REVIEW

Polychlorinated biphenyls (PCBs) and neurological development in children: a systematic review

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Abstract

***Background*—Polychlorinated biphenyls (PCBs) are complex mixtures of persistent contaminants that are widespread in the environment. Newborns are exposed across the placenta and through breast feeding. Experimental animal studies have indicated that PCBs are neurotoxic. The neurological effects of these compounds on children are not clear.**

***Methods*—A systematic review of literature on the relation between neurological development in children and exposure to polychlorinated biphenyls.**

***Results*—Seven follow up studies evaluated the effect of prenatal exposure to PCBs. Two of these studies evaluated highly exposed children. In newborns, an increase of the abnormal reflexes was observed in all four studies evaluating it. During the first months of life, a decrease in motor skills was observed in four of the five studies that investigated psychomotor development; deficits in the acquisition of cognitive skills were observed only in one study assessing non-highly exposed populations. At 4 years of age, an effect on the cognitive areas was observed in four of the five studies that evaluated it. Postnatal exposure to PCBs through breast feeding was not clearly related to any effect on neurological development.**

***Conclusions*—These studies suggest a subtle adverse effect of prenatal PCBs exposure on child neurodevelopment. Differences in study design, inconsistency in some of the results, and the lack of adequate quantitative exposure data, do not allow the derivation of the degree of risk associated with neurodevelopmental effects at current levels of exposure.**

(*J Epidemiol Community Health* 2001;**55**:537–546)

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Accepted for publication
15 February 2001

There is growing evidence that some environmental chemicals can interrupt neurodevelopmental processes during critical periods of development, resulting in effects on behaviour, or cognitive function.[1] Awareness of the toxicity of organochlorine compounds was first established after two well documented episodes of accidental exposure to polychlorinated biphenyls (PCBs) via contaminated cooking oil in Japan (Yusho)[2] and Taiwan (Yucheng).[3] Public health interest about the potential impact of environmental exposure to organochlorine compounds on child neurodevelopment has recently increased and several observational studies have been conducted.[4–32] However, the considerable heterogeneity among these studies in the selection of adequate markers of exposure, in the measure of the outcomes and in the control for possible confounder factors complicates the derivation of firm conclusions about the possible neurodevelopmental effects of these compounds.[33 34]

Properties of PCBs

PCBs are complex mixtures of persistent contaminants that are ubiquitous in the environment. They have been in widespread use, since the 1930s, as dielectric fluids in transformers and capacitors and in a variety of other applications.[35] Most, but not all,[36] industrialised countries have now banned or severely restricted their production.

PCBs are a family of chemicals including 209 different congeners. However, the number of the congeners present in extracts from biotic samples is much lower than the theoretical numbers.[37] The mechanisms of toxicity of these congeners are not similar and the doses at which they are active vary by orders of magnitude.[38] The planarity of the molecule is very important in both biostability and toxicology. Planar PCBs bind to the aryl-hydrocarbon (Ah) receptor resulting in some dioxin-like effects.[39]

Because of their high biostability and lipophilicity and because they are resistant to both chemical and biological degradation they accumulate in food chains and can be found in the tissues of wildlife, domestic animals, and humans worldwide.[40] Nowadays the sources of human exposure to PCBs are food, particularly fish and fish products and animal fats. PCBs are preferentially stored in adipose tissue and are also present, to a smaller extent, in serum and human milk. The concentrations of PCBs in the different organs depend on the lipid content of such organs, with the exception of the brain, where the concentration is lower than the lipid content would indicate. These lower concentrations are attributable to the nature of brain lipids that are more polar than

adipose tissue lipids.[41] PCBs also pass through the placenta and through human milk.

Experimental studies on neurotoxicity of PCBs

During the past 20 years, there has been an attempt to understand the cellular bases of PCB induced behavioural and neurological effects in animal and in vitro models. In vitro models have shown a decrease of cell dopamine content after PCB exposure.[42–44] Experimental studies with laboratory rodents and non-human primates have indicated changes in dopamine function.[45–47] Changes in locomotion activity,[48 49] in behaviour[50 51] and in learning and memory functions in the adult animal[48 52] have also been described after prenatal exposure to PCBs. These effects have been mainly described for non-dioxin-like ortho substituted PCBs congeners[53] as well as for the lower chlorinated PCBs.[54] Recent research also suggests that PCBs can change a number of other physiological processes that may be important for development. For example, PCB induced alteration in thyroid function during development may underline some of the developmental effects of PCBs reported in humans and animal models.[55 56]

Assessment of neurodevelopment in newborns and infants

Interpretation of studies on possible adverse developmental effects in infants from perinatal exposure to PCBs, in contrast with experimental models, is hampered by a high number of potential confounding factors and by difficulties in evaluating exposure and outcome measures. In studying human development, besides behaviour and cognition, it is difficult to define what is "normal". Human behaviour and intellect has been assessed by comparison to the "norm", and for this reason, different developmental tests based on general population development have been created. Neonatal tests mainly assess tonicity, reflexes, alertness, responsiveness and state regulation of the newborn. Child tests are constructed with the premise that an ability may or may not have been acquired in a given age for the children.[57] Child tests are divided into mental (that is, language, cognition, memory and social patterns), motor (that is, gross and fine motor functions) and behavioural (that is, activity rating and behaviour) scales. These tests are reliable, well standardised and have specific items for the assessment of motor, mental and behavioural development. Their use facilitates comparison of results from the different studies. All mental and motor standardised tests have a mean full scale score around 100, with the exception of the Fagan Test of Visual Recognition Memory (FTVRM), which calculates the percentage of success. For the behavioural tests a higher score indicates a higher frequency of behavioural or activity problems in the child. The neurodevelopmental assessment tools mentioned in this review are briefly described in table 1.

