Table 3 Concentrations (Mean ± SD, ng/g) in maternal and cord red blood cells (RBCs), the cord/maternal ratios, and the correlation coefficients of mercury, lead, arsenic, cadmium, and selenium in 81 pairs (99)

	Mercury	Lead	Cadmium	Arsenic	Selenium
Concentration in maternal RBCs	9.41 ± 4.19	26.4 ± 9.74	1.97 ± 0.72	6.16 ± 3.40	192 ± 25.1
Concentration in cord RBCs	15.3 ± 7.43	13.2 ± 4.12	0.22 ± 0.20	3.76 ± 2.27	227 ± 33.9
Cord/maternal RBCs ratio	1.63 ± 0.28	0.52 ± 0.11	0.12 ± 0.08	0.62 ± 0.17	1.18 ± 0.11
Correlation coefficient (r)	0.91**	0.79**	0.31*	0.89**	0.76**

* $P<0.05$; ** $P<0.01$.

方が母体血赤血球濃度より高かった。このため，臍帯と母体の赤血球濃度比は水銀とセレンで1より大きくなり，これら2金属の胎児への胎盤移行度は高いと推定された。メチル水銀は必須アミノ酸と結合した形で胎児に選択的に移行するものの (100, 101)，母親から児へのメチル水銀の移行度は母子ペアで大きく異なっていた (29)。セレンはSakamotoらの報告 (99) と同様の結果もあるが (102)，逆に臍帯血セレンが母体血セレンよりも低いとする結果 (103, 104) もあり，人種や食習慣の相違によって異なるかもしれない。一方，カドミウムの胎盤経由の移行はこれら金属の中で最も低く，同様の報告は多数ある (103, 105-110)。胎盤でのカドミウム蓄積量が母体血や臍帯血よりも高いことはよく知られており (105, 109, 111)，これは胎盤で発現するメタロチオネインがカドミウムを捕捉することによる (112-114)。以上より，臍帯血の代りに母体血を採取し，その濃度を胎児期の曝露指標として使用することの可否は検討する有害化学物質と影響指標によって異なるようである。すなわち，胎盤血流に起因すると考えられる影響指標（出生体重など）に対しては母体血の曝露指標が有用であるが (88, 95)，発達段階にある神経系などの影響指標に対しては臍帯由来の曝露指標の方が推奨されよう (29)。実際，小児の心臓性自律神経機能に及ぼすメチル水銀影響は臍帯血水銀濃度や臍帯組織メチル水銀濃度で有意な関連を示したが，母親毛髪水銀濃度では有意とならなかった (22, 61)。

必須金属であるセレンは魚介類 (115-117) のほかに穀類や肉 (118) からも摂取される。このため，魚を食べる習慣のある集団では血液中の水銀とセレンが正の相関を示す (115, 119, 120)。セレンはグルタチオンペルオキシダーゼやチオレドキシンレダクターゼの抗酸化酵素の構成成分として重要な役割を果たすと考えられている (121)。加えて，多くの動物実験の結果から，水銀と共存する，あるいは同時的に投与されたセレンは無機水銀やメチル水銀の毒性を減弱させることが認められており (122-126)，ヒトでもその効果が期待されている。しかし，フェロー諸島出生コホート研究ではセレンがメチル水銀の神経毒性に対する保護作用を示す証拠は示されなかったし (127)，心血管系疾患に対してセレンの役割が不明瞭であった (70, 71)。魚介類は，メチル水銀のみならず，PCBなどの発達毒性を示す有機塩素化合物や，セレンと同様にメチル水銀毒性に拮抗する作用が期待される n-3 PUFAも含む。また，セレンは無機セレンの他に，セレノシステイン，セレノメチオニン，セレノプロテインあるいはセレノネインなど多様な形態がある。どの形態がメチル水銀に対する防御的役割を担うのかを含め，魚介類摂取に伴うメチル水銀の評価を慎重に行う必要がある。

神経系に影響する有害化学物質として，メチル水銀のほかに，鉛，ヒ素，マンガンなどが知られている (59, 128-130)。1990年代には10 μg/dl以下の血中鉛であれば小児への影響はないと考えられ (131)，メチル水銀の神経発達影響に関する出生コホート研究で低濃度であった鉛は重回帰分析の説明変数から外された (18, 19)。2000年代になって，Canfieldらは172名の子ども達の血中鉛を経時的に測定し (132)，5歳児の知能指数 (IQ) が血中鉛濃度10 μg/dl以下で直線的かつ急激に低下し，それ以上の血中鉛濃度ではIQの低下が緩やかになると報じた。その後，血中鉛濃度5 μg/dl前後から小児の神経影響が現れ始めると考えられるようになり (128, 133, 134)，鉛とメチル水銀の同時曝露による神経影響について再検討することが必要となってきた。Yorifujiら (135) はフェロー諸島出生コホートの胎児期メチル水銀曝露を調整した後の鉛影響を解析し，臍帯血鉛（集団平均1.6 μg/dl，最大値11 μg/dl）が認知機能に有害影響を及ぼすことを報告した。しかし，鉛がメチル水銀の神経毒性に対し相補的あるいは単独で作用するのかどうかについては今後さらに検討する余地があろう。いずれにしても，低濃度曝露による神経影響を評価する際には，単にメチル水銀とその交絡因子を解析するのではなく，関連する有害化学物質も併せて分析する姿勢が望まれよう。

毒性研究を解釈するにあたり，過去に示された臨界濃度域を含まない集団を用いてリスク評価（特に，量−反応評価）した研究には注意が必要である。この種の論文はデータ信頼性の指標として大きな標本数を強調する。例えば，魚摂取に由来する水銀曝露が冠動脈疾患や心筋梗塞発作の発症に影響を及ぼす証拠はないと結論したMozaffarianらが解析に用いた米合衆国男性は51, 529名，女性121, 700名（実際のnested case-control studyでは3, 427名）であるが，最も高い5分位集団の毛髪換算水銀の中央値は2. 70 μg/gであった (70)。National Academy of Scienceはメチル水銀の臨界濃度を毛髪水銀で11 μg/g

