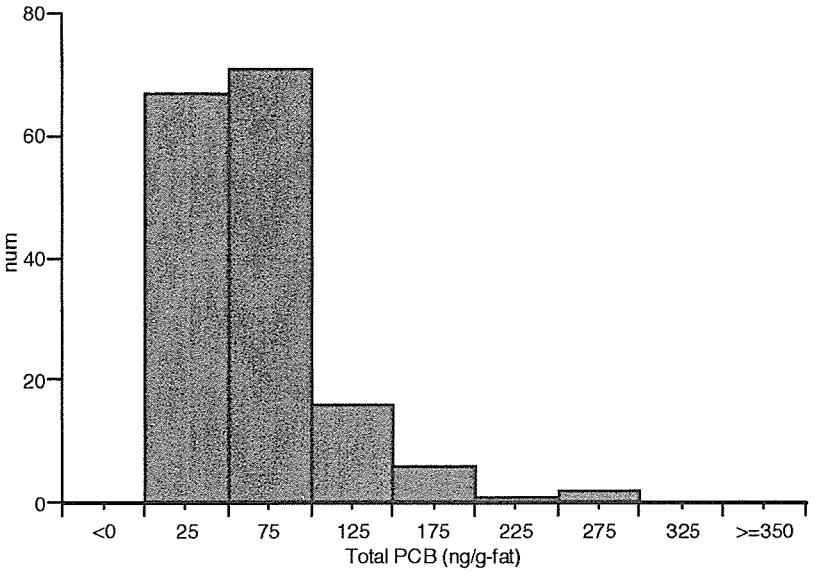

Fig 1. The distribution of total PCBs in whole cord blood

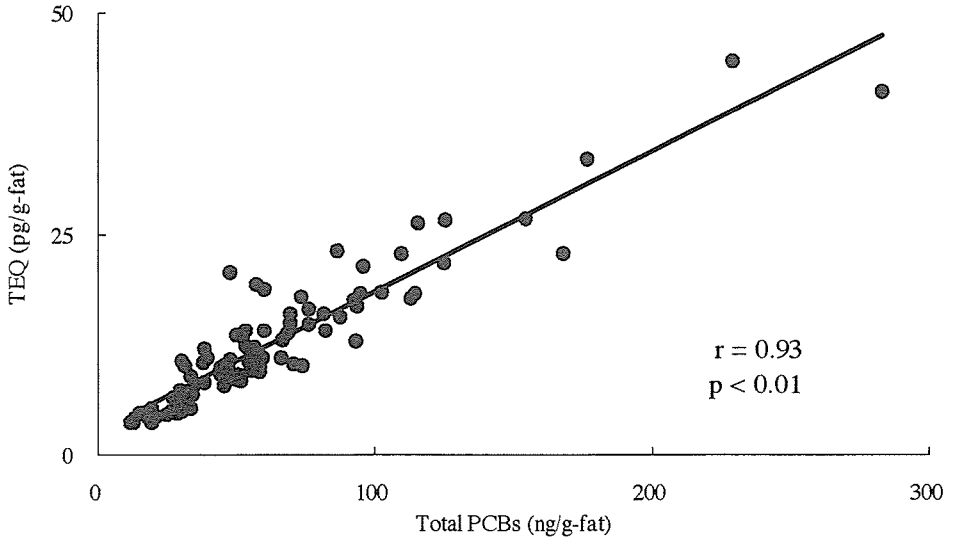

Fig 2. The correlation between total PCBs and TEQ

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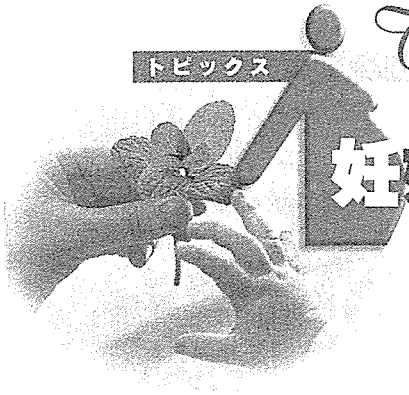

トピックス Topics

妊婦における魚摂取の考え方

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はじめに

厚生労働省は，薬事・食品衛生審議会食品衛生分科会乳肉水産食品・毒性合同部会の検討結果より「水銀を含有する魚介類等の摂食に関する注意事項」を平成15年6月3日発表した．しかしながら，この注意事項があまりに唐突に，しかも十分な説明がなされないまま公表され，水産業界に風評被害を出したこと，さらに発表直後の同年6月中旬にイタリアで開催された第61回FAO/WHO合同食品添加物専門家会議（JECFA）がメチル水銀の暫定的耐容週間摂取量を1.6 μg/kg体重/週としたことなどを踏まえて，厚生労働省は平成16年7月23日に内閣府食品安全委員会にメチル水銀のリスク評価を依頼した．食品安全委員会は，メチル水銀の健康影響評価を1年以上審議した末，「魚介類等に含まれるメチル水銀に係わる摂食に関してハイリスクグループを胎児，また耐容週間摂取量としてメチル水銀2.0 μg/kg体重/週（Hgとして）とする」旨の通知を平成17年8月4日に厚生労働大臣に届けた．ここでの対象集団は，胎児への影響を重視していることから，妊娠中あるいは妊娠している可能性のある人である．

