REVIEW

Background exposure to PCDDs/PCDFs/PCBs and its potential health effects : a review of epidemiologic studies

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Abstract : Here we review epidemiologic studies dealing with the dietary intake and the body burden of polychlorinated dibenzo-*p*-dioxins (PCDDs)/polychlorinated dibenzo-furans (PCDFs)/ polychlorinated biphenyls (PCBs) in the general population, and potential adverse health effects of these substances, especially on the risk of diabetes mellitus and endometriosis, and on thyroid function and the neurodevelopment of infants. The mean or median intake of dioxin-related compounds among the general populations of various countries is lower than the maximum tolerable daily intake (TDI) set by the WHO in 1998 (4pg TEQ/kg/day). However, there have been few reports on the distribution of intake and the proportion of subjects whose exposure levels exceed the maximum TDI. At present, it remains unclear whether background exposure to dioxin-related compounds is associated with increased risk of diabetes (because of lack of longitudinal studies), endometriosis (because of lack of studies with sufficient statistical power), or altered thyroid function (because of inconsistent results on humans). Consistent results have been reported for the association between exposure to background levels of PCBs/dioxins, especially trans-placental PCBs, and defective neurodevelopment of infants in the U.S. and Europe. Thus, efforts should be made to further decrease the body burden among women of reproductive age by reducing the release of PCDDs/PCDFs/PCBs into the environment. J. Med. Invest. 52 : 10-21, February, 2005

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INTRODUCTION

Polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzo-furans (PCDFs) are a group of toxic chemical substances that are produced unintentionally during thermal and industrial processes, such as incineration of wastes, production of organic chlorinated herbicides and bleaching of papers (1). Humans are exposed to low levels of PCDDs/PCDFs through food, water, the atmosphere and soil even in the absence of occupational or accidental exposure. Because of their lipophilic and persistent nature,

PCDDs/PCDFs are accumulated in various organs of wild animals and the human body, in adipose tissue and liver in particular, through the food chain. The toxic and biochemical responses induced by PCDDs/ PCDFs include carcinogenicity, endocrine, reproductive, neurobehavioral and immune effects, and induction of drug metabolizing enzymes such as CYP1A1(1). PCDDs/PCDFs are considered to exert their toxic effects through a common mechanism mediated through the aryl hydrocarbon receptor (AhR) (binding to AhR, formation of heterodimers with AhR nuclear translocator [ARNT] in the nucleus and binding to the xenobiotic response element and regulation of the expression of various genes). The strength of the toxicity of PCDDs/PCDFs is expressed relative to that of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) using the Toxic Equivalency Factor (TEF, with the

TEF of 2,3,7,8-TCDD=1) (2,3). Polychlorinated biphenyls (PCBs) are another group of persistent anthropogenic organic pollutants. Although their production and use in open systems was banned in the early 1970's, PCBs are ubiquitously detected in various tissues of wildlife and the human body. Some forms of PCBs with coplanar structures (coplanar-non-*ortho* and mono-*ortho* PCBs [co-PCBs]) have toxicities similar to that of 2,3,7,8-TCDD. So far, TEFs have been estimated for 7 PCDDs, 10 PCDFs and 12 co-PCBs.

In 1998, the WHO set the tolerable daily intake (TDI) of PCDDs/PCDFs/co-PCBs (dioxins or dioxin-related compounds) as 1-4 pg Toxicity Equivalents (TEQ)/kg/day (4). The TDI is defined as the maximum daily intake of an undesirable toxic substance that would not lead to the development of adverse health effects with lifetime exposure. The TDI of dioxins was calculated on the basis of the following equation, using the lowest body burden of animals at which adverse developmental and/or reproductive effects have been observed (5,6), the biological half-life (7.5 years) and absorption rate (50%) of dioxins, and the safety factor of 10 (4).

Intake (ng/kg/day)=Body Burden (ng/kg) × (ln [2]/biological half-life)/(absorption rate)

At present, except in special populations with heavy exposure, the mean or median intake levels among the general populations of various countries are considered to be below the TDI, as discussed later. However, it is of concern to researchers whether there are subtle adverse health effects of PCDDs/PCDFs/PCBs among human populations even at background exposure levels. Here we review epidemiologic studies dealing with the dietary intake and the body burden of dioxin-related compounds and their potential adverse health effects, especially increased risk of diabetes mellitus or endometriosis, and alterations of thyroid function or the neurodevelopment of infants, at the current background exposure levels. Effects on cancer risk were excluded because the association may not be strong (standardized mortality ratio for all cancers combined=1.6) even among a population whose exposure level is two to three orders of magnitude higher than the general population (7).