Epidemiological studies

IDENTIFICATION OF EPIDEMIOLOGICAL STUDIES AND ANALYSIS

All the available studies about the effects of PCBs on children's neurobehavioural development published from 1976 to January 2000 were reviewed. We searched the computerised database of Medline by using "polychlorinated biphenyls", "development", and "neurotoxicology". We also reviewed conference proceedings of related topics as well as citations in the identified reports. We only included papers that had been written in English. A total of 29 publications coming from seven independent populations were identified.

Results have been grouped by effect studied (motor, mental or behavioural) and age at evaluation (newborn (<1 month) and children (>3 months–11 years)). Some studies presented the mean scores of the test used, while others provided a β coefficient of the increment or decrement in the scale score as a function of PCB exposure. To allow comparisons among all studies, we presented 95% confidence intervals of the mean difference or the β coefficients, which were derived from standard deviations or from graphical presentations.[8 9 11] As in one publication[32] the scores were reported in a raw form, we transformed them to the standard index score using the *Bayley scales for infant development* (2nd ed).[57]

Table 1 Standardised neurodevelopmental tests mentioned in the publications reviewed

Test	*Age*	*Assessment*	*Reference*
Neonatal tests			
Brazelton neonatal scales (BNBAS)	<3 days	Reflexes, responsiveness, state regulation	67
Newborn neurological exam (Prechtl)	10–21 days	Age-appropriated neurodevelopment	24
Children tests			
Mental			
Fagan test of visual recognition memory (FTVRM)	3–12 months	Novelty preference; short-term memory; "infant intelligence"	80
Bayley scales of infant development (MDI)	<2.5 years	Age-appropriate cognitive ability	57
Stanford-Binet (SB)	2.5–6 years	General intelligence	66
Kaufman assessment battery for children (KABC)	2.5–12.5 years	Age-appropriate cognitive ability	66
McCarthy scales of children's abilities (MCSCA)	>3 years	Age-appropriate cognitive ability	66
Wechsler Intelligence Scale for children (WISC)	>6 years	General intelligence	66
Reynell developmental scales (RDS)	—	Age-appropriate development of language	28
Chinese Child Developmental Inventory (CCDI)*	6m–6y	General developmental status†	12
Motor			
The Neurological exam for toddler age (Hempel)	Toddlers	Age-appropriate motor ability	27
Bayley scales of infant development (PDI)	<2.5 years	Age-appropriate motor ability	57
Behavioural			
Rutter's child behaviour scale (RCBS-A)	0–12 years	Child behavioural problems, hyperactivity	66
Werry-Weiss-Peters activity scale (WWPAS)	3–11 years	Children's activity level	66

*Adopted and modified in 1978 from Minnesota Child Developmental Inventory. †CCDI has seven subscales: two for motor development and five for mental development.

Table 2 Studies about the effects of PCBs on neurodevelopment in children included in this review

Location	Type of study	Year of start	Study period	Population	Measurement of PCBs exposure	Mean PCBs concentration (biological sample)	Min–max PCBs concentration (biological sample)	Other detected organochlorine compounds	Effect studied
Japan[4]	Prospective	1968	7 years	Children born to poisoned women in Japan in 1968	Location	6.0 ppb (exposed children's blood[40])	?	—	Mental, motor, behavioural
Taiwan[5–12]	Matched pair cohort study*	1985–87	6 years	Children born to poisoned women in Taiwan in 1979 and their controls	Questionnaire on location and diet	0.99 ppb (exposed children's blood)‡	0–77.8 ppb (exposed children's blood)	Polychlorinated dibenzofurans (PCDFs)	Mental, motor, behavioural
North Carolina, USA[13–16]	Prospective	1978–82	5 years	General community	PCB† and DDE in biological samples	1.5–2 ppm (colostrum)	0–>4 ppm (colostrum)	Dichlorodiphenyl dichloroethene (p,p'DDE)	Neonatal, mental, motor
Michigan, USA[17–23]	Prospective	1980–81	11 years	Children born to Lake's Michigan fish eater women	PCB† in biological samples/questionnaire on diet	2.5 ng/ml (cord blood)#	0–12.3 ng/ml (cord blood)	Polybrominated biphenyls (PBBs), DDT	Neonatal, mental, behavioural
Rotterdam-Groningen, the Netherlands[24–29]	Prospective	1990–92	4 years	General community	$PCB_{118,138,153,180}$ and PCDDs in biological samples	0.38 ng/ml (cord blood)‡ 2.04 ng/ml (maternal plasma)‡	0.18–0.86 ng/ml (cord blood)§§	PCDFs, polychlorinated dibenzo-*p*-dioxins (PCDDs)	Neonatal, mental, motor
Oswego, USA[30 31]	Prospective	1991–94	4 years (in course[87])	Children born to Lake's Ontario fish eater women	69 PCB congeners in biological samples/ Questionnaire on diet	0.52 ng/g wet (cord blood)‡	Not reported	Hexachlorobenzene, dieldrin, lindane, chlordane, PCDDs, mirex	Neonatal
Düsseldorf, Germany[32]	Prospective	Not reported	7 months	General community (middle and upper class families)	$PCB_{138,153,180}$ in biological samples	0.55 ng/ml (cord blood)	Not reported	—	Mental, motor

*Cross sectional in reference 5. †Congeners of PCB not reported. ‡Median. #Detection limit: 3 ng/ml. §p5–p95. — Not applicable. ? Not known.

