Several studies have shown that prenatal and/or postnatal background-level exposure to environmental chemicals, such as polychlorinated biphenyls (PCBs) and dioxins, induces adverse effects on the neurodevelopment of children. However, other studies have not detected any harmful influences on neurodevelopment. Furthermore, except in western countries, no developmental tests have been carried out in relation to detailed assessment of exposure to PCBs and dioxins. In this study (the Hokkaido Study on Environment and Children’s Health), the effect of prenatal exposure to background levels of PCBs and dioxins on infant neurodevelopment in Japan/Sapporo was elucidated. The associations between the total or individual isomer level of PCBs and dioxins in 134 Japanese pregnant women’s peripheral blood and the mental or motor development of their 6-month-old infants were evaluated using the Bayley Scales of Infant Development. The mean level of total toxicity equivalency quantity (TEQ) was 18.8 (4.0–51.2) pg/g lipid in blood of 134 mothers. After adjustment for potential confounding variables, the total TEQ value was shown not to be significantly associated with mental developmental index (MDI) or psychomotor developmental index (PDI). However, the levels of one polychlorinated dibenzo-p-dioxin (PCDD) isomer, total PCDDs, and total PCDDs/polychlorinated dibenzofurans (PCDFs) were significantly negatively associated with MDI, and the levels of two PCDD isomers and three PCDF isomers were significantly negatively associated with the PDI. In conclusion, the background-level exposure of several isomers of dioxins during the prenatal period probably affects the motor development of 6-month-old infants more than it does their mental development. 

Key words: dioxins, infant development, maternal blood, polychlorinated biphenyls (PCBs), prenatal exposure. Environ Health Perspect 114:773–778 (2006). doi:10.1289/ehp.8614 available via http://dx.doi.org/ [Online 15 December 2005]
Materials and Methods

Study population. We recruited pregnant women between July 2002 and July 2004 from the Sapporo Toho Hospital in Hokkaido, Japan (this study became known as the Hokkaido Study on Environment and Children’s Health). All the subjects were native Japanese and were resident in Sapporo and the surrounding areas. The subjects completed the self-administered questionnaire survey after the second trimester during their last pregnancy. The questionnaire provided information relating to their dietary habits, exposure to chemical compounds in their daily life and at their work site, home environment, smoking, and medical histories of themselves and their partners. The prenatal information of the mothers and their children was collected from their medical records. This study was conducted with all the subjects’ written informed consent and was approved by the institutional ethical board for epidemiologic studies at Hokkaido University Graduate School of Medicine.

Exposure measures. A 40-mL blood sample was taken from the maternal peripheral vein after the second trimester during their last pregnancy. When we were not able to take mother’s blood due to the mother’s anemia during pregnancy, we took the blood during hospitalization after delivery. All samples were stored at −80°C until analysis.