としている（20）。また，血中鉛濃度3.63～9.99 μg/dl群は1.94 μg/dl未満群に比べて心血管系死亡リスクが1.55倍（95%信頼区間1.08～2.24）であると報告したMenkeらの対象者数は13,946名であった（136, 137）。これらの統計解析に問題があるとは思わないが，著名雑誌であるNew England Journal of Medicineに掲載された有料でないAbstractの結論（70）を読んだ一般人がメチル水銀を多く含む魚を多食するようになるかもしれない。すなわち，毒性物質の量一反応評価は過去に提示された臨界濃度を含む曝露データの中で検討されるべきであり，そうでない評価は一般人に「百害あって一利なし」となる恐れもある。

今後のメチル水銀の疫学研究として，耐容週間摂取量（TWI）を算出する際のone compartment pharmacokinetic modelに使われる生物学的半減期や毛髪／血液濃度比などの仮説を再検討することが挙げられるかもしれない。メチル水銀の生物学的半減期は，これまで2つの論文で算出された52±4（標準誤差）日（68）と50±1日（69）の値から50日とされ，上のモデルの排出定数として0.014（$=ln2/50$）が使われている。実際には，イラクで高濃度メチル水銀曝露を受けた患者で算出した生物学的半減期72日や（138），魚摂取を介して高濃度メチル水銀に曝露したボランティアから算出された半減期80日も存在する（67）。また，メチル水銀の毛髪／血液濃度比は，過去に報告された値は140～370であり，250が一般に用いられている（74, 75, 139）。しかし，フェロー諸島出生コホートの7歳と14歳児の濃度比は中央値で370と264であった（140）。また，スウェーデン成人の中央値は373であり（141），日本人妊婦の平均値は約350であった（142）。このように，最近報告された毛髪／血液濃度比は過去に算出された値と大きく乖離している可能性があるが，メチル水銀のPTWIやTWI算出に際して保守的な値が使われている（75）。したがって，どの値が薬物動態学的に最適であるのか吟味する研究は将来のリスク管理に不可欠であろう。

Ⅷ. 結　　語

PubMedを用いて最近のメチル水銀に関する疫学研究を概観し，以下の結論を得た。①2008年以降，メチル水銀を扱った論文の中で疫学研究の割合は減少傾向にある。②魚摂取による胎児期メチル水銀影響は，例え低濃度であっても，PCBや妊娠中の母親魚摂取量を調整すると小児発達に軽微のマイナス影響を及ぼす。③メバチマグロやメカジキのような高濃度メチル水銀を含む魚を長期間多量に摂食し続けると交感副交感神経バランスの不均衡に由来する心疾患の潜在的リスクを高める可能性がある。④1945～89年に水俣地域で生まれた住民から収集した臍帯組織のメチル水銀レベルを測定すると，1 μg/g以上に高くなった濃度は主に1947～68年に生まれた住民で観察され，そのピークは水俣におけるアセトアルデヒド生産量のピークと一致していた。⑤いくつかの途上国は日本の高度経済成長期の重化学工業生産の活動状況と酷似しており，そのような国々では，危険物質の早期認知とともに，それに対する予防対策に注意を払う必要がある。

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東日本大震災特集

被災地公務員の心的負担

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■ プロローグ

2009年頃の日本学術会議の子どもの健康分科会で環境リスクについて触れ，その中で「子どもの放射線被曝からの予防は，まさに原子力発電所の安全基準および安全対策に取り組む国家の威信に関わる問題である．すなわち，地震などの自然災害時，あるいは原子力発電所で働く人々のヒューマンエラーが発生した時にどれ程の安全性が保証されるのかが問われる．チェルノブイリ原発事故の経験を共有している世界に向けて，万一いままでに経験したことのない強い地震であったので，放射性物質が大気中に放出したという弁解が発せられるとするならば，恥の上塗り以外の何物でもない」と警告した．これが現実味を帯びたのは2011年3月11日であった．

その日は東京出張の予定であったが，翌日に行われる秋田大学後期入学試験の準備を理由に，結果として，2分以上続く震度5強の横揺れに学内で遭遇した．建物が揺れ始め，10秒も経たないうちにコンピュータ画面は真黒になった．秋田県内はその後30時間以上停電が続いたが，緊急時や停電時には解錠されると大学当局が説明していた非常用ドアは余震の続くあいだ開かずのままであった．また，帰宅難民にならずに済んだが，秋田県内のJR線，遠距離バス，飛行機は全て止まり，陸の孤島と化した．乾電池式ラジオから流れるNHK第一放送の地震情報と言えば，一度聞けば理解できる県内の些細な震災状況をエンドレステープの如く繰返していた．

■ 東日本大震災

東日本大震災の全体像—東北地方沿岸部の大津波や福島第一原発崩壊など—の情報を知ったのは震災翌日の午後7時のテレビニュースが観られるようになってからであった．停電中に行われた後期入学試験に来た受験生には八戸，仙台，千葉，大阪の出身者がおり，彼等が無事帰宅できるだろうか，そればかりを面接試験終了の夕方まで心配した．ひとりの面接者は「君は春休みに復旧ボランティア活動に参加するつもりはあるか？」と，未だ震災被害の把握もできていない状況下で質問していた．

東北大学医学系研究科は，人的被害こそなかったそうだが，8階に位置する環境保健医学教室は書庫の本，測定機器，コンピュータなどが足の踏み場もないくらい床に落下したと聞いた．また，同教室は昨年夏より東北コホート調査で東北沿岸部に住む7歳児の神経発達影響の評価を行っており[1]，現地事務所で働いている検査者の安否が気になった．被災直後に携帯メールをすると，検査者たちは津波を避けるために市立病院に避難したとの返事であったが，連絡はその後途絶えた．東京出張中に帰宅困難者になられた東北大学の佐藤　洋教授から「山形県米沢市から仙台市に移動する」とのメールが震災後3日目に届き，安否を気遣っておられた人々にこの旨をお伝えした．さらに2日ほどして，現地事務所は大津波で1.5m程度浸水した旨の連絡が届いた．現地は大津波警報が発令されていたため，検査者は個人情報や一部データの入った外部記憶装置を持参して避難したという．しかし，震災前に測定していた子ども達の脳波検査データは脳波計・コンピュータの水没（写真1）とともに消えてしまった！