CHARACTERISTICS OF THE STUDIES

Table 2 summarises the design and reporting of the seven studies considered in this review. All studies were prospective. The Japanese and the Taiwanese studies reported data from children highly exposed to PCBs. In Taiwan, for every exposed child, two control children matched on neighbourhood, age, sex, mother's age and parent's combined education level were used. The studies in Michigan and Oswego were based on children born to women who ate contaminated fish. The other three studies were based on children from general populations. The measure of exposure varied significantly between studies. In the Japanese and Taiwanese studies, information of children's exposure was only based on place of residence and on a mother's questionnaire on diet, respectively. However, in both studies, levels of PCBs in exposed children's sera were analysed in a subsample. In the rest of the studies information of children's exposure was specifically based on levels of PCBs measured in different biological samples. In Michigan and in Oswego, a questionnaire was also used to assess exposure to PCBs. Prenatal exposure was estimated through the measure of PCBs in cord blood and maternal plasma close to delivery or colostrum. Postnatal exposure was measured through the quantification of PCBs in milk samples or in child sera. Specific information about the congeners analysed was only given in the Netherlands, German and Oswego studies. The North Carolina and the Netherlands cohorts also studied the effects of other organochlorine compounds on neurodevelopment in children. The reported PCBs concentrations among children (sera or cord blood) in the highly exposed cohorts (Japan, Taiwan) seem to be orders of magnitude higher than among children from general populations (the Netherlands and Germany). Levels of PCBs in the sera of Yusho children are the highest.

NEURODEVELOPMENTAL EFFECTS OF PCB EXPOSURE AMONG NEWBORNS

A neonatal effect was studied in North Carolina, Michigan, the Netherlands and Oswego. Results from all the four studies suggest some negative effects on neonatal development. In North Carolina, higher PCB levels in maternal milk at birth were associated with hypotonicity and hyporeflexia.[13] Maternal consumption of contaminated fish in Michigan was predictive of newborn motor immaturity, poorer lability of states, a greater amount of startle, and more abnormally hypoactive reflexes in the Neonatal Behavioral Assessment Scale (NBAS)[17] but higher cord serum PCB levels were not related to any adverse outcomes. In the Netherlands, exposure through breast milk to PCBs, polychlorodibenzo-p-dioxins (PCDDs) and polychlorodibenzofurans (PCDFs) was associated with a reduced neonatal neurological optimality, but levels of PCB in cord blood were not related to nervous system dysfunction.[24] The Oswego study found that newborns highly exposed to highly chlorinated PCBs scored more poorly on the autonomic and habituation

Table 3 Main characteristics of the reports in the different publications of prenatal exposure to PCBs and mental, motor and behavioural development at different ages