Dietary intake of PCDDs/PCDFs/co-PCBs

Evaluation of dietary intake is crucial in the exposure assessment of dioxin-related compounds because more than 90% of exposure occurs via foods. Two methods have been used to estimate the dietary intake among populations, i.e., the market basket method and the duplicate portion analysis. In the former method, the dietary intake is estimated based on the dioxin content in various food samples (usually measured by high resolution gas chromatography/mass spectrometry [GC/MS]), and multiplied by the average or individual consumption of corresponding foods, which is derived from nutrition surveys. In the latter method, the respondents of the survey prepare two sets of identical meals, and one of them is directly analyzed for dioxin content.

Table 1 presents the mean or median dietary intake of PCDDs/PCDFs (8-19) and PCDDs/PCDFs/co-PCBs (14,16,17,20-26), expressed as pg TEQ/kg/day or pg TEQ/day, among adults, children and breast-fed infants in various countries. All studies but two (17, 25) were based on the market basket method. It should be pointed out that some researchers did not analyze all 29 congeners/isomers of PCDDs/PCDFs/co-PCBs for which TEF have been assigned. In addition, different (Nordic, International, WHO 1994, 1998) TEFs and body weights were used to calculate dioxin intake. Despite these methodological differences, except in one Spanish study with high PCDDs/PCDFs intake (19), the mean or median intake of dioxins among adults of most countries ranged from 0.33 to 3.57 pg TEQ/kg/day, which is lower than the maximum TDI set by the WHO in 1998 (4 pg TEQ/kg/day) (4).

It has been reported that in most Western countries, dioxin intake originated from various foods, such as meat, meat products, milk, dairy products and fish, whereas in Japan, Finland and Norway, the dioxin intake, especially co-PCBs, was predominantly derived from fish and fish products (16, 23). Although Japanese people consume large amounts of fish, the dietary intake of dioxins seems not to be higher than in Western countries (Table 1).

One problem that should be addressed is that the distribution (variance or standard deviation) of dioxin intake remains unknown, or reflected only that of the short-term intake in most previous reports. Usually, the short-term intake exhibits larger variance than the long-term intake because it contains not only between-subject variation but also within-subject variation (27). Therefore, use of short-term intake may lead to over-estimation of the proportion of subjects whose dioxin exposure is higher than the TDI. In one study (24), however, the 95th percentile of the dioxin intake was estimated at 2.0 pg TEQ/kg/day by using repeated measurements on the same individuals and statistically accounting for the within-person variance. Such an approach may be useful for clarifying the distribution

Table 1. Estimated mean dietary intake of dioxin-related compounds in adults, children and breast-fed babies in various countries

Country	pg TEQ/kg/day	pg TEQ/day	Year of survey	References
PCDDs+PCDFs				
US	0.52-2.57		1995	Shecter, *et al*.(1996)
Germany	1.3	93.5		Beck, *et al*.(1989)
Germany	2 (breast-fed infants 149)			Beck, *et al*.(1992)
Germany	1.2	85	1984-88	Furst, *et al*.(1990)
Germany	0.88		1993-1996	Rainer, *et al*.(1998)
Germany	1.60 (children 14-47 mo. old)		1998	Wittsiepe, *et al*.(2000)
New Zealand	0.18-0.44	14.5-30.6		Buckland, *et al*.(1998)
Venetia		42	1994-1996	Zanotto, *et al*.(1999)
Japan	0.89	44.69	1999-2000	Tsutsumi, *et al*.(2001)
Japan	0.47		2002	Ministry of Environment (2003)
Belgium	1.00	65.3	2000-2001	Focant, *et al*.(2002)
Spain		210	1996	Domingo, *et al*.(1999)
Spain		63.8	2002	Bocio, *et al*.(2005)
PCDDs+PCDFs+PCBs				
Netherlands	1(median), 2(95 percentile)		1987-88	Theelen, *et al*.(1993)
UK	(breast-fed infants 26-110)	140	1992	Wearne, *et al* (1996)
UK	2.4(breast-fed infants 39-170)		1992	Harrison, *et al*.(1998)
US	1.16-3.57		1995	Shecter, *et al* (1996)
US	2.2-2.4(breast-fed infants 42)		1995	Shecter, *et al* (2001)
Norway		137-190	1992-194	Becher, *et al*.(1998)
New Zealand	0.33-0.76			Buckland, *et al*.(1998)
Japan	2.25	112.61	1999-2000	Tsutsumi, *et al*.(2001)
Japan	1.3		2002	Ministry of Environment (2003)
Belgium	2.04	132.9	2000-2001	Focant, *et al*.(2002)
Netherlands	1.2(median), 1.9(90 percentile)		1998-99	Barrs, *et al*.(2004)

* Duplicate portion analysis. All other studies are based on the market basket method.

of the long-term intake, which is necessary for risk assessment of dioxins.

