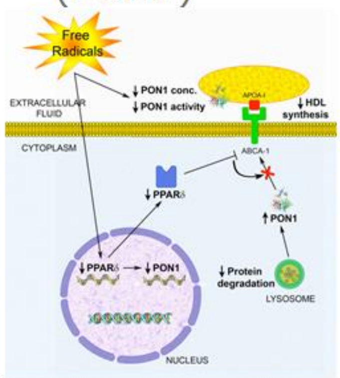
Mercury mainly affects brain development

MeHg and Cardiovascular diseases



Roman et al 2011

Serum paraoxonase 1 (PON1)



- a major anti-atherosclerotic component of high-density lipoprotein (HDL)
- The PON1 gene is activated by PPAR-γ, which increases synthesis and release of paraoxonase 1 enzyme from the liver, reducing atherosclerosis

PON1 is inversely associated with increased risk of cardiovascular disease

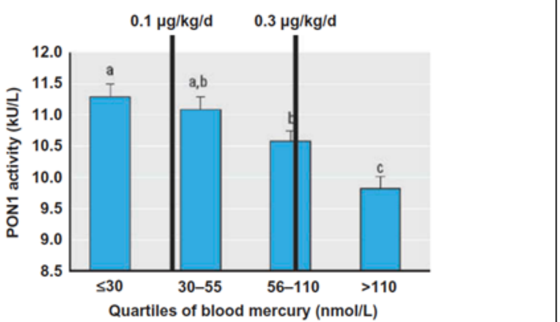
TABLE 1. Cardiovascular Events in Relation to Baseline PON1 Activity After 3-Year Follow-up[1]

PON1 baseline activity (nmol/ml/min)	Quartile 4 >1640	Quartile 3 899–1640	Quartile 2 450–899	Quartile 1 <450
N (overall)	315	325	326	311
Adjusted HR[a] for MI/CVA (95% CI)	1.0	2.9 (1.3–6.4)	3.1 (1.4–7.0)	4.4 (2.0–9.6)
n (no CVD at baseline)	80	61	57	56
Adjusted HR for first cardiovascular event	1.0	0.6 (0.1–3.1)	1.2 (0.3–5.3)	1.7 (0.5–6.4)

Note. Adapted from Bhattacharyya et al. (2008). Quartile 4, the reference group contains the greatest PON1 activity at baseline. Abbreviations: PON1, paraoxonase-1; HR, hazard ratio; MI, myocardial infarction; CVA, cerebrovascular accident; CVD, cardiovascular disease.

[a]Hazard ratio adjusted for a variety of traditional cardiovascular risk factors including diabetes status, C-reactive protein, body mass index, and medication use.

Previous study has shown MeHg is negatively associated with PON1



Ayotte et al 2001

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journal homepage: www.elsevier.com/locate/chemosphere

Relationship between the esterase paraoxonase-1 (PON1) and metal concentrations in the whole blood of Inuit in Canada

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Inuit Health Survey 2007 and 2008

34 communities participated

1800 participants

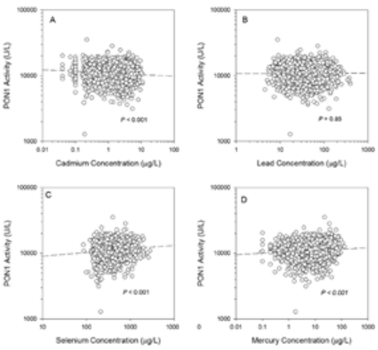
Blood PON1 and metals were measured in 2172 participants

Table 1
Descriptive statistics of the demographic study variables, paraoxonase (PON1) activity, and metal concentrations in adult participants of the International Polar Year Inuit Health Survey 2007–2008.

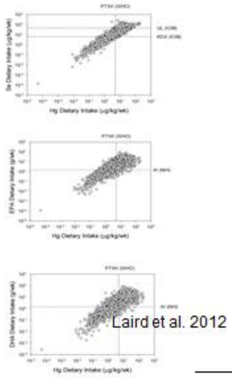
Covariates	n	Range	Geometric mean (95% CI)	Mean ± SD	Median (IQR)
Age (y)	2595	18–100	39.4 (38.9–40.0)	42.1 ± 15.2	41.0 (30.0–52.0)
BMI[a] (kg m^{-2})	2178	16.2–62.6	27.7 (27.4–27.9)	28.3 ± 6.5	27.4 (23.3–32.3)
Sex[b] (% female)	2595	–	–	61.5 ± 48.6	–
Smoking[c] (% yes)	2206	–	–	94.3 ± 23.1	–
Alcohol[d] (% yes)	2035	–	–	61.4 ± 48.6	–
HDL (mmol L^{-1})	2200	0.39–4.8	1.43 (1.41–1.45)	1.5 ± 0.5	1.4 (1.2–1.8)
Omega-3 (% fatty acid)	2201	0.14–22.2	4.6 (4.4–4.7)	5.8 ± 3.4	5.4 (3.3–7.7)
PON1 (U/L)	2214	1290–35 400	10900 (10800–11000)	11 300 ± 2960	11 100 (9330–13000)
Mercury (µg L^{-1})	2172	0.09–130	7.0 (6.6–7.3)	12.6 ± 14.0	7.8 (3.2 -17)
Cadmium (µg L^{-1})	2172	0.039–11	1.6 (1.5–1.7)	2.6 ± 2.0	2.5 (0.69–3.8)
Lead (µg L^{-1})	2172	4.5–400	35 (34–36)	46.8 ± 39.6	35 (20–61)
Selenium (µg L^{-1})	2172	85–2800	319 (312–327)	381 ± 281	280 (210–450)

[a] Body mass index.
[b] Dichotomous variable: 0 = Male; 1 = Female.
[c] Dichotomous variable: 0 = Never-smoker; 1 = Ever-Smoker.
[d] Dichotomous variable: 0 = No alcohol consumption in past 12 months; 1 = Alcohol consumption in past 12 months.