耐容週間摂取量とは

メチル水銀の代表的中毒災禍として，工場が排出したメチル水銀に汚染された魚介類を食べて起こった「水俣病」がある[1]．しかしながら，水俣におけるメチル水銀中毒の研究報告は，耐容週間摂取量の算出に役立つデータを含んでいなかった．水俣病から得られた教訓は「胎児性水俣病」患者の存在であり，メチル水銀を多量摂取した妊婦から生まれた子どもがメチル水銀にもっとも感受性が高くかつ脆弱な集団であることを，世界の研究者に示した点である．

耐容週間摂取量の計算に寄与したのは，有機水銀殺菌剤で汚染された小麦（種籾）をパンにして食べたイラク農民の妊婦から生まれた子どもたちに関する研究であった．曝露後に出産した母親の毛髪水銀濃度を測定し，かつ生まれた子どもたちの18カ月時の神経症状の有無を診察した米国ロチェスター大学のClarkson教授らのグループは，メチル水銀による健康影響（歩行障害など）が現われはじめる水銀の最小濃度を，数理モデルを用いて，毛髪水銀濃度で10 μg/gと推定した[2]．米国環境保護庁は，この値に相当する摂取量を算定し，さらに個人によって代謝速度や感受性が異なることから1/10の安全係数を乗じ，1日当たりのメチル水銀の耐容摂取量（**リファレンスドース**，毎日摂取しても健康影響が現われない限界量）を0.1 μg/kg体重/日と定めた．

耐容週間摂取量は，リファレンスドースを1週間当たりとして算出した値である．多くの人が日々食材を変えて食べることが多いので，特定の食材を多く摂取する日もあれば，まったくとらない日もありうる．つまり，日々の摂取量を厳密に規定するより，1週間という枠内で規制するほうが便利であると考えたのである．

なぜ魚が問題視されるのか

水銀蒸気は自然界（火山活動など）や産業界（火力発電などの化石燃料の燃焼）から主に放出され，酸化されて水溶性（たとえばHg^{++}）となり，降雨で土壌や水域に沈積する．さらに，その一部は主に水圏の非酵素的あるいは微生物の作用によりメチル化合物にその化学形態を変える[3]．こうして生成されたメチル水銀は，水中生物圏で食物連鎖と生物濃縮により，人が食べる大型の肉食魚やハクジラなどの海棲哺乳類に多く蓄積する．したがって，メチル水銀の存在は大型魚やクジラのみでなく魚介類全体にいえることであるが，

その濃度は魚種間で大きく異なり，小型の魚（イワシ，アジ，サバ）では低い．

食品中に含まれるメチル水銀は消化管から高率（95～100％）に吸収される．吸収されたメチル水銀は，血液中では90％以上が赤血球中に存在するが，SH基に対する親和性が高いため，システイン，グルタチオンのようなアミノ酸と結合し，とくにシステイン-メチル水銀複合体はアミノ酸輸送系を介して血液-脳関門および血液-胎盤関門を通過し，脳内および胎児に入る．この結果，メチル水銀は強い中枢神経毒性を（とくに胎児において）示すと考えられている．

ヒトのメチル水銀の主な曝露源は魚介類であり，また魚介類に含まれる総水銀の75～100％はメチル水銀であると推定されている．このため，魚介類摂取が問題視されたのであり，魚介類を多食するデンマーク領フェロー諸島やセイシェル共和国の人々が，水俣・新潟やイラクのメチル水銀中毒禍以後の胎児影響検証の場として選択された．

魚多食集団における研究

ノルウェーとアイスランドのほぼ中央に位置するフェロー諸島では，ゴンドウクジラを長年にわたって捕獲し，住民のたんぱく源として食していた．この地で1986年以降デンマーク・オデンセ大学Grandjean教授のグループがフェロー出生コホート研究を実施した[3]．出生時にメチル水銀の曝露評価を行い，子ども1,022名が7歳および14歳になったときに神経への影響評価を行った．この集団の曝露レベルは出産時の母親毛髪水銀濃度で0.2～39.1（中央値4.5）μg/gであり，メチル水銀濃度が高くなるにつれ記憶，注意，言語などの能力が低下し，また神経生理学的検査（聴性脳幹誘発電位や心電図RR間隔変動）の指標もメチル水銀の曝露量の増加にともなって変化した．さらに，ゴンドウクジラの脂身にはポリ塩化ビフェニル（PCB）が多いのであるが，神経心理・行動学的検査の成績はPCB濃度と有意な関係をもたず，水銀濃度とのみ有意な関連を示した．この出生コホート研究と同様の結果は，ニュージーランドの前向きコホート研究[4]，秋田・鳥取の後向きコホート研究でも認められている[5]．