大津波後に放映されるニュース画像は惨憺たるものであった（写真2）．日毎に増える死者数の合間に，震災後10日近く経て生存が確認された若者の画像は，あたかも戦後復興期の逞しさすら感じさせた．しかしながら，連日のテレビ報道の中で日増しに気掛かりになってきたのは，岩手，宮城，福島の沿岸部市町村職員の健康状態であった．津波により家屋を失った避難住民の世話を24時間行っているものの，職員自身の家族や家屋も震災・津波・放射線被曝の犠牲になっている人もいるであろう．支援物資が十分に届かない中で，公僕ということで自らの生命を縮めても良いと言うのであろうか．一方，「私にできることはないのか？」と自問が続いた．

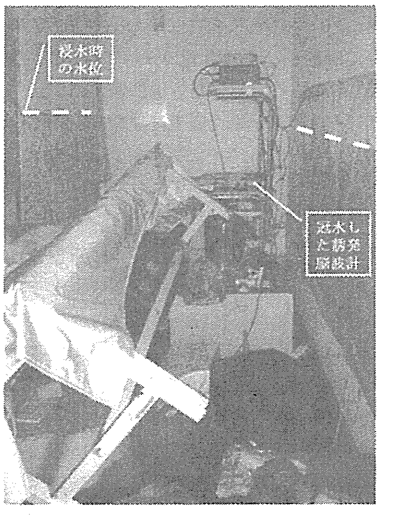

写真1

写真2

■ 過重労働の健康影響

Sokejima & Kagamimoriは，急性心筋梗塞患者195名と年齢，職業を一致させた心疾患を有さない対照群331名の患者対照研究を行った[2]．心筋梗塞患者群では高血圧，血清コレステロール高値，耐糖能異常，肥満，喫煙の割合が高く，一方，精神的ストレスには差が認められなかった．発症前1ヶ月の就労時間でも患者群と対照群で有意差は認められなかった．就労が1日平均7-9時間の労働者群の発症リスクを1とした時，平均11時間以上の労働者群の急性心筋梗塞の発症リスク比は2.44（95％信頼区間，1.26-4.73）であり，また7時間未満の労働者群の発症リスク比も3.07（同，1.77-5.32）であった．すなわち，平均就労時間と急性心筋梗塞の発症リスクの関係はU字曲線であるものの，残業時間の延長に伴って発症リスクは増加する．

2006年3月17日の基発第0317008号の「過重労働による健康障害防止のための総合対策」が発せられ，その中で「過重労働による業務上の疾病を発生させた事業場であって労働基準関係法令違反が認められるものについては，司法処分を含めて厳正に対処する」と記されている．このためか，厚生労働省は「長時間労働者に対する医師による面接指導制度の認知別事業所割合」を発表している．もっとも，2010年7月29日の朝日新聞によると，前年度の中央省庁における月平均残業時間は旧労働省系が73.4時間，旧厚生省系が71.1時間，経済産業省が45.9時間であった．これら過重労働の職員に対して制度下の面接指導を実施したのか，また過労死が発生した場合，誰（所轄大臣？）を処分するのか国民に明示して頂きたいと思う．もし「省庁は本制度下にない」と放言するならば，それは正に“お役所仕事”の典型例となろう．

いずれの被災地でも市町村職員の多くは過重労働者と言える状況にあるだろう．私が被災地で調べたいと思ったのは職員の睡眠時間と心的負荷についてであった．これは以下の根拠による．7時間睡眠群の対照群と比較して，平均睡眠時間が5時間以下の成人群の冠動脈性心疾患死亡リスクは1.57倍（95％信頼区間，1.32-1.88）高くなり，また9時間以上の睡眠群で1.79倍（同，1.48-2.17）高くなると報じられている[3]．同様に，閉経後の米国女性を対象にした睡眠研究でも似通った数値が報告されている[4]．すなわち，睡眠不足も寝過ぎも冠動脈性心疾患発症のリスクを高めるということにある[5]．また，Jouvenらはフランス・パリ市在住の健康障害症状を持たない男性労働者5,713名で，かつ臨床的に検出可能な心血管疾患のなかった人達を約23年間にわたり追跡調査した結果を，世界的に有名な米国医学雑誌に発表した[6]．主たる結果は，75以上の安静時心拍数を持ったヒトは心筋梗塞による突然死の発症リスクが，心拍数60未満のヒトと比べて，3.92倍（95％信頼区間，1.91-8.00）高くなるというものであった．すなわち，安静時心拍数が75より高いかどうかは，将来の突然死を左右する可能性があるかもしれないのである．フランスの労働者が我が国の労働条件や日常生活に合致するかどうかについて吟味する必要があるものの，安静時心拍数の意義を考える上で重要なエビデンス（証拠）である．

■ ボランティア活動

ガソリン事情も多少良くなった4月初旬，東北大学の仲井邦彦教授から沿岸部自治体に家庭用血圧計を届けに行きませんかとお誘いのメールがあった．前述の東北コホート調査で子どもの家庭血圧を測定しているが，震災に際して血圧計の提供を受けていたオムロンヘルスケア社より支援の申し出があり，沿岸部自治体に届けることになったのである．医師として診療活動に携わることは能力的に無理であるが，自治体職員の健康状態を把握することはできるかもしれないと考え，手持ちの血圧測定装置と自律神経機能測定用心電計を準備し，ボランティア特別休暇届（4月8-10日）を大学に提出した．申請した翌日の7日夜半，第二波と思われる大余震（仙台で震度6強）が東北地方を襲い，東北電力管内は一斉停電に陥った．秋田の停電は8日の正午前に復旧したが，東北自動車道の水沢－平泉間はしばらくのあいだ通行止めとなった．このため，8日は秋田に留まり，9日朝秋田自動車道～東北自動車道を走って水沢インターまで移動し，そこから震災で壊れた橋を回避しながら一般道を通ってボランティアセンターのある市民健康管理センターに入った．しかし，関東地方から東京都衛生局，聖マリアンナ医科大学ほか，多くの医療チームが同センター近くに既に居を構え（写真3），私が自治体職員の健康を把握するための店開きをする余地はなかった．震災直後はカップ麺などが職員の唯一の食料であり，その後全国から送られてきた缶詰製品，菓子類，ペットボトル飲料を食しておられたが，震災前の食事とは程遠いものであろう．

