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**Article title**

Prenatal Exposure to PCDDs/PCDFs and dioxin-like PCBs in relation to Birth Weight

**Authors' full name**

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## Abstract

Several human studies have shown that low-level exposure to environmental contaminants, such as polychlorinated biphenyls (PCBs) and organochlorine pesticides, negatively influences birth outcomes. However, the effects of low-level exposure to polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and dioxin-like PCBs (DL-PCBs) on birth outcomes have not been clarified in human studies.

A prospective cohort study was established to investigate the possible adverse effects of PCDDs/PCDFs and DL-PCBs on fetal growth and neurodevelopment. We recruited 514 pregnant women between July 2002 and October 2005 in Sapporo, Japan. We measured 29 congener levels of PCDDs/PCDFs and DL-PCBs in maternal blood.

Using multiple linear regression analysis of the association between birth weight and the levels of PCDDs/PCDFs and DL-PCBs with full adjustments for potential confounders, a significant adverse effect was observed regarding total PCDDs toxic equivalents (TEQ) levels (adjusted  $\beta = -231.5$  g, 95% CI:  $-417.4$  to  $-45.6$ ) and total PCDFs TEQ levels (adjusted  $\beta = -258.8$  g, 95% CI:  $-445.7$  to  $-71.8$ ). Among male infants, significant adverse associations with birth weight were found for total PCDDs TEQ level, total PCDDs/PCDFs TEQ level, and total TEQ level. However, among female infants, these significant adverse associations were not found. With regard to individual congeners of PCDDs/PCDFs and DL-PCBs, we found significantly negative association with the levels of 2,3,4,7,8-PeCDF (adjusted  $\beta = -24.5$  g, 95% CI:  $-387.4$  to  $-61.5$ ).

Our findings suggest that prenatal low-level exposure to PCDDs and PCDFs, especially 2,3,4,7,8-PeCDF, may accumulate in the placenta and retard important placental functions, which result in lower birth weight.

**Key words**

Birth weight, Fetal growth, Dioxin, Maternal blood, Prenatal exposure

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**Approval**

This study was conducted with all the subjects' written informed consent and approved by the institutional ethical board for epidemiological studies at Hokkaido University Graduate School of Medicine.

## **Introduction**

Polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and polychlorinated biphenyls (PCBs) are highly toxic compounds that have become distributed in all environments worldwide. These compounds may have numerous adverse health effects, including growth retardation in fetuses and infants, neurodevelopmental dysfunction, thyroid deficiency, immune deficiency, reproductive effects and cancer (Brouwer et al., 1999; Rogan and Ragan, 2003; Schantz et al., 2003; Toft et al., 2004). One of the most significant concerns regarding health effects is the harmful influence of PCBs and PCDDs/PCDFs on future generations, stemming from prenatal and/or postnatal exposure. Pregnant and nursing women pass these pollutants to their babies both trans-placentally and lactationally (Suzuki et al., 2005; Wang et al., 2004).

Human trans-placental exposure to high-levels of PCBs and PCDFs is certainly neurotoxic. Yusho and Yu-cheng children, who were trans-placentally exposed to PCBs and PCDFs from rice oil incidents in Japan and Taiwan, displayed growth retardation, delayed cognitive development, and behavioral problems (Rogan et al., 1988; Guo et al., 2004). Moreover, they exhibited a higher proportion of low birth weight (LBW) and premature births than those of the control population (Yamashita and Hayashi, 1985; Yen et al., 1994).

Dozens of studies concerning low-level exposure to these contaminants in recent years have primarily looked at organochlorine pesticides and PCBs, but there are very few studies on prenatal exposure to PCDDs/PCDFs and dioxin-like PCBs (DL-PCBs) exposure. Several studies of lower-level PCBs exposure during pregnancy observed associations with decreased birth weight and other growth parameters (Fein et al., 1984; Rylander et al., 1996; Rylander et al., 1998; Patandin et al., 1998; Karmaus and Zhu, 2004; Hertz-Picciotto et al., 2005; Sagiv et al., 2007; Sonneborn et al., 2008). In the

Lake Michigan fish consumer study, cord serum PCBs levels predicted LBW and smaller birth head circumference (Fein et al., 1984). Furthermore, in the Netherlands general population study, both cord and maternal plasma PCBs levels were negatively associated with birth weight (Patandin et al., 1998). However, these associations have not been demonstrated in other studies (Rogan et al., 1986; Dar et al., 1992; Grandjean et al., 2001; Longnecker et al., 2005; Weisskopf et al., 2005; Baibergenova et al., 2003). Higher PCBs exposure correlated with higher birth weight in fish consumers from the Green Bay, Wisconsin, area (Dar et al., 1992). Moreover, the U.S. Collaborative Perinatal Project study found that maternal PCBs levels during pregnancy were essentially unrelated to premature birth, birth weight, or length of gestation, although an association of PCBs with SGA birth was observed (Longnecker et al., 2005). Thus, consistent results regarding the influence of prenatal low-level exposure to PCBs on birth outcomes have not been obtained.

The influence of low-level exposure to PCDDs/PCDFs and DL-PCBs on birth size has not been reported as frequently as exposure to organochlorine pesticides and PCBs. A Finnish study reported that birth weight, especially of boys, correlated negatively with TEQ levels of PCDDs/PCDFs in breast milk (Vartiainen et al., 1998). Another recent study examining the effects of individual congeners of PCDDs/PCDFs and DL-PCBs on birth weight reported that only OCDD levels in breast milk had a significant negative correlation (Tajimi et al., 2005). However, there were no significant relationships between birth weight and PCDDs/PCDFs congeners in maternal breast milk (Nishijo et al., 2008). Thus, reported results on the relationship between birth weight and the levels of PCDDs/PCDFs and DL-PCBs are currently limited and inconsistent. Furthermore, some studies have reported a difference between genders with regard to the effects of PCBs and PCDDs/PCDFs on birth outcomes (Rylander et al., 1996; Baibergenova et al., 2003; Sonneborn et al., 2008; Hertz-Picciotto et

al., 2005; Vartiainen et al., 1998).