In contrast to adults, breast-fed babies have an extremely high dioxin intake. Based on the dioxin content in breast milk and the volume of milk consumed daily, the dioxin intake among breast-fed babies was estimated at 26-170 pg TEQ/kg/day (11, 20-22), which is much higher than the TDI. However, currently it is not recommended to refrain from breast-feeding, considering the relatively short duration of exposure and the overall merits of breast-feeding, such as immunologic protection, nutrition and mother-to-infant bonding. Several researchers reported that after the 1970s-1980's the content of PCDDs/PCDFs/PCBs in breast milk sharply declined in developed countries (28,29).

Blood levels of PCDDs/PCDFs/co-PCBs and related factors

The body burden of dioxins can be assessed by measuring dioxin levels in blood lipid. However, the relationship of the blood levels with the total body burden and the concentrations in various organs may be influenced by factors such as the presence of severe weight loss (28) and hyperlipidemia, and percent body fat. Table 2 presents the mean or median dioxin concentrations in the blood among populations with no known accidental or occupational exposure (17, 30-39). Within the same population, the arithmetic mean is usually higher than the median, since the distribution of the blood levels of dioxins is positively skewed. As was the case for dietary intake, some reports did not analyze all 29 congeners/isomers of PCDDs/PCDFs/co-PCBs with known TEFs, and not all studies used the same TEFs. The mean or median blood levels of PCDDs/PCDFs ranged from 9.8 to 40.8 pg TEQ/g lipid, and the mean or median blood contents of PCDDs/PCDFs/co-PCBs ranged from 16 to 43.8 pg TEQ/g lipid, with co-PCBs accounting for approximately 40% of the total TEQs.

Several researchers investigated the factors associated with the blood levels of dioxins. In general, blood concentrations of dioxins increase with age (28,32,38,40). Serum levels of triglyceride were positively correlated with levels of dioxins in the blood not only in heavily exposed populations (41,42) but also in the general population, even when expressed as pg TEQ/g lipid (38), which suggests that dioxins are more concentrated in triglyceride than other fractions of blood lipid. In Japan, serum levels of ω-3 polyunsaturated fatty acids (eicosapentaenoic acid and docosahexaenoic acid), a biomarker of fish intake, and intake frequency of raw fish were reported to be positively

Table 2.   Blood levels of dioxin-related compounds (pg TEQ/g lipid) in general populations of various countries

Country	No. of subjects	Mean or median	Range	Year of survey	References
PCDDs+PCDFs					
Canada	pooled sample	14.6(mean)		1992	Ayotte et al.(1997)
Canada	30	20.6(mean)		1994	Ryan et al.(1997)
Germany	139	16.1(mean)		1996	Papke et al.(1998)
Germany	507	19.2-40.8(median)	6.1-113.6	1991-6	Wittsiepe et al.(2000)
Finland	45	32(median)	12.0-81.0	1998	Kiviranta et al.(2000)
Spain	28	27.6(mean)	13.4-84.0	1999	Domingo et al.(2001)
Japan	50	16.4(mean)		1993-4	Iida et al.(1999)
Japan	50	17.2-22.9(median)	10.9-48.7	1998	Kumagai et al.(2000,2002)
Japan	253	9.8(median)	0.91-33	1999	Arisawa et al.(2003)
Japan	8	20.2(mean)		2000	Tsuchiya et al.(2003)
Japan	259	14(median)	0.61-56	2002	Ministry of Environment(2003)
PCDDs+PCDFs+PCBs					
Canada	pooled sample	26.1(mean)		1992	Ayotte et al.(1997)
Canada	30	36.3(mean)		1994	Ryan et al.(1997)
Japan	39	21(mean)	9.1-37	1993-4	Iida et al.(1999)
Japan	253	16-17(median)	1.3-53	1999	Arisawa et al.(2003)
Japan	8	43.8(mean)		2000	Tsuchiya et al.(2003)
Japan	259	23(median)	1.6-110	2002	Ministry of Environment(2003)

associated with the total TEQs (38). In a Taiwanese population living in the vicinity of waste incinerators (mean PCDDs/PCDFs in blood=14-16 pg TEQ/g lipid), intake frequency of sea fish, sea food and canned fish over the previous 10 years was positively associated with higher blood levels of PCDDs/PCDFs (40). A survey conducted by the Japanese Ministry of the Environment (17) showed that median blood level of PCDDs/PCDFs/co-PCBs among persons living in dioxin-polluted areas in Osaka and Saitama Prefectures was 27 pg TEQ/g lipid, which was not significantly different from that of the control population (23 pg TEQ/g lipid), suggesting that the contribution of air/soil pollution to the total body burden of dioxins was small. Among women, a larger number of breast-fed children and longer duration of breast-feeding were associated with lower levels of PCDDs/PCDFs/co-PCBs in the blood (28). Regarding the host factors, single nucleotide polymorphism of the *CYP1A1* gene was not associated with total TEQs in blood (39). It has been reported that dioxin levels in blood have been gradually decreasing with time in developed countries (28,32).