役場の健康増進課と打合わせの後，オムロンヘルスケア社から預かった自動血圧計を陸前階上駅近くの避難所に届けた．この辺りは海岸線に沿って電車が走っているが，線路が根こそぎ津波に攫われている箇所も散見された．被災者が400名近くいるこの避難所には体育館の片隅に診療室が設けられ，3名の看護師が交替で大半の医療業務を支えていた．また，市医師会に所属する2名の医師も時折回診されていると聞いた．高血圧症をもつ高齢者の多くは家庭用血圧計で自己管理していたが，被災時に家財道具とともに血圧計も流失してしまい，（避難所の診療室入口付近に自動血圧計は設置されていたが）自らの血圧管理を実行しづらい状況にあった．血圧計はそのような血圧計を失った被災者に配布されたが，この程度の規模の避難所でも62名の希望者がいた．血圧計の取扱い操作を説明する際に一

写真3

写真4

人の被災者を測ると，収縮期血圧195 mmHg，拡張期血圧110 mmHg，心拍数96とかなり高かった．大勢の被災者がプライバシーのない広い体育館に4週間近くも寝泊まりし，止まぬ余震，寒さ，低栄養からくるストレス下で生活していると，自ずと血圧も脈拍数も上がってくるに違いない．看護師の話では，まもなく間仕切り用段ボールが届く予定とのことだった．

津波後の光景を自分の目で直接確認すると想像を絶するものがある．南三陸町や仙台市若林区などでは多くの住宅が平地にあり，隣接する住居の大半が壊滅状態となった．一方，私が見た市街地には起伏があり，例えば港と小高い所にある役場までの道路約500 mを車で通過すると，港付近の木造家屋は全壊，その途中は床上浸水や半壊，役場近くでは無傷のままであった．緩やかな坂道の上下関係は津波の被災状況にも差をもたらし，日々挨拶を交わしていた隣人同士の感情にも影響を及ぼしかねない．また，JR大船渡線に沿って陸前高田方向に移動すると，鹿折唐桑駅がある．この地域は湾の奥座敷に相当し，最大級の津波被害とともに，港湾にあった船舶用燃料タンクの火災も重なり，あたかも焦土と化していた．その中に目を凝らすと，背景色と同じ色の服を着た自衛官や警察官が被災者の捜索にあたっていた（写真4）．

■ エピローグ

災害関連死は，被災後の数こそ減少しつつあるものの，5月13日現在で500名を超えたと言う．死因の多くは循環器疾患であり，また7割強は60歳以上の高齢者であった．これらの人々の健康管理を担うのは，正に地域医療そのものである．一方，東京電力福島第一，第二原子力発電所の非常勤産業医でもある愛媛大学の谷川　武教授は，現地で日夜働いている東京電力社員の健康管理に尽力されている．しかしながら，被災地元で働いている地方公務員の過重労働の実態は把握されているのであろうか．国・地方行政府の被災地復興に向けた計画立案が終わり，その描かれた図面に従って邁進し始める頃が彼等の心労の極限になるかもしれない．この場合，虚血性心疾患や脳卒中に対して特別の注意を払わねばならないが，彼等の保健指導を誰が行うのか．今，被災地の医療施設が徐々に復旧し，全国各地から集まっていた医療チームが被災地を離れている．"過労死"というのは日本人の心を震撼する言葉のひとつであるが，もし被災地の地方公務員ばかりがその犠牲になることがあるならば，それはあまりに哀しい話となろう．

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Prenatal exposures to environmental chemicals and birth order as risk factors for child behavior problems ☆

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ABSTRACT

Objectives: To assess whether polychlorinated biphenyls (PCBs), methylmercury, lead, or parental child-rearing attitudes was most crucial for maladaptive behavior problems, we examined Japanese 30-month-old children followed up from pregnancy.
Methods: The Child Behavior Checklist (CBCL) was used to assess the behavior problems in 306 children. The associations of cord-blood total PCBs (ΣPCB), total mercury (THg), and lead with each CBCL subscale were examined by multivariate analyses.
Results: The median values in cord blood of the 306 children were 48.3 (5 and 95 percentiles, 18.6–116.3) ng/g-lipid for ΣPCB, 10.2 (4.1–24.5) ng/g for THg, and 1.0 (0.5–1.7) μg/dl for lead. The internalizing score of the CBCL was significantly correlated with ΣPCB ($r=0.113$) in the children, though no significant correlation was seen between any CBCL score and either THg or lead. The significant correlation disappeared when conducting multiple regression analysis with possible confounders; at that time, the birth order, home environment, and maternal intelligence quotient were significantly related to the internalizing score. Three CBCL scores and ΣPCB levels were significantly higher in the first-born children than in the second-born or following children, and the partial correlation coefficient with the adjustment for all confounders except birth order was significant between the internalizing score and ΣPCB in the latter children ($r=0.175$).
Conclusions: Internalizing behavior appears to be affected by prenatal exposure to PCBs at low levels. Under lower-level exposures, however, behavior problems may be more strongly associated with parental child-rearing attitudes involved in birth order, than with such hazardous chemicals.

1. Introduction

Polychlorinated biphenyls (PCBs), methylmercury (MeHg), lead, and parental child-rearing attitudes have been suggested as the causes inducing behavioral problems such as attention deficit/hyperactivity disorder (ADHD) of children in the literature, but which of them has the most crucial effect is unclear. For instance, the impact of perinatal exposure to PCBs on neurobehavioral and neuropsychological functions remains controversial. The adverse effects of PCBs on child neurodevelopment were demonstrated by cohort studies in Michigan (Jacobson and Jacobson, 1996), Oswego (Stewart et al., 2008), the Netherlands (Patandin et al., 1999), and Germany (Walkowiak et al., 2001). In the North Carolina cohort, the effects of perinatal exposure to PCBs changed with time (Rogan et al., 1986; Rogan and Gladen, 1992); i.e., significant associations observed in neonates and 2-year-old children disappeared when the subjects became three to five years old. In contrast, some cohort studies failed to find a significant link between perinatal exposure to PCBs and neurobehavioral endpoints (Grandjean et al., 2001; Daniels et al., 2003; Suzuki et al., 2010). There are several possible reasons for these inconsistent results. In some studies, the other toxic chemicals, e.g. MeHg and lead, were not simultaneously assessed. The neurodevelopmental outcomes used may have been reversible

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in childhood. In addition, nutrients such as polyunsaturated fatty acids (PUFAs) and selenium might affect the outcomes.

