Effects of PCB Exposure on Neuropsychological Function in Children

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In the last decade advances in the analytic methods for quantification of polychlorinated biphenyls (PCBs) have resulted in widespread availability of congener-specific analysis procedures, and large amounts of data on PCB congener profiles in soil, air, water, sediments, foodstuffs, and human tissues have become available. These data have revealed that the PCB residues in environmental media and human tissues may not closely resemble any of the commercial PCB mixtures, depending on source of exposure, bioaccumulation through the food chain, and weathering of PCBs in the environment. At the same time, toxicological research has led to a growing awareness that different classes of PCB congeners have different profiles of toxicity. These advances in analytic techniques and toxicological knowledge are beginning to influence the risk assessment process. As the data from ongoing PCB studies assessing the mediators of neurobehavioral outcomes in children are published, the weight of evidence for PCB effects on neurodevelopment is growing. Studies in Taiwan, Michigan (USA), New York (USA), Holland, Germany, and the Faroe Islands have all reported negative associations between prenatal PCB exposure and measures of cognitive functioning in infancy or childhood. The German study also reported a negative association between postnatal PCB exposure and cognitive function in early childhood—a result that had not been found in previous studies. Only one published study in North Carolina (USA) has failed to find an association between PCB exposure and cognitive outcomes. Despite the fact that several more recent studies have used congener-specific analytic techniques, there have been only limited attempts to assess the role of specific PCB congeners or classes of congeners in mediating neurodevelopmental outcomes. From a statistical standpoint, attempts to determine the role of individual congeners in mediating outcomes are hampered by the fact that concentrations of most individual congeners are highly correlated with each other and with total PCBs. From a toxicological standpoint, these efforts are hampered by the fact that many of the PCB congeners present in human tissues have never been studied in the laboratory, and their relative potency to produce nervous system effects is unknown. More complete information on the health effects of various congeners or congener classes would allow more informed scientific and risk assessment decisions. *Key words:* **children's health, congeners, neurobehavioral outcomes, neuropsychological function, polychlorinated biphenyls.** *Environ Health Perspect* **111:357–376 (2003). doi:10.1289/ehp.5461 available via** *http://dx.doi.org/* **[Online 29 January 2003]**

A number of epidemiological studies to assess the neuropsychological consequences of developmental exposure to PCBs have been initiated over the last decade or so. These studies have extended previous epidemiological research on the developmental neurotoxicity of PCBs, as well as used modern analytic technology for quantification of individual PCB congeners. The U.S. Environmental Protection Agency (EPA) intends to reassess the health effects of PCBs, incorporating information on health effects of PCB congeners or groups of congeners to the extent possible. This review focuses on recent epidemiological studies for which congener-specific exposure data are available. Findings from earlier studies reporting only total PCB concentrations are also summarized to facilitate cross-study comparisons for consistency of the association between PCB exposure and neurodevelopment.

In 1989 the World Health Organization (WHO) released data showing that contamination of breast milk with PCBs and dioxins is higher in the Netherlands, Belgium, Germany, and the United Kingdom than in most other parts of the world (WHO 1989). The same year, the Dutch government responded by launching a longitudinal prospective study known as the Dutch PCB/Dioxin Study to investigate the possible adverse effects of elevated exposure to PCBs and dioxins on growth and development of healthy, full-term infants. The Dutch study was the first study of neurodevelopment to use congener-specific analytic procedures to assess PCB exposure. More recently, several additional studies have been initiated using comparable analytic techniques, but few of the results from the newer studies have been published at the time of this writing. For this reason, the Dutch study is the primary focus of this review. We also describe other studies applying congener-specific analytic techniques and report initial findings that are available.

Recent Studies Using Congener-Specific PCB Analysis

The Dutch Cohort

The Dutch cohort included approximately 400 healthy pregnant women, half of whom intended to breast-feed their infants and half of whom intended to bottle-feed their infants. Exposure indices included PCBs in maternal blood during the last month of pregnancy, PCBs in umbilical cord serum, and, for the breast-fed group, PCB, dioxin, and furan levels in milk. Four nonplanar PCB congeners (PCBs 118, 138, 153, and 180) were quantitated in maternal and cord serum, and 17 dioxins and furans, 6 coplanar PCBs, and 20 *ortho*-substituted PCBs were quantitated in milk. Neurodevelopment was assessed at 3, 7, 18, 42, and 84 months of age using neurological exams (birth and 18 and 42 months), the Bayley Scales of Infant Development (3, 7, and 18 months), the Kaufman Assessment Battery for Children (42 months), the Reynell Language Development Scales (42 months), and the McCarthy Scales of Children's Abilities (84 months).

Description. The Dutch study cohort consisted of 418 healthy, pregnant women recruited between June 1990 and June 1992. Half of the women had been living in Rotterdam or the heavily industrialized areas surrounding Rotterdam in the western part of the Netherlands for at least 5 years. The other half had lived in Groningen or the surrounding rural region in the northern part of the Netherlands for at least 5 years. Half of the women recruited in each region intended to breast-feed their infants for at least 6 weeks. The other half intended to bottle-feed their infants. All bottle-fed infants received formula from a single batch (Almiron M2; Nutricia NV, Zoetermeer, the Netherlands) from birth through 7 months of age.

The women were encouraged to volunteer for the study by their obstetrician or midwife during the last trimester of their pregnancies. Those who did were visited at their homes for further explanation of the study protocol. The women and infants included in the study had to meet a number of inclusion criteria. Only

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Table 1. PCB congeners, dioxins, and furans analyzed in the Dutch study.

Exposure variable, IUPAC no.	Chorine substitution pattern	No.	Mean tissue level	Mean TEQ
ΣPCBs in maternal plasma[a]				
118	2,3´,4,4´,5	415	0.16 ng/g	
138	2,2´,3,4,4´,5´	415	0.60 ng/g	
153	2,2´,4,4´,5,5´	415	0.91 ng/g	
180	2,2´,3,4,4´,5,5´	415	0.54 ng/g	
		ΣPCBs = 2.21 ng/g		
ΣPCBs in cord blood[a]				
118	2,3´,4,4´,5	373	0.04 ng/g	
138	2,2´,3,4,4´,5´	382	0.13 ng/g	
153	2,2´,4,4´,5,5´	382	0.18 ng/g	
180	2,2´,3,4,4´,5,5´	382	0.10 ng/g	
			ΣPCBs = 0.45 ng/g	
ΣPCBs in breast milk[b]				
118	2,3´,4,4´,5	195	35.5 ng/g	3.6
138	2,2´,3,4,4´,5´	195	129.9 ng/g	
153	2,2´,4,4´,5,5´	195	186.3 ng/g	
180	2,2´,3,4,4´,5,5´	195	76.8 ng/g	0.8
			ΣPCBs = 428.5 ng/g**	
Nondioxin-like PCBs measured in breast milk[b]				
28	2,4,4´	195	12.1 ng/g	
52	2,2´,5,5´	195	2.6 ng/g	
66	2,3´,4,4´	195	11.6 ng/g	
70	2,3´,4´,5	195	18.5 ng/g**	
99	2,2´,4,4´,5	195	19.7 ng/g**	
101	2,2´,4,5,5´	195	1.5 ng/g	
128	2,2´,3,3´,4,4´	195	4.0 ng/g	
137	2,2´,3,4,4´,5	195	16.8 ng/g	
138	2,2´,3,4,4´,5´	195	129.9 ng/g**	
141	2,2´,3,4,5,5´	195	1.1 ng/g	
151	2,2´,3,5,5´,6	195	0.9 ng/g	
153	2,2´,4,4´,5,5´	195	186.3 ng/g**	
177	2,2´,3,3´,4´,5,6	195	6.3 ng/g*	
183	2,2´,3,4,4´,5´,6	195	12.2 ng/g*	
187	2,2´,3,4´,5,5´,6	195	20.0 ng/g*	
194	2,2´,3,3´,4,4´,5,5´	195	8.6 ng/g	
195	2,2´,3,3´,4,4´,5,6	195	2.9 ng/g	
202	2,2´,3,3´,5,5´,6,6´	195	0.9 ng/g	
			ΣPCBs = 455.9 ng/g	
Mono-*ortho* PCBs in breast milk[b]				
105	2,3,3´,4,4´	195	9.4 ng/g	0.9
118	2,3´,4,4´,5	195	35.5 ng/g**	3.6
156	2,3,3´,4,4´,5	195	21.0 ng/g**	10.5
			ΣPCBs = 65.9 ng/g	ΣTEQ = 15.0**
Di-*ortho* PCBs in breast milk[b]				
170	2,2´,3,3´,4,4´,5	195	37.1 ng/g*	3.7
180	2,2´,3,4,4´,5,5´	195	76.8 ng/g	0.8
			ΣPCBs = 113.9 ng/g	ΣTEQ = 4.5*
Planar PCBs in breast milk[b]				
77	3,3´,4,4´	194	0.0193 ng/g	0.01
126	3,3´,4,4´,5	194	0.152 ng/g	15.2
169	3,3´,4,4´,5,5´	194	0.0843 ng/g**	0.8
			ΣPCBs = 0.2556 ng/g	ΣTEQ = 16.0
Dioxins in breast milk[b]				
48	2,3,7,8	176	0.004 ng/g	4.0
54	1,2,3,7,8	176	0.0106 ng/g*	5.3
66	1,2,3,4,7,8	176	0.0087 ng/g*	0.9
67	1,2,3,6,7,8	176	0.0474 ng/g**	4.7
70	1,2,3,7,8,9	176	0.0067 ng/g*	0.7
73	1,2,3,4,6,7,8	176	0.0632 ng/g*	0.6
75	1,2,3,4,6,7,8,9	176	0.7996 ng/g	0.8
			ΣDioxins = 0.9402 ng/g	ΣTEQ = 17.0
Furans in breast milk[b]				
83	2,3,7,8	176	0.0008 ng/g*	0.08
94	1,2,3,7,8	176	0.0003 ng/g	0.01
114	2,3,4,7,8	176	0.0227 ng/g*	11.3
118	1,2,3,4,7,8	176	0.0066 ng/g	0.7
121	1,2,3,6,7,8	176	0.0057 ng/g	0.6
130	2,3,4,6,7,8	176	0.0036 ng/g	0.4
124	1,2,3,7,8,9	176	0.0003 ng/g	0.03
131	1,2,3,4,6,7,8	176	0.0079 ng/g	0.08
134	1,2,3,4,7,8,9	176	0.0002 ng/g	0.0
135	1,2,3,4,6,7,8,9	176	0.0022 ng/g**	0.0
			ΣFurans 0.0505 ng/g	ΣTEQ = 13.2
				Total dioxin ΣTEQ = 65.7

[a]Levels in maternal and cord plasma calculated on whole weight basis (ng/g plasma). [b]Levels in breast milk calculated on lipid weight basis (ng/g fat). Asterisks denote significant relationship with neurological optimality score: *$p < 0.05$; **$p < 0.01$ (Huisman et al., 1995).

Caucasian first- or second-born full-term infants (37–42 weeks of gestation) delivered vaginally and without the assistance of forceps or vacuum extraction were included. In addition, pregnancy and delivery had to occur without serious illness or complications, and a maternal blood sample from the last month of pregnancy as well as a cord blood sample had to be available.

Exposure indices. The exposure indices used in this study included PCB levels in maternal blood collected during the last month of pregnancy, PCB levels in umbilical cord blood collected shortly after birth, and for the breast-fed group, PCB, dioxin, and furan levels in a 24-hr representative breast milk sample collected 2 weeks after delivery. The exposure variables derived from these measures are listed in Table 1. Four nonplanar PCB congeners [International Union for Pure and Applied Chemistry (IUPAC) nos. 118, 138, 153, and 180] were quantitated in maternal and cord blood. These four congeners were selected because they are the predominant congeners found in human tissue worldwide and typically account for around 50–60% of the total PCBs (Hansen 1998). The sum of the four congeners was calculated for maternal blood and cord blood to create two exposure variables: ΣPCB maternal and ΣPCB cord, both representing prenatal exposure.

It was not feasible to measure dioxins, furans, or coplanar PCBs in maternal or cord blood because the amount of sample available was small. However, the levels of 17 dioxins and furans, 6 coplanar or mono-*ortho* coplanar PCBs, and 20 *ortho*-substituted PCBs were quantitated in milk (see Table 1), providing several additional exposure variables for the breast-fed children. The dioxin, furan, and coplanar PCB data were used to calculate dioxin toxic equivalents (TEQs) (Ahlborg et al. 1994). Five exposure variables were created based on the TEQs: dioxin TEQs, planar PCB TEQs, mono-*ortho* PCB TEQs, di-*ortho* PCB-TEQs, and total TEQs (Table 1). In addition, the four *ortho*-substituted PCB congeners that were also measured in maternal and cord blood (IUPAC nos. 118, 138, 153, and 180) were summed to create a variable called ΣPCBs in breast milk. Because the levels of PCBs and dioxins in maternal milk shortly after birth are highly correlated with the levels in maternal and cord blood (Van den Berg et al. 1994), these measures were used as additional indicators of prenatal exposure in the subset of children who were breast-fed. To assess postnatal lactational exposure, the calculated values were multiplied by the number of weeks of breast-feeding.

The levels of PCB 118, 138, 153, and 180 in maternal and cord plasma are shown in Table 1. For all four PCB congeners, the levels

in maternal plasma were about 4–5 times higher than in cord plasma (Koopman-Esseboom et al. 1994a). However, the percentage of lipid in cord blood is much lower than in maternal blood, and when the PCB levels in maternal and cord plasma were expressed on a lipid basis, they were similar. It is difficult to compare absolute levels of exposure in this cohort to those in most other published studies because the analytic methods differ from study to study. Also, in the other studies PCBs are either reported as total PCBs (e.g., Michigan, North Carolina, Faroe Islands, and German studies) or as homologue groups (Oswego, NY, study). In the Faroe Islands and German studies, three of the same four congeners were quantitated, but they were reported either as the sum (German cohort) or the geometric mean of the sum multiplied by two (Faroe Islands cohort). The concentrations of individual congeners in maternal or cord plasma were not reported in either study. However, the total of congeners 138, 153, and 180 in cord plasma appears to be similar in the Dutch and German cohorts (0.41 vs. ~0.55 ng/g), and about 3-fold higher in the Faroe Islands cohort. Recently the levels of individual PCB congeners in cord serum were reported for a cohort of 751 infants assembled in New Bedford, Massachusetts, between 1993 and 1998 (Korrick et al. 2000). The levels of PCBs 138, 153, and 180 were all about 2-fold higher in the Dutch cohort than in the American cohort. The levels of PCB 118 were similar in the two cohorts. Exposure data were recently published for an Inuit cohort in northern Québec (Muckle et al. 2001). The PCB concentrations in cord plasma were not as high as expected on the basis of other Arctic cohorts. Concentrations of PCB 153 were similar to those in the Dutch cohort.