南インド洋に浮かぶセイシェル共和国では，1989年以降米国ロチェスター大学Clarkson教授のグループがセイシェル小児発達研究を実施し，子ども779名が5.5歳と9歳になったときに認知能力，言語や理解能力，計算能力などの神経発達検査を行った．出産時の母親毛髪水銀濃度は0.5～26.7（平均6.8）μg/gであったが，ここでは有意な量-反応関係は認められなかった[3]．

日本人の水銀摂取量

日本人の食品からの水銀（総水銀）の摂取量は，厚生労働省のトータルダイエット調査によると，2003年において8.1 μg/日（体重50 kgの人で1.1 μg/kg体重/週），このうち84％が魚介類からの摂取とされている．秋田・鳥取の7歳児をもつ母親327名（24～49歳，平均36歳）に対して食品摂取頻度調査法で魚介類25種類の実物大写真を提示しながら調べた結果によると[6]，総水銀摂取量は0.77～144.9（中央値15.0）μg/日であった（メチル水銀摂取量は1.75 μg/kg体重/週）．この摂取量と毛髪水銀濃度（0.11～6.86 μg/g，中央値1.63 μg/g）の間には有意な正の関係があった（r_s＝0.245）．

産褥婦および胎児の水銀濃度

胎児は母親から胎盤を介して成長に必要な栄養分や酸素を取り込み，また乳児は母乳を介して栄養などを取り込む．日本人産褥婦63名から母体血と胎盤血（胎児の血液）を採取し，赤血球中の水銀濃度を測定した研究によると[7]，出産直後の母親の平均赤血球中水銀濃度は8.4 ng/g，臍帯血のそれは13.4 ng/gであり，胎児のほうが有意に高かった．また，生後3カ月の乳児の平均赤血球中水銀濃度は6.5 ng/gであり，乳児のメチル水銀濃度は3カ月間で約半分まで減少した[8]．以上のことから，体内に取り込まれるメチル水銀は，妊婦から胎児に選択的に移行するが，母乳中のメチル水銀濃度は0.21 ng/gと低く，乳児期には発育にともなって濃度が急激に減少すると考えられる．

ドコサヘキサエン酸（DHA）は魚介類に含まれる多価不飽和脂肪酸であり，ヒトの脳発達に重要で

あると考えられている．産褥婦およびその臍帯から血液を収集し，赤血球中水銀濃度とDHAを測定すると，臍帯血中DHA濃度と母親血中DHA濃度の間には有意な正の関係がみられ，かつ臍帯血においてもDHA濃度と水銀濃度に有意な正の関係が観察された[7]．すなわち，メチル水銀もDHAも魚介類摂取によりヒト体内に入り，いずれも母体から胎児へ移行する．

魚摂取の利点

魚を摂食していない妊婦から産まれた子どもよりも週4回以上魚を摂食していた妊婦から産まれた子どものほうが，言語およびコミュニケーション能力の発達得点は高かったとする報告がある[9]．米国科学アカデミーのメチル水銀毒性影響に関する委員会は，魚はビタミンD，多価不飽和脂肪酸（DHAなど），たんぱく質，セレン，一部の食事には十分含まれていない他の栄養素などを豊富に含むことから，魚を多く摂取する食事の栄養学的優位性を認め，魚を習慣的に消費することにより，心血管系疾患，骨粗鬆症，がんをある程度予防できる可能性があると結論している[2]．また，米国環境保護庁のMahaffey博士は，水銀含有量が0.1 μg/g以下でDHAやエイコサペンタエン酸（EPA）を多く含む魚もいる反面，水銀を多く含みDHAやEPAがあまり豊富でない魚もいるので，水銀濃度の高い魚の摂食にとくに注意すべきであると述べている[10]．

妊婦における魚摂取量

魚に含まれる水銀量は，魚種だけでなく漁獲される海域で異なる．厚生労働省がまとめた国内の魚介類に含まれる水銀の調査結果によると[11]，たとえ同じカレイ類であっても，平均総水銀濃度は0.015 μg/g（クロガシラカレイ）から0.305 μg/g（カラスガレイ）まで多様である（詳細はWeb上にある文献11の別添1）．また，前述の食品中に占める魚介類の水銀摂取割合0.84を四捨五入して0.8とするならば，魚介類から摂食して支障のないメチル水銀量は，**[耐容週間摂取量（2.0 μg/kg体重/週）]×[妊婦の体重(kg)]×0.8**と算出され，体重75 kgの妊婦の耐容摂取量（120 μg/週）は50 kgの妊婦（80 μg/週）に比べ1.5倍多くなる．魚介類に含まれる総水銀がすべてメチル水銀と仮定した場合，体重50 kgの妊婦が1週間に食べる魚をメカジキ（総水銀濃度0.97 μg/g）のみとするならば摂食してよい量は約80 gであるが，シマアジ（同0.122 μg/g）なら約650 gも摂食可能となる．