The concentrations of PCBs and dioxins in the maternal blood 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 Fukuo University Institute of Health and Environmental Sciences. The gas chromatograph was an Agilent 6890 (Agilent Technologies Inc., Palo Alto, CA, USA) equipped with an AutoSpec Ultima NT (Micromass Ltd., Manchester, UK). The levels of PCBs and dioxins were measured in each isomer [seven polychlorinated dibenzo-p-dioxins (PCDDs): 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDDD), 1,2,3,7,8-pentachlorodibenzo-p-dioxin (PeCDD), 1,2,3,4,7,8-hexachlorodibenzo-p-dioxin (HxCDD), 1,2,3,6,7,8-HxCDD, 1,2,3,4,6,7,8-HpCDD, octachlorodibenzo-p-dioxin (OCDD); 10 polychlorinated dibenzo furans (PCDFs): 2,3,7,8-tetrachlorodibenzofuran (TCDF), 2,3,7,8,9-pentachlorodibenzofuran (PeCDF), 2,3,4,7,8-PeCDF, 1,2,3,4,7,8-hexachlorodibenzofuran (HxCB), 1,2,3,6,7,8-HxCB, 1,2,3,4,6,7,8-HpCDF, octachlorodibenzofuran (OCDF); four non-ortho PCBs: 3,3′,4,4′,5-pentachlorobiphenyl (PeCB) (congener 120), 3,3′,4,4′,5′-hexachlorobiphenyl (HxCB) (congener 169); eight mono-ortho PCBs: 2,3,4′,5′-PeCB (congener 105), 2,3,4,5-PeCDF (congener 114), 2,3′,4,4′,5-PeCB (congener 118), 2,3′,4,4′,6-PeCB (congener 123), 2,3′,4,5,5′-HxCB (congener 156), 2,3′,4,5,5′-HxCB (congener 157), 2,3′,4,5,5′,6′-HxCB (congener 167), 2,3′,4,5,5′,6′-heptachlorodibenzofuran (HxCB) (congener 189); and two di-ortho PCBs: 2,2′,3′,4′,5′-HpCB (congener 170), 2,2′,3′,4′,5′-HpCB (congener 180)], and the total toxicity equivalency quantity (TEQ) levels were calculated (Iida and Todaka 2003; Todaka et al. 2003). Furthermore, for several subjects, 68 PCBs (including mono-ortho PCBs), which remained behind in the blood, were measured using HRGC/HRMS.

Developmental measures. We used BSID-II (Bayley 1993) to assess the infants’ mental and psychomotor development (mental, motor) at 6 months of age. BSID-II is a developmental test tool that is standardized for use in the United States and is most widely used as an infant assessment instrument in both clinical and research settings in the United States. The BSID-II mental scale assesses the age-appropriate children’s level of cognitive, language, and personal/social development. The motor scale assesses fine and gross motor development. Mental and motor scores are based on the calibration scale from raw score and are represented as index scores. The mean values of the mental developmental index (MDI) and the psychomotor developmental index (PDI) were 100, and the standard deviation was 15. Although BSID-II has a lot of strengths and weaknesses (Bayley 1993), it is a most useful test to measure the present attainment of developmental abilities of normal children (Bradley- Johnson 2001).

Because BSID-II was not standardized in Japan, we translated a BSID-II manual in consultation with a manual for BSID, which was used in the development study reported by Kato et al. (1987, 1988). The children were brought to the community center in Sapporo, where they were tested in a quiet, private room in the presence of the parent(s) by one examiner. The development evaluation was performed by three occupational therapists who have clinical experience in the field of developmental disabilities. The examiners were unaware of the infants’ PCB and dioxin exposure levels. First, for all examined children, the scoring was performed by the examiner who performed the examination, and then the scoring was double-checked by two other examiners based on a video that recorded the examination.

We investigated the environmental conditions of the subjects using the questionnaire of home environment devised by Anne et al. (1997).

Data analysis. We used the following eligibility criteria for analysis of subjects: no serious illnesses or complications during pregnancy and delivery, singleton babies born at term (37–42 weeks’ gestation), Apgar score of > 7 at 1 min, infants without congenital anomalies or diseases, and BSID-II completed.

We performed multiple-regression analysis to examine the association between BSID-II scores (MDI, PDI) and the levels of PCBs and dioxins in maternal blood. The levels of PCBs and dioxins in maternal blood were logarithmically transformed, and the analysis was adjusted for gestational age (days), smoking during pregnancy, and caffeine intake during pregnancy (milligrams per day). When we
examined the levels of PCBs and dioxins among blood sampling time (during pregnancy and after delivery) by the Mann-Whitney test, there were significant differences in the levels of OCDD (<0.001), 1,2,3,4,6,7,8-HpCDD (<0.001), total PCDDs (<0.01), and total PCDDs/PCDFs (<0.05) (data not shown). So the blood sampling time was adjusted in multiple regression analysis. Results were considered significant if p < 0.05.