Perinatal exposures to MeHg and lead are known to restrain child neurodevelopment. Although the conclusions on the effect of prenatal MeHg exposure at hair levels of less than 40 μg/g differed between the Faroes birth cohort study and the Seychelles child development study (Grandjean et al., 1997; Davidson et al., 1998), the addition of maternal fish intake or *n*-3 PUFA at parturition as confounders elicited the developmental toxicity of MeHg (Budtz-Jørgensen et al., 2002; Strain et al., 2008). Blood lead has been reported to induce lower intelligence quotient (IQ) and ADHD scores in children (Lanphear et al., 2005; Roy et al., 2009). Thus, all crucial chemicals must be considered at the stage of the study design because developmental effects of environmental exposures to such chemicals at low levels are very delicate. Namely, a research model with concomitant exposures is necessary for assessing subtle effects on child development.

Of the various kinds of behavioral tests, the Child Behavior Checklist (CBCL) can evaluate maladaptive behavioral and emotional functioning of children (Visser et al., 2006), and has been used to assess the effects of each of PCBs, MeHg, and lead on behavior problems (Davidson et al., 1998; Wasserman et al., 1998; Burns et al., 1999; Myers et al., 2000, 2009). Apart from behavioral effects of hazardous chemicals, one study using the CBCL reported that more behavior problems in school-aged children were associated with first-born children (Wasserman et al., 1998). Thus, our attention was directed to possible confounders affecting child behavior, along with toxic substances. We have conducted the Tohoku Study of Child Development (TSCD), focusing on both the potential risks and benefits of fish intake during pregnancy (Nakai et al., 2004). In the present study, the CBCL was employed to clarify whether prenatal low-level exposures to PCBs, MeHg, and lead affected behavior in 30-month-old children. Whether the links between such concomitant exposures and behavior problems were distorted by a certain confounder such as birth order or home environment was also investigated.

2. Materials and methods

2.1. Study design and subjects

The study protocol of the TSCD has been described elsewhere (Nakai et al., 2004). The medical ethics committee of the Tohoku University Graduate School of Medicine approved this protocol. The research field was comprised of two areas, an urban area and a coastal area in the Tohoku district of Japan (Suzuki et al., 2010), but the subjects in the urban area were employed in this study because their ΣPCB concentrations in cord blood had already been determined. To establish an optimal study population, the eligibility criteria included a singleton pregnancy, Japanese as the mother tongue, and neonates born at term (36–42 weeks of gestation) with birth weight of more than 2400 g and no congenital anomalies or diseases. Information about pregnancy, delivery and the characteristics of infants at birth was obtained from medical records.

We enrolled 687 pregnant women with their written informed consent to participate in this study, and 599 mother–child pairs were registered according to the eligibility criteria. The CBCL was sent to the mothers when their children became 30 months old. Of the 506 CBCL sheets sent back, 455 had complete data. Finally, 306 complete data sets on ΣPCB, total mercury (THg), and lead concentrations in cord blood, maternal seafood intake, and possible confounders such as the home environment and maternal IQ, in addition to the CBCL, were available for the present study population.

2.2. Exposure markers

Umbilical cord blood was obtained immediately after birth, and stored at −80 °C until analysis. All 209 PCB congeners were analyzed by high-resolution gas chromatography and high-resolution mass spectrometry using the isotope dilution method. Laboratory analytical methods and quality control procedures were described elsewhere (Suzuki et al., 2010). All sample analyses were performed by IDEA Consultants, Inc. (Tokyo, Japan) and Shimadzu Techno-Research, Inc. (Kyoto, Japan). The quality of PCB analyses in these laboratories was validated using an external quality assurance program (Nakamura et al., 2008). The calculated limit of detection (LOD) was 0.03 pg/g-wet, which was identified by the signal-to-noise ratio. The amounts of congeners below the LOD were set at zero. The ΣPCB concentration represents the sum of the all measured congeners, expressed as ng/g-lipid.

THg and lead concentrations in whole cord blood collected after delivery were analyzed by IDEA Consultants, Inc., using cold vapor atomic absorption spectrometry and inductively coupled plasma mass spectrometry, respectively (Suzuki et al., 2010). The data quality was validated by external quality assurance programs.

Maternal fish intake was estimated from a food frequency questionnaire (FFQ) consisting of 122 individual foods, recipes, and 13 additional items regarding fish and shellfish. Detailed information on eating frequency and the amounts of 13 specific seafood types has already been reported (Suzuki et al., 2010). The FFQ was administered four days after delivery. Trained examiners showed a real-size photograph of each food to the mothers, and they answered about the frequency and the amount of intake per meal. Total seafood intake (kg/year) was calculated as the sum of the intake of the 13 seafood types.

2.3. Outcome variables

The CBCL/2–3, designed to obtain parental ratings of problem behaviors in 2- to 3-year-old children (Achenbach, 1992), was applied to our 30-month-old children. We used the Japanese-version of the CBCL/2–3 (Nakata et al., 1999). Ninety-nine items of the CBCL/2–3 describing different behavior problems were classified under seven major problems. Of them, three scores were used, i.e., the externalizing score (oppositional, aggressive, and overactive problem) and internalizing score (withdrawn and anxious problems), as well as the total CBCL score. These were converted to age-standardized scores (*T* scores having a mean=50 and SD=10). *T*-scores of 60–63 and of more than 63 on the total CBCL score were regarded as the borderline range and the clinical range, respectively.

2.4. Possible confounders

Major potential confounders included child age in the month at examination, birth weight, child gender, maternal age at parturition, delivery type, birth order (first-born or not), drinking and smoking habits during pregnancy, and the duration of breastfeeding. The maternal IQ was evaluated using the Raven standard progressive matrices (Raven, 1958). We employed the raw score because it has not been standardized in Japan. The home environment was assessed using the Evaluation of Environmental Stimulation (EES) (Anme et al., 1986), i.e., a modified version of the Home Observation for Measurement of the Environment (HOME) (Caldwell et al., 1984). The mother was asked to fill in the EES when her child was 18 months old. The correlation coefficient between the EES and HOME scores was 0.80, and the reliability and validity of the Japanese version of the EES have already been confirmed (Anme et al., 1990).