食の基本的考え方

食の安全性は，厚生労働省の「妊婦における食事の注意事項」を遵守すればメチル水銀の曝露がなくなるというものではない．妊婦がたとえクジラ，キンメダイ，クロマグロを妊娠中にまったく食べなくとも，注意事項に含まれないカツオ（水銀含有量0.154 μg/g）を日々多食すれば毛髪水銀濃度は高値になる．また，十分な科学的根拠は示されていないものの，メチル水銀以外の有害物質（PCBやカドミウムなど）の影響を否定できないので，「DHAやEPAを多く含み，メチル水銀含有量の少ない小魚を毎日たくさん食べると，胎児の発達にとって有益である」と過信することは，別の危険性を孕んでいるといえる．魚介類に限らず，野菜，穀類，食肉においても農薬，土壌・水質汚染，家畜飼料などの問題が残り，有害性を100％除外できているという確証はない．したがって，筆者らが推奨する食品摂取の基本的考え方は「**多種類の食品を，偏ることなく日々品を変え，少量ずつ，バランスよく摂取する**」ことに尽きる[12]．

おわりに

ヒトは環境中の健康促進因子とともに健康有害因子にさらされながら生活している．予防原則は後者のリスクをゼロにすることを目指しているが，ゼロリスクのみ追求すると安全な食材など存在しなくなるように思われる．このため「特定の食材を常に使用する」ことを避け，多種類の食品をバランスよく摂食することが，環境からの有害リスクを軽減する最善の方法と考えられるのである．

地球温暖化による異常気象と砂漠の拡大は陸の幸の枯渇をもたらす可能性を示唆している．このため，われわれは海の幸を資源として大切にし，有効利用する方法を身につける必要がある．そして，一人ひとりが環境に配慮しながら，

季節ごとのおいしい食材をみつけて調理しよう．しかし，日々の食材に変化を求める心を忘れないように．

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Correlations between mercury concentrations in umbilical cord tissue and other biomarkers of fetal exposure to methylmercury in the Japanese population

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Abstract

Methylmercury (MeHg) is one of the most risky substances to affect humans through fish consumption, and the fetus is known to be in the most susceptible group. Our objective in this study is to examine the relationships of total mercury (THg) and MeHg concentrations between umbilical cord tissue and other tissues as biomarkers of fetal exposure to MeHg in the Japanese population. In total, 116 paired samples were collected in three Japanese districts, the Tsushima Islands, Fukuoka City, and Katsushika ward of metropolitan Tokyo. THg was measured for hair and THg and MeHg were measured in cord tissues, maternal blood, and cord blood. The relationships among tissues in Hg concentrations were similar among districts. Therefore, we analyzed the relationships using all the samples. More than 90% of Hg in cord tissue, cord blood, and maternal blood was MeHg. THg and MeHg in cord blood was about two times higher than in maternal blood. A strong correlation was found between THg and MeHg in cord tissue. The cord tissue THg and MeHg showed a strong correlation with cord blood Hg, which is recognized as the best biomarker for fetal exposure to MeHg. The findings of this study indicate the significance of cord tissue THg and MeHg as biomarkers for fetal exposure to MeHg at parturition.

Keywords: Mercury; Methylmercury; Exposure; Umbilical cord tissue; Umbilical cord blood; Maternal blood; Hair; Parturition; Biomarkers; Fetus; Parturition

1. Introduction

Fetuses are known to be a high-risk group for methylmercury (MeHg) exposure because of the high susceptibility of the developing brain itself (Choi, 1989; Sakamoto et al., 1993; World Health Organization (WHO), 1990). Moreover, MeHg easily crosses the blood–placenta barrier, accumulating more in the fetus than the mother (Choi, 1989; Sakamoto et al., 2002, 2004; Stern and Smith, 2003; WHO, 1990). Therefore, the effect of MeHg exposure on pregnant women is an important issue for elucidation, especially in Japanese and some other populations that consume much fish and sea mammals (Grandjean et al., 1997, 2005; Myers et al., 1995a, b, 2003; National Research Council (NRC), 2000; WHO, 1990).