Effect studied, study and publication	*Code**	*Age at evaluation***	*Test used*	*Number‡*	*Age adjusted mean full scale score of all children*	*Covariates#*
Mental						
Taiwan						
Rogan, 88	5a	<2.5y	MDI	45/45	103	Socioeconomic status (2), mother's age, gender, age
	5b	2.5–6y	SB	52/52	87	Socioeconomic status (2), mother's age, gender, age
	5c	>6y	WISC	21/21	86	Socioeconomic status (2), mother's age, gender, age
Yu, 91	6a	<2.5y	MDI†	28/28	101.1	Socioeconomic status (2), mother's age, gender, age
	6b	<2.5y	MDI†	19/19	101.9	Socioeconomic status (2), mother's age, gender, age
	6c	2.5–6y	SB†	25/25	101.7	Socioeconomic status (2), mother's age, gender, age
	6d	2.5–6y	SB†	69/69	94.1	Socioeconomic status (2), mother's age, gender, age
	6e	>6y	WISC	30/30	91	Socioeconomic status (2), mother's age, gender, age
Lai, 94	9a	6m	MDI	6/6	107.5	Socioeconomic status (2), mother's age, gender, age
	9b	1y	MDI	15/15	113	Socioeconomic status (2), mother's age, gender, age
	9c	1.5y	MDI	24/24	101	Socioeconomic status (2), mother's age, gender, age
	9d	2y	MDI	40/40	102	Socioeconomic status (2), mother's age, gender, age
	9e§	4y	SB	86/86	94.5	Socioeconomic status (2), mother's age, gender, age
	9f§	7y	WISC	101/101	94.5	Socioeconomic status (2), mother's age, gender, age
	9g	11y	WISC	30/30	105	Socioeconomic status (2), mother's age, gender, age
Chen, 94	10	7–12y	WISC	27/27	96.3	Socioeconomic status (2), mother's age, gender, age
Guo, 94	12	6m–6y	CCDI ‖	66/66	103.1	Socioeconomic status (2), mother's age, gender, age
North Carolina, USA						
Gladen, 88	14a	6m	MDI	787	114.6	Socioeconomic status (2), parental factors (5), perinatal factors (5), gender, age, duration of breast feeding, examiner
	14b	1y	MDI	720	108.9	Socioeconomic status (2), parental factors (5), perinatal factors (5), gender, age, duration of breast feeding, examiner
Michigan, USA						
Jacobson, 85	18a	7m	FTVRM	123	57%	Socioeconomic status, parental factors (2)
	18b	7m	FTVRM	123	57%	Perinatal factors (3)
Jacobson, 90	20	4y	MCSCA-GCI	146	na	Socioeconomic status (7), parental factors (6), perinatal factors (2), gender, age, examiner, PBBs, DDT, lead
Jacobson, 96	22	11y	WISC	178	107	Socioeconomic status (2), parental factors (2)
Rotterdam-Groningen, the Netherlands						
Koopman-Esseboom, 96	26	7m	MDI	206	113	Socioeconomic status (3), parental factors (3), perinatal factors (3), gender, duration of breast feeding
Patandin, 99	28a	4y	K-ABC	373	111	Socioeconomic status (2), parental factors (4), perinatal factors (2), gender, duration of breast feeding
	28b	4y	RDS	190	105	Socioeconomic status (2), parental factors (4), perinatal factors (2), gender, duration of breast feeding
Düsseldorf, Germany						
Winneke, 98	32a	7m	MDI	131	94.5	Socioeconomic status (3), parental factors (3), perinatal factors (3), age, duration of breast feeding, lead
	32b	7m	FTVRM	131	59%	Socioeconomic status (3), parental factors (3), perinatal factors (3), age, duration of breast feeding, lead

*Useful for interpreting the figures (the number coincides with the reference). **In the Taiwanese cohort, we only included <2y, 4, 7 and 11 years. †Different visits. ‡In matched paired cohort studies, number of subjects exposed/non-exposed. #In parentheses, number of covariates. §Also reported in reference 4. ¶Also reported in reference 8. ‖ General developmental score (motor, mental and social). na: Not available.

Table 3 Continued

Effect studied, study and publication	Code*	Age at evaluation**	Test used	Number‡	Age adjusted mean full scale score of all children	Covariates#
Motor						
Taiwan						
Rogan, 88	5	<2.5	PDI	45/45	104.5	Socioeconomic status (2), mother's age, gender, age
Yu, 91	6a	<2.5	PDI†	28/28	105.2	Socioeconomic status (2), mother's age, gender, age
	6b	<2.5	PDI†	19/19	107.6	Socioeconomic status (2), mother's age, gender, age
Lai, 94	9a	6m	PDI	6/6	110	Socioeconomic status (2), mother's age, gender, age
	9b	1y	PDI	15/15	110	Socioeconomic status (2), mother's age, gender, age
	9c	1.5y	PDI	24/24	108	Socioeconomic status (2), mother's age, gender, age
	9d	2y	PDI	40/40	99	Socioeconomic status (2), mother's age, gender, age
North Carolina, USA						
Gladen, 88	14a	6m	PDI	787	114.7	Socioeconomic status (2), parental factors (5), perinatal factors (5), gender, age, duration of breast feeding, examiner
	14b	12m	PDI	787	108.6	Socioeconomic status (2), parental factors (5), perinatal factors (5), gender, age, duration of breast feeding, examiner
Rogan, 91	15a	1.5y	PDI	676	108	Socioeconomic status (2), parental factors (5), gender, age, examiner
	15b	2y	PDI	670	114	Socioeconomic status (2), parental factors (5), gender, age, examiner
the Netherlands						
Huisman, 95	25	18m	Hempel	373	na	Socioeconomic factors (1), parental factors (1), study centre
Koopman-Esseboom, 96	26	3m	PDI	198	117	Socioeconomic factors (3), parental factors (2), perinatal factors (4), gender, duration of breast feeding
Germany						
Winneke, 98	32	7m	PDI	131	83	Socioeconomic status (3), parental factors (3), perinatal factors (3), age, duration of breast feeding, lead
Behavioural						
Taiwan						
Rogan, 88	5	3y–12y	RCBS-A	117/119	10.2	Socioeconomic status (2), mother's age, gender, age
Chen, 94	8a¶	4y	RCBS-A	na	14.8	Socioeconomic status (2), mother's age, gender, age
	8b¶	7y	RCBS-A	na	12.2	Socioeconomic status (2), mother's age, gender, age
	8c¶	11y	RCBS-A	na	10.1	Socioeconomic status (2), mother's age, gender, age
	8d	4y	WWPAS	na	48	Socioeconomic status (2), mother's age, gender, age
	8e	7y	WWPAS	na	37	Socioeconomic status (2), mother's age, gender, age
	8f	11y	WWPAS	na	25	Socioeconomic status (2), mother's age, gender, age
Guo, 94	12	3y–6y	RCBS-A	40/40	12.9	Socioeconomic status (2), mother's age, gender, age

*Useful for interpreting the figures (the number coincides with the reference). **In the Taiwanese cohort, we only included <2y, 4, 7 and 11 years. †Different visits. ‡In matched paired cohort studies, number of subjects exposed/non-exposed. #In parentheses, number of covariates. §Also reported in reference 4. ¶Also reported in reference 8. ‖ General developmental score (motor, mental and social). na: Not available.