Taking the above considerations into account, the aim of the present study was to examine the influence of low-levels PCDDs/PCDFs and DL-PCBs on birth weight, and also identified which individual congeners of PCDDs/PCDFs and DL-PCBs have harmful effects on birth weight.

## **Materials and Methods**

Study, subjects, and data collection. In 2002, the Hokkaido University Graduate School of Medicine established a hospital-based prospective cohort study entitled the “Hokkaido Study on Environment and Children’s Health” to investigate the possible adverse effects of PCBs, PCDDs/PCDFs, perfluorinated chemicals, and many other environmental contaminants on fetal growth and neurodevelopment (Sasaki et al., 2006; Sasaki et al., 2008; Nakajima et al., 2006; Washino et al., 2009). This birth cohort study is based on the inborn infants delivered at the Sapporo Toho Hospital in Sapporo, Hokkaido, Japan, which is obstetrics and gynecology hospital and treated the largest number of delivery in Sapporo City. Between July 2002 and October 2005, we approached pregnant women who were between the 23rd and 35th weeks of gestation, and no serious illness or any other medical complications. All potential subjects were native Japanese living in Sapporo and the surrounding industrialized areas. The following were exclusion criteria for study subjects: the women had incomplete partner’s information, the women had decided to enroll in the Japanese cord blood bank (22% of those of approached), or the women decided to deliver the baby at another hospital (3% of those of approached). Some of the women we approached did not express interest in our study, and some were unable or unwilling to participate in this study. Ultimately, 514 pregnant women (30% of those approached) were enrolled in this cohort study. All of these women have been taking medical examination during pregnancy at the hospital. This study was conducted after all participating women provided written informed consent and was approved by the institutional ethical board for epidemiological studies at the Hokkaido University Graduate School of Medicine.

The self-administered questionnaire survey provided us with potential confounding variables in relation to the past medical history of the mothers and their partners, demographic characteristics,

health status during pregnancy, smoking habits (including environmental tobacco smoke), educational level, economic status, work history during pregnancy, dietary intake during pregnancy (including inshore fish and deep-sea fish), caffeine intake, alcohol intake, and exposure to chemical compounds in their daily life. For estimating caffeine and alcohol intake, we used the modified self-administered questionnaire described by Nagatani et al. (Nagata et al., 1997). Dietary intake during pregnancy was obtained from the food frequency questionnaire, which is divided into five categories: Never, 1 to 2 times/month, 1 to 2 times/week, 3 to 4 times/week, or almost every day. With regard to maternal smoking habits during pregnancy, 21% of the women quit smoking in the first trimester and most of them quit smoking before 10 weeks of gestation, which is quite soon after cognition of their pregnancy. Therefore, the women who quit smoking in the first trimester were included in the group of non-smokers. Maternal smoking status during pregnancy was categorized into two groups: women who were non-smokers during pregnancy and those who quit smoking during the first trimester (non-smoking group), and women who smoked during pregnancy and those who quit smoking after the first trimester (smoking group).

Maternal and infant medical information, including multiple births, infant gender, gestational age, birth weight, birth length, birth head circumference, maternal age, maternal height, maternal weight before pregnancy, parity, and medical history during pregnancy, were collected from their medical records at the hospital.

Exposure measures. Analyses of PCDDs/PCDFs and DL-PCBs were performed according to a previously published method (Iida and Todaka, 2003; Todaka et al., 2003). Briefly, a 40-ml blood sample was taken from the maternal peripheral vein at the time of the next prenatal hospital examination after recruitment. If we were not able to take the blood during pregnancy due to maternal

anemia, we took the blood during hospitalization within a week after delivery. All samples were stored at  $-80^{\circ}\text{C}$  until analysis. The levels of PCDDs/PCDFs and DL-PCBs in the maternal blood samples were measured using high-resolution gas chromatography/high-resolution mass spectrometry (HRGC/HRMS) equipped with a solvent-cut large-volume injection system (SGE Ltd., Victoria, Australia) at Fukuoka Institute of Health and Environmental Sciences. The gas chromatograph was an Agilent 6890 (Agilent Technologies Inc., Palo Alto, CA, USA) equipped with an AutoSpecUltima NT (Micromass Ltd., Manchester, UK). Specific congeners of seven PCDDs, ten PCDFs, four non-ortho PCBs, and eight mono-ortho PCBs were analyzed. The World Health Organization (WHO) toxic equivalent factor approach was used to express the toxic potency of the mixture of PCDDs, PCDFs, non-ortho PCBs, and mono-ortho PCBs. The TEQ levels were calculated by multiplying the levels of individual congeners by its toxic equivalency factor (TEF) values of the WHO 1998 (Van den Berg et al., 1998) and the WHO 2006 (Van den Berg et al., 2006). We measured the levels of PCDDs/PCDFs and DL-PCBs in 426 maternal blood samples. The remaining maternal blood samples in this study were not analyzed because they were not available or lacked sufficient blood volume for the measurement. One mother's sample was excluded from the study because the PCDFs levels were extremely high. The blood sampling period was categorized into four groups: 23-31 weeks of gestation, 32-34 weeks of gestation, 35-41 weeks of gestation, within a week after delivery.

Data analysis and statistical methods. Ten registered women were lost from the study due to miscarriage, stillbirth, removal before delivery, or dropping out from the study at the beginning of the follow-up period. The following subjects were excluded from analysis: those with maternal pregnancy-induced hypertension (n=11), diabetes mellitus (n=1), fetal heart failure (n=1), and multiple births (n=7). We also excluded premature births (n=23)—defined as birth at less than 37 weeks of

gestation—from the data analysis to keep the focus on fetal growth, resulting in a sample size of 461. Finally, the available sample size for the statistical analysis was 398 subjects who completed the measurements of PCDDs/PCDFs and DL-PCBs in the 461 subjects.