PON1 increased with Hg and Se and decreased with Cd



Risk-Benefit Assessment



Se has a strong effect on increase of PON1

Table 4
Stepwise multiple regression analysis of $\log_{10}$-transformed paraoxonase (PON1) activity on mercury and selenium blood concentrations for adult participants ($n = 2172$) of the International Polar Year Inuit Health Survey with adjustment for demographic and clinical variables.[a]

	β ± SE	*P*-value
Mercury[b]	0.0002 ± 0.0082	0.980
Selenium[b]	0.056 ± 0.017	0.001
Age	−0.040 ± 0.019	0.0328
BMI	0.189 ± 0.030	<0.0001
HDL	0.221 ± 0.0220	<0.0001
Alcohol	0.013 ± 0.0064	0.0043
Sex	0.012 ± 0.0064	0.0514

[a] Demographic and clinical variables inputted stepwise in the model included high-density lipoprotein (HDL), erythrocyte omega-3, age, sex, body mass index (BMI), smoking status, and alcohol consumption.
[b] Blood metal concentrations constrained in the model.

Everybody loves their food!

Why do we care about the Arctic?

Acknowledgements

All Aboriginal organizations and participating communities

Northern Contaminants Program
ArcticNet
CIHR IRSC
NSERC CRSNG

Methylmercury exposure and neurological outcomes by ingesting whale meat

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Background: Methylmercury (MeHg) is a major environmental neurotoxicant that causes damage to the central nervous system. In Japan, industrial emission of MeHg has resulted in MeHg intoxication in Minamata and Niigata, the so-called Minamata disease. Humans are exposed to MeHg derived from natural sources, primarily fish and fish predators. Therefore, MeHg continues to be an environmental risk to human health, particularly in susceptible populations that frequently consume substantial amounts of fish or fish predators such as whale.

Objective: This study aimed to investigate the health effects (especially neurological abnormalities) of MeHg exposure in adults.

Methods: The subjects were 194 residents (117 males, 77 females; age 20–85 years) who resided in the coastal town of Taiji, the birthplace of traditional whaling in Japan. We analyzed hair for mercury content and performed detailed neurological examinations and dietary surveys. Audiometry, magnetic resonance imaging, and electromyography were performed to diagnose neurological defects. Whole blood mercury and selenium (Se) levels were measured in 23 subjects.

Results: The geometric mean of the hair mercury levels was 14.9 μg/g. Twelve subjects revealed hair mercury levels >50 μg/g (NOAEL) set by WHO. Hair mercury levels significantly correlated with daily whale meat intake. These results suggested that residents in Taiji were highly exposed to MeHg by ingesting MeHg-contaminated whale meat. Multivariate regression analysis demonstrated no significant correlations between hair mercury levels and neurological outcomes, whereas some of the findings significantly correlated with age. A significantly positive correlation between whole blood mercury and Se levels was observed and the whole blood mercury/Se molar ratios of all subjects were <1.

Conclusions: We investigated the health effects of MeHg exposure in 194 adult Taiji residents who were considered to be highly exposed to MeHg by ingesting MeHg-contaminated whale meat. No significant correlations were determined between hair mercury levels and neurological outcomes. The results of whole blood mercury/Se molar ratios of all subject suggests that sufficient Se intake might be one of causes of the absence of adverse effects of MeHg exposure in this study.

NIMD

Methylmercury exposure and neurological outcomes by ingesting whale meat

National Institute for Minamata Disease

Masaaki Nakamura

Background

1. WHO has announced in 1990 that a hair mercury level of 50–125 ppm corresponds to "no observed adversary effect level" (NOAEL) of MeHg for adults.

2. Afterwards, however, there have been some reports (Amazonian studies) suggesting the possible MeHg intoxication in adults whose hair mercury levels are below 50 ppm.

↓

The threshold level that MeHg toxicity elicits in adults is still controversial.

Taiji

- The birthplace of traditional whaling in Japan
- The majority of the townsman engaged in whaling and whaling-related work in the past.

Taiji

Purpose

This study aimed to investigate the health effects of MeHg exposure in adults.

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High mercury levels in hair samples from residents of Taiji, a Japanese whaling town

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ARTICLE INFO

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Short-finned pilot whale (Globicephala macrorhynchus)
Yellowfin tuna
Albacore

ABSTRACT

We investigated the mercury concentrations in red meat from pilot whales consumed by some residents of the Japanese whaling town, Taiji, and in hair samples from 50 residents for their maker of mercury burden. The methyl mercury (M-Hg) level in the red meat was 5.9 μg/wet g, markedly higher than the US FDA action level and Cordex Alimentarius guideline level for predatory fish (1.0 μg/wet g). The average level of total mercury (T-Hg) in the hair from residents who ate whale meat more than once a month was 24.6 μg/g, whereas the average from the residents who did not consume any whale meat was 4.3 μg/g. The T-Hg concentrations in the hair from three donors exceeded 50 μg/g, the level for NOAEL set by WHO. The T-Hg level found in the Taiji whale meat consumers was markedly higher than that observed in the Japanese population overall (about 2 μg/g).