KEY POINTS

- Health risk of the human intake of persistent organochlorine compounds to child neurodevelopment is a matter of worldwide concern.
- The existing research suggests that polychlorinated biphenyls (PCBs) hinder neurodevelopment to children exposed early in life.
- Considerable heterogeneity between study designs does not permit a joint quantitative measure of the association.
- The universal exposure to organochlorine compounds makes necessary further research of populations exposed to the current levels of these contaminants.

clusters of the NBAS and, although not significantly, had more abnormal reflexes.[30 31]

NEURODEVELOPMENTAL EFFECTS OF PCB EXPOSURE AMONG CHILDREN

Prenatal exposure to PCBs

Original quantitative data of the effects of prenatal exposure to PCBs on children from 6 months to 11 years were reported in 15 publications from Taiwan, North Carolina, Michigan, the Netherlands and Germany (table 3).

A negative association between PCBs and mental development was found in children born to mothers who had consumed contaminated oil in 1979 in Taiwan (fig 1A). In most of the evaluations at different ages, the average difference between exposed and non-exposed was around −4 to −6 points. In the studies based on non-highly exposed populations a negative effect on the acquisition of cognitive skills during the first months of life was only observed in the Michigan study (fig 1B). In addition, a significant association between prenatal PCBs exposure and mental impairment was observed at 4 years of age in the Netherlands and 11 years in Michigan (fig 1B). When memory was specifically assessed, an inverse association could also be observed in Michigan at 4 years of age.[20 21] In contrast, the North Carolina study reported that no effects were observed at 3, 4 or 5 years.[16]

An inverse association with the psychomotor scale scores was also observed both in children prenatally exposed in Taiwan and in children highly exposed in North Carolina compared with the non-exposed and the less exposed, respectively (fig 2A). In North Carolina and in the Netherlands, negative associations with psychomotor scales were observed during the first year of life, particularly at 3 months (fig 2B). In the Netherlands study the authors also reported that cord blood PCB levels did not predict poorer scores in motor development at either 7 months[26] or at 42 months.[27]

Behavioural scales were only studied in Taiwan and Michigan. In all the publications from the Taiwanese study there was a negative association between children born to women who had consumed contaminated oil and higher scores in the behavioural scales (fig 3). In Michigan, prenatal PCB exposure was not