Associations between variables were analyzed by the Student's t-test, Spearman's correlation coefficient test, and analysis of variance (ANOVA). Multiple linear regression models were used to examine the association between birth weight and the levels of PCDDs/PCDFs and DL-PCBs in maternal blood. This analysis was adjusted for relevant covariates, such as predictors of birth weight and other known potential confounders for birth weight. We examined potential confounders from the following risk factors: infant gender, gestational age, birth length, birth head circumference, maternal age, maternal height, maternal weight before pregnancy, parity, maternal smoking status during pregnancy, alcohol intake during pregnancy, caffeine intake during pregnancy, inshore fish intake during pregnancy, deep-sea fish intake during pregnancy, educational level, household income and blood sampling period (Table 1). The final multiple linear regression models included risk factors associated with birth weight at p-values < 0.20 or risk factors known to be associated with the outcomes from the literature (e.g., maternal age, parity, maternal smoking status). When we considered fish intake during pregnancy, only inshore fish was associated with birth weight at p-values < 0.20 of the model, so it was also included in the final models while deep-sea fish was not. We also considered whether the levels of PCDDs/PCDFs and DL-PCBs in maternal blood change depending on the period in which blood was drawn during pregnancy or after delivery. When we examined the levels of PCDDs/PCDFs and DL-PCBs in maternal blood among four blood sampling periods by the Kruskal-Wallis test, there were significant differences in the levels of total PCDDs, total PCDFs, and total PCDDs/PCDFs ( $p < 0.001$ ) (data not shown). Therefore the blood sampling period was also

included in the final models.

It was also important to clarify the interaction with the infant's gender, so the final multiple linear regression model was also stratified by infant gender. The levels of PCDDs/PCDFs and DL-PCBs were lipid adjusted (pg/g lipid) and were assumed a value equal to half the limit of detection (LOD) when the levels were below the LOD for individual congeners (Longnecker et al., 2000). The levels of PCDDs/PCDFs and DL-PCBs displayed a log-normal distribution. Therefore, we treated the levels of PCDDs/PCDFs and DL-PCBs primarily on  $\log_{10}$ -transformed values for the multiple linear regression models. We also conducted linear regression diagnostics to identify outliers and influential cases using Cook's distance and the leverage. All statistical analyses were performed using the Statistics Package for Social Sciences (SPSS, Inc., USA) software for Windows version 13.0 J.

## Results

Infant and maternal characteristics are presented in Table 1. The 189 infants (47.5%) were male, and the mean gestational week and birth weight were 39.1 ( $\pm 1.2$ ) weeks and 3,100 ( $\pm 349$ ) g, respectively. Mothers ranged in age from 18 to 42 years, with a mean age of 31.0 ( $\pm 4.7$ ) years. Mothers were primiparous (48.2%), smoking during pregnancy (17.1%) and more than 13 years of education (57.5%). The number of women who provided a blood sample after delivery was 121 (30.4%). Among the women who could provide a blood sample during pregnancy, 90.6% of maternal blood samples were taken during the third trimester (data not shown).

The relationships between birth weight and infant and maternal characteristics, which were potential confounders of birth weight, are also presented in Table 1. We did not find a significant relationship in this study with maternal smoking status during pregnancy and parity, but the mean birth weight was lower in the smoking group (3,065 g) versus the non-smoking group (3,107 g) and in primiparous (3,073 g) versus multiparous (3,125 g) mothers.

The levels of PCDDs/PCDFs and DL-PCBs in maternal blood are presented in Table 2. We present the total concentration levels (pg/g lipid) and total TEQ levels according to the WHO 1998 and WHO 2006 (TEQ pg/g lipid). The WHO 2006 mean and range of total PCDDs TEQ, total PCDFs TEQ, total non-ortho PCBs TEQ, total mono-ortho PCBs TEQ, and total TEQ were 7.4 (1.7–29.3), 2.6 (0.6–7.8), 4.6 (0.7–23.2), 0.4 (0.1–1.5), and 14.9 (3.2–43.4) TEQ pg/g lipid, respectively.

Table 3 shows the results of the multiple regression analysis for the association between birth weight and both the total concentration levels and total TEQ levels of PCDDs/PCDFs and DL-PCBs, with full adjustments for potential confounders. For the total TEQ levels of PCDDs/PCDFs and DL-PCBs, only the levels according to WHO 2006 are presented in Table 3 because the results of the

multiple regression analysis were similar to the WHO 1998 and WHO 2006 total TEQ levels. Because the models were run with the levels of PCDDs/PCDFs and DL-PCBs on the  $\log_{10}$  scale, a unit of increase implies a 10-fold increase in the levels of PCDDs/PCDFs and DL-PCBs. We found a 272.7 g decrease in birth weight with a 10-fold increase in total PCDFs levels (95% CI: -505.8 to -39.5) and similar relations in total PCDDs TEQ level (adjusted  $\beta = -231.5$  g, 95% CI: -417.4 to -45.6), total PCDFs TEQ level (adjusted  $\beta = -258.8$  g, 95% CI: -445.7 to -71.8), total PCDDs/PCDFs TEQ level (adjusted  $\beta = -256.4$  g, 95% CI: -448.6 to -64.2) and total TEQ level (adjusted  $\beta = -220.5$  g, 95% CI: -399.2 to -41.9) among all infants. Among male infants, significant inverse associations with birth weight were found for total PCDDs TEQ level, total PCDDs/PCDFs TEQ level, and total TEQ level. However, among the female infants, these significant associations were not found.

Figure 1 shows scatterplots and the predicted line for the  $\log_{10}$ -transformed total PCDDs TEQ and total PCDFs TEQ levels in maternal blood and birth weight, and the superimposed predicted line fully adjusted for potential confounders. The birth weight was significantly reduced in association with increasing  $\log_{10}$ -transformed total PCDDs TEQ and PCDFs TEQ values (Table 3). The trend remains after removal of the two high birth-weight outliers on PCDDs TEQ values (not shown). For PCDDs TEQ values, there was milder slope among female infants than among male infants.