The levels of individual dioxin, furan, and PCB congeners in breast milk were also determined for women who breast-fed their infants (Koopman-Esseboom et al. 1994a; Table 1). The total dioxin TEQs averaged 65.7 pg/g milk fat. Dioxins and furans contributed 46%, planar PCBs contributed 24%, mono-*ortho* PCBs contributed 23%, and di-*ortho* PCBs contributed 7%. The total dioxin TEQs are somewhat elevated compared to those of the Scandinavian countries, Spain, and the United States, but they are comparable to the total TEQs in other highly industrialized, densely populated countries in Western Europe such as Belgium, the United Kingdom, and Germany (WHO 1989). The ΣPCBs in milk fat based on the four congeners assessed in maternal and cord blood as well as breast milk was 428.5 ng/g, whereas the ΣPCBs based on all 23 congeners quantitated in breast milk averaged about 636 ng/g milk fat. As with the cord plasma concentrations, these levels are similar to those in the German cohort and about 3-fold lower than those reported in the Faroe Islands cohort.

It is difficult to make quantitative comparisons to the total PCBs in milk fat reported in earlier studies because packed-column gas chromatography based on Aroclor standards was used to calculate total PCBs in those studies. However, with that caveat in mind, the total PCBs in milk collected shortly after birth in the Michigan and North Carolina cohorts were 812 and 1,770 ng/g milk fat, respectively (Schwartz et al. 1983; Rogan et al. 1986a). As discussed below, the analytic method used in the North Carolina study probably overestimated total PCBs by a factor of about 2 (Jensen 1987).

Neuropsychological measures. The neuropsychological development of the Dutch children was evaluated shortly after birth and again at 3, 7, 18, 42, and 84 months of age. Data were collected on a large number of potential covariates, including smoking and alcohol consumption during pregnancy, maternal education and IQ, intellectual stimulation in the home, and maternal age and weight.

Neurological optimality. The Prechtl neurological exam was administered to all infants between 10 and 21 days after birth to assess neonatal neurological condition (Huisman et al. 1995a). The exam consisted of two clusters of items, one describing postural tone (10 items) and one describing other reflexes and responses (11 items). Infants received a score of 0–2 on each item, and the scores for individual items within each cluster were then summed to get cluster scores. Each infant was also assigned a neurological optimality score based on 60 items for which an optimal range was defined. Infants received a point for each item on which they met the optimality criteria, and these points were summed to obtain the neurological optimality score.

After adjusting for the age of the mothers, area of residence (Rotterdam or Groningen), maternal alcohol consumption, and an interaction between maternal age and alcohol consumption, no significant relationship between individual PCB congeners or ΣPCBs in maternal or cord blood and neurological optimality scores was found. Similarly, scores on the Prechtl postural tone and reflexes and responses clusters were unrelated to maternal or cord blood PCB levels. In contrast, both ΣPCBs in maternal milk (sum of PCBs 118, 138, 153, and 180) and total dioxin TEQs (sum of PCB, dioxin, and furan TEQs) in maternal milk were negatively associated with neurological optimality scores. This suggests that postnatal exposure may play a role in mediating effects. Alternatively, breast milk may be a marker for prenatal exposure and, because of its high fat content and the large amount of sample available for analysis, may simply be a more reliable measure than either maternal blood or cord blood.

Seven of 17 individual dioxin and furan congeners and 10 of 20 individual *ortho*-substituted PCB congeners were negatively associated with neurological optimality. With the exception of PCB 180, which was not related to neurological optimality, the *ortho*-substituted PCB congeners for which significant associations were found tended to be those present in the highest concentrations in milk fat (Table 1). The 10 congeners did not appear to be structurally or toxicologically similar in any obvious way. They included congeners with four to seven chlorine substitutions. Some were aryl hydrocarbon (Ah) receptor agonists, whereas others were not. Thus, the significant associations could be related to the fact that these congeners *a*) were most likely present in a larger percentage of the sample population (although no data on prevalence are presented) and *b*) could be measured more reliably due to their higher concentrations rather than to any specific structural or toxicological aspects of the congeners. If Ah receptor binding is an important mechanism for neurotoxicity, one would predict that congeners with higher TEQs would be most likely associated with negative outcomes. However, no obvious relationship between TEQs and neurological outcome was observed (Table 1).

In summary, the regression analyses using individual PCB, dioxin, and furan congeners provided little information about potential structure–activity relationships for neurological outcomes in humans, either with respect to nondioxin-like versus dioxin-like compounds or with regard to structure–activity relationships within each of these broad classes. As Koopman-Esseboom et al. (1994a) have shown, the levels of the various PCB and PCDD/PCDF congeners in human tissues are highly intercorrelated. This will undoubtedly complicate any attempts to determine structure–activity relationships based on human data. It may be necessary to rely on laboratory animal studies for such insights.

The neurological condition of the children was assessed again at 18 (Huisman et al. 1995b) and 42 months of age (Lanting et al. 1998). At 18 months the children were assessed using an age-specific neurological exam that focused on observations of motor functions including milestones such as grasping, sitting, crawling, standing, and walking. The neurological findings were also evaluated in terms of optimality. A list of 57 items was compiled, and the child was given 1 point for each item meeting the criteria for optimality. As in the neonatal assessments, points were totaled to obtain a neurological optimality score. Unlike the neonatal findings, neither PCB nor dioxin exposure via breast milk was associated with neurological optimality at 18 months of age. In contrast, transplacental

PCB exposure, measured either as ΣPCB cord or ΣPCB maternal, was associated with a small but measurable deficit in neurological condition at 18 months. Children at the 95th percentile for PCB exposure scored, on average, about 2 points lower than children at the 5th percentile. A cluster score derived from the neurological exam was not significantly associated with any of the outcome measures. At 42 months of age, the neurological condition of the children was reassessed using similar methodology (Lanting et al. 1998). In addition to the exposure measures used at the earlier time points, the child's serum PCB concentration at 42 months (ΣPCBs 118, 138, 153, 180) was also used as an exposure variable. No significant associations between PCB or dioxin/furan exposure and neurological condition were observed at 42 months of age.

Bayley Scales of Infant Development. The mental and psychomotor development of the children in the Rotterdam portion of the sample was assessed at 3, 7, and 18 months of age using the Dutch version of Bayley Scales of Infant Development, a frequently used standardized test of infant cognitive development (Koopman-Esseboom et al. 1996). *In utero* PCB exposure as measured by the sum of PCBs in maternal blood (ΣPCB maternal) was negatively associated with the psychomotor development score at 3 months of age. A doubling of the PCB concentration in maternal plasma corresponded to a decrease of approximately 3 points in the child's score on the psychomotor index (PDI). Neither the sum of PCBs in cord blood (ΣPCB cord) nor the sum of PCBs in breast milk was associated with the PDI score, but the total dioxin TEQs in milk at 2 weeks of age was negatively related to the PDI score at 3 months. Postnatal exposure, determined by multiplying the ΣPCBs or the total dioxin TEQs in breast milk by the number of weeks of breast-feeding, was not related to PDI scores at 3 months.

In contrast, at 7 months of age there were no associations with prenatal PCB or dioxin exposure, but there did appear to be a small negative association with total postnatal dioxin TEQ exposure on PDI scores. This was somewhat obscured by the fact that breast-feeding had a positive influence on PDI scores. Infants breast-fed for 6–16 weeks scored, on average, 7 points higher than formula-fed infants, and those breast-fed for 17–30 weeks scored 14 points higher. The association with exposure to PCBs via breast milk only became evident when the infants were divided into low (168–769 pg TEQ/g), medium (770–1,289 pg TEQ/g), and high (1,290–4,340 pg TEQ/g) exposure groups based on their total postnatal exposure to dioxin TEQs. When this approach was taken, breast-fed infants with low postnatal exposure to dioxin-like compounds scored significantly higher than formula-fed infants on the PDI, whereas breast-fed infants with medium or high exposure did not show a similar advantage. In essence, exposure to dioxin-like compounds eliminated the significant positive influence of breast-feeding on PDI scores. However, the most highly exposed breast-fed infants still did not perform more poorly than formula-fed infants, even among the most highly exposed women in the general population. Unlike dioxin TEQs, postnatal exposure to nondioxin-like PCBs was not related to PDI scores at 7 months.

Neither prenatal nor postnatal exposure to PCBs or dioxins was related to PDI scores at 18 months, and there were no associations of either pre- or postnatal exposure to PCBs or dioxins with the Bayley mental development index (MDI) at 3, 7, or 18 months of age. MDI scores were positively influenced by breast-feeding, but the advantage was not as great as for the PDI. Infants breast-fed for 6–16 weeks or 17–30 weeks scored 2 or 4 points higher than formula-fed infants, respectively. There was no relationship between neonatal thyroid hormone levels and mental or psychomotor development at any age.

The Bayley Scales of Infant Development were also used to assess infant mental and psychomotor development in several of the earlier studies. Jacobson et al. (1986) administered the test to a cohort of Michigan children at 5 months of age and did not find any association between pre- or postnatal PCB exposure and either MDI or PDI scores. In contrast, Gladen and colleagues (1988; Rogan and Gladen 1991) administered the test at 6, 12, 18, and 24 months of age and found that higher prenatal PCB exposure was associated with lower psychomotor scores at 6, 12, and 24 months of age. A similar trend was seen at 18 months, but the difference was not statistically significant at that age. The reasons for the discrepancies between the three studies are not readily apparent. However, the North Carolina cohort studied by Rogan and Gladen was considerably larger (880 children) than either the Michigan cohort (313 children) or the Dutch cohort (207 children assessed on the Bayley Scales). The larger sample may simply have provided better statistical power.

Neither research group found any relationship between postnatal exposure and PDI scores. However, in both cases, the only measure of PCB exposure was total PCBs determined by packed-column gas chromatography. It was not feasible at the time these earlier studies were conducted to analyze for individual coplanar PCBs, dioxins, or furans. The postnatal effect observed in the Dutch cohort was associated with exposure to dioxin TEQs and was unrelated to total PCBs. Thus, the findings are not necessarily inconsistent with those from the earlier studies.

Cognitive assessments. At 42 months of age, the cognitive development of the Dutch children was assessed with the Dutch versions of the Kaufman Assessment Battery for Children (K-ABC) and the Reynell Language Development Scales (RDLS) (Patandin et al. 1999). The entire cohort (Rotterdam and Groningen samples) was assessed on the K-ABC, but only the Rotterdam sample was assessed on the RDLS. The K-ABC is a standardized test of intellectual function similar to the McCarthy Scales of Children's Abilities and consists of 11 subtests, which yield two scaled scores. The sequential processing scale includes various types of problems that must be solved by arranging input in serial order. The simultaneous processing scale consists of problems that are spatial, analogic, or organizational in nature. The test yields an overall cognitive score as well as the two scaled scores. The RDLS is a test of verbal comprehension.

As in the previous assessments, prenatal PCB exposure was estimated from the ΣPCBs in maternal and cord plasma. In the breast-fed group, breast milk concentrations of dioxin TEQs and nondioxin-like PCBs (sum of 20 congeners) were used as additional estimates of prenatal exposure. Lactational exposure was estimated by multiplying breast milk concentrations of total dioxin TEQs or total PCBs by the number of weeks of breast-feeding. Both the sum of the four PCBs (IUPAC nos. 118, 138, 153, 180) analyzed in maternal and cord plasma and the total of all 20 nonplanar PCBs were assessed as measures of nondioxin-like PCBs. Current PCB body burden was assessed using the sum of PCBs 118, 138, 153, and 180 in plasma samples obtained from the children at 42 months.

A total of 395 children (193 from Rotterdam and 202 from Groningen; 94% of the original cohort) were evaluated at 42 months of age. Fifteen of the 395 children did not cooperate with the testing procedures and had to be excluded from the final analysis of the K-ABC data. However, the excluded children did not differ from the others in terms of PCB or dioxin exposure. All 193 children from Rotterdam completed the RDLS. As was reported for the Bayley Scales of Infant Development, the breast-fed group scored significantly higher than the formula-fed group on both the K-ABC and the RDLS. This might be explained by the fact that breast-fed children came from a more advantaged background, rather than by breast-feeding per se. Several important covariates including parental education, parental IQ, and Home Observation for Measurement of the Environment (HOME) scores were higher for the breast-fed group. After adjusting for these covariates, the scores of the two feeding groups no longer differed. However, because of this difference, the data

were analyzed for the entire cohort and also for the breast-fed and formula-fed groups individually.

After controlling for covariates, prenatal PCB exposure (ln ΣPCB maternal) was associated with lower scores on all three scales of the K-ABC (Patandin et al. 1999; Table 2). A similar trend was observed for the RDLS verbal comprehension scale, but the relationship was not statistically significant. When the breast-fed and formula-fed groups were assessed separately, an interesting pattern emerged: All of the outcome measures were highly significant in the formula-fed group, but none was significant in the breast-fed group. The most highly exposed children in the formula-fed group scored 6–8 points lower than the least exposed children on both the K-ABC and RDLS (Patandin et al. 1999). When ln ΣPCB in cord plasma was entered as the PCB exposure variable, the pattern of the results was similar, but fewer significant associations were observed. Formula-fed children scored lower on the simultaneous processing scale of the K-ABC and on the RDLS.

As discussed above, several additional measures of exposure were assessed in the breast-fed children. Prenatal dioxin TEQ exposure, lactational dioxin TEQ exposure, and lactational PCB exposure were all unrelated to performance on the K-ABC and the RDLS. However, the positive influences of their more advantaged background may have compensated for any negative impact from PCB/dioxin exposure in these children. Unfortunately, there is no way to estimate prenatal dioxin TEQs in the formula-fed group. It would be enlightening to know whether a similar lack of association would be observed in these children. Finally, current body burdens of PCBs as measured by the ln ΣPCB in plasma samples taken from the children at 42 months were not related to any of the measures of cognitive ability in the group as a whole or in either of the groups individually. Deficits in childhood intellectual functioning have been reported in the Michigan cohort (Jacobson et al. 1990a; Jacobson and Jacobson 1996) and in children exposed to PCB-contaminated rice oil in Taiwan (Chen et al. 1992), but not in

Table 2. Neurobehavioral, neuropsychological, and neuroendocrine effects of the Dutch study.