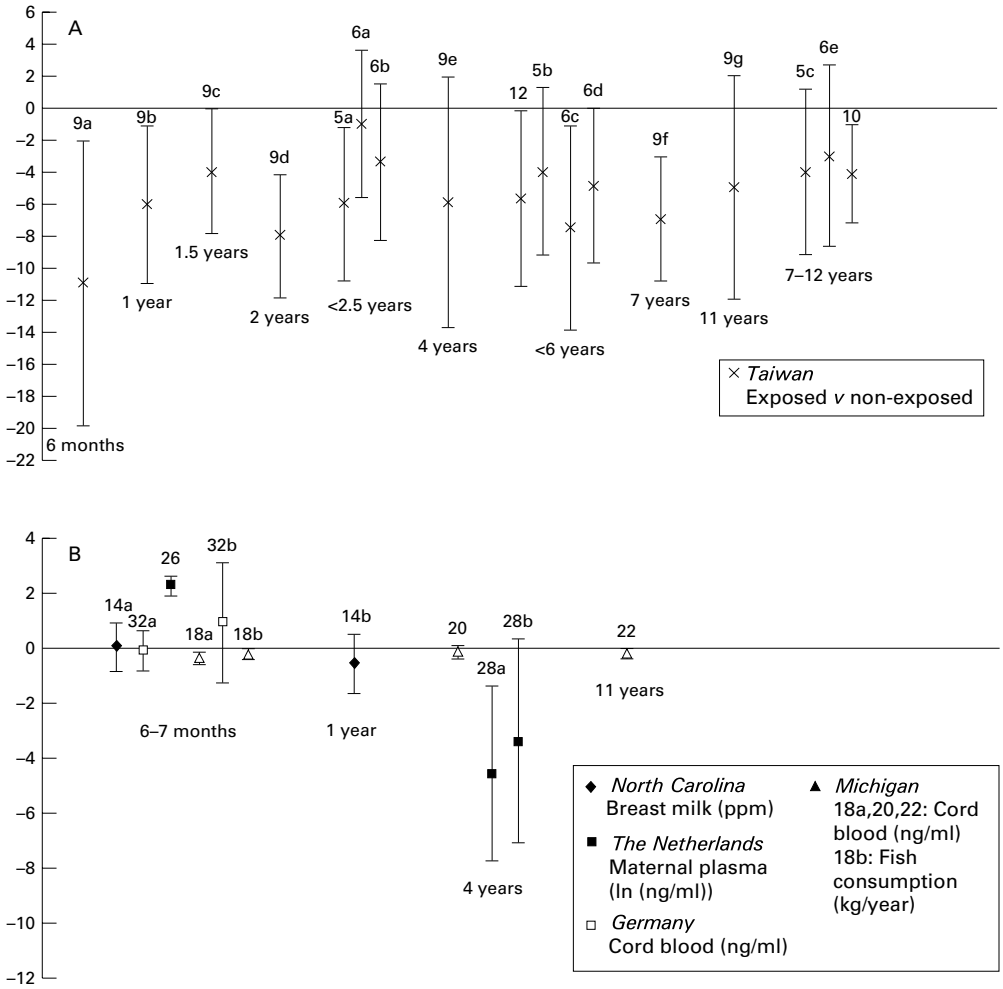

Figure 1 Mean difference in full mental scales (and 95% confidence intervals): (A) between prenatally exposed and non-exposed children to PCBs and (B) for a change in one unit of prenatal exposure to PCBs; ordered by age of the infant and type of test of the different studies.

associated with worse behavioural score in either the composite activity rating[19] or sustained attention rating[21] at 4 years of age.

The Japanese study did not use any specific standardised test and did not report quantitative data. However, a clinical examination of 127 exposed children showed that they had a mean IQ of 70, had hypotonia and appeared to be sullen, expressionless and hypoactive.[4] Overall, in addition to the effects found in the Japanese and the Taiwanese accidents, prenatal PCB exposure seems to be related to a decrease in motor skills during the first months of life and to an effect on the cognitive areas among children older than 4 years.

POSTNATAL EXPOSURE TO PCBS

Postnatal exposure was studied in North Carolina, Michigan, the Netherlands and Germany. Unlike prenatal exposures, postnatal exposures have rarely been found to be associated with any neurodevelopmental effect. In North Carolina, postnatal exposure to PCBs, based on a function of the concentration of the chemical in milk and the duration of breast feeding, was not related to worse performance in any of the tests and ages studied.[14–16] In Michigan, levels of PCBs in maternal milk were unrelated to recognition memory performance at 7 months,[18] cognitive performance at 4 years,[20 21] and at 11 years.[22] Only the composite activity rating at 4 years was negatively related to both the maternal milk PCBs level and the four year serum PCBs level.[19] In the Netherlands, postnatal exposure to PCBs was analysed together with the effects of dioxins. According to the toxic equivalent factor of each congener, a total of 17 dioxins and three PCBs were added and summarised as a total PCB-dioxin toxic equivalent concept (TEQ). Examination of the postnatal exposure revealed no significant effect of the total PCB-dioxin TEQ exposure at 3 months of age. At 7 months higher amounts of PCBs and dioxin exposure through breastfeeding had a significant adverse effect on the psychomotor outcome among breast feeders.[26] At 18 months[25 26] and at 24 months,[27 28] an effect of lactational exposure to these compounds could not be detected.[25 26] In Germany, only the Bayley mental developmental index exhibited a significant negative association with PCBs levels in breast milk at 7 months.[32]

Discussion

The reviewed studies have shown that PCBs exposure through the mother might be related