We also examined the association between birth weight and the levels of individual congeners of PCDDs/PCDFs and DL-PCBs. For all or more than 90% of the subjects with a level below the LOD of the congeners, such as 1,2,3,7,8-PeCDF, 2,3,4,6,7,8-HxCDF, 1,2,3,7,8,9-HxCDF, 1,2,3,4,7,8,9-HpCDF, OCDF, and 3,4,4'-TCB(#81), calculations could not be performed or were lack of available subjects for the multiple linear regression models, so they are expressed as a hyphen in Table 4. We found significantly negative association with the levels of 2,3,4,7,8-PeCDF (adjusted  $\beta =$

–224.5 g, 95% CI: –387.4 to –61.5), and marginally negative associations with the levels of 1,2,3,7,8-PeCDD (adjusted  $\beta$  = –136.0 g, 95% CI: –296.8 to 24.9), 1,2,3,6,7,8-HxCDD (adjusted  $\beta$  = –164.7 g, 95% CI: –333.8 to 4.3), 1,2,3,6,7,8-HxCDF (adjusted  $\beta$  = –121.2 g, 95% CI: –252.8 to 10.5), and 23'44'55'-HxCB (#167) (adjusted  $\beta$  = –42.4 g, 95% CI: –291.4 to 6.5).

## Discussion

Data from this hospital-based study show that low-levels of PCDDs and PCDFs are associated with lower birth weight. The levels of PCDDs/PCDFs and DL-PCBs in maternal blood during pregnancy more directly evaluate the fetal exposure levels than those levels in breast milk. Our study is the first to report the influence of the levels of PCDDs/PCDFs and DL-PCBs in maternal blood on birth weight, although Vartiainen et al., Tajimi et al. and Nishijo et al. have studied the effects on birth weight using those levels in breast milk (Vartiainen et al., 1998; Tajimi et al., 2005; Nishijo et al., 2008). We also examined which individual congeners of PCDDs/PCDFs and DL-PCBs have harmful effects on birth weight.

The exposure levels of PCDDs/PCDFs and DL-PCBs. The mean total TEQ level (WHO 1998) of maternal blood in this study was 17.5 TEQ pg/g lipid, which was lower than that of the subjects in another study in domestic areas with ages similar to this study; the other study reported 22.1 TEQ pg/g lipid (n = 53; mean age, 30.0 years) (Masuda et al., 2005). It was reported that maternal exposure levels of PCDDs/PCDFs and DL-PCBs in this study was lower than recently reported in Japan (Todaka et al., 2008a, b). Recent German study reported that the mean total TEQ level of maternal blood was 28.4 TEQ pg/g lipid (n = 169; mean age, 31.2 years) (Wittsiepe et al., 2007). Furthermore, the mean total TEQ level in women of child-bearing age in Taiwan was 13.6 TEQ pg/g lipid (n = 20; mean age, 28.3 years), which was the lowest level compared with those in eight U.S and Europe studies (including the Japan study) (Wang et al., 2004). Therefore, the exposure levels of PCDDs/PCDFs and DL-PCBs in this cohort study were one of the lowest levels in Japan as well as in U.S. and Europe human studies.

The effects of PCDDs/PCDFs and DL-PCBs on birth weight. In this study, we found that

total PCDDs TEQ, total PCDFs TEQ, total PCDDs/PCDFs TEQ, and total TEQ levels in maternal blood were significantly negatively associated with birth weight among all infants after adjustment for potential covariates of birth weight. A Finnish study reported that birth weight was negatively correlated with PCDDs/PCDFs TEQ levels in breast milk (Vartiainen et al., 1998). This result was consistent with our results, although the Finnish study did not adjust for potential confounders and used breast milk with smaller sample sizes (n=167) than our study. However, a previous Japanese study, which has examined 240 breast milk samples, reported that only the OCDD level was significantly correlated with birth weight by multiple regression analyses with potential cofounders (Tajimi et al., 2005), we did not find negative correlations with the OCDD level in our study. Because their multiple regression models have not included important potential confounders such as gestational age and infant sex, we could not simply compare between their results and our results. Another Japanese study, which has examined 42 breast milk samples, reported that there were no significant relationships between birth weight and the level of individual PCDDs/PCDFs congeners after adjustments for confounding factors, but significant relationships were shown between infant head circumference and 2,3,7,8-TCDD and 2,3,4,7,8-PeCDF levels (Nishijo et al., 2008). We also examined the influence of PCDDs/PCDFs and DL-PCBs on birth length and head circumference at birth, but there were no significant relationships between these birth outcomes and the levels of PCDDs/PCDFs and DL-PCBs (data not shown), only a significant relationship with birth weight. Our total TEQ level in breast milk (Todaka et al., 2008a) was lower than those of the three previous studies of prenatal exposure of PCDDs/PCDFs and DL-PCBs. The inconsistencies among the studies could be due to the smaller sample sizes than our study, different samples such as maternal blood or breast milk, different level of exposure, different statistical analyses such as simple or multiple regressions; in addition, these

multiple regression models were adjusted with different covariate. Why this inconsistency for birth weight varies across studies remains unclear, so additional studies are needed to further clarify this issue.

Gender difference in the effects. There were few results reported gender difference, they frequently indicated a stronger negative effect on the birth weight among male infants (Rylander et al., 1996; Baibergenova et al., 2003; Sonneborn et al., 2008; Hertz-Picciotto et al., 2005; Vartiainen et al., 1998). Previous reports have indicated that increased maternal serum PCBs levels are associated with reduced birth weight in male infants and have suggested a greater susceptibility of male conceptuses, either in the fetal or embryonic period (Sonneborn et al., 2008; Hertz-Picciotto et al., 2005). Some of the studies reporting gender difference in the PCBs effects did not actually measure PCBs levels, but used a surrogate for exposure such as estimated fish consumption (Rylander et al., 1996) or residential information (Baibergenova et al., 2003), which may entail greater errors in exposure classification. However, there was a study reported gender difference for PCDDs/PCDFs, the study reported the birth weight was negatively correlated with PCDDs/PCDFs TEQ levels in breast milk, especially of male infants (Vartiainen et al., 1998).