Test	Age (months)	Outcome	Exposure	ΣPCB in cord blood	ΣPCB in maternal blood	ΣPCB in milk	Total dioxin/ PCB TEQs	References
Birth size and growth								Patandin et al. (1998)
Birth weight	0	↓	BF + FF	$p = 0.03$ (179)[a]	$p = 0.057$ (203)			
Length	0.3	—	BF + FF	NS	NS			
Head circumference	3	—	BF + FF	NS	NS			
Prechtl's neurological exam	0.5	↓	BF	NS	NS	$p < 0.01$ (194)	$p < 0.01$ (168)	Huisman et al. (1995)
Bayley Scales of Infant Development								Koopman-Esseboom et al. (1996)
MDI	3	—	BF + FF	NS	NS	NS	NS	
PDI	3	↓	BF + FF	NS	$p = 0.02$ (198)	NS	NS	
MDI	7	—	BF + FF	NS	NS	NS	NS	
PDI	7	↓	BF + FF	NS	NS	NS	$p = 0.05$ (182)	
MDI	18	—	BF + FF	NS	NS	NS	NS	
PDI	18	—	BF + FF	NS	NS	NS	NS	
Neurological optimality	18	↓	BF + FF	$p = 0.003$ (373)	NS	NS	NS	Huisman et al. (1995)
Fluency of motility	18	—	BF + FF	NS	NS	NS	NS	Huisman et al. (1995)
Touwen/Hempel neurological exam	42	—	BF + FF	NS	NS	NS	NS	Lanting et al. (1998)
K-ABC								Katandin et al. (1999)
Overall cognitive	42	↓	BF + FF	NS	$p = 0.005$ (373)	NS	NS	
Sequential		↓	BF + FF	NS	$p = 0.02$ (373)	NS	NS	
Simultaneous		↓	BF + FF	$p = 0.02$ (384)	$p = 0.02$ (384)		NS	NS
Reynell language		—	BF + FF	NS	NS	NS	NS	
Overall cognitive	42	—	BF	NS	NS	NS	NS	
Sequential		—	BF	NS	NS	NS	NS	
Simultaneous		—	BF	NS	NS	NS	NS	
Reynell language		—	BF	NS	NS	NS	NS	
Overall cognitive	42	↓	FF	NS	$p = 0.0006$ (178)	NS	NS	
Sequential		↓	FF	NS	$p = 0.002$ (178)	NS	NS	
Simultaneous		↓	FF	$p = 0.02$	$p = 0.007$ (186)	NS	NS	
Reynell language		↓	FF	$p = 0.01$	$p = 0.03$ (90)	NS	NS	
Thyroid status								Koopman-Esseboom et al. (1994)
Maternal pregnancy TT3		↓		NS	NS	NS	$p < 0.001$ (78)	
Maternal pregnancy FT4		—		NS	NS	NS	NS	
Maternal pregnancy TT4		—		NS	NS	NS	NS	
Maternal pregnancy TSH		—		NS	NS	NS	NS	
Maternal postdelivery TT3		↓		NS	NS	NS	$p < 0.001$ (77)	
Maternal postdelivery FT4		—		NS	NS	NS	NS	
Maternal postdelivery TT4		↓		NS	NS	NS	$p < 0.01$ (77)	
Maternal postdelivery TSH		—		NS	NS	NS	NS	
Infant TT3	0.5	—	BF	NS	NS	NS	NS	
Infant FT4	0.5	↓	BF	NS	NS	NS	$p < 0.05$ (78)	
Infant TT4	0.5	—	BF	NS	NS	NS	NS	
Infant TSH	0.5	↑	BF	NS	NS	NS	$p < 0.001$ (78)	
Infant TT3	3	—	BF	NS	NS	NS	NS	
Infant FT4	3	—	BF	NS	NS	NS	NS	
Infant TT4	3	—	BF	NS	NS	NS	NS	
Infant TSH	3	↑	BF	$p < ??$	$p < ??$	NS	$p < 0.001$ (78)	

Abbreviations: ↓, decrease; ↑, increase; ??, *p*-value not given; BF, breast fed; FF, formula fed; FT4, free T4; TSH, thyroid-stimulating hormone; TT3, total triiodothyronine; TT4, total thyroxine; NS, nonsignificant. [a]Numbers in parentheses represent sample size (*n*).

the North Carolina cohort (Gladen and Rogan 1991). Interestingly, 88% of the women in the North Carolina cohort breast-fed their children (Rogan et al. 1986a). The authors reported that this was a highly educated group of women, most of whom were professionals or white-collar workers, so it is possible that the advantaged background of the children in this cohort diminished or masked the impact of prenatal PCB exposure on later cognitive function.

A reevaluation of the Rotterdam children was undertaken at 84 months of age (Vreugdenhil et al. 2002). Assessments included the McCarthy Scales of Children's Abilities, several motor tests including finger tapping and the Purdue Pegboard Test, and several auditory tests including otoacoustic emissions and brain stem auditory evoked responses (Weisglas-Kuperus N. Personal communication).

Only results relating prenatal PCB exposure to performance on the McCarthy scales are available at this time. When effects of prenatal PCB exposure on the general cognitive index (GCI), the memory scale score, and the motor scale score from the McCarthy were assessed, after adjustment for covariates there was no relationship between prenatal PCB exposure and the GCI, memory, or motor scores. Similarly, when the breast-fed and bottle-fed children were considered separately, there was no relationship between PCB exposure and McCarthy scores. However, when interactions of PCB exposure with maternal age, parental education, parental verbal IQ score, and HOME score were considered, several interesting patterns emerged. Prenatal PCB exposure was associated with poorer cognitive and memory performance in the children born to younger mothers, parents with lower verbal IQ, and parents with less education. PCB exposure was associated with poorer motor performance in children whose parents had lower verbal IQ scores or lower HOME scores. These results illustrate the critical role that key covariates can play in mediating subtle PCB-related relationships and suggest that the differences in vulnerability between the breast-fed and bottle-fed children at 42 months of age were most likely related to parental and home characteristics rather than to beneficial effects of breast-feeding per se.

Other measures. Additional non-neuropsychological outcome measures were also assessed in a subset of the children from the Dutch cohort. These included body weight, body length, and head circumference, which were assessed in the Rotterdam children (Patandin et al. 1998), as well as measures of immune function (not discussed here, but see Weisglas-Kuperas et al. 1995) and thyroid hormone function (Koopman-Esseboom et al. 1994b), which were assessed in a subset of the Rotterdam children. After adjustment for covariates, both cord and maternal blood PCB levels were negatively associated with birth weight (Patandin et al. 1998). Infants with cord PCB levels at the 90th percentile (0.80 μg/L) weighed 165 g less than infants with cord PCB levels at the 10th percentile (0.20 μg/L). Similar results were obtained using ΣPCB in maternal plasma as the exposure measure. The size of the body weight deficit in the more highly PCB-exposed infants was similar to that reported some years earlier in the Michigan cohort (Fein et al. 1984). However, unlike in the Michigan study, there were no significant negative associations between PCBs in cord or maternal plasma and body length or head circumference. Both cord and maternal PCB levels were also associated with a lower growth rate between birth and 3 months of age in the formula-fed group, but there was no negative association with growth rate from 0 to 3 months in the breast-fed group or from 3 to 7, 7 to 18, or 18 to 42 months in either the formula- or breast-fed groups. The influence of postnatal PCB and dioxin exposure on growth rate was also examined in the breast-fed group, but no association was found.

Thyroid hormones, including total thyroxine (TT4), total triiodothyronine (TT3), free T4 (FT4), and thyroid-stimulating hormone (TSH) were measured in a subset of 105 mother–infant pairs in the Rotterdam area (Koopman-Esseboom et al. 1994b). Except for one mother with a high TSH level, the TT3, TT4, FT4, and TSH levels of all mother–infant pairs were within the clinically defined normal range. However, higher TEQs correlated with lower maternal TT3 and TT4 during the last month of pregnancy as well as at 2 weeks after delivery, with higher infant TSH levels both 2 weeks and 3 months after birth, and with lower infant TT4 and FT4 2 weeks after birth (Table 2). Higher ΣPCBs in maternal and cord plasma were also associated with higher TSH levels in infants 2 weeks after birth. A recent publication reported that mild, asymptomatic maternal hypothyroidism during pregnancy can lead to subtle intellectual impairments in children (Haddow et al. 1999). However, the potential role of subtle PCB-induced changes in circulating thyroid hormones in mediating the neuropsychological effects described above remains undetermined. Thus far, animal studies have failed to establish a relationship between PCB-induced reductions in thyroid hormones during development and later deficits in cognitive function (Schantz et al. 1997), suggesting that the hypothyroxinemia that accompanies PCB exposure may not mediate the cognitive deficits.

Comments and discussion: Dutch cohort. In summary, the Dutch collaborative PCB/dioxin study assessed neuropsychological, physical, hormonal, and immune outcomes in a cohort of children from Rotterdam and Groningen at various time points from birth to 84 months of age. Congener-specific analytic techniques were used, a number of indices of pre- and postnatal exposure to PCBs and dioxin were calculated (Table 1), and several important developmental outcomes were found to be negatively impacted by prenatal or lactational exposure to PCBs and/or dioxins (Table 2). Because so many different outcomes were assessed in relation to so many different exposure variables, the results are very complex.

Complexities of the data set include the fact that the neuropsychological domains affected by exposure were not consistent across age of assessment. Early in development (3–18 months of age), psychomotor and neurological development was negatively impacted by PCB/dioxin exposure (Huisman et al. 1995a, 1995b; Koopman-Esseboom et al. 1996), whereas mental development did not appear to be affected (Koopman-Esseboon et al. 1996). Conversely, later in development (42 and 84 months of age), neurological function appeared to be normal (Lanting et al. 1998), but cognitive function was impaired (Patandin et al. 1999; Vreugdenhil et al. 2002). Despite these seeming inconsistencies, aspects of the findings are consistent with those of several earlier studies. The psychomotor differences reported at 3 and 7 months of age are consistent with the findings reported earlier by Rogan, Gladen, and colleagues (Gladen et al. 1988; Rogan and Gladen 1991), although in that case psychomotor differences persisted through 24 months of age. The cognitive differences are consistent with findings reported by Jacobson and colleagues, who found that children with higher PCB exposure scored lower on tests of cognitive function in infancy (Jacobson et al. 1985) and later in childhood (Jacobson et al. 1990a; Jacobson and Jacobson 1996). The Dutch children did not show any evidence of cognitive deficits associated with PCB exposure in infancy (Koopman-Esseboom et al. 1996). However, this could be related to the use of different assessment tools. Early cognitive development was assessed using the Bayley MDI in the Dutch study, whereas a very different test, the Fagan Test of Infant Intelligence, was used in the Michigan study. Many developmental psychologists believe that the Bayley MDI measures primarily sensorimotor function rather than cognitive function (e.g., McCall et al. 1977). In contrast, the Fagan test involves relatively complex information processing and is considered to be a purely cognitive test.

Another complexity relates to the fact that the measures of exposure associated with the outcomes varied depending on the outcome and the age of assessment. For example, scores on the Bayley psychomotor index (PDI) were negatively affected at both 3 and 7 months of age, but at 3 months poorer performance was related to prenatal PCB exposure. In contrast, at 7 months lower scores were related to postnatal dioxin TEQ exposure via breast milk (Koopman-Esseboom et al. 1996). Neurological optimality was negatively affected at birth and 18 months of age, but the neonatal scores were negatively associated with PCBs and dioxin TEQs in milk (Huisman et al. 1995a), whereas the 18-month scores were associated with PCBs in cord plasma (Huisman et al. 1995b).

At first glance the cognitive results appear to be more straightforward. That is, the cognitive differences at both 42 and 84 months of age were related to prenatal PCB exposure as measured by the ΣPCBs in either cord or maternal plasma (Patandin et al. 1999; Vreugdenhil et al. 2002). There was no relationship between dioxin TEQs in milk fat at 2 weeks postpartum (considered to be an estimate of prenatal dioxin TEQ exposure) and cognitive function. Similarly, there was no indication that postnatal PCB or dioxin TEQ exposure (concentration in breast milk multiplied by number of weeks the infant was breast-fed) was related to cognitive function.

However, interpretation of these findings is complicated by the fact that the breast- and formula-fed infants differed in the extent to which prenatal PCB exposure affected cognitive function. At 42 months of age, there were highly significant negative relationships between prenatal PCB exposure and scores on both the K-ABC and RLDS in the formula-fed infants (Patandin et al. 1999). In contrast, none of the correlations between PCB exposure and performance on these tests approached statistical significance in the breast-fed infants. As discussed above, the mothers of the breast-fed infants were older and more highly educated, had higher verbal IQs, and had higher HOME scores. Thus, it is likely that they provided a more optimal rearing environment for their children. This higher quality intellectual stimulation could have helped children in the breast-fed group overcome the relatively subtle cognitive deficits caused by PCB exposure.

Because dioxin TEQs could not be measured in the small amounts of cord and maternal plasma that were available, no measurements were available for the formula-fed children, and the impact of exposure to dioxins on neurodevelopment could be assessed only in the breast-fed children. Less optimal neurological condition at birth and a slight delay in psychomotor development at 7 months were the only outcomes associated with dioxin exposure. However, the more advantaged background of the breast-fed children may have protected them from the negative impact of dioxin exposure. Recent advances in analytic techniques allowing the measurement of specific PCB and dioxin congeners in smaller volume samples should make it feasible to quantitate dioxin TEQs in maternal plasma of formula-fed infants in ongoing and/or future studies.

The tendency for women who breast-feed their infants to be more advantaged also complicates the assessment of the impact of postnatal exposure to PCBs and dioxins on cognitive function because the more enriching rearing environment these women provided for their infants may have also compensated for the negative effects of postnatal exposure to the chemicals. Previous studies in Michigan and North Carolina also failed to find a relationship between lactational exposure to PCBs and neuropsychological outcomes but shared similar confounds with breast-feeding (Jacobson and Jacobson 1993; Rogan et al. 1986a; Schantz 1996). Recently Jacobson and Jacobson (2002) divided the Michigan cohort into children who were breast-fed for more than 6 weeks and children who were either not breast-fed at all or breastfed only briefly, and reanalyzed the data. They found the same pattern as was reported in the Dutch cohort. PCB-related decrements in cognitive functioning were observed only in the nonbreast-fed group.

Animal studies in both rodents (e.g., Holene et al. 1998; Eriksson and Fredriksson 1996) and primates (Rice 1999) convincingly demonstrate that postnatal exposure to PCBs can dramatically influence later behavioral function. The primate studies are particularly telling because the PCB levels in plasma were similar to those observed in the human population and striking deficits were observed on several cognitive tasks. Because of the complex interrelationships between sociodemographic variables and exposure via breast-feeding, it may be difficult to determine whether postnatal exposure to PCBs and dioxins is a risk factor in humans. However, study designs that match women who breast- and formula-feed their infants on key sociodemographic variables known to influence childhood cognitive function (e.g., parental IQ and HOME scores), and/or that specifically seek to include breast-fed infants from both advantaged and disadvantaged backgrounds could go a long way toward addressing this problem.