The epidemic called "Minamata disease" is well known as the first instance on record of severe MeHg poisoning caused by manmade environmental pollution, which occurred mainly among fishermen and their families in and around Minamata City. It originated from the consumption of large amounts of fish and shellfish contaminated with MeHg discharged from a chemical plant (Irukayama and Kondo, 1966). The principal

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symptoms included neurological disorders such as sensory disorders, cerebellar ataxia, contraction of the visual field, hearing impairments, and disequilibrium (Takeuchi et al., 1962). The first patient was reported in 1953, and the number of patients rapidly increased after 1955. Up to the present, more than 2000 people have been certified to have Minamata disease. Furthermore, many fetuses exposed to MeHg through the placenta of the exposed mother showed severe cerebral-palsy-like symptoms, while their mothers had mild or no manifestation of the poisoning (Harada, 1978). Outbreaks of the typical fetal-type Minamata disease occurred during 1955–1959 when the mercury pollution appears to have been most severe, judging from the incidence of patients (Harada, 1978) and the MeHg concentration in the preserved umbilical cords of inhabitants of the area (Nishigaki and Harada, 1975). During the period, a deceased male birth ratio associated with increased male fetal death was observed in Minamata City pollution, indicating its severity and widespread distribution (Sakamoto et al., 2001). This landmark epidemic was the first to bring worldwide attention to the high risk of fetal exposure to MeHg.

Thereafter, large prospective cohort studies were conducted in the Seychelles (Myers et al., 1995a, b, 2003) and the Faroe Islands (Grandjean et al., 1997, 1999, 2005), where fish or sea mammal consumption is high. Though the MeHg exposure level was similar in these studies, different conclusions were reached (NRC, 2000). The exposure level in the epidemic in Minamata is thought to have been much higher than in those studies. Therefore, the study of Minamata disease is still very important, and it will provide more obvious health effect information by using recently developed neurological test batteries. Fortunately, Japanese people have a custom of preserving a small piece of the dried umbilical cord tissue as a birth memento in a wooden or plastic box deep inside a chest of drawers. MeHg in the tissue will not be reduced by microorganisms, because it is completely dried. By measuring the Hg concentrations in this preserved dry cord sample, we can estimate the individual MeHg exposure level at birth. Grandjean et al. (2005) revealed that cord tissue Hg as well as cord blood Hg was useful as a predictor of the effect of fetal exposure to MeHg. However, the preserved cord tissues had often been treated with mercurochrome at the period when cut off at parturition. The mercurochrome can easily dissociate into Hg ions in the solution and the ions act as a disinfectant. Then the cord tissue treated with mercurochrome shows a very high Hg concentration when total mercury (THg) is measured. Accordingly, we need to measure not THg but MeHg in the preserved cord tissue in Japan, especially in the samples treated back in those days. Some studies (Akagi et al., 1998; Nishigaki and Harada, 1975) have revealed exposure of the fetus to MeHg in the Minamata area by measuring it in the preserved cord tissue. The present study investigates the relationships between THg and MeHg in cord tissue and the relationships between other biomarkers of fetal exposure to MeHg in the Japanese population to evaluate the significance of the Hg concentrations in cord tissue.

2. Materials and methods

2.1. Subjects and sampling

In total, 116 healthy Japanese pregnant women without any special exposure to mercury, ranging in age from 19 to 41 yr (average 30.0 ± 5.0), gave informed consent to take part in the present trial. The samples were collected in the Tsushima Islands in Nagasaki Prefecture (30 cases), Fukuoka City in Fukuoka Prefecture (68 cases) and Katsushika, a special ward of metropolitan Tokyo (18 cases). Blood samples from the mothers and umbilical cord were collected immediately after birth in 1996. Whole length of maternal hair and cord tissue near the fetus were also collected at parturition. Samples were stored at −80 °C until analysis. About 1 cm of umbilical cord from the fetus side was rinsed in physiological saline solution to remove blood and body fluid and pressed between paper towels to remove the saline solution. Further, they were dried at 40 °C for 3 days and were kept in desiccators. No further weight loss occurred after the dehydration, ensured by weighing for 3 days. The dried tissues were then cut into small pieces with scissors and around 0.1–0.2 g of the tissues were moistened with 0.5 ml of water one day prior to the Hg analysis. This study was approved by the Ethics Committee of the National Institute for Minamata Disease (NIMD).

2.2. Mercury analysis

THg in the samples was determined by cold vapor atomic absorption spectrophotometry (CVAAS) according to the method of Akagi et al. (2000). The method involves sample digestion with HNO_3, $HClO_4$, and H_2SO_4 (1 + 1 + 5), followed by reduction to elemental Hg vapor by $SnCl_2$. The detection limit was 0.01 ng/g. MeHg in the samples was determined by gas chromatography with electron capture detection (GC-ECD) according to the method of Akagi et al. (2000). The method involves sample digestion with KOH–ethanol and subsequently, under slightly acidic conditions, the fatty content is removed using *n*-hexane. After extraction with dithizone–toluene, MeHg is back-extracted with a slightly alkaline sodium sulfide solution. The excess sulfide ions are then removed as hydrogen sulfide by purging with nitrogen gas after slight acidification with HCl solution. MeHg is then re-extracted with a small portion of dithizone–toluene; the extract is washed with NaOH solution to remove the excess dithizone, and then slightly acidified with HCl and analyzed by GC-ECD. The detection limit was 0.01 ng/g. Accuracy of THg was ensured by using reference blood material Level 2, MR9067 (Seronorm201605: Nycomed Co., Oslo, Norway): the THg determined averaged 7.5 μg/L, as compared to the range of 6.8–8.5 μg/L recommended by ICP-SFMS. The precision of the method, expressed as coefficient of variation, was 0.8%. Analysis of a MeHg standard solution containing 5 μg/L gave a recovery of almost 100%. The precision and accuracy of THg and MeHg were repeatedly verified by interlaboratory calibration exercises, including the analysis of standard reference material such as IAEA-085, 086, and 142 (Horvat et al., 1988).