In this study, we found that the adjusted regression coefficients of total PCDDs TEQ and PCDDs/PCDFs TEQ levels among male and female infants were  $-331.4\text{g}$  and  $-126.3\text{g}$ , and  $-338.7\text{g}$  and  $-173.9\text{g}$ , respectively. It was possible that male infants had more reduced birth weight at higher PCDDs and PCDDs/PCDFs TEQ levels in the maternal blood than did female infants. Our finding that male infants were more susceptible to PCDDs/PCDFs TEQ levels than female infants was consistent with the Finnish study (Vartiainen et al., 1998). However, studies of the specific gender difference in the effects of PCBs and PCDDs/PCDFs are a part of the larger discussion of endocrine disruption, so

we need more evidence from larger studies with exposure measurement.

The effects of PCDDs/PCDFs and DL-PCBs congeners on birth weight. Identification of the potent biological properties of PCDDs/PCDFs and DL-PCBs, and which individual congeners of PCDDs/PCDFs and DL-PCBs affect birth outcomes has been an important goal in investigating the mechanism and preventing harmful influences on fetuses.

Yu-Cheng children's serum concentrations of 2,3,4,7,8-PeCDF and 1,2,3,4,7,8-HxCDF were still 10 to 25 times higher than those from a matched control group of children (Guo et al., 2004), the PCDFs group, including the penta-CDF and hexa-CDF congeners, was more responsible for the observed health effects than other groups of PCBs/PCDFs congeners in the Yu-Cheng children. Moreover, 70% of the toxicity level of TEQ was contributed by 2,3,4,7,8-PeCDF in Yusho patients (Masuda Y., 2001). A previous Finnish study reported that the 2,3,7,8-TCDD, 1,2,3,7,8-PeCDD, and 2,3,4,7,8-PeCDF levels in breast milk were negatively correlated with birth weight (Vartiainen et al., 1998). However, another Japanese study reported that there were significant relationships between infant head circumference and 2,3,7,8-TCDD and 2,3,4,7,8-PeCDF levels (Nishijo et al., 2008). We found significantly negative associations between 2,3,4,7,8-PeCDF levels and birth weight after we adjusted for potential confounders. In total, these data suggest that 2,3,4,7,8-PeCDF is one of the most suspect congeners in this regard.

Previous studies showed that the PCDDs/PCDFs levels in the placenta are higher than the levels in venous serum and breast milk. In particular, 2,3,7,8-TCDD, 1,2,3,7,8-PeCDD, and 2,3,4,7,8-PeCDF are found in significantly greater amounts in the placenta. Thus, there is a specific accumulation of these three PCDDs/PCDFs congeners in the placenta due to their high affinity for the Ah receptor (Wang et al., 2004; Suzuki et al., 2005). These three TEF values (0.3 to 1) are higher than

those of other congeners (0.00003 to 0.1) (Van den Berg et al., 2006). Thus, their TEQ levels in maternal blood were relatively high, even though their concentrations measured low. The placenta has an important function in transporting nutrients and oxygen to the fetus via cord blood. Indeed, impairment of placental function can result in intrauterine growth retardation in the fetal or embryonic period, and in lower birth weight and SGA birth. Taking the above considerations into account, we suggest that PCDDs/PCDFs congeners, especially 2,3,4,7,8-PeCDF, may accumulate in the placenta and retard important placental functions, which may result in lower birth weight. Further studies are required to identify which properties of PCDDs/PCDFs and DL-PCBs and which individual congeners of PCDDs/PCDFs and DL-PCBs have an effect on birth weight. Our study should be useful to assess more accurately the human health risks of these congener levels.

Limitations. Interpretation of our results is limited by several conditions. First, our sample size was small for representatives of the general population, even larger sample size than previous studies of PCDDs/PCDFs and DL-PCBs. Second, the selection bias may have occurred because this cohort was based on one area hospital, which treated pregnant women in Sapporo and the surrounding areas. The specific newborns, those who needed to high grade neonatal care, were not available in our study population because such specific newborns were transferred to other facilities from the hospital. Third, it is possible that women who have much awareness of environmental contamination preferentially participated in this study. In addition, the participation rate in our cohort study was low, which also may have caused selection bias. These may limit extrapolation of our results to the general population.

In conclusion, our findings suggest that prenatal exposure to low-levels of PCDDs and PCDFs, especially 2,3,4,7,8-PeCDF, were significantly negatively associated with birth weight.

PCDDs/PCDFs may accumulate in the placenta and retard important placental functions, which may result in lower birth weight. However, our results for birth weight vary across previous studies, so additional studies are needed to further clarify this issue.

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## **Abbreviations**

DL-PCBs, dioxin-like polychlorinated biphenyls

HRGC/HRMS, high-resolution gas chromatography/high-resolution mass spectrometry

LBW, low birth weight

LOD, limit of detection

Mono-ortho PCBs, mono-ortho coplanar polychlorinated biphenyls

Non-ortho PCBs, non-ortho coplanar polychlorinated biphenyls

OCDD, octachlorodibenzo-p-dioxin

OCDF, octachlorodibenzofuran

PCBs, polychlorinated biphenyls

PCDDs, polychlorinated dibenzo-p-dioxins

PCDFs, polychlorinated dibenzofurans

TEF, toxic equivalency factor

TEQ, toxic equivalents

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Table 1. Infant and maternal characteristics, and their association with birth weight (n=398)