Results
One hundred thirty-five mother–infant pairs fulfilled the determined eligibility criteria of this study; they completed exposure measurements and BSID-II. One pair was excluded from the study because the PCB and dioxin levels in the maternal blood were extremely high. So, in total, 134 mother–infant pairs were included in the study.

Characteristics of mothers and infants are presented in Table 1. The mean (± SD) maternal age was 31.1 ± 4.7 years; 13.4% of mothers continued smoking during pregnancy. Forty-four percent of mothers are inshore fish during pregnancy at least once per week, and 58.2% of mothers ate deep-sea fish during pregnancy at least once per week. Fifty percent of infants were first-born, and 58.2% of infants had been breast-fed >3 months. The mean scores of MDI and PDI were 91.9 ± 5.8 and 89.3 ± 10.5, respectively. Both values were lower than the standardized score.

The relationships between MDI and PDI scores and the subjects’ characteristics are presented in Table 2. For mothers’ characteristics, caffeine intake during pregnancy was significantly negatively associated with PDI scores (r = -0.177, p = 0.04). For infants’ characteristics, gestational age (days) was significantly positively associated with MDI scores (r = 0.178, p = 0.039) and PDI scores (r = 0.289, p = 0.001).

The levels of PCBs and dioxins (picogram per gram lipid) in maternal blood are presented in Table 3. For subjects with a level below the detection limit, we used a value equal to half the detection limit (Longnecker et al. 2000). The means (ranges) of levels of total PCDD/PCDF TEQ, total coplanar PCB TEQ, and total TEQ were 11.9 (2.1–31.2), 6.9 (1.1–22.2), and 18.8 (4.0–51.2) pg TEQ/g lipid, respectively. The mean level of dioxins in this study was slightly lower than that of the subjects in other studies of domestic areas with ages similar to that in this study. In addition, the median level of PCB-153 in the maternal blood of 64 subjects in this study was 22.9 ng/g lipid, which was lower than that in the previous study (Longnecker et al. 2003).

Table 4 shows the results of the multiple regression analysis of the association between the levels of PCBs and dioxins in maternal blood and MDI and PDI scores. After adjustment for blood sampling time, gestational age (days), smoking during pregnancy, and caffeine intake during pregnancy (milligrams per day), PCDD isomer 1,2,3,4,6,7,8-HpCDD (<0.05), total PCDDs (<0.01), and total PCDDs/PCDFs (<0.05) were significantly negatively associated with MDI. On the other hand, PCDD isomers 1,2,3,7,8,9-HxCDD (<0.05) and 1,2,3,4,6,7,8-HxCDF (<0.01), 2,3,7,8-TCDF (<0.05), 1,2,3,7,8-PeCDF (<0.05), and PCDF isomer 1,2,3,6,7,8-HsCDF (<0.05) were significantly negatively associated with PDI. The total levels of PCBs and dioxins were not significantly associated with PDI, and the TEQ values were not significantly associated with MDI or PDI.

Discussion
To the best of our knowledge, this is the first report to investigate the association between the early neurodevelopment of infants and the total level and individual isomer level of Japanese pregnant women’s blood at background levels. As a result, there was no association between the TEQ value of the maternal blood and the PDI levels of Japanese pregnant women’s blood at background levels. The correlation coefficient between the developmental scores and the TEQ value of the maternal blood and the PDI levels of Japanese pregnant women’s blood at background levels was -0.016. The correlation coefficient between the developmental scores and the TEQ value of the maternal blood and the PDI levels of Japanese pregnant women’s blood at background levels was 0.085.