Methods- 1

1) receding hair mercury survey: 724 residents (344 males and 380 females)

2) Detailed neurological examination

a) Objects:194 residents (117 males and 77 females)

b) Dietary survey

c) Neurological examination: three certified neurologists, authorized by the Japanese Society of Neurology

d) Detailed examination: audiometry: 32 subjects
MRI: brain: 8 subjects;
cervical: 10 subjects;
lumbar: 9 subjects)
EMG: 24 subjects

Methods- 2

3) Analysis of health consequence by MeHg

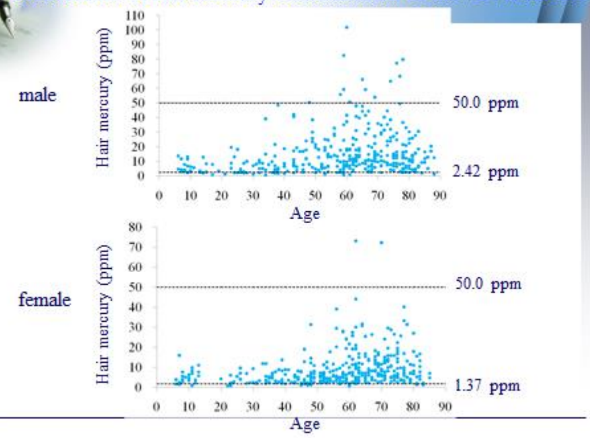
   a) Clinical evaluation

   b) Associations between the neurological outcomes and hair mercury concentration, age and gender

   c) Detailed assessment of 12 residents whose mercury concentrations were over 50 ppm, the level for NOAEL set by WHO

4) Assessment of whole blood mercury and Se (n=23)

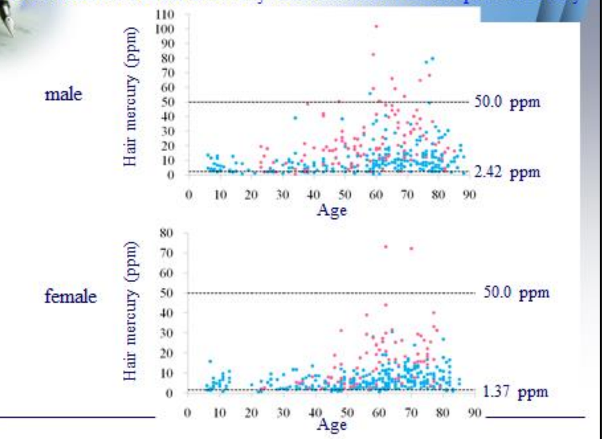
Distribution of hair mercury concentration of the 724 residents



Distribution of hair mercury concentration of the 724 residents

Gender	male	female	total
N	344	380	724
Age (years)			
Min	6	6	6
Max	88	92	92
Arithmetic mean	57.5	56.4	56.9
Hair mercury (μg/g)			
Min	0.6	0.7	0.6
25 Percentile	5.1	3.5	4.0
Median	10.6	5.9	7.7
75 Percentile	19.5	11.0	14.6
Max	101.9	73.1	101.9
Geometric mean	10.0	6.2	7.8
Hair mercury ≧ 50 μg/g (N)	14	2	16

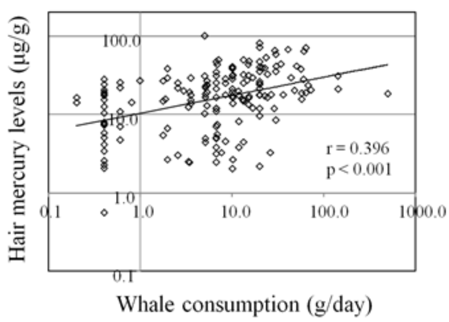
Distribution of hair mercury concentration of the present study



Distribution of hair mercury concentration of the present study

Gender	male	female	total
N	117	77	194
Age (years)			
Min	20	24	20
Max	85	79	85
Arithmetic mean	56.7	59.5	57.8
Hair mercury (μg/g)			
Min	1.1	2.1	1.1
25 Percentile	11.1	5.9	7.9
Median	18.7	15.1	17.8
75 Percentile	32.7	24.3	28.7
Max	101.9	73.1	101.9
Geometric mean	17.2	12.1	14.9
Hair mercury ≧ 50 μg/g (N)	10	2	12

Relative distributions of daily whale meat consumption and hair mercury levels



Summary of neurological findings

- We determined 35 clinical endpoints.
- Audiometry (32 subjects)
  - ⇒ sensorineural hearing loss (10 subjects)
- MRI: cervical: 10 subjects
  - lumbar: 9 subjects
- EMG: 24 subjects
  - ⇒ sensory disturbances were peripheral origin (radiculopathy or peripheral neuropathy)
- Brain MRI (8 subjects)
  - ⇒ old cerebral infarction (4 subjects)

Associations of neurologic findings with hair mercury concentrations, age and gender