Another problem relates to the fact that it is difficult to estimate accurately PCB exposure via breast milk. In most studies milk samples are collected only once, typically soon after birth, and breast milk exposure is estimated by multiplying the PCB concentration in breast milk at that time by the number of weeks of breast-feeding. However, breast milk PCB levels have been shown to decline over the course of breast-feeding, so this approach could lead to misclassification errors. To address this problem it would be necessary to collect multiple breast milk samples at regular intervals over the course of breast-feeding.

It is important to note that subjects in the Dutch study were volunteers. Posters explaining the study were displayed in the offices of obstetricians and midwives throughout Rotterdam and Groningen, and women wishing to participate called a contact person to volunteer. Some, but not all, women were encouraged to volunteer by their obstetricians or midwives (Weisglas-Kuperus N. Personal communication). A number of studies have shown that volunteers tend to differ from the general population in several important ways that could result in the tendency to underestimate PCB-related effects. For example, volunteers are less likely to smoke cigarettes, are more likely to be concerned about their health, are more likely to be members of community organizations, and tend to be more active in community affairs (Lilienfeld 1994). Volunteers also have more formal education as well as higher cognitive test scores and are more likely to be employed in professional and skilled positions (Ganguli et al. 1998; Lilienfeld 1994). As alluded to above, parents who are more concerned about their health, have more formal education, and are employed in higher paying professional occupations are likely to provide a more enriching rearing environment for their children. This more enriching environment may partially compensate for the negative effects of PCB exposure. Thus, there is the possibility that reliance on a volunteer sample may have underestimated the actual risks from PCB exposure in the Dutch population at large.

In the Dutch study, the issue of volunteer bias was further complicated by the fact that women who were planning to breast- or formula-feed their infants received different incentives to participate. Those who chose to formula-feed their infants received a 7-month supply of infant formula free of charge, whereas those who chose to breast-feed their infants were not compensated in any way for their participation in the study. This may have served to accentuate the sociodemographic differences between the two groups, attracting lower income women for whom the free formula was a significant incentive to the formula-feeding group and highly self-motivated women who were interested in learning about their children's development to the breast-feeding group. The end result could be an underestimate of

the actual risks from PCB exposure in breast-fed children.

Strengths of the Dutch study over earlier studies are that congener-specific analytic procedures were used and that dioxins and furans were measured in addition to PCBs. In theory, this approach should be very powerful, permitting assessment of the relative importance of *ortho*-PCBs versus coplanar PCBs, dioxins, and furans (expressed as dioxin TEQs) in mediating neurodevelopmental effects, as well as allowing investigation of the roles of individual PCB congeners with different structural and toxicological properties in determining effects. However, in practice, several limitations restricted the extent to which these goals could be accomplished. Some are complexities that would be inherent in virtually any epidemiological study of this nature, whereas others are problems specific to the design of the Dutch study, and still others relate to our incomplete knowledge of specific PCB congeners, their mechanisms of neurotoxicity, and the relevant structure-activity relationships.

As discussed above, assessment of the importance of *ortho*-PCBs versus coplanar PCBs, dioxins, and furans in mediating neurodevelopmental outcomes was limited by the fact that dioxins and furans could be measured only in breast milk. As a result, dioxin TEQs were available for only half of the cohort, significantly reducing the power to detect associations. Furthermore, the same factors that appear to have mitigated against PCB-related cognitive deficits in the breast-fed children also could have biased against finding dioxin-related associations. Additional studies that measure dioxin TEQs in maternal plasma and thus provide measurements of dioxin exposure in both breast- and formula-fed infants will be needed before definitive answers about the role of dioxin TEQs in mediating neurodevelopmental outcomes can be reached.

Assessment of the role of individual PCB congeners with different structural and toxicological properties in mediating effects is a much more complex problem. Although the Dutch study did use congener-specific analytic techniques, it was not designed to address the impact of individual congeners. Only a few "marker" congeners (IUPAC nos. 118, 138, 153, and 180) were measured in maternal and cord plasma. A more extensive list of 20 congeners were quantitated in milk (Table 1), but, as discussed above, the one study that did attempt to relate neurodevelopmental outcomes to concentrations of individual congeners did not shed much light on the issue (Huisman et al. 1995a).

From a statistical perspective, attempts to determine the role of individual congeners are hampered by the fact that the concentrations of most of the individual congeners are highly correlated with each other (Koopman-Esseboom et al. 1994a) and with total PCBs. This will make attributing effects to individual congeners extremely difficult. From a toxicological perspective, this approach is limited by our incomplete knowledge of the mechanisms of action and structure–activity relationships for *ortho*-substituted PCBs. It is unlikely that we will gain significant insights by looking for associations between health outcomes and concentrations of individual PCB congeners in human tissue. Except for a handful of prominent congeners such as PCBs 138, 153, and 180, individual congeners are present at such low concentrations in human tissue that it is extremely unlikely they would be acting individually to produce effects. However, classes of congeners that share similar mechanisms of action are likely acting in concert to produce certain effects.

A potentially powerful approach would be to weight congeners according to their relative potency to produce a given effect (e.g., reduce dopamine or thyroid hormone concentrations or alter calcium signaling) and sum the weighted values to come up with toxic equivalents similar to those now widely used for coplanar PCBs, dioxins, and furans (Pessah and Wong 2001; Seegal 2001; Zoeller 2001). This approach would focus on the subsets of congeners that are likely to produce given effects and thus could increase predictive validity over that for total PCBs, as well as provide valuable information about which subset of PCB congeners should be the target of regulatory action. Unfortunately, we have not reached the stage where we can successfully use this approach. A large number of the PCB congeners present in human tissue have never been studied in the laboratory, so the relative potency of these congeners to produce nervous system effects is unknown. Furthermore, even for congeners that have been studied in the laboratory, the relationship between underlying molecular or cellular changes such as reductions in dopamine concentrations or changes in ryanodine binding and functional effects such as learning or memory deficits is not understood. We hope that significant toxicological insights will be forthcoming. When they are, some of the ongoing studies that have quantitated large numbers of individual congeners in plasma and milk samples will be poised to take advantage of the information.

The Oswego Cohort

The Oswego cohort consisted of 309 mother–child pairs who were followed longitudinally with assessments at birth, 6, 12, 36, and 54 months of age. The primary exposure indices were PCBs in umbilical cord serum and placenta. Milk samples were also available from a subset of the women who breast-fed. A congener-specific analytic technique that permitted quantitation of 68 individual PCB congeners was used. Infants were assessed on the Brazelton Neonatal Assessment Scale at birth, the Fagan Test of Infant Intelligence at 6 and 12 months, and the McCarthy Scales of Children's Abilities at 36 and 54 months.

Description. The Oswego Newborn and Infant Development Project was initiated in 1991 to follow up on earlier findings showing a relationship between PCB exposure from maternal consumption of Great Lakes fish and cognitive impairments in children (Jacobson et al. 1985, 1990a). Oswego is located on the southeastern shore of Lake Ontario and is a mecca for sport fishing. Fishing in the area increased dramatically during the 1980s despite fishing advisories issued by the New York State Department of Health (Dawson and Brown 1989). In 1990, a survey of 655 pregnant women from the Oswego area found that 8.2% had eaten large quantities of Lake Ontario fish (> 26 lb in the past 6 years). Forty-six percent of the women interviewed reported eating at least some Lake Ontario fish (Lonky et al. 1996), highlighting the need for further research on the health impacts of *in utero* exposure to contaminants in Great Lakes fish.

All of the participants for the Oswego study were recruited between June 1991 and June 1994 at the county's sole obstetric practice (Lonky et al. 1996). Of the 2,587 women visiting the clinic for a mid-gestation sonogram during that time period, 1,337 (52%) agreed to be interviewed. Based on the interviews, all fish eaters and a random subset of non-fish eaters were enrolled in the study, for a total initial sample size of 602 women. Attrition reduced that number to 559 (395 fish eaters and 164 non-fish eaters) at birth. A subset of 309 of the women and their infants were followed longitudinally, with assessments at birth, 6, 12, 36, and 54 months of age. The rest of the children were evaluated only at birth. The women were of low to middle socioeconomic status, and nearly all of them were Caucasian. Women who participated in the study did not differ from other women seen at the same clinic on demographic variables such as age, parity, and marital status, or on most aspects of labor and delivery (Lonky et al. 1996). However, fewer of the women who participated in the study delivered by cesarean section, and the Apgar scores of the infants born to study participants were slightly but significantly higher than those of infants born to the women who did not participate (Lonky et al. 1996).

Exposure indices. The primary measure of exposure used in this study was the concentration of PCBs in umbilical cord plasma

collected at birth. Samples of placenta were also collected, but the placental PCB concentrations have not been published yet. A subset of 83 women provided a breast milk sample collected during the first 6 months after birth. The cord plasma, placenta, and milk samples were all analyzed using a congener-specific analytic technique that permitted quantitation of 68 individual PCB congeners (Stewart at al. 1999). The median concentrations of total PCBs were 0.52 ng/g in cord serum and 153 ng/g in milk fat (Darvill et al. 2000). PCB exposure in this more recently assembled Great Lakes cohort appears to be somewhat lower than in the earlier Michigan cohort, where the median cord plasma PCB concentration (based on packed column chromatography) was 2.0 ng/g (Schwartz et al. 1983). However, the cord serum PCB levels are similar to those in another U.S. cohort assembled during the 1990s in New Bedford, Massachusetts (Korrick et al. 2000). In that study, the median cord serum PCB concentrations of 751 infants born between 1993 and 1998 was 0.38 ng/g.

The individual congener data have not been published yet, but concentrations of PCB homologue groups (Cl 1–3, Cl 4–6, and Cl 7–9) in cord plasma have been reported (Stewart et al. 1999). Fish eaters and non-fish eaters did not differ in their degree of exposure to PCB homologues with 1–3 or 4–6 chlorine substitutions, but infants born to fish eaters did have greater exposure to PCBs with 7–9 chlorines. On the basis of these findings, Stewart and colleagues (1999, 2000) argued that the concentration of these highly chlorinated PCBs in cord plasma is a better indicator of prenatal PCB exposure from fish than is the concentration of total PCBs. Part of the reason for this may be that few other contaminants interfere with the measurement of these more highly chlorinated PCBs. As a result, these PCBs can be measured more reliably than other congeners at the low concentrations found in cord plasma. Accordingly, neurodevelopmental outcomes in this study were assessed with respect to total PCBs and total highly chlorinated PCBs (Darvill et al. 2000; Stewart et al. 2000). Hexachlorobenzene (HCB) and dichlorodiphenyl dichloreethene (DDE) were also measured in cord plasma, and methyl mercury (MeHg) was measured in maternal hair samples. Dioxins, furans, and coplanar congeners were not measured in this cohort. Contaminant exposure data are available only for the longitudinal portion of the cohort.

Neuropsychological measures. The neurodevelopmental findings from birth and 6 and 12 months of age were recently published (Darvill et al. 2000; Stewart et al. 2000), but the results from 36 and 54 months are still being analyzed. Shortly after birth the infants were evaluated on the Brazelton Neonatal Assessment Scale (NBAS). The NBAS is a widely used assessment of infant interactive, reflex, and motor behavior that yields seven cluster scores. The data from the whole cohort were evaluated using fish consumption as the exposure variable (Lonky et al. 1996). The data from the subset of infants in the longitudinal sample were also evaluated using total highly chlorinated PCBs (7–9 chlorines) in cord plasma as the exposure variable (Stewart et al. 2000). The NBAS was administered twice, once between 12 and 24 hr after birth and once between 25 and 48 hr after birth. Change scores representing the change in behavior from the first assessment to the second were computed and used as the outcome variables in the analyses. After controlling for confounding variables, contaminated fish consumption was associated with poorer scores on the reflex, autonomic, and habituation clusters (Lonky et al. 1996). The deficits were similar to those reported a decade earlier in Michigan infants whose mothers consumed sport-caught Great Lakes fish (Jacobson et al. 1984b) and in North Carolina infants whose mothers were exposed to PCBs from background environmental sources (Rogan et al. 1986b).

Because greater exposure to highly chlorinated PCBs was associated with consumption of Lake Ontario fish, the investigators predicted that this exposure would predict poorer performance on the same behavioral clusters negatively affected by fish consumption. As predicted, exposure to heavily chlorinated PCBs was negatively associated with scores on both the autonomic and habituation clusters (Stewart et al. 2000). However, the reflex cluster score was not significantly affected by PCB exposure. The most highly PCB-exposed infants also had a greater proportion of cluster scores that were more than 1 standard deviation below the mean. None of the other contaminants that were assessed (DDE, HCB, MeHg, or lead) were related to NBAS performance.

At 6 and 12 months of age, the Oswego infants were tested on the Fagan Test of Infant Intelligence, a measure of visual recognition memory (Darvill et al. 2000). In the Fagan test, the infant is shown a visual stimulus. Later, the familiar stimulus is paired with a novel one. The normative response is to spend more time looking at a novel stimulus. Preference for the novel stimulus indicates the capacity to recall the original stimulus and discriminate it from the novel one. The Fagan test has become a popular assessment tool because it requires relatively complex information processing, including stimulus discrimination, memory storage, and retrieval. Also, it can be performed on young infants, it is sensitive to a range of at-risk conditions, and the scores are a reasonably good predictor of later verbal IQ (Fagan and McGrath 1981; Rose and Wallace 1985). Finally, the test was used by Jacobson and colleagues (1985) to assess infant cognition in their Michigan fish exposure cohort, and *in utero* PCB exposure was associated with less preference for novelty. Total PCBs (sum of 68 congeners) and total highly chlorinated PCBs (sum of 16 septa-, octa-, and nona-chlorinated congeners) in cord plasma and milk fat were used as the exposure measures. Fixation time to the novel stimulus was the outcome variable. After control of covariates, higher total cord PCBs were associated with lower fixation times at both 6 and 12 months. Highly chlorinated PCBs showed a similar association with fixation time at 6 months but were not related to fixation time at 12 months (Darvill et al. 2000).

PCB concentrations in breast milk were not related to fixation scores on the Fagan test. However, breast milk samples were available from only 83 of the women, so statistical power was limited. Also, the time at which breast milk was collected was highly variable. The potential relationships of non-PCB contaminants including MeHg, lead, and DDE to performance on the Fagan test were investigated, but none of these other contaminants had any association with fixation scores. Furthermore, the significant negative relationship between PCB exposure and fixation scores did not change when these other contaminants were included as covariates in the analysis.