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Table 2. BSID-II mental (MDI) and psychomotor (PDI) development scores for infants in relation to mother and infant characteristics (n = 134).

| Characteristic                          | No. | MDI Mean ± SD | p-value | PDI Mean ± SD | p-value |
|----------------------------------------|-----|--------------|---------|--------------|---------|
| **Maternal characteristics**           |     |              |         |              |         |
| Age (years)                            |     | r = 0.042    | 0.626   | r = -0.059   | 0.498   |
| Educational level                      | 52  | 92.2 ± 5.0   | 0.647   | 89.8 ± 10.8  | 0.676   |
| ≤12 years                              |     | 91.7 ± 6.2   | 0.617   | 89.0 ± 10.4  | 0.617   |
| ≥13 years                              |     | 92.3 ± 5.8   | 0.444   | 89.4 ± 10.4  | 0.875   |
| Economic status: annual income         |     |              |         |              |         |
| <5,000,000 yen                         | 81  | 91.6 ± 5.8   | 0.444   | 89.4 ± 10.4  | 0.875   |
| ≥5,000,000 yen                         | 53  | 92.3 ± 5.8   | 0.617   | 89.1 ± 10.7  | 0.670   |
| Worked during pregnancy                | 112 | 91.5 ± 5.7   | 0.107   | 89.1 ± 10.3  | 0.697   |
| No                                     | 22  | 93.7 ± 6.0   | 0.118   | 90.1 ± 11.8  | 0.183   |
| Smoked during pregnancy                |     |              |         |              |         |
| No                                     | 113 | 93.8 ± 5.8   | 0.027   | 89.3 ± 10.3  | 0.789   |
| Yes                                    | 56  | 93.7 ± 6.0   | 0.627   | 89.8 ± 10.6  | 0.526   |
| Inshore fish intake during pregnancy   |     |              |         |              |         |
| <1 time/week, rarely/never             | 75  | 91.6 ± 6.0   | 0.018   | 89.9 ± 11.3  | 0.670   |
| ≥1 time/week                           | 59  | 92.2 ± 5.5   | 0.198   | 89.7 ± 9.4   | 0.542   |
| Deep-sea fish intake during pregnancy  |     |              |         |              |         |
| <1 time/week, rarely/never             | 56  | 92.6 ± 5.3   | 0.470   | 89.9 ± 10.6  | 0.542   |
| ≥1 time/week                           | 76  | 91.3 ± 6.0   | 0.177   | 88.8 ± 10.5  | 0.542   |
| Caffeine intake during pregnancy (mg/day)| | r = -0.050 | 0.089 | r = -0.089 | 0.256 |
| Alcohol intake before pregnancy (g/day)| | r = 0.137 | 0.011 | r = 0.114 | 0.142 |
| Blood sampling time                    |     |              |         |              |         |
| During pregnancy                       | 86  | 92.0 ± 5.5   | 0.767   | 88.8 ± 10.3  | 0.472   |
| After delivery                         | 48  | 91.7 ± 6.3   | 0.095   | 90.2 ± 10.9  | 0.095   |
| **Child characteristics**              |     |              |         |              |         |
| Sex                                    |     |              |         |              |         |
| Male                                   | 68  | 91.6 ± 5.8   | 0.595   | 87.8 ± 9.9   | 0.084   |
| Female                                 | 66  | 92.1 ± 5.8   | 0.627   | 90.9 ± 10.9  | 0.084   |
| Gestational age (days)                 |     | r = 0.178   | 0.039   | r = 0.289    | 0.001** |
| Birth weight (g)                       |     | r = 0.103    | 0.039   | r = 0.086    | 0.323   |
| Length (cm)                            |     | r = 0.098    | 0.039   | r = 0.086    | 0.323   |
| Head circumference (cm)                |     | r = 0.071    | 0.039   | r = 0.086    | 0.323   |
| First-born                             |     | r = 0.146    | 0.039   | r = 0.086    | 0.323   |
| Duration of breast-feeding, ≥3 months  |     | r = -0.050   | 0.089   | r = -0.089   | 0.256   |
| Yes                                    | 78  | 92.1 ± 5.0   | 0.356   | 89.7 ± 10.5  | 0.617   |
| No                                     | 56  | 91.5 ± 5.5   | 0.557   | 89.9 ± 10.5  | 0.422   |

Student’s t-test, Pearson’s correlation coefficient test: *p < 0.05; **p < 0.01.
there were few human or animal experimental studies investigating the association between individual isomer levels of PCBs and dioxins and neurodevelopment. So, at low-level exposure, total, and total TEQ values had only a minimal effect on mental and motor development. However, we found that several specific chemical compounds would have an adverse influence on motor development, whereas total PCDDs or total PCDDs/PCDFs would have an adverse influence on mental development.