A. Correlation with log transformed hair mercury concentration

Neurological findings		Age	Male (femal as a referent)	Hair mercury concentration Log (ppm)
		Adjusted odds ratios or adjusted regression coefficients* (95% confidence intervals if calculated)		
Cranial nerve	Saccadic pursuit	1.24 (0.79,1.96)	0.00 (0.00, –)	59.6 (0.008, 4.24×10^{8})
	Sensorineural hearing loss	1.05 (1.00, 1.10)	1.56 (0.44, 5.49)	1.22 (0.22, 6.89)
	Dysarthria	0.14 (0.87, 1.25)	9.49×10^{8} (0.00, –)	6.74 (0.005, 1.55×10^{4})
Muscular weakness	Upper limb	0.94 (0.86, 1.03)	0.13 (0.010, 1.65)	3.37 (0.13, 85.7)
	Lower limb	1.02 (0.91, 1.14)	0.12 (.010, 1.31)	47.7 (0.77, 2950)
Tremors	Resting	0.95 (0.82, 1.10)	0.00 (0.00, –)	11.1 (0.012, 1.04×10^{4})
	Kinetic	1.13 (0.85, 1.50)	6.49×10^{8} (0.00, –)	26.3 (0.003, 2.11×10^{5})
	Postural	1.12 (1.04, 1.21) **	1.10 (0.29, 4.21)	2.63 (0.031, 22.2)
Rigidity		1.24 (0.79, 1.96)	0.00 (0.00, –)	59.6 (0.008, 4.24×10^{8})
Coordinated movements	Diadochokinesis	1.25 (1.03, 1.51) *	1.32 (0.12, 15.0)	16.6 (0.22, 1280)
	Finger-to-nose test	1.19 (0.98, 1.44)	3.35×10^{7} (–)	3.22 (0.03 413)
	Heel-knee test	1.12 (1.03, 1.21) **	5.14 (0.57, 46.2)	0.67 (0.07, 6.61)
	Knee tapping test	1.11 (1.00, 1.24)	4.86×10^{7} (–)	4.87 (0.14, 172)
One foot standing	Right foot < 5s	1.12 (1.02, 1.23) *	1.36 (0.23, 8.15)	1.97 (0.14, 27.3)
	Right foot < 15s	1.11 (1.06, 1.16) ***	0.70 (0.30, 1.67)	2.05 (0.58, 7.25)
	Left foot < 5s	1.11 (1.02, 1.21) *	0.64 (0.15, 2.76)	2.55 (0.25, 25.9)
	Left foot < 15s	1.12 (1.07, 1.17) ***	0.83 (0.35, 1.97)	1.87 (0.53, 6.59)
Simple gait		1.11 (0.98, 1.25)	1.65 (0.16, 16.7)	31.1 (0.56, 1740)
Tandem gait		1.23 (1.03, 1.48) *	3.22×10^{7} (–)	5.60 (0.08, 392)
Reflex	Upper limb	1.05 (1.02, 1.08) **	2.84 (1.25, 6.45) *	1.04 (0.36, 2.99)
	Lower limb	1.05 (1.02, 1.09) **	1.67 (0.77, 3.65)	1.22 (0.42, 3.57)
	Babinski	1.15 (0.96, 1.35)	0.36 (0.043, 3.36)	11.2 (0.16, 681)
	Chaddock	1.15 (0.96, 1.35)	0.36 (0.043, 3.36)	11.2 (0.16, 681)
Touch sensation		1.07 (1.03, 1.12) **	1.58 (0.53, 4.65)	0.55 (0.13, 2.39)
Pain sensation		1.06 (1.02, 1.10) **	1.03 (0.40, 2.66)	0.79 (0.21, 3.02)
Position sense		0.97 (0.78, 1.20)	0.00 (0.00, –)	1.1 57(0.013, 1.57×10^{4})
Vibratory sensation (s)	Right upper limb	−0.087 (−0.12, −0.055) ***	0.21 (−0.69, 1.11)	−0.68 (−1.90, 0.55)
	Left upper limb	−0.081 (−0.11, −0.052) ***	−0.018 (−0.83, 0.80)	−0.38 (−1.49, 0.74)
	Right lower limb	−0.15 (−0.18, −0.13) ***	0.24 (−0.57, 1.05)	−0.35 (−1.46, 0.75)
	Left lower limb	−0.15 (−0.18, −0.13) ***	−0.062 (−0.84, 0.71)	0.12 (−0.94, 1.18)
Two-point discrimination (mm)	Right index finger	0.017 (−0.002, 0.036)	−0.37 (−0.89, 0.15)	0.31 (−0.41, 1.02)
	Left index finger	0.022 (0.000, 0.043)	−0.24 (−0.85, 0.36)	0.26 (−0.57, 1.09)
Graphesthesia (/4)	Right palm	−0.001 (−0.002, 0.001)	−0.004 (−0.042, 0.033)	−0.009 (−0.060, 0.042)
	Left palm	−0.001 (−0.003, 0.001)	0.039 (−0.021, 0.10)	−0.049 (−0.13, 0.033)
Stereognosis (/3)		0.000 (−0.001, 0.001)	−0.016 (−0.046, 0.013)	−0.002 (−0.044, 0.040)

Associations of neurologic findings with hair mercury concentrations, age and gender