2.5. Data analysis

The Mann–Whitney *U* test and χ^2 test were used to compare the 306 mother–child pairs with complete data and the remaining pairs of the whole cohort and for comparison of the 155 first-born and 151 other pairs with complete data. ΣPCB, THg, and lead in cord blood and maternal seafood intake were logarithmically transformed because of skewed distributions. Pearson product-moment correlation coefficients (r) were calculated to determine the association between the CBCL scores and exposure markers. Multiple regression analysis was used to adjust for possible confounders, i.e. birth weight, child gender, maternal age at parturition, birth order, delivery type, drinking and smoking habits during pregnancy, the Raven and EES scores, and the duration of breastfeeding. All analyses, with two-sided p values, were performed using SPSS Ver. 17.0 (SPSS Japan, Tokyo) and the significance level was set at $p<0.05$.

3. Results

Table 1 provides descriptive information for all mother–child pairs who were eligible to participate in this study. No parameters, except the Raven score and breastfeeding, differed significantly between the children with complete data and the remaining children (maximally, 209) who had incomplete information on exposure biomarkers, CBCL/2–3 scores, and confounder measures. The mean age of children of the mothers who answered the questionnaire was 31.6 ± 1.7 (SD) months. The cord-blood PCB-153 was significantly higher in the 306 children with

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Table 1
Exposure biomarkers, endpoints, and confounders in 306 mother–child pairs of this study population and remaining mother–child pairs that were excluded because of incomplete data.

	The present study population Mean ± Standard deviation (or median and 5–95 percentiles or number and % in parenthesis)	Remaining mother–child pairs Mean ± Standard deviation (or, median and 5–95 percentiles or number and % in parenthesis)	p-value[a]
Exposure biomarkers			
Cord-blood ΣPCB (ng/g-lipid)[b]	48.3, 18.6–116.3	42.9, 19.4–101.2	0.057
Cord-blood THg (ng/g)[b]	10.2, 4.1–24.5	9.7, 4.5–21.9	0.306
Cord-blood lead (μg/dl)	1.0, 0.5–1.7	1.1, 0.6–1.7	0.366
Scores of the CBCL/2–3 (*T* score)[b]			
Internalizing score	47.5 ± 9.2	48.1 ± 9.7	0.846
Externalizing score	48.2 ± 9.8	47.8 ± 9.1	0.835
Total score	48.1 ± 9.8	48.5 ± 9.5	0.963
Confounders			
Birth weight (g)	3062 ± 322	3083 ± 357	0.450
Child gender (boys, %)	157 (51.3)	158 (53.9)	0.521
Maternal age at parturition (years)	31.7 ± 4.0	31.0 ± 4.7	0.038
Birth order (first child, %)	155 (50.7)	153 (52.2)	0.702
Delivery type (spontaneous, %)	220 (72.2)	210 (71.7)	0.952
Drinking habit during pregnancy (drinkers, %)	100 (32.7)	90 (30.7)	0.606
Smoking habit during pregnancy (smokers, %)	19 (6.2)	28 (9.6)	0.128
Seafood intake during pregnancy (kg/year)	20.7, 5.4–50.8	19.0, 3.2–53.3	0.393
Raven score	52.0 ± 5.7	50.7 ± 7.0	0.019
Score of EES at 18 months[b]	28.1 ± 3.4	28.4 ± 3.2	0.408
Breastfeeding (months)	8.4 ± 4.1	7.6 ± 3.8	0.026

[a] Mann–Whitney *U* test or χ^2 test.
[b] PCB: polychlorinated biphenyls; THg: total mercury; CBCL: Child Behavior Checklist; EES: Evaluation of Environmental Stimulation.

Table 2
Pearson product-moment correlation coefficients between exposure markers and CBCL scores in 306 pairs with complete data.

	CBCL/2–3		
	Internalizing score	Externalizing score	Total score
$\log_{10}$ [Cord-blood ΣPCB]	0.113*	0.046	0.068
$\log_{10}$ [Cord-blood THg]	0.001	−0.036	−0.039
$\log_{10}$ [Cord-blood lead]	−0.083	−0.036	−0.077
$\log_{10}$ [Maternal seafood intake]	−0.067	−0.108	−0.102

** $p < 0.01$.
* $p < 0.05$.

complete data (median, 28.0 ng/g-lipid; 5 and 95 percentiles, 10.4–82.5 ng/g-lipid) than in the remaining children (median 24.7 ng/g-lipid; 9.5–66.6 ng/g-lipid), but the ranges and distributions of ΣPCB and PCB-153 were similar between the two groups (the correlation coefficient between ΣPCB and PCB-153, $r=0.901$). The median THg levels in 3 cm of maternal hair from the occipital area at parturition were 1.98 μg/g in the 306 pairs with complete data and 1.99 μg/g in the remaining pairs. Judging from the total score of the CBCL/2–3, 263 children of the 306 pairs with complete data (85.9%) had normal scores, 26 children (8.5%) were thought to be in the borderline range, and 17 children (5.6%) were within the clinical range.

Table 2 shows simple correlation coefficients between the CBCL/2–3 scores and exposure markers. Only the internalizing score was significantly correlated with cord-blood ΣPCB. As illustrated in Fig. 1, cord-blood PCB-153 was also significantly correlated with the internalizing score ($r=0.127$). There was no significant correlation between any CBCL score and either cord-blood THg or maternal hair THg at parturition, inasmuch as the correlation coefficient between THg levels in maternal hair and cord blood was 0.839 in the 306 mother–child pairs. As shown in model 1 of Table 3, however, the significant association of ΣPCB (and PCB-153) with the internalizing score disappeared after adjusting for all possible confounders. The Raven and EES scores and birth order had a significant relation to that score. However, the significant association of ΣPCB (and PCB-153) with the internalizing score reappeared after removing the "birth order" variable from model 1, as shown in model 2. In both models, the EES score and maternal age at parturition were significantly related to the internalizing, externalizing, and total scores of the CBCL/2–3.

Table 4 presents results of the comparison between the first- and second-born or following children in the 306 pairs. The ΣPCB (and PCB-153) concentrations, along with three CBCL scores, were significantly higher in the former (median, 31.6 ng/g-lipid) than in the latter (22.1 ng/g-lipid). In examining the two groups separately, the partial correlation coefficient, with adjustment for all variables employed in model 2 of Table 3, between the internalizing score and ΣPCB was statistically significant ($r=0.175$, $p=0.039$) for the second-born or following children.