The size of the effect on visual recognition memory in the Oswego cohort, although statistically significant, was smaller than that reported a decade earlier in the Michigan cohort (Darvill et al. 2000; Jacobson et al. 1985). This is consistent with the lower exposure to PCBs in the more recently recruited Oswego cohort. It is interesting that PCB-related impairments in infant cognition have now been reported in two fish exposure cohorts, both of which used the Fagan Test of Infant Intelligence (Darvill et al. 2000; Jacobson et al. 1985). Meanwhile, no impairments in infant cognition were observed in three other cohorts exposed to PCBs from background environmental sources in North Carolina (Gladen et al. 1988; Rogan and Gladen 1991), the Netherlands (Koopman-Esseboom et al. 1996), and Germany (Winneke et al. 1998). The studies in North Carolina and the Netherlands used the MDI from the Bayley Scales of Infant Development to measure cognitive development in infancy, whereas the German study used the Fagan test. However, the German investigators stated that there were problems with the administration of the Fagan test in their cohort, which could explain the absence of an association (Winneke

et al. 1998). The differences between the two sets of studies could be related to differences in contaminant exposure in the two types of cohorts. Alternatively, they could be related to differences between the tests used to measure cognitive function in the Michigan and Oswego cohorts versus the North Carolina and Dutch cohorts. Novelty preference is different from other standard measures of infant intelligence in that it taps aspects of higher-order cognitive functioning, including recognition memory, visual discrimination, and speed of visual processing, that are common to infants, older children, and adults. Perhaps the relatively more complex processing involved in performing the Fagan task makes it a more sensitive measure of PCB exposure than more traditional tests such as the Bayley MDI.

It is also noteworthy that the findings on both the NBAS and the Fagan test in the Oswego cohort of Lake Ontario fish eaters are similar to those reported over a decade earlier in the infants of Lake Michigan fish eaters. As summarized below, the Michigan children continued to show PCB-related impairments in intellectual function later in childhood (Jacobson et al. 1990a; Jacobson and Jacobson 1996). Data from follow-up testing of the Oswego children at 36 and 54 months of age are currently under analysis and will reveal whether this more recent and less highly exposed group of children continue to show intellectual deficits as they mature.

Comments and discussion: Oswego cohort. Although the Oswego investigators used a sophisticated analytic technique that involved quantitating more than 60 individual PCB congeners, the studies published to date relate outcomes to total PCBs or to PCB homologue groups. Thus far, no attempt has been made to assess the importance of individual congeners or classes of congeners in mediating neurodevelopmental outcomes. As discussed above, analysis of human data for congener-specific effects will be challenging. However, if useful strategies for assessing the roles of different classes of congeners can be developed, the Oswego group will have a rich data set and should make a valuable contribution. The results of congener-specific PCB analysis of placental tissue should be particularly valuable because the higher concentrations of PCBs and larger amounts of tissue available for analysis should permit accurate quantitation of a large number of congeners.

Strengths of the Oswego study include the fact that detailed information was collected on a large number of potential confounding variables and that comparisons of study participants with nonparticipants indicate few differences. Also, the sophisticated analytic method used to quantitate PCBs should permit analysis of the neurodevelopmental data for congener-specific effects in the future. The fact that placental samples are available for analysis should greatly enhance these efforts. Finally, tissue samples in this study were analyzed for the presence of other key environmental contaminants including lead, mercury, and DDE, so the potential impact of these other environmental neurotoxicants can also be assessed. Dioxins and furans were not measured, but if enough placental tissue is available the investigators may be able to perform some analyses on stored tissue samples in the future.

Weaknesses of the Oswego study include the fact that few maternal milk samples are available. Furthermore, those that do exist were not collected at a consistent time point. As a result, it will probably not be possible to assess the impact of postnatal lactational exposure to PCBs in the cohort. This is unfortunate because the women in this sample are described as "lower middle class" (Lonky et al. 1996). Thus, covariates that are typically associated with breast-feeding might not play as prominent a role in this cohort as they appear to in some of the other cohorts that have been studied (e.g., Patandin et al. 1999). Another weakness is that no maternal serum samples were collected for PCB analysis. This may limit cross-study comparisons because PCBs in maternal serum were used as one of the primary exposure variables in most other studies.

The German Cohort

The German cohort consisted of 171 mother–infant pairs. Exposure indices included PCBs in umbilical cord serum and milk. Three marker congeners (PCBs 138, 153, and 180) were measured. Neurodevelopment was assessed at 7, 18, 30 and 42 months of age using the Bayley Scales of Infant Development, at 7, 18 and 30 months, and the Kaufman Assessment Battery for Children and Heidelberg Test for Language Development (Table 3) at 42 months.

Description. In 1993, the European Union provided funding to expand the Dutch PCB/dioxin study into a transnational, multicenter cooperative study, which included a German cohort in Düsseldorf and a Danish cohort in the Faroe Islands (Winneke et al. 1998). The German cohort consisted of 171 mother–infant pairs consecutively recruited from the obstetric wards of three Düsseldorf hospitals in 1993 (Winneke et al. 1998). Only first- or second-born infants from German-speaking families with Apgar scores of at least 7 and no illnesses or complications during pregnancy or delivery were included. The families were primarily middle and upper class.

Exposure indices. Prenatal PCB exposure was assessed by measuring the sum of three marker congeners (PCBs 138, 153, and 180) in cord blood. Milk samples were also collected from women who were breast-feeding when infants were 2 and 4 weeks of age, and milk was analyzed for the same three congeners assessed in blood. A total of 169 cord blood samples and 131 breast milk samples were available for analysis. As discussed above, the sum of PCBs 138, 153, and 180 in cord blood and milk fat were similar to the sum of these three congeners in the Dutch cohort.

Neuropsychological measures. The German children were assessed on the Fagan Test of Infant Intelligence at 7 months of age, the Bayley Scales of Infant Development at 7, 18, and 30 months of age, and the Kaufman Assessment Battery for Children (K-ABC) and Heidelberg Test for Language Development at 42 months of age. The findings from 7 months of age have been published (Winneke et al. 1998).

Multiple linear regression analyses were run using ln ∑PCBs in cord blood or breast milk as the two independent variables. The outcome variables were the Bayley MDI and PDI scores as well as fixation time to the novel stimulus on the Fagan test. One-tailed significance tests were used. After controlling for confounding variables, the only significant association was a negative relationship between ln ∑PCB milk and the Bayley MDI score.

Others have either failed to find any relationship between PCB exposure and Bayley Scores (Jacobson et al. 1986) or have reported a negative relationship between PCB exposure and Bayley PDI scores (Gladen et al. 1988; Koopman-Esseboom et al. 1996; Rogan and Gladen 1991). The German study was the first to report a link between PCB exposure and Bayley MDI scores. In contrast, other groups have reported significant negative associations between prenatal PCB exposure and Fagan test scores (Darvill et al. 2000; Jacobson et al. 1985), but there was no association between PCB exposure and Fagan test scores in the German cohort (Winneke et al. 1998). The reasons for this discrepancy are unclear. The investigators suggest that the lack of an association on the Fagan test could be due to the low test–retest and inter-rater reliability of the Fagan test in their study (Winneke et al. 1998). However, when exposure is near background and effect sizes are small, it is not unusual for the outcomes that are most affected to vary from study to study.

In a later report the results from the 7-, 18-, and 30-month Bayley assessments and 42-month Kaufman ABC assessment are discussed (Walkowiak et al. 2001). A negative relationship between maternal milk PCB concentrations (sum of congeners 138, 153, and 180) and mental/motor development was observed at all four ages, but statistically significant associations were observed only at

30 and 42 months of age. After adjustment for covariates, including scores on the HOME scale, significant negative associations between maternal milk PCB concentration 2 weeks after birth and scores on both the Bayley mental and motor development scales were observed at 30 months of age. At 42 months of age a negative association with the mental processing composite index of the Kaufman ABC was observed. As PCB concentrations increased from the 5th percentile to the 95th percentile, scores on the Bayley MDI decreased by 9.9 points.

Quality of the home environment has been shown to have a strong positive impact on child development. Therefore, Walkowiak and colleagues (2001) compared the magnitude of the PCB-related decrement on the Bayley MDI to the magnitude of the increase associated with a positive home environment. The difference in scores on the Bayley MDI for those scoring at the 5th versus the 95th percentile on the HOME was 17.7 points. When one considers that the quality of intellectual stimulation provided by the parents is one of the strongest predictors of childhood intellectual functioning, it is impressive that the magnitude of the effect associated with PCB exposure was roughly half that associated with the HOME score.

Walkowiak and colleagues (2001) also investigated the impact of postnatal PCB exposure via breast-feeding on mental and motor development using two exposure variables: the PCB concentration in maternal breast milk times the number of months of breast-feeding and the child's serum PCB level at 42 months of age. Both of these postnatal exposure variables were corrected for prenatal exposure. In both cases a significant negative association between postnatal PCB exposure and Kaufman ABC scores at 42 months of age was observed.

Comments and discussion: German cohort. The German findings are consistent with those from the Michigan, Oswego, and Dutch cohorts in that all four studies found negative associations between prenatal PCB exposure and some measure or measures of cognitive development. However, the German study differs from these other studies in that it also found a relationship between postnatal PCB exposure via breast-feeding and mental development. Previously, only behavioral endpoints such as activity level (Jacobson et al. 1990b) had been associated with postnatal PCB exposure. The reason for this discrepancy remains unclear. As discussed earlier, there is strong evidence that early postnatal exposure to PCBs can dramatically influence later cognitive function in both rodents (e.g., Holene et al. 1998) and primates (Rice 1999), yet all of the previous human studies have failed to find a relationship between postnatal PCB exposure and childhood cognitive functioning. It has been suggested that the failure to find such a relationship in humans may be related to the fact that women who breast-feed their infants tend to have higher IQ scores, more education, and more financial resources. As a result, they typically provide a more intellectually enriching rearing environment for their children. This high-quality rearing environment may help breast-fed children overcome the relatively subtle cognitive deficits resulting from PCB exposure. However, HOME scores in the German cohort were near the upper end of the continuum, so it is unlikely that a poorer rearing environment can explain the difference between this and earlier studies.

In summary, the findings from the German study are important in several respects: They add to the overall weight of evidence for neurodevelopmental effects of early PCB exposure, and they also demonstrate for the first time that postnatal PCB exposure via breast-feeding may, in fact, contribute to the negative impact of PCBs on childhood intellectual functioning. However, because only three marker PCB congeners were measured, findings from the German cohort are unlikely to contribute to our understanding of the contribution of individual PCB congeners or classes of congeners on neurodevelopment.

The Faroe Islands Cohorts

Two cohorts that could contribute to our knowledge of PCB effects on neurodevelopment are currently under study in the Faroe Islands (Grandjean et al. 1997; Steuerwald et al. 2000). Both cohorts were recruited with the goal of evaluating the effects of methylmercury exposure on neurodevelopment. However, the primary source of methylmercury exposure in the Faroe Islands—pilot whale meat and blubber—is also contaminated with significant amounts of PCBs. Thus, the role of PCBs in mediating neurodevelopmental outcomes is also being considered in both Faroese cohorts.

1986–1987 Cohort. The first cohort was assembled in 1986–1987 and consisted of 1,022 singleton births (Grandjean et al. 1997). Mercury concentrations were determined in cord blood, maternal hair at parturition, child blood at 12 months, and child blood at 7 years. PCBs were determined in stored samples of umbilical cord from a subset of 443 children. The sum of three major congeners (PCBs 138, 153, and 180) was multiplied by 2.0 and used as an estimate of total PCBs.

Neuropsychological measures. Detailed neuropsychological evaluations of the children were performed at 7 years of age. A total of 917 (90.3%) of the original 1,022 children completed the neuropsychological testing. The battery was extensive and included tests of visual and auditory evoked potentials, postural sway, and autonomic nervous system function, as well as a large number of neurobehavioral tests. These included computerized tests from the Neurobehavioral Evaluation System (NES) including finger tapping, hand–eye coordination, tactual performance, and the NES continuous performance task (CPT). Also included were the digit-span, similarities, and block design subtests from the Wechsler Intelligence Scale for Children-Revised (WISC-R), the Bender Gestalt Test, the California Verbal Learning Test for Children (CVLT-C), the Boston Naming Test, and the Nonverbal Analogue Profile of Mood States. After controlling for covariates, outcomes on a number of the tests including finger tapping, the NES CPT, WISC-R digit span, the Boston Naming Test, and the CVLT-C were negatively associated with cord blood mercury concentrations (Grandjean et al. 1997). The results from a subset of these outcomes (CPT, Boston Naming Test, and CVLT-C) were subsequently reanalyzed to determine the potential role of PCBs in mediating the effects. After adjustment for PCB exposure, only the association of mercury with the CPT remained significant, suggesting that PCBs may have played some role in mediating the mercury effects on the other tests.

Further analyses specifically designed to assess the role of PCBs in mediating the mercury effects were conducted by dividing the subset of children for which PCB exposure measures were available into PCB exposure tertiles (Budtz-Jorgensen et al. 1999). One outcome variable was selected to reflect each of five different domains of brain function (motor, attention, visuospatial, language, and memory). Regression equations were then fitted to the data for each of the three PCB subgroups. The three regression coefficients for the three PCB tertiles did not differ for any of the outcomes, suggesting that increasing exposure to PCBs did not modify the effects of exposure to mercury.

Possible effect modification by PCBs was also investigated in regression analyses, which treated PCB exposure as a continuous variable and included both the mercury and PCB exposure variables as well as a PCB–mercury interaction term. The *p*-value for the PCB–mercury interaction term was not significant for any of the outcomes, providing further evidence that PCB exposure did not modify the effects of mercury. However, the results did suggest an independent association with PCBs on one of the outcome measures (Boston Naming Test). This is a test in which the child is presented with line drawings of objects and asked to name them. If a correct response does not occur in 20 sec, a semantic cue is given. If a correct response still does not occur, a phonemic cue consisting of the

first two letters of the word is given. The total correct with and without cues is scored. The test is considered to be a measure of language development. Language development was also negatively impacted by PCB exposure in the Dutch cohort (Patandin et al. 1999), and both word and reading comprehension were negatively impacted in the Michigan cohort (Jacobson and Jacobson 1996).