B. Correlation with hair mercury level classified as the first or forth quartiles

Neurological findings		Age	Male (femal as a referent)	Hair mercury concentration Quartile 4 (Quartile 1 as a referent)
		Adjusted odds ratios or adjusted regression coefficients* (95% confidence intervals if calculated)		
Cranial nerve	Saccadic pursuit	NA †		
	Sensorineural hearing loss	1.05 (0.98, 1.12)	5.80 (0.57, 59.2)	0.45 (0.07, 2.95)
	Dysarthria	1.03 (0.83, 1.28)	9.38×10^{6} (0.00, –)	9.11×10^{6} (0.00, –)
Muscular weakness	Upper limb	0.91 (0.77, 1.08)	2.96×10^{-8} (–)	5.23×10^{-7} (–)
	Lower limb	1.02 (0.87, 1.19)	0.28 (0.02, 4.83)	8.91×10^{7} (–)
Tremors	Resting	NA †		
	Kinetic	1.16 (0.80, 1.74)	6.22×10^{6} (0.00, –)	5.48×10^{6} (0.00, –)
	Postural	1.15 (0.96, 1.38)	0.17 (0.02, 1.76)	1.37×10^{8} (–)
Rigidity		NA †		
Coordinated movements	Diadochokinesis	1.18 (0.89, 1.57)	1.35×10^{7} (–)	1.22×10^{7} (–)
	Finger-to-nose test	1.03 (0.83, 1.28)	9.38×10^{6} (–)	9.11×10^{6} (–)
	Heel-knee test	1.09 (0.98, 1.22)	1.23×10^{8} (–)	0.58 (0.04, 7.58)
	Knee tapping test	1.12 (0.92, 1.35)	2.46×10^{7} (–)	1.64×10^{7} (–)
One foot standing	Right foot < 5s	1.42 (1.03, 1.98) *	1.53×10^{8} (–)	0.50 (0.00, 82.0)
	Right foot < 15s	1.21 (1.08, 1.35) **	1.15 (0.21, 6.34)	2.40 (0.35, 16.6)
	Left foot < 5s	1.03×10^{10} (–)	7.62×10^{-9} (–)	8.12×10^{11} (–)
	Left foot < 15s	1.21 (1.08, 1.35) **	1.15 (0.21, 6.34)	2.40 (0.35, 16.6)
Simple gait		1.03 (0.91, 1.18)	2.97×10^{7} (–)	2.83×10^{7} (–)
Tandem gait		1.22 (0.94, 1.58)	1.97×10^{7} (–)	2.23×10^{7} (–)
Reflex	Upper limb	1.03 (0.98, 1.08)	4.57 (0.89, 23.6)	1.45 (0.33, 6.31)
	Lower limb	1.08 (1.02, 1.13) **	1.19 (0.36, 3.96)	0.94 (0.26, 3.36)
	Babinski	1.03 (0.83, 1.28)	9.38×10^{6} (–)	9.11×10^{6} (–)
	Chaddock	1.03 (0.83, 1.28)	9.38×10^{6} (–)	9.11×10^{6} (–)
Touch sensation		1.04 (0.98, 1.11)	0.85 (0.15, 4.79)	0.92 (0.15, 5.78)
Pain sensation		1.04 (0.97, 1.11)	0.51 (0.10, 2.54)	1.51(0.26, 8.79)
Position sense		NA †		
Vibratory sensation (s)	Right upper limb	−0.076 (−0.12, −0.029) **	−0.018 (−1.36, 1.33)	−0.95 (−2.46, 0.57)
	Left upper limb	−0.081 (−0.12, −0.039) ***	−0.21 (−1.41, 1.00)	−0.40 (−1.75, 0.96)
	Right lower limb	−0.15 (−0.19, −0.11) ***	0.63 (−0.59, 1.84)	−0.84 (−2.21, 0.53)
	Left lower limb	−0.14 (−0.18, −0.10) ***	0.37 (−0.76, 1.49)	−0.38 (−1.65, 0.89)
Two-point discrimination (mm)	Right index finger	0.008 (−0.017, 0.032)	−0.42 (−1.14, 0.29)	0.50 (−0.30, 1.31)
	Left index finger	0.017 (−0.015, 0.048)	−0.43 (−1.34, 0.48)	0.36 (−0.66, 1.38)
Graphesthesia (/4)	Right palm	0.000 (−0.002, 0.001)	−0.012 (−0.058, 0.033)	−0.013 (−0.064, 0.038)
	Left palm	−0.001 (−0.004, 0.002)	0.010 (−0.067, 0.087)	−0.050 (−0.14, 0.037)
Stereognosis (/3)		NA †		

Associations of neurologic findings with hair mercury concentrations, age and gender

B. Correlation with hair mercury level classified as the first or forth quartiles

Range of hair mercury concentration of four quartiles	
1	1.1 ppm to 7.9 ppm
2	7.9 ppm to 17.8 ppm
3	17.8 ppm to 28.7 ppm
4	28.7 ppm to 101.9 ppm

Associations of neurologic findings with hair mercury concentrations, age and gender

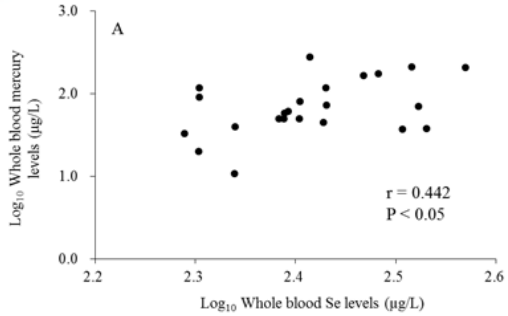
C. Correlation with hair mercury level higher than 50 ppm