Characteristics	No. (%)	Birth weight	
		Mean $\pm$ SD	<i>p</i> -value <sup>a</sup>
		Correlation coefficient	
<Infants>			
Gender			
Male	189 (47.5)	3160 $\pm$ 351	0001 **
Female	209 (52.5)	3046 $\pm$ 338	
Gestational age (weeks)	39.1 $\pm$ 1.2 <sup>b</sup>	r = 0.345	<0.001 **
Birth weight (g)	3100.3 $\pm$ 348.5 <sup>b</sup>	-	-
Birth length (cm)	48.2 $\pm$ 1.8 <sup>b</sup>	r = 0.681	<0.001 **
Birth head circumference (cm)	33.3 $\pm$ 1.3 <sup>b</sup>	r = 0.491	<0.001 **
<Mothers>			
Maternal age (years)	31.0 $\pm$ 4.7 <sup>b</sup>	r = 0.013	0.794
Maternal height (cm)	58.2 $\pm$ 5.3 <sup>b</sup>	r = 0.102	0.041 *
Maternal weight before pregnancy (kg) <sup>d</sup>	52.7 $\pm$ 8.0 <sup>b</sup>	r = 0.165	<0.001 **
Parity			
Primiparous	192 (48.2)	3073 $\pm$ 355	0.137
Multiparous	206 (51.8)	3125 $\pm$ 341	
Maternal smoking status during pregnancy			
Non-smoking	330 (82.9)	3107 $\pm$ 359	0.365
Smoking	68 (17.1)	3065 $\pm$ 294	
Alcohol intake during pregnancy			
No	271 (68.1)	3091 $\pm$ 353	0.462
Yes	127 (31.9)	3119 $\pm$ 339	
Alcohol consumption in drinkers (g/day)	1.2 (0.3 - 51.8) <sup>c</sup>	r = 0.034	0.493
Caffeine intake during pregnancy (g/day)	118.1 (1.5 - 646.3) <sup>c</sup>	r = -0.065	0.198
Fish intake during pregnancy			
Inshore fish			
$\leq$ 1-2times/month	220 (55.3)	3111 $\pm$ 339	0.508
$\geq$ 1-2times/week	178 (44.7)	3087 $\pm$ 360	
Deep-sea fish			
$\leq$ 1-2times/month	185 (46.5)	3092 $\pm$ 379	0.672
$\geq$ 1-2times/week	213 (53.5)	3107 $\pm$ 321	
Educational level (years)			
$\leq$ 12	169 (42.5)	3071 $\pm$ 367	0.180
$\geq$ 13	229 (57.5)	3120 $\pm$ 333	
Annual household income (million yen) <sup>d</sup>			
<5	264 (66.3)	3108 $\pm$ 353	0.590
$\geq$ 5	133 (33.5)	3088 $\pm$ 339	
Blood sampling period (gestational weeks)			
23-31	66 (16.6)	3137 $\pm$ 314	0.121
32-34	108 (27.1)	3040 $\pm$ 367	
35-41	103 (25.9)	3147 $\pm$ 333	
Within a week after delivery	121 (30.4)	3094 $\pm$ 358	

<sup>a</sup> Student's t-test, Spearman's correlation coefficient test, ANOVA<sup>b</sup> Mean  $\pm$  SD.<sup>c</sup> Median (min - max)<sup>d</sup> Missing data: maternal weight before pregnancy (2), annual household income (1)\**p*<0.05, \*\**p*<0.01

Table 2. Levels of PCDDs/PCDFs and dioxin-like PCBs in maternal blood (n=398)

	Mean $\pm$ SD	Min	Median	Max
<Total level> (pg/g lipid)				
Total PCDDs	510.9 $\pm$ 224.4	99.0	457.1	1602.4
Total PCDFs	20.5 $\pm$ 12.0	9.5	18.4	192.4
Total PCDDs/PCDFs	531.3 $\pm$ 230.7	109.9	476.3	1637.5
Total non- <i>ortho</i> PCBs	81.2 $\pm$ 44.6	20.0	75.0	553.6
Total mono- <i>ortho</i> PCBs	12381.6 $\pm$ 6500.4	1777.9	11128.8	49632.0
Total DL-PCBs	12462.8 $\pm$ 6531.7	1797.9	11227.9	49813.4
Total PCDDs/PCDFs and DL-PCBs	12994.2 $\pm$ 6633.6	2104.9	11855.9	50477.5
<WHO-98 <sup>a</sup> > (TEQ pg/g lipid)				
Total PCDDs TEQ	7.3 $\pm$ 3.3	1.6	6.8	29.2
Total PCDFs TEQ	3.8 $\pm$ 1.6	0.7	3.6	11.8
Total PCDDs/PCDFs TEQ	11.1 $\pm$ 4.8	2.5	10.4	36.8
Total non- <i>ortho</i> PCBs TEQ	4.0 $\pm$ 2.5	0.6	3.6	22.3
Total mono- <i>ortho</i> PCBs TEQ	2.4 $\pm$ 1.2	0.3	2.2	10.1
Total DL-PCBs TEQ	6.4 $\pm$ 3.5	0.9	5.9	26.4
Total TEQ	17.5 $\pm$ 7.7	3.4	16.5	51.2
<WHO-2006 <sup>b</sup> > (TEQ pg/g lipid)				
Total PCDDs TEQ	7.4 $\pm$ 3.3	1.7	6.9	29.3
Total PCDFs TEQ	2.6 $\pm$ 1.1	0.6	2.4	7.8
Total PCDDs/PCDFs TEQ	10.0 $\pm$ 4.3	2.5	9.3	34.4
Total non- <i>ortho</i> PCBs TEQ	4.6 $\pm$ 2.7	0.7	4.2	23.2
Total mono- <i>ortho</i> PCBs TEQ	0.4 $\pm$ 0.2	0.1	0.3	1.5
Total DL-PCBs TEQ	4.9 $\pm$ 2.9	0.7	4.5	23.9
Total TEQ	14.9 $\pm$ 6.6	3.2	14.0	43.4

<sup>a</sup> The calculation of TEQ was estimated based on the WHO 1998 toxic equivalent factor values (Van den Berg 1998).

<sup>b</sup> The calculation of TEQ was estimated based on the WHO 2006 toxic equivalent factor values (Van den Berg 2006).