Later the investigators did a more detailed analysis of the data from the 435 children for which PCB exposure data were available, specifically looking for PCB-related effects (Grandjean et al. 2001). These analyses confirmed a relationship between umbilical cord PCB concentrations and poorer performance on the Boston Naming Test, and suggested a relationship between high cord PCB concentrations and slower reaction times on the NES2 CPT as well. However, previous analyses had demonstrated an association of both of these measures with mercury exposure (Grandjean et al. 1997). After adjusting for mercury exposure in the statistical analysis, the association of test scores with PCB exposure was reduced to a nonsignificant level on both the Boston Naming Test and the CPT. To explore further the possibility of an interaction between PCBs and methylmercury, the children were divided into tertile groups based on mercury exposure, and separate regression coefficients were calculated for each outcome variable within each tertile group of mercury exposure. The strongest association with PCB was seen in the children with the highest mercury exposure. However, none of the within-tertile regression coefficients were statistically significant. In summary, it appears that in the Faroese population methylmercury is the greater hazard. The investigators suggest that PCB exposure could be augmenting the neurobehavioral effects of methylmercury in children with the highest mercury exposure, but it is not clear that their results support this conclusion. Recently a National Research Council (NRC) committee scrutinized the Faroese data set and came to the conclusion that the effects of methylmercury and PCBs appeared to be independent (NRC 2000).

Sensory measures. In sensory testing, no associations of PCB exposure with visual function were noted, but cord PCB concentrations were a significant predictor of increased auditory thresholds (Grandjean et al. 2001). However, only two frequencies, one low and one high, were affected, and the deficits were present only on the left side. Hearing has not been assessed in any of the other developmental studies in humans, but low-frequency hearing loss has been reported in laboratory rats exposed to PCBs during early development (Crofton et al. 2000a; Goldey et al. 1995). Crofton and colleagues (2000a) hypothesized that the hearing loss resulted from PCB-induced hypothyroxinemia during a critical period of cochlear development. Later they demonstrated that the PCB-induced deficit could be partially ameliorated by thyroxine replacement (Goldey and Crofton 1998), and they identified the outer hair cells of the cochlea as the histologic site of the damage (Crofton et al. 2000b). Lasky and colleagues (2002) used distortion product otoacoustic omissions, which measure the mechanical response of the cochlea to different frequency tones, to provide further evidence that the PCB-induced hearing loss is a functional deficit associated with damage to the outer hair cells of the cochlea. With this more sensitive method for measuring cochlear hearing loss, they also found that hearing loss was present across a broader range of frequencies than had been demonstrated previously. Given the effect of PCBs on hearing in animal models and the suggestion of PCB effects on hearing in this human population, additional studies of auditory function in PCB-exposed humans seem warranted. Otoacoustic emissions are frequently used to assess cochlear hearing loss in humans and can be recorded reliably and efficiently in newborn infants and young children. Thus, this approach could be a very useful tool for further assessments of auditory function in PCB-exposed children.

1994–1995 Cohort. The other Faroese cohort was recruited in 1994 through 1995 as part of the European Union-sponsored multicenter project (Steuerwald et al. 2000). A total of 182 singleton infants born at term were recruited from consecutive births at the National Hospital in Thorshavn, Faroe Islands. Sixty-four percent of all births during a 12-month period were included in the sample. Maternal serum, maternal hair, breast milk, and umbilical cord blood were collected and analyzed for contaminants. Maternal serum, breast milk, and 10% of cord serum samples were analyzed for 28 individual PCB congeners and 18 pesticides and pesticide metabolites. Whole cord blood and maternal hair were analyzed for mercury. Levels of essential fatty acids and selenium were also determined in the cord blood. PCB exposure in this cohort was roughly 3-fold higher than in the Dutch cohort (Steuerwald et al. 2000).

Neuropsychological measures. Each infant's neurological optimality was assessed at 2 weeks of age using the Prechtl neurological exam, which measures reflexes and responses as well as the stability of the infant's behavior during the examination. After adjustment for confounders, a 10-fold increase in cord blood mercury concentration was associated with a 2-point decrease in the neurological optimality score. In contrast, PCB exposure had no effect on neurological optimality. In the Dutch cohort, PCB concentrations in maternal milk collected 2 weeks after birth were associated with a decrease in neurological optimality of neonates (Huisman et al. 1995a). The reasons for a lack of effect in the more highly exposed Faroese infants are not immediately obvious.

The Inuit Cohort

Like the Faroese, the Inuit people who reside in Arctic regions of Quebec and Greenland rely on sea mammals (mainly seal, beluga whale, and walrus) as the primary sources of protein and lipids in their diet. As a result, they have unusually high body burdens of PCBs and other organochlorine compounds. In the early 1990s, PCB concentrations in breast milk samples collected from Inuit women were about 7 times higher than the PCB concentrations in Caucasian women residing in southern Quebec (Dewailly et al. 1993). The high PCB body burdens previously identified in the Inuits identify them as an important at-risk population.

Muckle and colleagues have initiated a neurodevelopmental study of Inuit children in northern Québec and Greenland (Muckle G. Personal communication). The study was designed to extend the findings reported in earlier PCB-exposed cohorts by studying more highly PCB-exposed infants and by using new infant assessment procedures that have been linked to specific brain regions and neural pathways. This approach is promising because it has the potential to provide information about which underlying neural systems are damaged by developmental PCB exposure. Also, the higher PCB exposure among the Inuits relative to other cohorts for which detailed congener-specific data exist (e.g., Oswego and New Bedford) should allow more accurate quantitation of specific PCB congeners in umbilical cord serum.

The cohort consists of approximately 300 Inuit mothers and infants (200 from Nunavik in northern Québec and 100 from Greenland). The women were recruited at their first or second prenatal medical exam, and the infants were assessed at birth, 6.5 and 11 months of age. Thyroid hormones, neurological status, physical maturity, and anthropometric measures were assessed in the newborns. At 6.5 and 11 months of age, numerous aspects of neurobehavioral and cognitive development were assessed. Tests included those used in previous PCB studies such as the Bayley Scales of Infant Development and the Fagan Test of Infant Intelligence, as well as several new tests such as the A-not-B object permanency test, the Haith Paradigm Test, and Teller Visual Acuity Cards. Physical growth, neuromotor and neurological functions, and overall health were also assessed. Five groups of potential confounding variables will be considered in

the statistical analyses. These include exposure to other toxic substances, dietary fat, perinatal medical complications, sociodemographic status, and psychosocial risk.

Statistical analyses of the data collected in this study are currently under way. The results from the neurodevelopmental assessments will not be available for some time, but an initial article reporting the concentrations of PCBs and other contaminants in umbilical cord serum, maternal serum, and maternal milk from 175 women in Nunavik has been published (Muckle et al. 2001). The samples in this study were analyzed using a congener-specific analytic procedure, which quantitated 14 specific PCB congeners. The concentrations of marker congener 153 in this cohort were similar to those in the Dutch cohort and about 2-fold higher than those in the New Bedford cohort. Biological samples in this study were also analyzed for various chlorinated pesticides and heavy metals, in addition to PCBs. Methylmercury concentrations in cord blood, maternal blood, and maternal hair were similar to those in the Faroe Islands, so this cohort may provide another opportunity to assess the potential for interactive effects of these two ubiquitous contaminants. Finally, dioxins and furans will reportedly be measured in a limited number of milk samples, which may permit further assessment of the role of dioxin exposure in mediating neurodevelopmental outcomes.

The New Bedford Cohort

New Bedford harbor in southeastern Massachusetts was designated a Superfund Site in 1982 because of PCB contamination in the sediments. In the early 1990s, concern over the potential for PCB exposure among area residents prompted a prospective study of mothers and infants residing in the towns bordering the harbor (Korrick et al. 2000). A total of 788 mother–infant pairs were recruited between March 1993 and December 1998 at one of the main hospitals serving the greater New Bedford area. All were enrolled at the time of birth, and participation was limited to mothers who had resided in the Massachusetts towns of New Bedford, Acushnet, Fairhaven, or Dartmouth for at least the duration of their pregnancies. Infants born by cesarean section or whose mothers did not speak English were excluded.

Umbilical cord serum and maternal milk were collected and analyzed for PCBs using a congener-specific technique that quantitated 51 individual PCB congeners (Korrick et al. 2000). Growth and developmental assessments were performed on the children from birth to 7 months of age, and assessments at early school age are currently under way. The results of the developmental assessments are not yet available, but the congener-specific analysis of PCBs in cord serum has been published (Korrick et al. 2000). Samples were available and successfully analyzed from 751 (95%) of the participating infants. The findings are notable in that the total PCB concentrations in cord serum are lower than in most previously published studies. The total cord serum concentration of PCBs averaged 0.54 ng/g, with a median of 0.38 ng/g. The concentrations of key individual congeners (PCBs 118, 138, 153, and 180) were about one-half the concentrations reported in the Dutch cohort (Koopman-Esseboom et al. 1994a). The levels in the New Bedford cohort are, however, quite similar to those reported in the Oswego, New York, fish-exposure cohort. The congener-specific results have not been published yet for the Oswego cohort, but the median total cord serum PCB concentration of 0.52 ng/g (Darvill et al. 2000) is similar to the median for the New Bedford cohort.

As discussed above, the Oswego research team recently reported PCB-related cognitive impairments on the Fagan Test of Infant Intelligence at 6 and 12 months of age (Darvill et al. 2000). Results from later cognitive testing at 36 and 54 months of age are currently under analysis and should be available soon. The New Bedford study includes cognitive testing during infancy using the Fagan test, as well as additional testing at early school age. It will be important to see whether impairments similar to those documented in the Oswego cohort are observed in the similarly exposed New Bedford cohort. Its large sample size and extensive congener-specific PCB analyses will also make the New Bedford cohort an important resource for exploring the relationships between exposure to specific congeners or congener classes and developmental outcomes.

The Collaborative Perinatal Project and Child Health and Development Study Cohorts

Several investigators have initiated studies designed to take advantage of archived data from two large-scale studies of child development conducted during the 1960s. This is a potentially powerful approach because these cohorts included thousands of children who were followed longitudinally from birth to school age. Furthermore, the use of an already established data set allows results to be obtained in a timely and economical way. The availability of archived serum samples permits state-of-the-art congener-specific analytic techniques to be applied to samples collected during a time period when PCB exposure was considerably higher than it is today.

Gray and colleagues (2000) have been working with archived data from the Collaborative Perinatal Project (CPP). The CPP was a joint effort of investigators at the National Institutes of Health and 12 academic centers throughout the United States (Klebanoff et al. 1999). The goal of the project was to investigate the causes of neurological disorders in children. More than 56,000 pregnant women from the 12 study centers were enrolled in the study between 1959 and 1966. Their children were followed longitudinally from birth to 7 years of age. Serum was collected from the women during the third trimester of pregnancy, and the samples have remained archived in glass containers at –20°C, with no recorded thaws. Neurodevelopmental measures assessed in the children included a neonatal neurological exam, the Bayley Scale of Infant Development at 8 months of age, the Wechsler Intelligence Scale for Children at 7 years of age, and audiograms at 7–8 years of age. For their study, Gray and colleagues (2000) selected a subset of 1,200 subjects from the CPP database. Serum samples obtained from the mothers of these children during the third trimester of pregnancy were analyzed for 11 specific PCB congeners at the Centers for Disease Control. Statistical analyses of the relationship between PCB exposure and neurodevelopmental outcomes are currently underway, and results should be available soon.

Hertz-Picciotto and colleagues (2000) are using a similar approach to assess the relationship between PCB exposure and developmental outcomes in children from the Child Health and Development Study (CHDS). In the early 1960s, 20,000 pregnant women in northern California were enrolled in the CHDS through the Kaiser Foundation health maintenance organization. The women were interviewed about their reproductive histories, medication use, medical conditions, smoking, alcohol use, demographic factors, and occupation. Serum samples were collected during each trimester of pregnancy and stored at –20°C. Subsets of the children were enrolled in specialized developmental studies.

Hertz-Piciotto and colleagues (2000) selected 414 children from the CHDS database who were born between April 1964 and April 1967 and had participated in a developmental examination at 5 years of age. The goal of the study is to relate exposure to specific PCB congeners with *in utero* and postnatal growth, measures of cognitive development, hearing, speech, vision, and morbidity. Maternal serum samples collected during the second or third trimester of pregnancy were analyzed for PCBs 118, 138, 153, 170, 180, and 187. The data are still under analysis, but preliminary results suggesting an association between PCB exposure and various growth parameters were presented at Dioxin 2000 (Hertz-Picciotto et al. 2000).

After adjustment for covariates including maternal smoking, alcohol consumption,

maternal and paternal height, maternal prepregnancy body mass index, race, maternal age, and parity, there was an inverse association between total PCBs (sum of six individual congeners) and several growth parameters including body weight, length, and head circumference at birth. The associations between PCB exposure and reduced fetal growth were seen in boys but not in girls. A number of other investigators have reported a relationship between PCB exposure and reduced birth weight, but in most cases the reductions were not reported to be sex specific (Fein et al. 1984; Patandin et al. 1998; Rylander et al. 1998; Taylor et al. 1989).

In the CHDS sample, several indicators of growth at 5 years of age were also inversely related to PCB exposure. Again, the relationship was seen only in boys. In contrast, several earlier studies have reported reduced postnatal growth in girls, but not in boys (Guo et al. 1994; Jacobson et al. 1990b). The reasons for these discrepancies remain unclear at the present time.

Historical Cohorts for Which Congener-Specific Data Are Not Available

The Yu-Cheng Cohort

The potential neurotoxicity of PCBs was first recognized after an outbreak of human PCB poisoning in Japan in 1968. In that incident, more than 1,000 people became ill after ingesting rice oil that had been contaminated with PCBs during the manufacturing process. The disease, which became known as Yusho or "rice oil disease," was first characterized by its dermal manifestations including acneform lesions, brown pigmentation of the skin, and ocular swelling. However, many Yusho patients also complained of neurological disorders including headache and memory loss as well as numbness, hypoesthesia, and neuralgia of the limbs (Urabe et al. 1979).

Pregnant women who had ingested the rice oil gave birth to babies that were small and had dark brown pigmentation of the skin (Yamashita and Hayashi 1985). Other abnormalities observed in the infants at the time of birth included hypersecretion of the Meibomian glands, orbital edema, gingival hyperplasia, natal teeth, abnormal calcification of the skull, and rocker bottom heel (Yamashita and Hayashi 1985). A follow-up study of a subset of the children reported a number of additional abnormalities including growth impairment, slowness, lack of endurance, hypotonia, jerkiness, clumsy movement, apathy, and IQs averaging around 70 (Harada 1976).

In 1979, a similar outbreak of PCB poisoning occurred in Taiwan. More than 2,000 people became ill. Again, the disease (called Yu-Cheng in Taiwan) was traced to rice oil contaminated during the manufacturing process (Hsu et al. 1985). The clinical manifestations were similar to those reported a decade earlier in Japan (Hsu et al. 1985).