Neurological findings		Age	Male (femal as a referent)	Hair mercury concentration ≥ 50 ppm (< 50 ppm as a referent)
		Adjusted odds ratios or adjusted regression coefficients* (95% confidence intervals if calculated)		
Cranial nerve	Saccadic pursuit	1.18 (0.84, 1.66)	0.00 (0.00, –)	0.00 (0.00, –)
	Sensorineural hearing loss	1.05 (1.00, 1.10) *	1.63 (0.46, 5.74)	7.80 (1.66, 36.29) **
	Dysarthria	1.05 (0.91, 1.22)	1.50×10^{7} (0.00, –)	0.00 (0.00, –)
Muscular weakness	Upper limb	0.97 (0.91, 1.04)	0.32 (0.02, 2.30)	6.49×10^{-8} (–)
	Lower limb	1.04 (0.94, 1.14)	0.15 (0.01, 1.55)	3.69×10^{-8} (–)
Tremors	Resting	0.98 (0.87, 1.10)	1.32×10^{7} (0.00, –)	0.00 (0.01, –)
	Kinetic	1.10 (0.90, 1.34)	1.39×10^{7} (0.00, –)	0.00 (0.01, –)
	Postural	1.12 (1.04, 1.20) **	1.34 (0.32, 4.79)	6.97×10^{-8} (–)
Rigidity		1.18 (0.84, 1.66)	0.00 (0.00, –)	0.00 (0.00, –)
Coordinated movements	Diadochokinesis	1.21 (1.03, 1.43) *	1.70 (0.15, 19.3)	1.99×10^{-7} (–)
	Finger-to-nose test	1.17 (0.99, 1.39)	2.85×10^{7} (–)	3.07×10^{-8} (–)
	Heel-knee test	1.12 (1.03, 1.22) **	4.65 (0.52, 41.7)	9.20×10^{-8} (–)
	Knee tapping test	1.11 (0.99, 1.24)	4.76×10^{7} (–)	1.40×10^{-8} (–)
One foot standing	Right foot < 5s	1.13 (1.02, 1.24) *	1.32 (0.022, 7.94)	1.30×10^{-8} (–)
	Right foot < 15s	1.11 (1.07, 1.16) ***	0.81 (0.34, 1.92)	1.02 (0.24, 4.38)
	Left foot < 5s	1.11 (1.03, 1.19) **	0.96 (0.23, 4.06)	1.04×10^{-8} (–)
	Left foot < 15s	1.13 (1.08, 1.18) ***	1.00 (0.42, 2.40)	0.88 (0.20, 3.84)
Simple gait		1.10 (0.99, 1.22)	1.90 (0.19, 19.3)	10.21 (1.29, 80.54) *
Tandem gait		1.31 (1.03, 1.66) *	2.22×10^{7} (–)	1.88×10^{-8} (–)
Reflex	Upper limb	1.05 (1.02, 1.08) **	3.21 (1.40, 7.38) **	0.42 (0.09, 2.10)
	Lower limb	1.06 (1.02, 1.09) ***	1.72 (0.79, 3.76)	1.37 (0.38, 4.99)
	Babinski	1.13 (0.99, 1.29)	0.58 (0.07, 4.82)	3.03×10^{-8} (–)
	Chaddock	1.13 (0.99, 1.29)	0.58 (0.07, 4.87)	3.03×10^{-8} (–)
Touch sensation		1.07 (1.02, 1.12) **	1.63 (0.55, 4.82)	0.64 (0.08, 5.47)
Pain sensation		1.06 (1.02, 1.10) **	1.10 (0.42, 2.84)	0.83 (0.07, 4.61)
Position sense		0.00 (0.00, 1.17)	0.00 (0.00, –)	0.00 (0.00, –)
Vibratory sensation (s)	Right upper limb	−0.093 (−0.12, −0.063) ***	0.14 (−0.76, 1.03)	−0.10 (−1.89, 1.64)
	Left upper limb	−0.088 (−0.11, −0.060) ***	−0.099 (−0.91, 0.71)	−0.33 (−1.96, 1.29)
	Right lower limb	−0.15 (−0.18, −0.13) ***	0.33 (−0.47, 1.13)	−0.84 (−2.44, 0.76)
	Left lower limb	−0.15 (−0.18, −0.13) ***	−0.003 (−0.77, 0.77)	−0.62 (−2.15, 0.92)
Two-point discrimination (mm)	Right index finger	0.019 (0.001, 0.037) *	−0.34 (−0.86, 0.18)	−0.20 (−1.24, 0.84)
	Left index finger	0.024 (0.004, 0.044) *	−0.22 (−0.82, 0.39)	−0.05 (−1.29, 1.13)
Graphesthesia (/4)	Right palm	−0.001 (−0.002, 0.001)	−0.006 (−0.043, 0.031)	0.024 (−0.050, 0.098)
	Left palm	−0.001 (−0.003, 0.001)	0.038 (−0.022, 0.098)	0.038 (−0.082, 0.159)
Stereognosis (/3)		−0.001 (−0.002, 0.000)	−0.022 (−0.0534, 0.008)	0.018 (−0.042, 0.079)

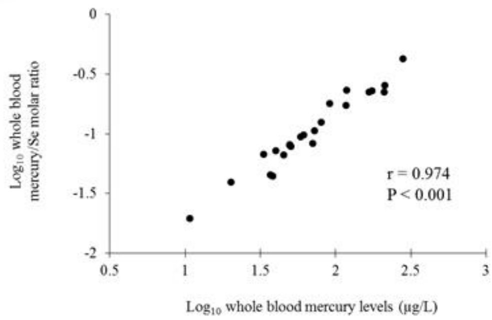
Summary of neurological findings of 12 residents whose hair mercury concentrations were over 50 ppm

No	Gender	age	Hair mercury (μg/g)	Wide-based gait	Sensorineural hearing loss	Cerebellar sign	Sensory disturbance and two-point discrimination (mm)
1	M	49	50.4	(−)	(−)	(−)	(−) Two-point discrimination: 6.0, 6.0
2	M	61	50.6	mild (+)	(−)	(−)	Decreased vibratory sensation of the lower limbs: 5s, 4s Two-point discrimination: 2.0, 2.6
3	M	70	54.0	(−)	left (+)	(−)	(−) Two-point discrimination: 1.5, 1.5
4	M	61	59.2	(+)	(+)	(−)	(−) Two-point discrimination: 2.1, 2.1
5	M	66	59.2	(−)	(−)	(−)	(−) Two-point discrimination: 4.0, 5.0
6	M	74	65.0	(−)	(−)	(−)	(−) Two-point discrimination: 2.5, 3.3
7	M	65	66.2	(−)	(+)	(−)	(−) Two-point discrimination: 5.0, 4.2
8	M	78	68.4	(−)	(+)	(−)	Dysesthesia (left L5, S1) Two-point discrimination: 3.2, 3.8
9	F	70	72.2	(−)	(−)	(−)	Decreased vibratory sensation of the lower limbs: 5s, 5s Two-point discrimination: 5.0, 5.0
10	F	62	73.1	(−)	(−)	(−)	(−) Two-point discrimination: 3.8, 3.8
11	M	60	82.6	(−)	(−)	(−)	(−) Two-point discrimination: 2.6, 2.2
12	M	60	101.9	(−)	(−)	(−)	Decreased vibratory sensation of the lower limbs: 6s, 7s Two-point discrimination: 2.7, 3.5