Gray et al. (2005) reported that the level of total PCBs in mothers in their study, which did not show a significantly negative association with the level of total PCBs and the outcome, was similar to those in other studies in which an adverse effect was found. On the other hand, the mixture of PCBs in their specimens was unusual compared with that in other studies. Levels of nonquantitated PCBs may also have varied in biologically significant ways. Thus, they speculated that they might have had a relatively benign mixture if the composition of PCBs affected neurotoxicity. Therefore, the minimal effect of total and total TEQ values on mental and motor development in this study might be caused by the composition of PCBs and dioxins.

### Table 3. Level of PCBs and dioxins (pg/g lipid) in maternal blood (n = 134).

| PCDDs | Detection limit (pg/g) | Mean | Geometric mean | Minimum | 25th | 50th | 75th | Maximum |
|-------|------------------------|------|----------------|---------|------|------|------|---------|
| 2,3,7,8-TCDD | 1.0 | 1.1 | 0.9 | ND | ND | 1.1 | 1.4 | 3.1 |
| 1,2,3,7,8-PeCDD | 1.0 | 4.4 | 3.9 | ND | 3.1 | 4.2 | 5.4 | 11.9 |
| 1,2,3,4,7,8-HxCDD | 2.0 | 1.8 | 1.6 | ND | ND | 2.3 | 13.6 |
| 1,2,3,6,7,8-HxCDD | 2.0 | 15.5 | 13.7 | 2.4 | 10.4 | 14.5 | 18.3 | 43.6 |
| 1,2,3,7,8,9-HxCDD | 2.0 | 2.3 | 1.9 | ND | ND | 2.2 | 3.7 | 7.4 |
| 1,2,3,4,6,7,8-HpCDD | 2.0 | 26.9 | 24.0 | 9.6 | 18.3 | 23.3 | 31.5 | 69.7 |

| OCDD | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 2,3,7,8-TCDF | 1.0 | 0.7 | 0.6 | ND | ND | ND | ND | 2.5 |
| 1,2,3,7,8-PeCDF | 1.0 | 0.6 | ND | ND | ND | ND | ND | 2.2 |

| PCDFs | Detection limit (pg/g) | Mean | Geometric mean | Minimum | 25th | 50th | 75th | Maximum |
|-------|------------------------|------|----------------|---------|------|------|------|---------|
| 2,3,7,8-TCDF | 1.0 | 0.7 | 0.6 | ND | ND | ND | ND | 2.5 |
| 1,2,3,7,8-PeCDF | 1.0 | 0.6 | ND | ND | ND | ND | ND | 2.2 |

### Abbreviations:
- ND: nondetectable
- WHO: World Health Organization.

### Notes:
1. For subjects with a level below the detection limit, we used a value equal to half the detection limit.
2. Percentiles.
3. The calculation of TEQ was estimated based on the toxic equivalent factor values proposed by the WHO (Van den Berg 1988).

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Japanese infant development research is still ongoing, with a focus on the potential effects of low-level exposure to environmental chemicals. The study in Japan aimed to elucidate the mechanisms underlying the association between low-level exposure to PCBs and dioxins and the development of infants and young children, considering the levels of various isomers of these chemicals. The results showed that specific isomers of PCBs and dioxins had a more significant influence on motor development, whereas there were negative associations between metal development and levels of isomers of PCDDs and PCDFs. In this respect, it was impossible to explain the mechanism of our findings because the levels of PCBs and dioxins in maternal blood were 18.8 (4.0–51.2) pg TEQ/g lipid in this study, lower than that of other studies.