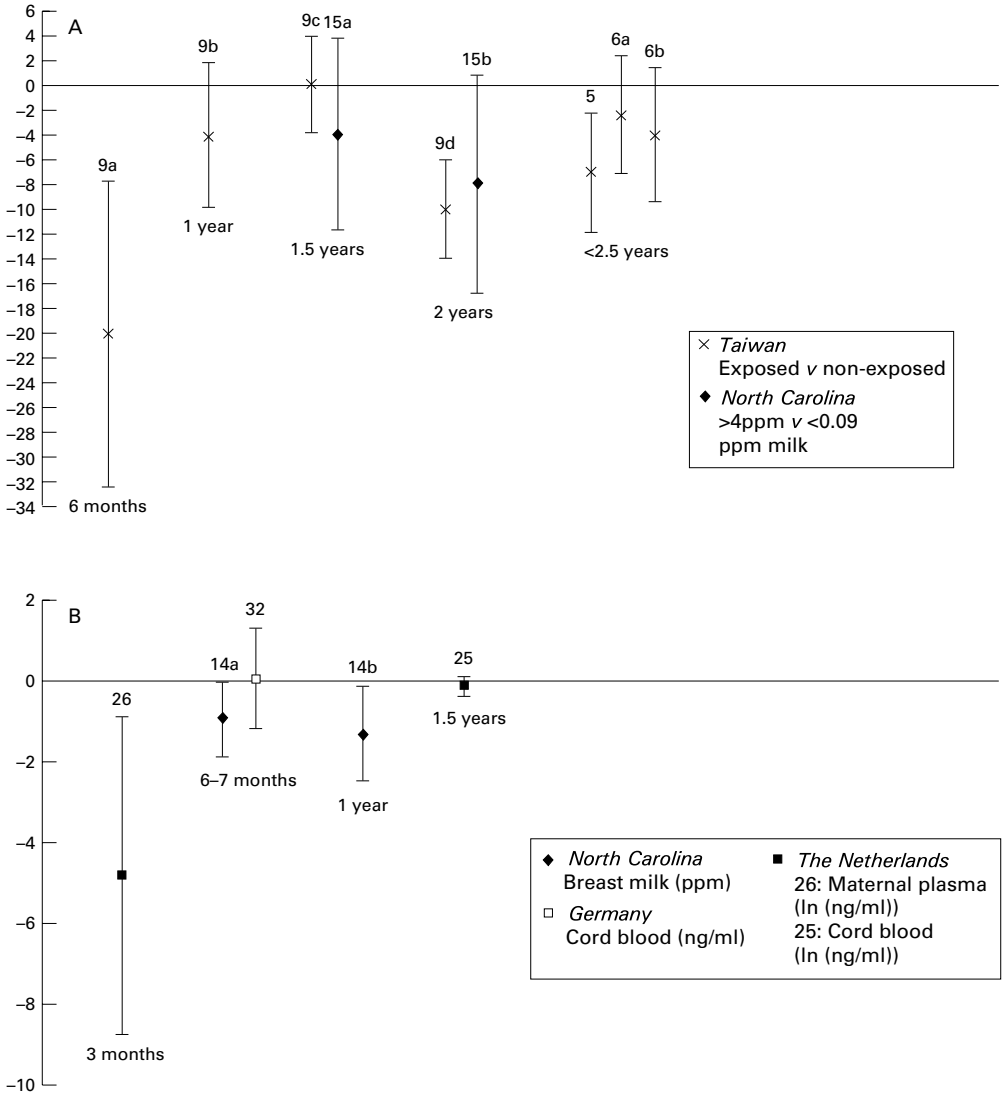

Figure 2 Mean difference in full motor scales (and 95% confidence intervals): (A) between prenatally exposed and non-exposed children to PCBs and (B) for a change in one unit of prenatal exposure to PCBs; ordered by age of the infant and type of test of the different studies.

to some small adverse effects on the neurodevelopment and behaviour of children. Seven follow up studies evaluated the effect of prenatal exposure to PCBs. Two of these studies evaluated highly exposed children. In newborns, an increase of the abnormal reflexes was observed in all four studies evaluating it. During the first months of life, a decrease on the motor skills was observed in four of the five studies that investigated psychomotor development; deficits in the acquisition of cognitive skills were observed only in one study assessing non-highly exposed populations. The studies based on general populations mainly evaluated motor development in infants up to 2 years, so it cannot be excluded that the observed psychomotor effects during the neonatal period and early infancy might disappear later in life. At 4 years of age, an effect on the cognitive areas was observed in four of the five studies that evaluated it. The strongest effects on motor and mental development were observed in Taiwan, in the reports at the age of 6 months. A possible explanation could be related to the fact that exposed mothers were encouraged not to breast feed their infants,[58] impeding the possible neurodevelopmental benefits of breast feeding to their newborn.[59 60] Effects on neurological development of postnatal exposure to PCBs through breast feeding were inconsistent among the studies and preponderantly non-significant. PCBs exposure is higher through breast feeding than in utero,[58 61] but intrauterine exposure seems to pose a greater threat to the infant than postnatal exposure as has been observed for other chemicals.[62]

Exposure to PCBs was assessed through biological samples or questionnaires on residence or diet. Questionnaires did not specifically discriminate between prenatal or postnatal exposure and were not sufficiently sensitive to detect either exposure to specific compounds or the magnitude of the exposure. In Taiwan, the authors tried to improve the exposure measurement provided by the questionnaire by using the physical signs observed in the children after PCBs intoxication, such as presence of nail abnormalities. No relation

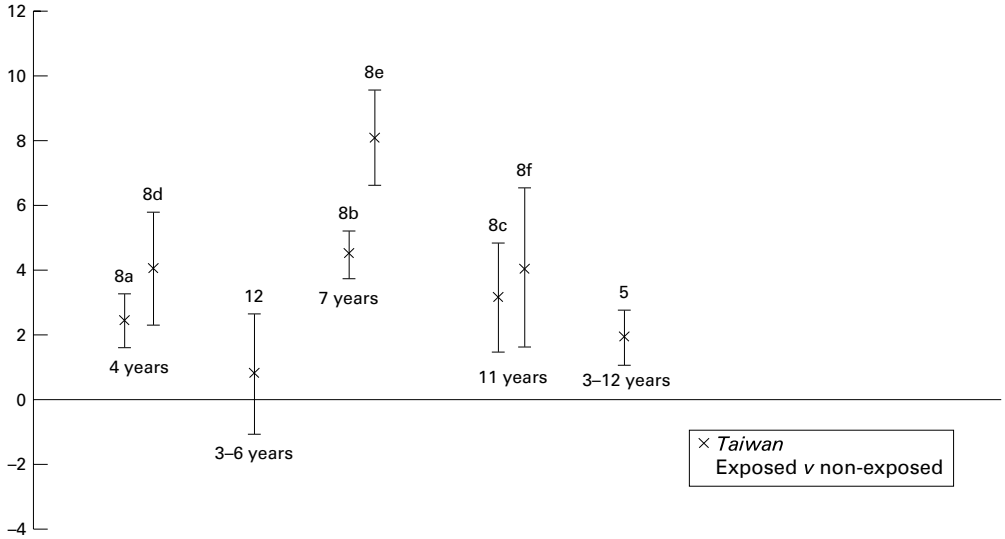

Figure 3 Mean difference in full behavioural scales (and 95% confidence intervals) between prenatally exposed and non-exposed children to PCBs; ordered by age of the infant and type of test of the different studies.