2.3. Statistics

THg and MeHg concentrations among the districts were analyzed by one-way analysis of variance (ANOVA). Similar correlations were observed between the Hg concentrations in each tissue among the districts. Therefore, all the data were combined and the associations between THg and MeHg among samples were studied by Pearson correlation analysis. Logarithmic transformation was used to correct the skewed distribution of the Hg concentrations. The differences in Hg concentrations between paired samples were determined by paired *t*-test. A *P*-value less than or equal to 0.05 was considered to demonstrate statistical significance.

Table 1
Geometric means and 25th–75th percentiles of total mercury (THg) in hair and total and methylmercury (MeHg) in cord tissue, maternal blood and cord blood in three districts in Japan

Districts (ng/g)	Hair	Cord tissue		Maternal blood		Cord blood	
	THg	THg	MeHg	THg	MeHg	THg	MeHg
Tsushima ($n = 30$)	1453 (1157–1950)	64.0 (46.7–87.9)	54.6 (38.1–71.8)	4.62 (3.02–7.55)	3.98 (2.75–5.95)	9.13 (6.37–12.4)	8.38 (5.84–10.7)
Fukuoka ($n = 68$)	1954 (1170–2293)	97.0 (80.6–125)	89.3 (75.8–121)	4.9 (3.65–6.44)	4.61 (3.61–5.73)	9.27 (7.03–13.9)	8.93 (6.57–11.5)
Katsushika ($n = 17$)	2120 (1810–2990)	137.7 (94.5–207)	130.8 (95.5–197)	7.91 (5.42–11.3)	7.54 (5.21–10.3)	13.9 (8.87–20.9)	11.4 (8.13–20.1)
Total ($n = 115$)	1624 (1175–2195)	91.7 (63.5–127)	83.1 (57.1–122)	5.18(3.63–7.34)	4.77 (3.5–6.54)	9.81 (6.96–13.6)	9.32 (6.56–13.4)
MeHg (%) Mean ± SD			90.6 ± 10.4		92.5 ± 8.1		95.2 ± 5.5

Note: The mean MeHg percentage (MeHg/THg × 100).

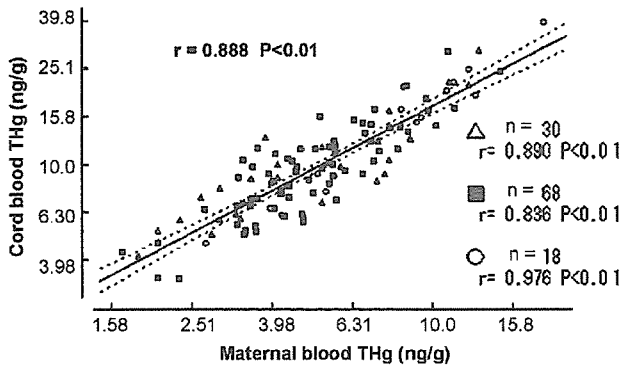

Fig. 1. Correlation between total mercury (THg) in maternal and cord blood: (△) Tsushima Islands; (■) Fukuoka City; and (○) Katsushika ward of metropolitan Tokyo. Dotted lines represent 95% confidence intervals for the regression line.

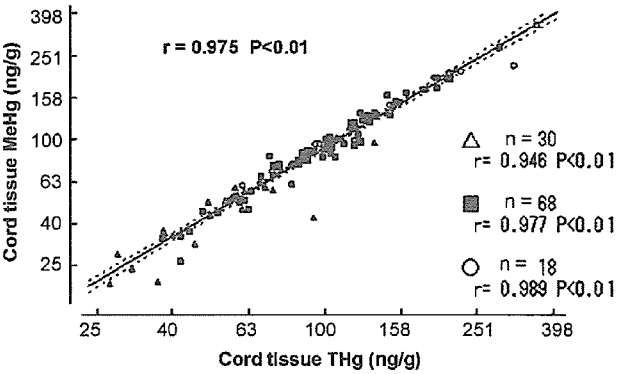

Fig. 2. Correlation between total mercury (THg) and methylmercury (MeHg) in cord tissue: (△) Tsushima Islands; (■) Fukuoka City; and (○) Katsushika ward of metropolitan Tokyo. Dotted lines represent 95% confidence intervals for the regression line.