Table 3. Multiple linear regressions for birth weight in relation to PCDDs/PCDFs and DL-PCBs

log10 scale	Overall <sup>a</sup>			Male <sup>b</sup>			Female <sup>b</sup>		
	Beta <sup>c</sup>	(95%CI)	<i>p</i> -values	Beta <sup>c</sup>	(95%CI)	<i>p</i> -values	Beta <sup>c</sup>	(95%CI)	<i>p</i> -values
<Total level> (pg/g lipid)									
Total PCDDs	-92.5	(-282.2 to 97.1)	0.338	-125.7	(-402.3 to 150.8)	0.371	-19.3	(-294.0 to 255.5)	0.890
Total PCDFs	-272.7	(-505.8 to -39.5)	0.022 *	-237.6	(-595.2 to 119.9)	0.191	-304.9	(-620.6 to 10.7)	0.058
Total PCDDs/PCDFs	-101.7	(-294.6 to 91.2)	0.301	-136.6	(-418.3 to 145.1)	0.340	-28.7	(-307.5 to 250.1)	0.839
Total non-ortho PCBs	-113.5	(-281.9 to 54.9)	0.186	-90.7	(-350.4 to 169.0)	0.491	-122.4	(-347.9 to 103.2)	0.286
Total mono-ortho PCBs	-125.3	(-277.4 to 26.8)	0.106	-138.6	(-372.7 to 95.4)	0.244	-104.3	(-308.7 to 100.1)	0.315
Total DL-PCBs	-125.9	(-278.2 to 26.4)	0.105	-138.7	(-373.1 to 95.7)	0.245	-105.3	(-309.9 to 99.3)	0.311
Total PCDDs/PCDFs and DL-PCBs	-131.5	(-288.7 to 25.6)	0.101	-148.5	(-391.1 to 94.1)	0.229	-106.8	(-317.6 to 103.9)	0.319
<WHO-2006 <sup>d</sup> > (TEQ pg/g lipid)									
Total PCDDs TEQ	-231.5	(-417.4 to -45.6)	0.015 *	-331.4	(-607.4 to -55.5)	0.019 *	-126.3	(-384.5 to 131.9)	0.336
Total PCDFs TEQ	-258.8	(-445.7 to -71.8)	0.007 **	-269.8	(-561.5 to 21.9)	0.070	-241.7	(-491.7 to 8.4)	0.058
Total PCDDs/PCDFs TEQ	-256.4	(-448.6 to -64.2)	0.009 **	-338.7	(-628.2 to -49.1)	0.022 *	-173.9	(-437.6 to 89.8)	0.195
Total non-ortho PCBs TEQ	-116.1	(-245.9 to 13.7)	0.079	-107.3	(-306.1 to 91.5)	0.288	-114.8	(-289.4 to 59.8)	0.196
Total mono-ortho PCBs TEQ	-125.3	(-277.4 to 26.8)	0.106	-138.6	(-372.7 to 95.4)	0.244	-104.3	(-308.7 to 100.1)	0.315
Total DL-PCBs TEQ	-119.9	(-252.3 to 12.6)	0.076	-112.1	(-315.1 to 91.0)	0.278	-117.5	(-295.6 to 60.5)	0.195
Total TEQ	-220.5	(-399.2 to -41.9)	0.016 *	-289.5	(-561.7 to -17.3)	0.037 *	-144.2	(-386.7 to 98.4)	0.243

<sup>a</sup> Results are calculated as multiple linear regression models adjusted for gestational age, maternal age, maternal height, maternal weight before pregnancy, parity, smoking status during pregnancy, inshore fish intake, blood sampling period, and infant gender.

<sup>b</sup> Results are calculated as multiple linear regression models adjusted for gestational age, maternal age, maternal height, maternal weight before pregnancy, parity, smoking status during pregnancy, inshore fish intake, and blood sampling period.

<sup>c</sup> Beta coefficients represent the change in birth weight (g) for a 10-fold increase in the levels of PCDDs/PCDFs and DL-PCBs.

<sup>d</sup> The calculation of TEQ was estimated based on the WHO 2006 toxic equivalent factor values (Van den Berg 2006).