Description. A cohort of 118 Yu-Cheng children and 118 matched control children has been followed since birth. The control children were matched to the Yu-Cheng children for neighborhood of residence, age, sex, maternal age, parental education, and parental occupation. A number of developmental abnormalities have been observed as they matured. These include lower body weight and height, hyperpigmentation of the skin, hypertrophy of the gums, deformities of the nails, increased frequency of bronchitis, and delays in neuropsychological development (Rogan et al. 1988).

Exposure indices. Unfortunately, little PCB exposure data are available for this cohort. Maternal blood, umbilical cord blood, and maternal milk samples were not collected at the time of birth. In 1991, a full 12 years after the poisoning episode, blood samples were collected from 45 (38%) of the children and analyzed for total PCBs (Ryan et al., 1994). Maternal blood samples were also collected at that time.

Neuropsychological measures. The neuropsychological functioning of the Yu-Cheng children and their matched controls has been assessed, and the results have been discussed in a series of reports (Chen et al. 1992, 1994; Chen and Hsu 1994; Guo et al. 1995) as well as in several previous reviews (e.g., Schantz 1996; Seegal 1996). The Yu-Cheng children scored, on average, about 5 points lower on standardized intelligence tests than control children matched for neighborhood, age, sex, maternal age, parental education, and parental occupation (Chen et al. 1992).

There was no apparent relationship between a child's IQ score and his or her serum PCB concentration in 1991. Maternal serum PCB concentrations in 1991 were also unrelated to the childrens' IQ scores. These results are not particularly surprising given that other studies have found an association between *in utero* PCB exposure and cognitive impairments, but not between postnatal PCB exposure and cognitive function (e.g., Jacobson and Jacobson 1996; Patandin et al. 1999). The childrens' serum PCB levels in 1991 probably represented primarily postnatal PCB exposure via breast-feeding and/or other environmental sources. In addition, the small number of children for which serum samples were available would have severely limited statistical power to detect an effect. The data were also analyzed to see if children born during or shortly after the episode were more severely affected than those born later, but there did not appear to be any relationship between timing of exposure and severity of effect.

The neurophysiological functioning of a subset of 27 Yu-Cheng children and their matched controls was assessed using auditory event-related potentials (P300), visual evoked potentials, and short-latency somatosensory evoked potentials (Chen and Hsu 1994). This subset of the children and their matched controls also underwent thorough neurological examinations, which included tests for signs of impaired motor development. The mean P300 latencies of the Yu-Cheng children were prolonged compared with those of their matched controls, and the longest P300 latencies were observed in exposed children with the lowest IQ scores. The mean P300 amplitudes of Yu-Cheng children were also reduced relative to controls. No abnormalities were found in the general neurological exams, and the Yu-Cheng children did not differ significantly from matched controls on the motor tests. Visual and somatosensory evoked potentials were also normal, implying that these sensory pathways were intact.

The full cohort of Yu-Cheng children was assessed on two behavior rating scales, the Rutter Child Behavior Scale, which is used to identify children with emotional or behavioral disorders, and the Werry-Weiss-Peters Activity Scale, which evaluates the child's activity level (Chen et al. 1994). A higher score on the Rutter scale indicates a higher frequency of behavioral problems, whereas a higher score on the Werry-Weiss-Peters scale indicates a more active child. The Yu-Cheng children consistently scored higher than their matched controls on both scales. The differences between the Yu-Cheng children and their controls did not lessen as the children grew older, and there was no evidence of decreased differences between exposed and control children as the interval between maternal exposure and year of birth increased. There was no correlation between physical signs of PCB intoxication and behavioral scores. Children with the severest physical symptoms were not necessarily those with the highest behavioral scores. Maternal serum PCB levels were also unrelated to the childrens' scores. As discussed above, a similar lack of relationship between exposure indices and IQ test scores was observed (Chen et al. 1992).

The possibility of sex-related effects has also been explored in the Yu-Cheng cohort (Guo et al. 1995). Changes in androgen status have been reported in animals exposed to PCBs and dioxins perinatally (e.g., Mably et al. 1992). Furthermore, cognitive development is sex dependent, and male–female differences in cognitive style develop as a result of the actions of sex steroids in the brain

during early development (Williams et al. 1990). Although the differences are small, males typically have better spatial abilities and females have better verbal abilities.

The Yu-Cheng children were tested on the Ravin Progressive Matrices, an intelligence test that measures primarily spatial abilities, at 6, 7, and 8 years of age. Overall, the Yu-Cheng children scored lower than their matched controls (Guo et al. 1995). However, when the children were grouped by sex, the Yu-Cheng boys had significantly lower scores than their matched controls, but the girls were not statistically different from their controls. The investigators hypothesized that the decrease in spatial ability in the Yu-Cheng boys could have been mediated by changes in the hormonal milieu during early development. We recently reported a male-specific spatial learning deficit in rats exposed to PCBs during early development (Roegge et al. 2000). Sex-related effects on cognitive function have not been reported in any of the other PCB-exposed human cohorts. However, it is not clear whether the investigators have specifically addressed the issue. This is something that should be investigated to determine if any similar sex-specific changes are occurring in less heavily PCB-exposed cohorts.

The Yu-Cheng studies appear to be methodologically sound. However, there was a lack of relationship between available indices of exposure (e.g., child's serum PCB level, maternal serum PCB level, time since maternal exposure, severity of physical symptomatology) and neuropsychological outcomes in this study. As discussed above, it is possible that the available measures of exposure do not accurately reflect the child's actual *in utero* PCB exposure. Blood samples were not collected from the mothers and children until 1991, a full 12 years after the poisoning episode occurred. Furthermore, exposure data were available only for a small subset of the cohort. Umbilical cord PCB levels, which would provide the most direct measure of *in utero* exposure, were not available for these children.

As a final note, it is important to point out that the PCBs to which the Yu-Cheng people were exposed were thermally degraded and thus contained unusually high concentrations of polychlorinated dibenzofurans and polychlorinated dibenzodioxins (Kunita et al. 1984). As a result, the effects observed in the Yusho and Yu-Cheng populations may not be representative of the effects that can be expected in other PCB-exposed populations.

The Michigan Cohort

After the Yusho and Yu-Cheng incidents, several studies were initiated to assess the potential neurobehavioral effects of *in utero* and lactational exposure to the lower levels of PCBs that are present in the environment. These included a study by Jacobson and colleagues (Fein et al. 1984; Jacobson et al. 1984a, 1984b, 1985, 1990a, 1990b, 1992; Schwartz et al. 1983) in the early 1980s. Their longitudinal prospective study investigated the relationship between low-level maternal PCB exposure from the food chain (Lake Michigan fish) and developmental outcomes in children. The study has been thoroughly reviewed by several authors, and its strengths and weaknesses have been debated at great length (e.g., Paneth 1991; Schantz 1996; Seegal 1996; WHO 1993). As in several other early studies, PCB concentrations in the Michigan study were determined by packed-column chromatography. As a result, no exposure data on specific PCB congeners are available for this cohort. The findings are summarized here to facilitate comparisons across the various human studies for consistency of the developmental effects. For a more detailed assessment of the strengths and weaknesses of this study, refer to the references cited above.

Description. More than 8,000 women who delivered babies in four western Michigan hospitals in 1980–1981 were interviewed on the day after delivery, and all women who had consumed 26 or more pounds of Lake Michigan fish during the preceding 6 years were asked to participate. Women who did not eat Lake Michigan fish were randomly selected and invited to serve as controls. The final sample consisted of 313 women, 77% who reported eating moderate to large quantities of Lake Michigan fish and 23% who reported eating no Lake Michigan fish. The details of sample selection are discussed in Jacobson et al. (1983, 1986) and critiqued by Paneth et al. (1991).

Exposure indices. PCB exposure measures included the mother's estimated total lifetime Lake Michigan fish consumption, the infant's umbilical cord serum PCB level, the maternal serum PCB level at birth, and the breast milk PCB level at birth and 5 months for women who breast-fed. Maternal serum PCB concentrations averaged 5.5 ng/mL, and umbilical cord serum PCB concentrations averaged 2.5 ng/mL (Schwartz et al. 1983). The PCB concentration in milk fat was 812 ng/mL in the first week after birth and 769 ng/mL at 5 months.

Neuropsychological measures. The children were evaluated at birth, 5 months, 7 months, 4 years, and 11 years of age. Neonatal behavioral function was assessed using the NBAS. Maternal consumption of contaminated fish was associated with several adverse behavioral outcomes on the NBAS (Jacobson et al. 1984b) (Table 3). Infants of women who ate the most fish exhibited motoric immaturity, poorer lability of states, a greater amount of startle, and more abnormally weak (hypoactive) reflexes. However, umbilical cord serum PCB level was not related to any adverse behavioral outcomes on the NBAS. Because of this, the NBAS results should be interpreted with caution. They may be related to other contaminants present in the fish or to some other aspect that differed between the fish eaters and non-fish eaters.

Infant cognitive functioning was assessed at 5 and 7 months of age (Jacobson et al. 1985, 1986). The Bayley Scales of Infant Development was administered at 5 months of age (Jacobson and Jacobson 1986), and Fagan's Test of Infant Intelligence, a measure of visual recognition memory, was administered at 7 months of age (Jacobson et al. 1985).

Neither maternal fish consumption, nor umbilical cord serum PCB level was related to scores on the Bayley scales (Jacobson and Jacobson 1986). In contrast, both contaminated fish consumption and umbilical cord serum PCB level were associated with less preference for the novel stimulus on the Fagan test (Jacobson et al. 1985). In this case, the more direct measure of exposure (umbilical cord serum PCB level) was the stronger predictor. Preference for novelty decreased in a dose-dependent fashion as prenatal exposure to PCBs increased. The observed association did not seem to be mediated by shorter gestation, reduced birth size, or poorer performance on the NBAS. In contrast to prenatal exposure, postnatal PCB exposure via breast milk was not related to visual recognition memory (Jacobson et al. 1985).

Children from the cohort were reassessed when they reached 4 years of age (Jacobson et al. 1990a, 1990b, 1992). They were tested on the McCarthy Scales of Children's Abilities and on several tests that focused on specific aspects of cognitive processing including reaction time, short-term memory processing efficiency, visual discrimination, and sustained attention. Higher levels of prenatal PCB exposure, as measured by umbilical cord serum PCB levels, were associated with poorer scores on two subtests of the McCarthy scales that measure verbal and numeric memory (Jacobson et al. 1990a). Higher PCB concentrations in breast milk were also associated with poorer performance on both of the subtests. In contrast, neither the quantity of breast milk consumed nor the child's current serum PCB level related to any of the outcomes. The authors concluded that the correlation with breast milk PCB levels probably derives from the fact that PCB concentrations in breast milk are representative of maternal body burden, and children of mothers with the highest PCB body burdens would have received the greatest transplacental exposure to PCBs. The fact

that two exposure indices correlate with the same set of outcome variables lends strength to these findings.

Prenatal exposure to PCBs was also associated with less efficient visual discrimination processing and more errors in short-term memory scanning (Jacobson et al. 1992). Reaction time on the visual discrimination task was correlated with maternal milk PCB level, and the number of errors on the short-term memory scanning task was correlated with umbilical cord PCB level. No associations with sustained attention were observed.

A relationship between PCB exposure and activity level was also observed. However, unlike the association with cognitive function, the changes in activity level were related to the child's current PCB body burden, the principal determinant of which was postnatal exposure to PCBs via breast milk (Jacobson et al. 1989). Reduced activity was also associated with postnatal PCB exposure in the Dutch cohort (Patandin et al. 1999b). Children with the highest PCB body burdens at 4 years were less active than children with lower body burdens. These were all children who were breast-fed for at least 1 year and had mothers with above average breast milk PCB levels. In contrast, the Yu-Cheng children were found to be more active than control children (Chen et al. 1994). However, Yu-Cheng mothers were encouraged not to breast-feed, and very few of them did. Thus, exposure of the Yu-Cheng children to PCBs was primarily *in utero*. This could account for the difference in outcome.

The children were reassessed a final time at 11 years of age (Jacobson and Jacobson 1996). A battery of IQ and achievement tests were administered, including the WISC-R, the spelling and arithmetic subtests of the Wide Range Achievement Test-Revised, and the word and passage-comprehension subtests of the Woodcock Reading Mastery Tests-Revised. To improve reliability and sensitivity of the prenatal exposure variable, the PCB concentrations in cord serum and in maternal serum and milk were converted to *z*-scores and averaged to create a composite measure of prenatal exposure. Postnatal exposure was assessed by three separate measures, the PCB concentration in breast milk multiplied by the number of weeks of breast-feeding, the child's serum PCB concentration at 4 years and the child's serum PCB concentration at 11 years.

Prenatal exposure to PCBs was associated with lower full-scale and verbal IQ scores (Jacobson and Jacobson 1996). After adjustment for confounding variables, the IQs of the most highly exposed group (children whose prenatal PCB exposure equivalent was at least 1.25 µg/g milk fat, 4.7 ng/g cord serum, or 9.7 ng/g maternal serum) averaged 6.2 points lower than the scores of the other children. Consistent with earlier findings in these children, the strongest associations were seen on subscales related to memory and attention. Prenatal exposure to PCBs was also associated with poorer word comprehension and overall reading comprehension. The most highly exposed children were 7.2 months behind their peers in word comprehension. In contrast, postnatal PCB exposure was not associated with poorer performance on any of the tests.

The functional importance of the PCB-related deficits was examined by looking at the number of children who scored more than 1 standard deviation below the mean for IQ or at least 2 years behind the age-based norms for reading mastery. The most highly exposed children were three times more likely to score more than a standard deviation below the mean on the WISC-R full-scale IQ and twice as likely to be at least 2 years behind in reading. The results indicated that *in utero* exposure to PCBs at levels only slightly higher than those typically seen in the general population can have a long-term impact on cognitive function. It will be important to follow the more recent and more lightly exposed PCB cohorts to school age to see if the cognitive deficits that have been reported in infants (Darvill et al. 2000) and preschoolers (Patandin et al. 1999) persist as the children grow older.