4. Discussion

In the environment, there are various hazardous chemicals such as PCBs, MeHg, and lead, affecting the nervous system, but the effects of concomitant exposures to such chemicals have not always been assessed. Another issue is that little comparable information is available concerning the levels of biomarkers. As an example of specimens for THg, maternal hair and cord blood were used for evaluating child neurodevelopment (Davidson et al., 1998; Grandjean et al., 1997) and toenails were employed for the risk assessment of coronary heart disease (Guallar et al., 2002; Yoshizawa et al., 2002). These issues make the interpretation of neurotoxicity complicated. The median PCB-153 level in cord blood of this study was near that of the Massachusetts study (30 ng/g-lipid in maternal serum), the lowest among 10 studies of the U.S.A, the Netherlands, Germany, Denmark, and northern

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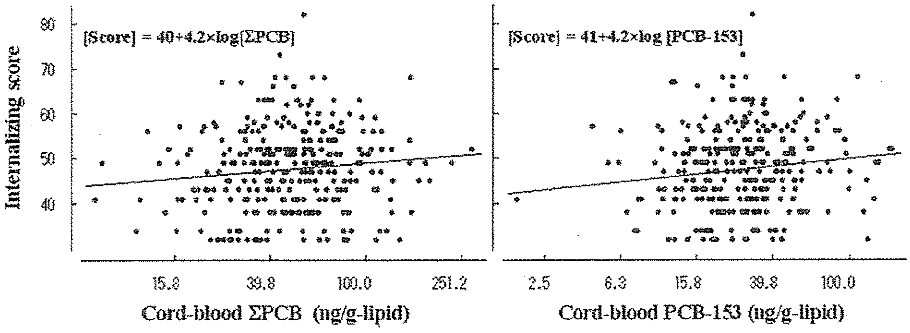

Fig. 1. Relations of cord-blood ΣPCB and PCB-153 to internalizing score of the CBCL/2–3 in 306 children.

Table 3
Relations of CBCL subscale scores to exposure markers[a] and confounders[a] in 306 pairs: results of multiple regression analysis (multiple regression and standardized regression coefficients).

	Internalizing score		Externalizing score		Total score	
	Model 1	**Model 2**	**Model 1**	**Model 2**	**Model 1**	**Model 2**
Multiple correlation coefficient (*R*)	0.418**	0.319**	0.320**	0.315**	0.376**	0.327**
$\log_{10}$ [Cord-blood ΣPCB]	0.063	0.158*	0.067	0.085	0.048	0.114
$\log_{10}$ [Cord-blood THg]	−0.005	−0.004	−0.033	−0.033	−0.038	−0.037
$\log_{10}$ [Cord-blood lead]	−0.107	−0.070	−0.038	−0.032	−0.092	−0.066
Birth weight	0.025	0.048	0.014	0.019	0.016	0.031
Child gender	−0.001	−0.010	0.027	0.026	0.019	0.013
Maternal age at parturition	−0.077	−0.216**	−0.143*	−0.170**	−0.105	−0.200**
Birth order	−0.313**		−0.059		−0.216**	
Delivery type	−0.024	0.010	−0.067	−0.061	−0.052	−0.028
Drinking habit during pregnancy	0.016	0.027	0.035	0.037	0.023	0.031
Smoking habit during pregnancy	0.018	−0.004	0.057	0.055	0.057	0.047
$\log_{10}$ [Maternal seafood intake]	−0.060	−0.076	−0.077	−0.080	−0.066	−0.077
Raven score	−0.116*	−0.074	−0.052	−0.044	−0.059	−0.030
Score of the EES at 18 months	−0.128*	−0.139*	−0.144*	−0.146*	−0.156**	−0.164**
Breastfeeding	−0.032	−0.038	−0.127*	−0.128	−0.089	−0.093

* $p < 0.05$.
** $p < 0.01$.
[a] See units in Table 1.

Quebec (Longnecker et al., 2003). The level in our study was extremely low compared to studies in the Faroe Islands (Grandjean et al., 2001) and northern Quebec (Muckle et al., 2001). The maternal hair THg levels at parturition (median, 1.98 μg/g) of our participants were about a half of those in the Faroese, Seychellois, and Nunavik Inuit infants (Muckle et al., 2001). The median cord-blood lead level was lower in the present study than in seven cohort studies of environmental lead exposure and IQ (Lanphear et al., 2005). Therefore, this study addressed the behavior effects of concomitant exposures at lower levels.

In the children of our study, an association of elevated PCBs at birth with internalizing behavior was suggested by correlation analyses, though the significant effect of PCBs disappeared when considering possible confounders such as birth order. Still, a significant relation was again found in the second-born or following children using the partial correlation coefficient. Many previous reports demonstrated the developmental effects of perinatal exposure to PCBs (Rogan et al., 1986; Rogan and Gladen, 1992; Jacobson and Jacobson, 1996; Patandin et al., 1999; Walkowiak et al., 2001; Stewart et al., 2008). Recently, Plusquellec et al. (2010) also observed a significant association between prenatal exposure to PCB-153 at relatively higher levels and behavioral outcomes relating unhappiness and anxiety. Taken together, the implication of this study is that prenatal exposure to PCBs at low levels may affect the internalizing behavior. Additional study using cord-blood/serum PCBs is needed to confirm the effects of prenatal exposure to PCBs at low levels on behavior problems, because maternal PCB levels may not exactly reflect cord-blood/serum ones in the assessment of child neurodevelopment, different from birth weight (Konishi et al., 2009).

In contrast to some studies showing MeHg-related neurotoxicity (Grandjean et al., 1997; Strain et al., 2008; Suzuki et al., 2010), our study could not find such an effect. This corresponds to the Seychelles child development study presenting no association between maladaptive behaviors assessed by the CBCL and either prenatal or postnatal MeHg exposure (Myers et al., 2000). In addition, Myers et al. (2009) reported that postnatal THg was adversely associated with Connor's Teacher Rating Scale ADHD index in Seychellois children aged 107 months, but they were suspicious of their result because "there was no clear evidence that behavioral changes could be expected with MeHg." In any case, prenatal exposure at maximal maternal hair THg levels of less than 9.4 μg/g may not lead to such behavior problems.

Our study failed to find a significant correlation between cord-blood lead (range, 0.4∼4.8 μg/dl) and any CBCL score. However, Lanphear et al. (2005) concluded that environmental lead exposure in children who have maximal blood lead levels of less than 7.5 μg/dl was associated with intellectual deficits. Yorifuji et al. (2010) also demonstrated the adverse effect on cognitive

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Table 4
Birth order-specific exposure biomarkers, CBCL scores, and basal characteristics in 306 pairs of this study population.