\**p*<0.05, \*\**p*<0.01

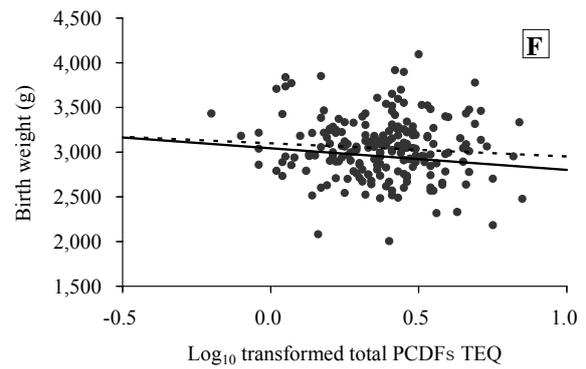
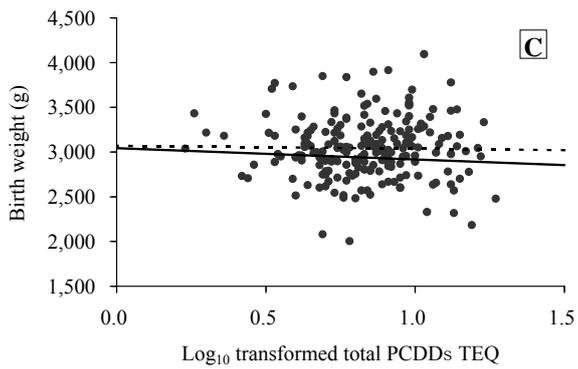
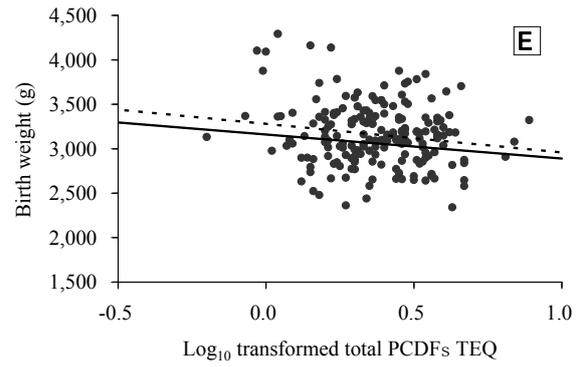
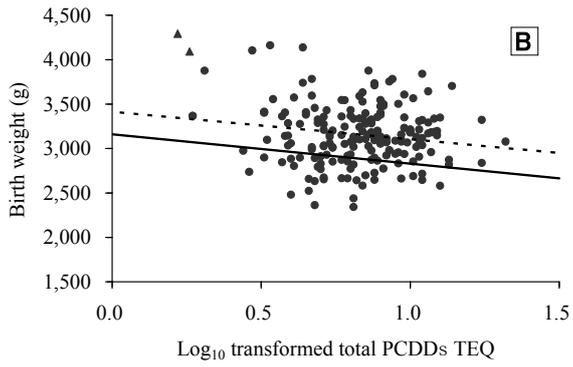
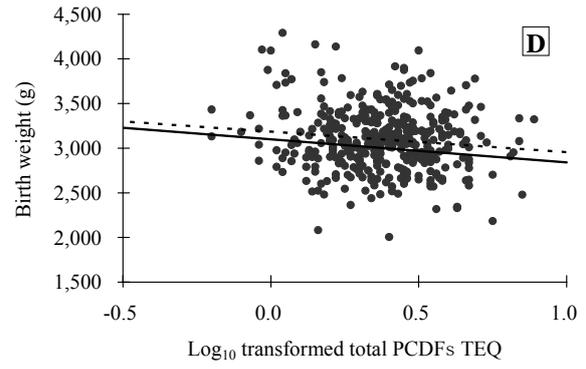
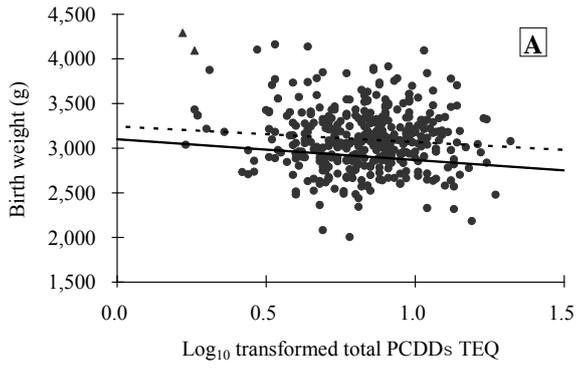
Table 4. Multiple linear regressions for birth weight in relation to congener levels of PCDDs/PCDFs and DL-PCBs

log <sub>10</sub> scale (pg/g lipid)	Birth weight (Overall) <sup>a</sup>		
	Beta <sup>b</sup>	(95%CI)	<i>p</i> -values
<PCDDs>			
2,3,7,8-TCDD	-65.3	(-203.5 to 72.9)	0.354
1,2,3,7,8-PeCDD	-136.0	(-296.8 to 24.9)	0.097
1,2,3,4,7,8-HxCDD	13.5	(-148.1 to 175.1)	0.870
1,2,3,6,7,8-HxCDD	-164.7	(-333.8 to 4.3)	0.056
1,2,3,7,8,9-HxCDD	-59.2	(-188.3 to 69.9)	0.368
1,2,3,4,6,7,8-HpCDD	-96.1	(-290.2 to 98.0)	0.331
OCDD	-83.8	(-268.1 to 100.5)	0.372
<PCDFs>			
2,3,7,8-TCDF	-94.3	(-275.0 to 86.5)	0.306
1,2,3,7,8-PeCDF	-	-	-
2,3,4,7,8-PeCDF	-224.5	(-387.4 to -61.5)	0.007 **
1,2,3,4,7,8-HxCDF	-71.1	(-208.4 to 66.2)	0.309
1,2,3,6,7,8-HxCDF	-121.2	(-252.8 to 10.5)	0.071
2,3,4,6,7,8-HxCDF	-	-	-
1,2,3,7,8,9-HxCDF	-	-	-
1,2,3,4,6,7,8-HpCDF	-74.5	(-185.6 to 36.6)	0.188
1,2,3,4,7,8,9-HpCDF	-	-	-
OCDF	-	-	-
<Non-ortho PCBs>			
344'5-TCB(#81)	-	-	-
33'44'-TCB(#77)	43.0	(-97.0 to 183.0)	0.546
33'44'5-PeCB(#126)	-98.7	(-218.9 to 21.4)	0.107
33'44'55'-HxCB(#169)	-112.8	(-258.0 to 32.4)	0.128
<Mono-ortho PCBs>			
2'344'5-PeCB(#123)	-91.7	(-208.4 to 25.0)	0.123
23'44'5-PeCB(#118)	-114.2	(-252.9 to 24.5)	0.106
2344'5-PeCB(#114)	-41.8	(-193.5 to 109.9)	0.588
233'44'-PeCB(#105)	-84.5	(-221.7 to 52.6)	0.226
23'44'55'-HxCB(#167)	-42.4	(-291.4 to 6.5)	0.061
233'44'5-HxCB(#156)	-116.7	(-284.3 to 51.0)	0.172
233'44'5'-HxCB(#157)	-116.0	(-271.7 to 39.7)	0.144
233'44'55'-HpCB(#189)	-46.9	(-210.7 to 116.9)	0.574

<sup>a</sup> Results are calculated as multiple linear regression models adjusted for gestational age, maternal age, maternal height, maternal weight before pregnancy, parity, smoking status during pregnancy, inshore fish intake, blood sampling period, and infant gender.

<sup>b</sup> Beta coefficients represent the change in birth weight (g) for a 10-fold increase in the congener levels of PCDDs/PCDFs and DL-PCBs.

\*\**p*<0.01



## Figure legend

Figure 1. Correlation between birth weight the  $\log_{10}$  transformed total PCDDs TEQ and total PCDFs TEQ levels in maternal blood samples, before and after adjustment for potential confounders. The dotted lines denote the predicted fit from a simple linear regression model. The lines denote the predicted fit from the fully adjusted multivariate regression model. Corresponding regression coefficients are presented in Table3. Among all infants (A, D). Among males (B, E). Among females (C, F).