3. Results

Table 1 presents the geometric means of THg in hair and THg and MeHg in cord tissue, maternal blood, and cord blood in three districts in Japan. There were significant differences among the districts in all the Hg concentrations ($P < 0.01$). The geometric means of Hg concentrations in all tissues were highest in Katsushika ward of metropolitan Tokyo, followed by Fukuoka City and the Tsushima Islands. All the data were combined, because similar correlations were observed among the Hg concentrations in all tissues among the districts as shown in Figs. 1–3. Significant correlations of THg and MeHg concentrations were observed among the biomarkers as shown in Table 2. THg and MeHg in cord tissue showed strong correlations with those in maternal and cord bloods (Table 2). However, the correlation coefficients of THg in maternal hair and THg and MeHg in other biomarkers were comparatively low and scattered, as shown in Table 2 and Fig. 3. As shown in Table 2 and Fig. 1, the geometric means of THg and MeHg in cord blood were 9.81 and 9.32 ng/g, respectively, and the concentrations were about two times higher ($P < 0.01$) than those of maternal blood (5.18 and 4.77 ng/g). THg and MeHg in cord tissue showed

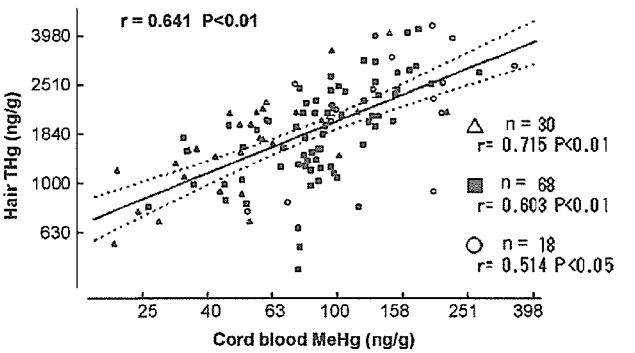

Fig. 3. Correlation between cord tissue methylmercury (MeHg) and hair total mercury (THg): (△) Tsushima Islands; (■) Fukuoka City; and (○) Katsushika ward of metropolitan Tokyo. Dotted lines represent 95% confidence intervals for the regression line.

strong correlation coefficients (Table 2 and Fig. 2), and the geometric means of THg and MeHg in cord tissue were 91.7 and 83.1 ng/g, respectively. The mean MeHg percentage (MeHg/THg × 100) in cord tissue was 90.6 ± 10.4%. MeHg percentages in cord blood and maternal blood were 95.2% and 92.5%, respectively (Table 1), and the mean MeHg percentage in cord blood was significantly ($P < 0.01$) higher than that of maternal blood.

Table 2
Correlation coefficients of logarithmic total mercury (THg) in hair and total and methylmercury (MeHg) in cord tissue, maternal blood and cord blood in the total of three districts in Japan

	Hair	Cord tissue		Maternal blood		Cord blood	
	THg	THg	MeHg	THg	MeHg	THg	MeHg
Hair THg	1						
Cord tissue THg	0.641	1					
Cord tissue MeHg	0.626	0.975	1				
Maternal blood THg	0.648	0.809	0.799	1			
Maternal blood MeHg	0.654	0.846	0.839	0.981	1		
Cord blood THg	0.651	0.848	0.815	0.888	0.885	1	
Cord blood MeHg	0.646	0.873	0.839	0.882	0.888	0.992	1

Note: All the correlation coefficients were significant ($P<0.01$).

4. Discussion

MeHg is one of the most risky substances for the fetal brain, and most of the human exposure to MeHg is through maternal fish consumption. MeHg easily passes through the placenta as a cysteine conjugate during intrauterine life (Aschner and Clarkson, 1987; Kajiwara et al., 1996). The National Research Council (NRC, 2000) recommended cord blood Hg as the best biomarker for fetal exposure to MeHg. In addition, cord tissue Hg concentration was revealed to be useful as a predictor of the effect of fetal exposure to MeHg (Grandjean et al., 2005). The MeHg concentration in preserved umbilical cord was also used as a biomarker of fetal-type Minamata disease patients (Akagi et al., 1998; Nishigaki and Harada, 1975). The present study investigated the relationships between THg and MeHg in cord tissue and other biomarkers of fetal exposure to MeHg in the Japanese population to evaluate the significance of Hg in the tissue.

The differences in MeHg exposure levels in various geographic areas were similar to the data from a recent Japanese hair mercury survey (Yasutake et al., 2004). The high Hg concentrations in katushika ward of Metropolitan Tokyo may also be explained by the high amount of tuna consumption in Tokyo and nearby Tokyo Metropolitan Prefecture (Yasutake et al., 2004). The correlations between the Hg concentrations in biomarkers were similar among areas. The geometric mean of THg in cord tissue in this study was 91.7 ng/g, and the level was approximately half that of the Faroe Islands study (Dalgard et al., 1994; Grandjean et al., 2005).