Other measures in the Michigan cohort. PCB exposure, measured both by maternal contaminated-fish consumption and by umbilical cord serum PCB levels, was associated with lower birth weight, smaller head circumference, and shorter gestational age (Fein et al. 1984). Exposed infants weighed 160–190 g less, their heads were 0.6–0.7 cm smaller, and they were born 4.9–8.8 days earlier depending on whether fish consumption or umbilical cord PCB level was used as the exposure measure. Head circumference was significantly smaller even after controlling for birth weight and gestational age. The size deficits were comparable to those associated with smoking during pregnancy (Jacobson and Jacobson 1988). Higher umbilical cord serum PCB levels continued to be correlated with smaller size at 5 months of age (Jacobson and Jacobson 1988). The physical growth of the children was also assessed at 4 years (Jacobson et al. 1990b). Prenatal PCB exposure continued to be associated with lower body weight at 4 years, but there was no relationship between prenatal PCB exposure and height or head circumference at 4 years. The decrease in body weight was more pronounced in girls than in boys.

The North Carolina Cohort

Another PCB exposure cohort study was initiated in North Carolina in 1978. The women in the North Carolina cohort were selected from the general population and had not been exposed to any known dietary source of PCBs other than the background levels that contaminate the general food supply. The children in the North Carolina cohort were assessed shortly after birth and were followed up at 6-month intervals until 2 years of age and then at yearly intervals until 5 years of age (Table 3).

Description. The original cohort consisted of 880 pregnant women recruited at term from three health centers in the Raleigh–Durham area (Rogan et al. 1986a). A few women dropped out of the study almost immediately, but most continued to participate beyond the initial neonatal contact (Rogan et al. 1986a), and more than 700 of the children were still available for follow-up at 3–5 years of age (Gladen and Rogan 1991).

Exposure indices. Maternal blood, umbilical cord blood, placenta, and milk/colostrum were collected at the time of birth for PCB analysis. Additional milk samples were collected from women who breast-fed at 6 weeks, and at 3, 6, and 12 months if the woman was still breast-feeding. The median maternal serum PCB concentration at the time of birth was 9.06 ng/mL (Rogan et al. 1986a). The median PCB concentration in maternal milk fat at birth was 1.77 mg/mL. After 12 months of breast-feeding, the milk fat concentration was reduced to 1.17 mg/mL. These exposures appear to be higher than those reported by Schwartz et al. (1983). However, differences in analytic techniques make it difficult to compare results from the two studies. As Jensen (1987) discusses, the method used by Rogan and colleagues probably overestimated the actual PCB concentration by about a factor of 2. Thus, the exposure may actually be somewhat higher in the Michigan cohort even though the reported values are lower. The PCB levels in umbilical cord blood were nearly all below the detection limit. Therefore, the investigators, assuming that mothers with higher PCB body burdens would transfer more PCB to their fetuses, used the PCB content of maternal milk fat at birth as an indicator of the child's prenatal exposure.

Neuropsychological measures. Outcome measures at birth included scores on the NBAS. Infants whose mothers had the highest PCB concentrations in their milk fat (> 3.5 mg/mL) had less muscle tone, lower activity levels, and were hyporeflexive (Rogan et al. 1986b). As reviewed above, the infants in the Michigan and Oswego cohorts whose mothers ate the largest quantities of Great Lakes fish were also hyporeflexive (Jacobson et al. 1984b; Lonky et al. 1996). However, in those cohorts there was no relationship between actual measures of PCB exposure and NBAS reflex scores, which makes it difficult to attribute the effects to PCBs.

Infant cognitive and motor development was assessed in the North Carolina study by administering the Bayley Scales of Infant Development at 6, 12, 18, and 24 months of age (Gladen et al. 1988; Rogan and Gladen 1991). Higher transplacental exposure to PCBs was associated with lower psychomotor scores at 6, 12, and 24 months of age. A similar trend was seen at 18 months, but the difference was not statistically significant. There was no relationship between transplacental PCB exposure and scores on the mental development scale, and postnatal exposure through breast-feeding was unrelated to performance on either scale. As discussed above, Jacobson and Jacobson (1986) tested the Michigan cohort on the Bayley scales and did not observe any relationship between psychomotor scores and PCB exposure. However, more recently Koopman-Esseboom et al. (1996) did find psychomotor delays at 3 and 7 months of age in their cohort of Dutch children.

The North Carolina children were later assessed on the McCarthy Scales of Children's Abilities at 3, 4, and 5 years of age, and neither transplacental or breast-feeding exposure was related to scores on any of the McCarthy scales (Gladen and Rogan 1991). Despite the early deficits in psychomotor performance on the Bayley scales, there was no indication of a relationship between PCB exposure and scores on the McCarthy motor scale. This scale is not an exact analogue of the Bayley psychomotor scale, but it is similar in that it uses common, age-appropriate tasks to assess motor function (Gladen and Rogan 1991). These findings suggest that the initial delay in psychomotor development associated with transplacental PCB exposure does not persist beyond 2 years of age.

There was no indication of a relationship between PCB exposure and scores on the McCarthy memory scale. Thus, Rogan and colleagues (Gladen and Rogan 1991) were not able to confirm the relationship between prenatal PCB exposure and verbal or memory deficits reported by Jacobson and colleagues (1990a, 1992; Jacobson and Jacobson 1996). As discussed above, this could be related to the fact that most of the women in the North Carolina cohort were professionals or white-collar workers, and 88% of them breast-fed their infants (Rogan et al. 1986a). In a more recent study in the Netherlands, Patandin et al. (1999) found that the more advantaged home environment provided by women who breast-fed their infants seemed to compensate for the negative impact of prenatal PCB exposure on cognitive function.

Other measures. Unlike the Michigan cohort (Fein et al. 1984), no association

Table 3. Neuropsychological outcomes of human PCB studies.[a]

Test	Age	Outcome	Exposure variable	References
Congener-specific studies				
Oswego cohort				
NBAS	Birth	↓ Autonomic	7–9 chlorinated PCBs	Stewart et al. (2000)
		↓ Habituation	7–9 chlorinated PCBs	
Fagan	6 months	↓ Fixation time	Cord blood PCBs, 7–9 chlorinated PCBs	Darvill et al. (2000)
	12 months	↓ Fixation time	Cord blood PCBs	Darvill et al. (2000)
German cohort				
Fagan	7 months	No effect		Winneke et al. (1998)
Bayley scales	7 months	↓ MDI	ln ∑PCBs (138, 153, and 180) breast milk	Winneke et al. (1998)
	18 months	No effect		Walkowiak et al. (2001)
	30 months	↓ MDI	ln ∑PCBs (138, 153, and 180) breast milk	Walkowiak et al. (2001)
Kaufman ABC	42 months	↓ Mental processing composite index	ln ∑PCBs (138, 153, and 180) breast milk	Walkowiak et al. (2001)
Faroe Islands cohort				
Boston Naming Test		↓ Performance	Cord blood PCBs	Grandjean et al. (2001)
Auditory function		↑ Auditory thresholds	Cord blood PCBs	Grandjean et al. (2001)
Noncongener-specific studies				
Michigan cohort				
Birth size/growth	Birth	↓ Birth weight	Cord blood PCBs	Fein et al. (1984)
		↓ Head circumference	Cord blood PCBs	
		↓ Gestational age	Cord blood PCBs	
	5 months	↓ Body weight	Cord blood PCBs	Jacobson and Jacobson (1988)
Bayley scales	5 months	No effect		Jacobson and Jacobson (1986)
Fagan	7 months	↓ Fixation time	Cord blood PCBs	Jacobson et al. (1985)
McCarthy scales	4 years	↓ Verbal memory	Cord blood PCBs, breast milk PCBs	Jacobson et al. (1990a)
		↓ Numerical memory	Cord blood PCBs, breast milk PCBs	
		↓ Visual discrimination	Breast milk PCBs	Jacobson et al. (1992)
		↓ Short term memory	Cord blood PCBs	
Birth size/growth	4 years	↓ Body weight	Total cord PCBs	Jacobson et al. (1990b)
		↓ Activity	Child's total PCBs	
WISC-R	11 years	↓ Full-scale IQ	Prenatal PCBs	Jacobson and Jacobson (1996)
		↓ Verbal IQ	Prenatal PCBs	
North Carolina cohort				
NBAS	Birth	↓ Muscle tone	Breast milk PCBs	Rogan et al. (1986b)
		↓ Activity	Breast milk PCBs	
		↓ Reflexes	Breast milk PCBs	
Bayley scales	6 months	↓ PDI	Breast milk PCBs	Gladen et al. (1988)
	12 months	↓ PDI	Breast milk PCBs	Gladen et al. (1988)
	18 months	No effect		Rogan and Gladen (1991)
	24 months	↓ PDI	Breast milk PCBs	Rogan and Gladen (1991)
McCarthy scales	3–5 years	No effect		Gladen and Rogan (1991)

Abbreviations: ↓, decrease; ↑, increase; Bayley scales, Bayley Scales of Infant Development; Fagan, Fagan Test of Infant Intelligence; Kaufman ABC, Kaufman Assessment Battery for Children; McCarthy scales, McCarthy Scales of Children's Abilities; NBAS, Brazelton Neonatal Behavioral Assessment Scale; Wisc-R, Wechsler Intelligence Scales for Children-Revised. [a]Dutch cohort is summarized in Table 2.

between birth weight or head circumference and PCB exposure was observed in the North Carolina cohort (Rogan et al. 1986b).

Summary and Conclusions

As the data from ongoing PCB studies are published, the weight of evidence for PCB effects on neurodevelopment is growing. In particular, studies in Taiwan (Chen et al. 1992), Michigan (Jacobson et al. 1985, 1990a; Jacobson and Jacobson 1996), Oswego, New York (Darvill et al. 2000), The Netherlands (Patandin et al. 1999), Germany (Walkowiak et al. 2001; Winneke et al. 1998), and the Faroe Islands (Budtz-Jorgensen et al. 1999; Grandjean et al. 2001) have now all reported negative associations between prenatal PCB exposure and measures of cognitive functioning in infancy or childhood. Only one published study in North Carolina has failed to find any association between PCB exposure and cognitive outcomes (Gladen and Rogan 1991). It is particularly noteworthy that the levels of exposure in some of the more recent studies, the Oswego cohort, for example, are significantly lower than in the earlier studies, yet negative impacts on cognitive functioning are still being reported.

As the evidence for a negative relationship between PCB exposure and cognitive function in children grows, it is important to consider the validity of the neurospychological tests that have been used to assess cognition in the various studies. A number of the studies, including the Michigan, North Carolina, Oswego, and Dutch studies, have used the McCarthy Scales of Children's Abilities to assess cognition. Critics of this test argue that it is an old test that has not been revised or restandardized since 1972 (McCarthy 1972; Sattler 1982). In particular, it has been argued that the so-called Flynn effect may lead to inflated scores on the McCarthy scales. The Flynn effect refers to the fact that average scores on IQ tests tend to rise over time (Flynn 1998). However, this should not be a problem for the internal validity of studies using the test. It is true that the absolute value of scores on an older test such as the McCarthy scales may be higher, but there is no reason to believe that interindividual variability and the determinants of that variability would be affected. In other words, an increase in the absolute values of scores on the test instrument would not change the order of test scores for individuals and therefore would not affect the results. Furthermore, several studies have shown a consistency of the negative association between PCB exposure and cognition across test instruments. In the Michigan cohort prenatal PCB exposure was negatively associated with IQ scores on both the McCarthy scales (Jacobson et al. 1990a) and the WISC-R (Jacobson and Jacobson 1996). Similarly, in the Dutch cohort, PCB exposure was negatively associated with IQ scores on both the Kaufman ABC (Patandin et al. 1999) and the McCarthy scales (Vreugdenhil et al. 2002).

In the last decade advances in the analytic methods for quantitation of PCBs have resulted in widespread availability of congener-specific analysis procedures for human tissue and environmental media. Several recent or ongoing epidemiological studies of PCB effects on neurodevelopment have used congener-specific analytic methods to determine the concentrations of individual PCB congeners in maternal serum, cord serum, and breast milk. Our purpose in this review was to provide an integrated overview of the human developmental studies that have used congener-specific analytic methods to point out consistencies and inconsistencies between the studies and to discuss the potential for the congener-specific exposure data to help us understand the role of individual PCB congeners or classes of congeners in mediating neurodevelopmental outcomes.

Despite the fact that a number of the recent studies have used sophisticated congener-specific analytic techniques, there have been only limited attempts to assess the role of specific PCB congeners or classes of congeners in mediating neurodevelopmental outcomes. In essence, most studies are still relying on total PCBs as the measure of exposure. In most studies only a small set of three or four marker congeners were measured in maternal and cord blood. These data may be adequate for estimating total PCB exposure but are clearly not sufficient to assess the role of specific congeners or classes of congeners in mediating outcomes. In the Dutch cohort, Huisman et al. (1995a) looked at the association between the concentrations of 20 individual *ortho*-substituted PCB congeners measured in breast milk and neonatal neurological optimality, but the results were not informative. Ten of the 20 congeners showed significant negative associations with neurological optimality scores. With one exception, these were the congeners that were present in the highest concentrations in milk fat (Table 1). The congeners did not appear to be structurally or toxicologically similar in any obvious way, and few insights were gained. In the Oswego cohort a large number of congeners were quantified, but so far no attempt has been made to assess the relationship of individual congeners or toxicological classes of congeners to outcomes. The investigators have used the congener-specific data to look at the relationship of PCB homologue groups (e.g., those with 1–3, 4–6, or 7–9 chlorine substitutions) to outcome and have reported negative associations with exposure to the most highly chlorinated PCB homologues. However, this approach provides little or no information about the relationship of individual PCB congeners to neuropsychological outcomes and is, in a sense, counterintuitive because the different PCBs congeners within homologue groups differ markedly in their chemical and physical properties and toxicity.

In theory, congener-specific PCB analysis should provide the data we need to explore the role of individual PCB congeners with different structural and toxicological properties in mediating health outcomes in humans. However, in practice, a number of obstacles must be overcome before we can take full advantage of the wealth of exposure data these methods generate. From a statistical perspective, attempts to determine the role of individual congeners in mediating outcomes are hampered by the fact that the concentrations of most individual congeners are highly correlated with each other and with total PCBs (DeVoto et al. 1997; Gladen et al. 1999; Koopman-Esseboom et al. 1994a). This creates colinearity problems, which could be difficult to address.

From a toxicological perspective, the approach is limited by our incomplete knowledge of the mechanisms of action and structure–activity relationships for PCB neurotoxicity. A potentially useful strategy would be to weight congeners according to their relative potency to produce a given effect and sum the weighted values to come up with toxic equivalents similar to those used for coplanar PCBs, dioxins, and furans. This would allow us to focus on subsets of congeners likely to produce given effects and could significantly increase predictive validity over that for total PCBs. Unfortunately, a large number of the congeners present in human tissue have never been studied in the laboratory, and their relative potency to produce nervous system effects is unknown. More complete information regarding the developmental neurotoxicity of individual congeners or congener groups would help to inform the risk assessment process.

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