between severity of the external clinical examination and the neurodevelopmental effects could be observed.[6] However, the measurement of exposure through an index of physical signs could be less valid than the questionnaire as individual susceptibility was not taken into account. Problems with biological measures of exposure were of a different nature. Some studies measured prenatal exposure of newborns through assays in maternal blood or milk close to delivery rather than cord blood. Although there is a correlation between maternal and child levels,[63] a within individual variability can be observed in the correlation between levels of specific PCBs' congeners in maternal milk close to delivery and levels in cord blood.[64] Differences in the analytical methods used could also explain some of the differences observed among studies. In Michigan and in North Carolina exposure was defined from total PCBs levels by summing different Webb-McCall peaks.[65] This method may have hampered the identification of specific PCB congeners, such as the non-dioxin like PCBs or the less chlorinated, which have been described to be the most neurotoxic in animals.[54]

The measure of the outcome was also significantly different among the studies. The age at evaluation and the specific use of the available standardised tests differed in each report. Mental development was assessed in all studies at 6–7 months of age. Only some of these studies followed up their children up to school ages. Motor development was mainly evaluated in children aged less than 2 years. The behavioural and mental repertoires of the younger child are more vulnerable to acute external influences difficult to control for than the motor skills, and therefore less reliable.[66] Clusters like mobility or reflexes, which predict better future motor function, tend to respond less to the environmental stimuli during the examination.[67] In addition, the mental skills early in life are less predictive of later functioning than motor skills.[68]

The major differences between studies laid in the methods of controlling for confounders. Socioeconomic status, prenatal maternal alcohol consumption, maternal smoking during pregnancy, maternal age, dietary habits, gender, the caregiving environment as measured by the HOME inventory[69] and breast feeding itself are strongly associated with neurodevelopment,[70] and adjustment for these factors was heterogeneous among studies and not comparable. Besides, humans are exposed to PCBs that are quite frequently present in mixtures with other organochlorine compounds or other chemical products, but only a few of the studies measured other compounds. Other organochlorine compounds were studied in North Carolina, Michigan and Oswego. The studies in Michigan, Germany and Oswego took into account levels of lead. Only the study in Oswego controlled for methylmercury, which has been reported to act synergistically with polychlorinated biphenyls in in vitro models,[71] and has been shown to be associated with deficits in language, attention and memory in children.[72] In a recent study in the Faroe Islands, an association with PCBs exposure disappeared after adjustment for methyl mercury.[73]

Systematic reviews are prone to publication bias[74] as those studies with negative findings are less likely to be published. However, it seems unlikely that any large study might have not been published because of negative findings. We are quite confident that all published studies about the effects of PCBs on child neurodevelopment have been considered in this review, but publication bias cannot be absolutely discarded.

Despite the relatively consistent results due to prenatal exposures, the lack of homogeneity between study designs does not allow having a joint quantitative measure of the association. The present studies do not provide enough information on type of dose-response relation and the presence of a threshold level. Taiwan and Japan, which had the highest levels of PCBs and PCDFs, did not use levels of

internal dose of PCBs to assess the association with neurodevelopmental tests and only quantified exposure in two levels (exposed/non-exposed). The critical temporal period during the brain growth spurt where the potential damage might occur is also not known. Measurements at birth averaged all prenatal exposures and could not differentiate acute exposures during pregnancy. Moreover, information on the possible transience of the effects, or the specific cognitive skills that might remain permanently affected in later childhood cannot be derived from the present studies. As was fully assessed in the case of lead, it is important to clarify the possible reversibility of the observed effects.[75]

Another important issue of concern is whether the small group average effects observed have a clinical significance at the individual level.[76] At current levels in the Great Lakes region, the effects of intrauterine PCBs exposure appeared to be so subtle that they would not have been evident in a routine clinical examination.[77] Studies on lead exposure have shown that a decrease of 4 points in average population intelligence increases the number of children with IQs of <80 by threefold and decreases the percentage of children with IQ scores of >125.[78] In a similar way, exposure to these ubiquitous environmental pollutants may have a seemingly small effect at individual level, but probably have a large impact at population level.[79]

We conclude that the available studies suggest an adverse effect of prenatal PCBs exposure on neurological development in children. However, differences in study design, some inconsistencies in the results, and the lack of homogeneous quantitative exposure data, do not allow the derivation of the degree of risk associated with neurodevelopmental effects at current levels of exposure. Future investigation, as well as ongoing cohort studies,[80–84] should guarantee standard evaluation of specific organochlorine exposure using biological samples, homogeneous outcome assessment through standardised tests and measurement of important covariates such as socioeconomic factors and other neurotoxic chemicals.[85] The universal exposure to these compounds and the importance of early assessment of signs of dysfunction to provide the best possible basis for decisions on prevention,[86] makes necessary the setting up and continuation of large follow up studies of populations exposed to the current levels of these contaminants.

We are grateful to Dave Macfarlane for his help in editing this manuscript.

Funding: supported in part by grants from "Fundació La Caixa" 97/009.00, and Generalitat de Catalunya-CIRIT 1999SGR 00241.

Conflicts of interest: none.

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