Thanks to the traditional Japanese custom of preserving umbilical cord tissue at the time of the infant's birth, we may use this dried cord tissue to estimate past MeHg exposure. The cord tissue is formed mainly during the second and third trimester, and cord blood is the blood circulating in the fetal body at parturition. Judging from the data on the biological half-life of MeHg of about 45 days (Smith and Farris, 1996), not only fetal blood but also cord tissue Hg will reveal the average MeHg burden of the fetus during the third trimester. In addition, rapid brain growth occurs primarily during the third trimester in humans (Dobbing and Sands, 1979) and the brain at the period is known to be most vulnerable to the toxicity of MeHg (Rice and Barone, 2000). Strong correlation coefficients were observed between cord blood THg, which is recommended as the best biomarker for fetal exposure to MeHg by the National Research Council (NRC, 2000). The strong correlation coefficient between THg and MeHg in cord tissue and the high MeHg percentage (about 90%) also suggest that cord tissue MeHg as well as THg concentrations are useful biomarkers for prenatal MeHg exposure.

Under the steady-state condition, the hair/blood mercury ratio is about 250 (WHO, 1990). However, in the present study, the maternal hair/maternal blood ratio was about 350, presumably due to the lower hematocrit (Htc, the ratio of the volume of red blood cells to the total volume of blood) during gestation (Bollini et al., 2005), especially in the last trimester as plasma volume increases. The low maternal Htc during gestation will explain the higher hair/blood ratio, because about 90% of Hg exists in red blood cells in a population that consumes much fish (Group, 1970; Sakamoto et al., 2002; Svensson et al., 1992). The difference in MeHg% between maternal blood (92.5%) and cord blood (95.2%) may also be explained by the low Htc in the former blood and the high Htc in the latter blood, as indicated by Sakamoto et al. (2002).

Maternal hair and maternal blood Hg concentrations are also important biomarkers for fetal MeHg exposure. Originally, maternal biomarkers reflect the exposure of the mother herself, and there is a certain variability between the maternal and fetal MeHg levels. Our recent study indicated that individual cord/maternal Hg concentrations in red blood cells varied from 1.08 to 2.19 in mother–infant 53 pairs at parturition, which show the individual differences in MeHg concentrations between maternal and fetal circulations at late gestation (Sakamoto et al., 2004). Stern and Smith (2003) also summarized the variability of cord/maternal blood Hg level ratio. Grandjean et al. (1997, 2005) revealed significant associations between the adverse effects and the Hg level in cord blood and cord tissue, but the effects were not well associated with the level in maternal hair. In the present study, THg

and MeHg in cord showed strong correlations with those in maternal and cord blood. However, the correlations of THg in maternal hair and either THg or MeHg in other biomarkers were comparatively low, and the 95% confidence interval of the intercept for the regression line did not include zero. This may have been due to the fact that we used the whole length of hair for Hg analysis in the present study, while Hg levels in newly formed hair reflect those in blood (Phelps et al., 1980) . In this way, the Hg concentrations in whole hair do not exactly reflect the Hg level in blood at parturition. In addition, another reason for the scattered distribution would be decrease in Hg level by artificial hair waving (Dakeishi et al., 2005; Yamamoto and Suzuki, 1978).

Some of the ratios among biomarkers calculated from our study were similar to those calculated from the Faroe Island study (Grandjean et al., 1997, 2005), suggesting that the ratios are applicable to estimation of the past Hg levels in other tissues at parturition in a population in which the MeHg exposure level is comparatively high. The mean cord tissue Hg level of fetal-type Minamata disease patients ($n = 24$, median MeHg = 1.63 μg/g; Akagi et al., 1998) was about eight times higher than that in the Faroe Islands ($n = 447$, geometric mean THg = 0.21 μg/g; Grandjean et al., 1997, 1999), and about 20 times higher than our present result (geometric mean MeHg = 0.083 ng/g). The estimated mean THg in maternal blood, cord blood, and maternal hair of the fetal-type of Minamata disease patients were approximately 100, 200 ng/g and 32 μg/g, respectively. However, the estimation of the maternal hair THg will be more uncertain as we mentioned earlier.

The findings of this study support the use of umbilical cord THg and/or MeHg as biomarkers of fetal exposure to MeHg. Further, the MeHg concentration in preserved cord tissue will be useful as the only biomarker available as a predictor of the retrospective dose–response (or dose–effective) study in the Minamata district even up to today.

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厚生労働科学研究費補助金　化学物質リスク研究事業

難分解性有機汚染物質（POPs）の胎児期暴露に関する研究
（Ｈ１８−化学−一般−００５）

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