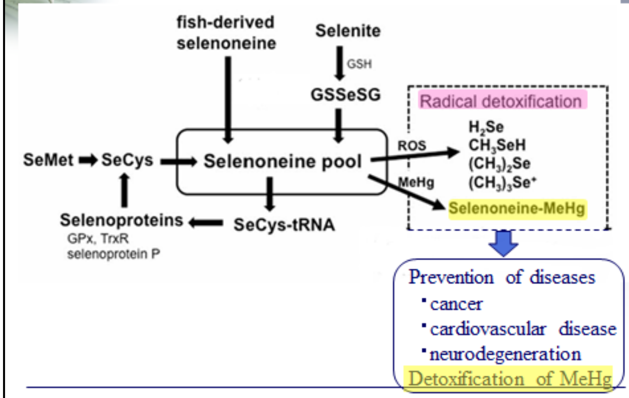
Correlation between whole blood mercury and Se levels



Correlation between whole blood mercury and the mercury/Se molar ratio



Possible metabolic pathway of selenoneine



Conclusions

1. We investigated the health effects of MeHg exposure in 194 adult Taiji residents who were considered to be highly exposed to MeHg by ingesting MeHg-contaminated whale meat.

2. Multivariate regression analysis demonstrated no significant correlations between hair mercury levels and neurological outcomes, whereas some of the findings significantly correlated with age.

3. Sufficient Se intake might be one of causes of the absence of adverse effects of MeHg exposure in this study.

Collaborators

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Negative Confounding by Essential Fatty Acids in Methylmercury Neurotoxicity Associations

Anna L Choi, Ulla B. Mogensen, Kristian S. Bjerve, Frodi Debes, Pal Weihe, Philippe Grandjean, Esben Budtz-Jørgensen

***** *Harvard University, USA***

Background: Methylmercury, a worldwide contaminant of fish and seafood, can cause adverse effects on the developing nervous system. However, long-chain n-3 polyunsaturated fatty acids in seafood provide beneficial effects on brain development. Negative confounding will likely result in underestimation of both mercury toxicity and nutrient benefits unless mutual adjustment is included in the analysis.

Methods: We first examined these associations in 176 Faroese children, in whom prenatal methylmercury exposure was assessed from mercury concentrations in cord blood and maternal hair. The relative concentrations of fatty acids were determined in cord serum phospholipids. Neuropsychological performance in verbal, motor, attention, spatial, and memory functions was assessed at 7 years of age. Multiple regression and structural equation models (SEMs) were carried out to determine the confounder-adjusted associations with methylmercury exposure. Supplementary SEM analyses on verbal and motor functions included a larger previous cohort with similar characteristics, but the fatty acid measurements were missing. A total of 1016 children with available data were included in the joint-cohort analyses with estimated fatty acid parameter for Cohort 1 using the meta-analysis method for SEM.

Results: A short delay recall (in percent change) in the California Verbal Learning Test (CVLT) was associated with a doubling of cord blood methylmercury (-18.9, 95% confidence interval [CI] = -36.3, -1.51). The association became stronger after the inclusion of fatty acid concentrations in the analysis (-22.0, 95% confidence interval [CI] = -39.4, -4.62). In structural equation models, poorer memory function (corresponding to a lower score in the learning trials and short delay recall in CVLT) was associated with a doubling of prenatal exposure to methylmercury after the inclusion of fatty acid concentrations in the analysis (-1.94, 95% CI = -3.39, -0.49). Similar results were found in the supplementary joint-cohort SEM analyses

Conclusions: Associations between prenatal exposure to methylmercury and neurobehavioral deficits in memory function at school age were strengthened after fatty acid adjustment, thus suggesting that n-3 fatty acids need to be included in analysis of similar studies to avoid underestimation of the associations with methylmercury exposure.

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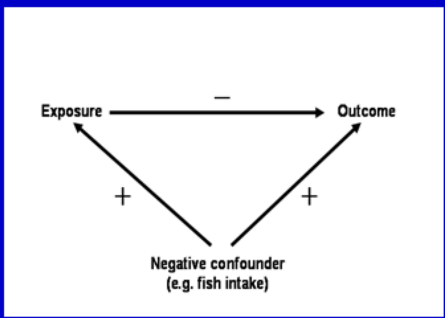
Nutrients in fish and seafood

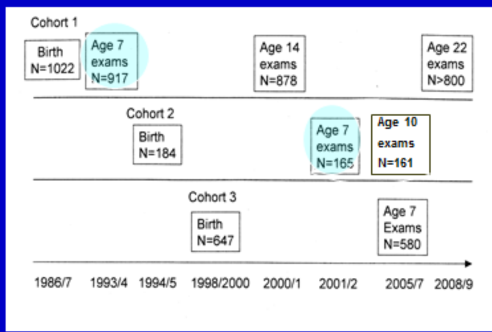
- Polyunsaturated fatty acids
  - essential for normal brain development
  - possibly protecting against cardiovascular diseases
- Selenium
  - a constituent of selenoproteins
- Others