There are many previous studies regarding low-level, early-life PCB exposure and its influence on the motor development of infants and young children rather than on their mental development. The total levels of PCDDs or total PCDDs/PCDFs were significantly associated with mental and motor development, whereas there were significant negative associations between the total levels of PCBs and dioxins in maternal blood and the mental development of children. Therefore, the minimal effect of total and total TEQ values on mental and motor development in this study might be caused by the composition of PCBs and dioxins.
In this study, we performed multiple-regression analysis to examine the association between BSID-II scores (MDI, PDI) and total and individual isomer levels of PCBs and dioxins. Because we performed 45 statistical tests for MDI or PDI, this study had a multiple-testing problem. If we performed the Bonferroni adjustment for addressing the multiple-testing problem, all the significances would have disappeared. Furthermore, this study has a small sample size. These are the limitations of this study.

However, because the measurement of PCBs and dioxins is highly complicated and is too expensive, it is difficult to measure these compounds in a large number of subjects. In recent studies of the associations between background-level exposure to PCBs and dioxins and infant neurodevelopment (Koopman-Esseboom et al. 1996; Walckowiak et al. 2001), the sample size was similar to our study. However, no studies have measured isomer levels of PCBs and dioxins to analyze the associations between individual isomer levels and infant neurodevelopment. Because exposure to PCBs and dioxins can be reduced to prevent their adverse effects on children’s development, even if the α error rate rises to some extent, we consider it important to catch these adverse effects on children’s development. Therefore, we believe that analysis of the associations between PCBs and dioxins and children’s development in this study was valuable.

In Japan, Nakai et al. (2004) also performed a prospective study to elucidate the influence of an endocrine-disrupting chemical on the neurodevelopment of children. Humans are the main source of various chemicals that are known pollutants, and food seems to be the main source of PCBs and dioxins in background-level exposure. Because the intake of marine products, such as fish or iodine, in an island country such as Japan would be greater than in western countries, a risk evaluation based on domestic dioxin/PCB data is important.

Vreugdenhil et al. (2002b) pointed out that an improving tendency was shown in children of school age, even if there was a significant negative association between endocrine-disrupting chemical level and neurodevelopment of children during infancy. Breast-feeding and a good home environment are regarded as important factors that improve the influence. Additional studies are needed to elucidate these results still further.

Table 4. BSID-II mental (MDI) and psychomotor (PDI) development scores for infants in relation to the level of PCBs and dioxins in maternal blood (n = 134).

| PCBs | MDI | PDI |
|------|-----|-----|
| β²  | t   | p-Value | β²  | t   | p-Value |
| 2,3,7,8-TCDD | 0.154 | −1.755 | 0.083 | −0.125 | −1.477 | 0.142 |
| 1,2,3,7,8-PeCDD | 0.074 | 0.847 | 0.398 | −0.063 | −0.758 | 0.450 |
| 2,3,4,7,8-HxPeCDD | 0.031 | −0.352 | 0.725 | −0.135 | −1.608 | 0.110 |
| 1,2,3,6,7,8-HxPeCDD | 0.033 | 0.395 | 0.716 | −0.074 | −0.873 | 0.394 |
| 2,3,7,8-TePeCDD | 0.006 | 0.067 | 0.946 | −0.209 | −2.549 | 0.012* |
| 1,2,3,4,6,7,8-HxCDD | −0.222 | −2.418 | 0.017* | −0.243 | −2.806 | 0.006** |
| OCDD | −0.177 | −1.897 | 0.060 | −0.168 | −1.895 | 0.060 |

Abbreviations: ND, nondetectable; WHO, World Health Organization.
*p < 0.05; **p < 0.01.

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