	155 first-born children Mean ± Standard deviation (or, median and 5–95 percentiles or number and % in parenthesis)	151 other children Mean ± Standard deviation (or median and 5–95 percentiles or number and % in parenthesis)	p-value[a]
Exposure biomarkers			
Cord-blood ΣPCB (ng/g-lipid)[b]	54.7, 25.0–117.7	42.5, 15.4–115.5	< 0.001
Cord-blood THg (ng/g)[b]	10.4, 4.4–22.1	10.2, 3.7–25.4	0.632
Cord-blood lead (μg/dl)	1.0, 0.5–2.2	0.9, 0.6–1.6	0.104
Scores of the CBCL/2–3 (T score)[b]			
Internalizing score	50.6 ± 8.9	44.4 ± 8.4	< 0.001
Externalizing score	49.4 ± 8.6	47.1 ± 10.9	0.043
Total score	50.5 ± 8.6	45.6 ± 10.4	< 0.001
Confounders			
Birth weight (g)	3054 ± 310	3070 ± 336	0.656
Child gender (boys, %)	79 (51.0)	78 (51.7)	0.852
Maternal age at parturition (years)	30.3 ± 3.6	33.1 ± 3.9	< 0.001
Delivery type (spontaneous, %)	108 (69.7)	113 (74.8)	0.379
Drinking habit during pregnancy (drinkers, %)	54 (34.8)	46 (30.5)	0.488
Smoking habit during pregnancy (smokers, %)	8 (5.2)	11 (7.3)	0.594
Seafood intake during pregnancy (kg/year)	19.0, 5.2–46.1	22.8, 5.9–54.8	0.942
Raven score	52.7 ± 5.4	51.3 ± 5.9	0.033
Score of EES at 18 months[b]	27.9 ± 3.0	28.4 ± 3.8	0.238
Breastfeeding (months)	8.5 ± 4.2	8.3 ± 4.1	0.806

[a] Mann–Whitney U test or χ^2 test.
[b] See Table 1.

functions of prenatal lead exposures corresponding to an average cord-blood concentration of 1.6 μg/dl (range, 0.1–11 μg/dl). Since such intellectual deficits may be independent of maladaptive behavior in view of the neurotoxic outcome, blood lead needs to be considered as one of concomitant exposure biomarkers affecting child neurodevelopment even though the maximum value for blood lead levels of a study population is less than 5 μg/dl.

As confounders for the CBCL/2–3, birth order, maternal age at parturition, and home environment were chosen in multiple regression analysis (Table 3). Parental child-rearing attitudes involved in birth order have been reported to affect behavior problems (Wasserman et al., 1998), whereas the authors did not examine environmental toxins other than lead. Of course, first-born children are more vulnerable to maternal persistent organic pollutants (POPs), including PCBs and pesticides, than second-born or following children (Kostyniak et al., 1999), as shown in Table 4. Likewise, higher scores of the CBCL/2–3 were associated with younger mothers, implying that most of them were primiparous rather than multiparous and that maternal age at parturition and birth order may have colinearity. Home environment, assessed by the EES score originating from the HOME, was also suggested to be associated with maladaptive behavior. This is accordant with a report by Davidson et al. (1998) that the quality of the home environment had a substantial impact on child performance, significantly affecting the results of all tests, including the CBCL scores. For that reason, these crucial confounders should be noted in future research, inasmuch as most of the reports supporting developmental effects of perinatal exposure to POPs, excluding one study (Jacobson and Jacobson, 1996), did not consider birth order.

Apart from an interrelation of the above confounders, the cord-blood ΣPCB levels were considerably higher in the first-born children than in the other children of the present study, along with our previous one (Nakamura et al., 2008), while seafood intake during pregnancy did not differ between mothers of the two groups. This implies that parity is an important factor affecting the exposure levels of POPs. In other words, such an association between birth order and prenatal exposure to POPs would complicate an interpretation of the developmental effect; as the result, the effect of prenatal PCB exposure on the internalizing behavior reappeared after removing birth order from independent variables (Table 3). Therefore, it is desirable that first-born children and the other children should be examined separately to avoid the effect of parity.

There may have been some potential limitations in the current study. We did not measure n-3 PUFA beneficial to child neurodevelopment, but maternal seafood intake was employed instead. Though dioxin-like PCBs were not analyzed in this study, a strong correlation between the dioxin-like PCB-TEQ and ΣPCB ($r=0.91$) was observed from 49 samples of our participants (Nakamura et al., 2008); and, a similar finding might have been obtained if we had used them. Judging from the fact that the contribution rates (R^2) of multiple regression analysis were small in Table 3, breast milk PCBs and other neurotoxicants (e.g., pesticides and manganese) should have been examined. Other possible confounders were considered in the data analysis. Owing to our eligibility criteria, the number of mother–child pairs in this study was smaller than that of the original TSCD, but the representativeness of the TSCD would have been preserved as demonstrated by the finding that there were no significant differences in basal characteristics between the 306 pairs with complete data and the remaining pairs (Table 1), so, uncertainty and ambiguity of the used data would have been avoided. Since the CBCL/2–3 uses a parent report form to measure behavior, it may have resulted in measurement bias. However, the CBCL data have been suggested to be a valid measure of behavior (Raven, 1958; Myers et al., 2000). Thus, it is suggested that our data were not heavily influenced by confounders, or sampling or measurement bias.

In conclusion, prenatal exposure to PCBs at low levels appears to affect maladaptive behavior. However, if the exposure levels are lessened by environmental regulation, children may be more susceptible to parental child-rearing attitudes involved in birth order, than to such chemicals. The results from the US National Children's Study (Downs et al., 2010) and the Japan Environment and Children's Study (Hasegawa and Tsukamoto, 2009), following 100,000 children in each country hopefully, will be able to answer these questions in the near future. In any case, if the range of an exposure biomarker in the study population is extremely narrow

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or below the critical concentration estimated previously, there may be no use investigating a dose–response, but not dose-effect, relationship between the exposure and outcomes, irrespective of the sample size.

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出生コホートによる難分解性有機汚染物質（POPs）ばく露の次世代影響の検証
(H21-科学-一般-007)
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