Negative Confounding



(Choi et al., 2009)

Faroe Islands prospective birth cohorts

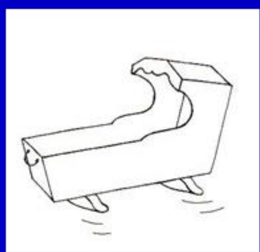


Neuropsychological Exams

Tests were chosen according to the brain function domains:

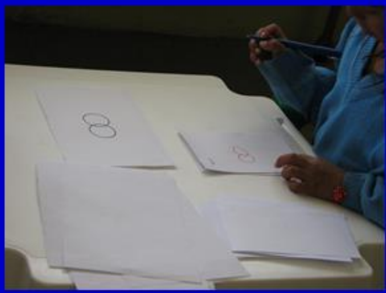
- Verbal
- Motor
- Attention
- Spatial
- Memory

Boston Naming Test



NES2 Continuous Performance Test

Stanford-Binet Copying



Distribution of Hg and PCB exposure among the birth cohort

Exposure Biomarker	Geometric Mean	Total Range	Correlation with Cord Blood Hg
Cord blood (µg/L)	21.4	1.90-101.8	**(1)**
Maternal hair (µg/g)	4.10	0.32-16.3	**0.84**
Serum PCB (µg/g lipid)	1.13	0.04-18.4	0.45

Choi et al. NTT 2014;42:85-92

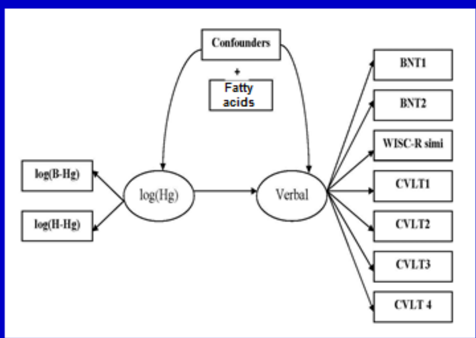
Distribution of Mean Relative Concentrations of Fatty Acids (%) Among the Birth Cohort

Fatty Acid	Mean (SD)	Total Range	Correlation with DHA+EPA
DHA + EPA	9.57 (1.71)	6.40-14.5	**(1)**
Total n-3	10.8 (1.91)	6.97-16.7	0.98
DHA + EPA / AA	0.59 (0.12)	0.50-0.67	0.86

Change in Neurobehavioral Outcomes Associated with 1 unit Increase of DHA+EPA, and a Doubling of the Cord Blood Hg Exposure

			Hg with DHA+EPA	
Outcomes	Hg only	DHA +EPA	Hg	DHA+EPA
CVLT learning	**-14.3 (-30.4, 1.87)**	-0.01 (-0.95,0.93)	**-15.7 (-32.3, 0.83)**	0.11 (-0.83, 1.05)
CVLT short delay	**-18.9(-36.3, -1.51)**	0.22 (-0.11, 0.55)	**-22.0(-39.4, -4.62)**	0.28 (-0.05, 0.60)

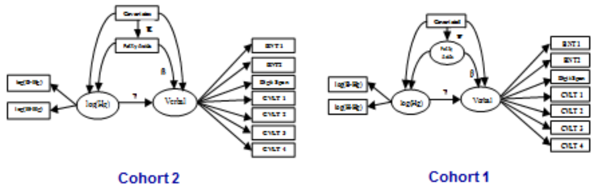
In a structural equation model, the latent exposure variable is optimized based on exposure predictors, confounders, and latent effect variable



Change in Neurobehavioral Outcome Associated with a Doubling in Hg Exposure *With and Without DHA+EPA Adjustment*

Outcome	Hg Exposure		DHA+EPA
	Without DHA+EPA	With DHA+EPA	
Memory	**-1.01 (-2.21, 0.20)**	**-1.94 (-3.30, -0.49)**	0.67 (-0.03, 1.36)
Verbal	-0.42 (-1.17, 0.32)	**-0.50 (-1.06, 0.06)**	0.15 (-0.12, 0.43)
Spatial	-0.13 (-0.32, 0.07)	-0.16 (-0.37, 0.05)	0.04 (-0.07, 0.15)

A joint SEM for verbal function combining cohorts 1 and 2



β = Association of fatty acids with the outcome
κ = Association between covariates and fatty acids
γ = Association of mercury exposure with the outcome

Change in outcomes associated with a doubling in Hg exposure and a one unit increase in fatty acids among the two Faroese cohorts

Outcome	Hg effects (95% CI)	
	No fatty acids	With fatty acids
Verbal	**-0.49 (-0.75,-0.23)**	**-0.49 (-0.76, -0.22)**
Motor	-0.17 (-0.45, 0.12)	-0.21 (-0.50, 0.09)

Conclusions

- Prenatal exposure to methylmercury was associated with deficits at school age in domains known to be sensitive to this neurotoxicant.
- Underestimation of mercury toxicity and fish benefits may result from a lack of mutual adjustment.
- All the study children in this fishing community with frequent consumption of seafood and pilot whale meat were fully PUFA sufficient.
- PCBs did not have any important impact on the neurodevelopmental outcomes in our cohort.
- There is considerable variability in mercury and PUFA concentrations within and across species of dietary fish.

Seafood diets	Toxicants	Nutrients
Salmon, mackerel	Low	High
Light tuna, lobster	Medium	Medium
Swordfish, tuna steak	High	Low

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