The reference range or upper normal limit for the blood levels of dioxins has not been determined. One reason for this may be that the association between exposure to low levels of PCDDs/PCDFs/co-PCB and health effects has not been definitely established. Another approach may be to estimate these values on the basis of the statistical distribution. In Japan, the 95th percentile of the blood levels of dioxins was around 65 pg TEQ/g lipid (17).

Potential health effects associated with low levels of exposure to PCDDs/PCDFs/PCBs
Diabetes mellitus

The association between dioxins and diabetes was firstly reported for occupationally exposed populations and subsequently investigated in the general population. In a longitudinal study with more than 20 years of follow-up, Henriksen et al. (43) found that the risk of diabetes significantly increased, and time to diabetes onset significantly decreased, among U.S. Air Force veterans who had been heavily exposed to Agent Orange and its contaminant, 2,3,7,8-TCDD, during the Vietnam War (serum 2,3,7,8-TCDD=10-618 pg/g lipid). In a cross-sectional study on chemical workers heavily exposed to 2,4,5-trichlorophenol (2,4,5-T) (National Institute for Occupational Safety and Health [NIOSH] cohort), the prevalence of diabetes among the exposed group (N=280, mean serum 2,3,7,8-TCDD=220 pg/g lipid) was not significantly different from that of the control group (N=260, mean=7 pg/g lipid). However, six of 10 workers with the highest serum 2,3,7,8-TCDD levels (≧1500 pg/g lipid) had diabetes (44). In a study by Steenland et al.(45), in which the data from the U.S. Air Force veterans (43) and the NIOSH cohort (44) were re-analyzed, a dose-response relationship between serum dioxin and prevalence of diabetes was observed only for Air Force veterans.

Longnecker et al.(46) reported that there was a significant dose-response relationship between the serum level of 2,3,7,8-TCDD and the prevalence of diabetes among 1,197 Air Force veterans with no history of occupational dioxin exposure. The prevalence odds ratio of diabetes in the highest quartile

(5.2 pg/g lipid) was 1.71 (95%CI 1.00-2.91) as compared with the lowest quartile (2.8 pg/g lipid). However, after adjustment for serum triglycerides, a potential confounder, the odds ratio was attenuated to 1.56 (95%CI 0.91-2.67). The same research group also reported higher serum levels of PCBs among pregnant women with diabetes than among controls (47). However, because these two studies were cross-sectional, it remains unclear whether exposure to 2, 3, 7, 8-TCDD/PCBs increased the prevalence of diabetes, or diabetes altered the metabolism of 2, 3, 7, 8-TCDD/PCBs in the body. Considering all these findings taken together, it seems premature to conclude that exposure to background levels of dioxins increases the risk of diabetes. In the future, cohort studies of populations with background levels of exposure will be required.

Endometriosis

The association between exposure to dioxin-related compounds and endometriosis was firstly found in animal experiments, and subsequently investigated in highly exposed human populations, followed by general populations. Endometriosis is important in that this is one of the most sensitive adverse effects observed in animal experiments, and has been used as a basis for the calculation of TDI (4). In 1993, Rier *et al*. (5) reported that the incidence and the severity of endometriosis increased in a dose-dependent manner in rhesus monkeys fed a diet containing 5-25 ppt of 2, 3, 7, 8-TCDD for 4 years. An additional study conducted 13 years after the termination of exposure showed that serum levels of not only 2, 3, 7, 8-TCDD but also dioxin-like PCBs (International Union for Pure and Applied Chemistry [IUPAC] No. 77 and 126) were increased in TCDD-treated monkeys, especially among those with endometriosis, suggesting the involvement of dioxin-like PCBs in the development of the disease (48).

In Seveso, Italy, where heavy exposure to 2, 3, 7, 8-TCDD occurred because of an explosion at a chemical plant, a historical cohort study was carried out (49). Among 601 women, 19 cases of endometriosis were identified during 20 years of follow-up. The multivariate relative risks for women with 2, 3, 7, 8-TCDD levels of 100 ppt and 20.1-100 ppt were 2.1 (95%CI 0.5-8.0) and 1.2 (95%CI 0.3-4.5), respectively, as compared with women with =20 ppt. It was pointed out that non-differential misclassification of disease status, because of inability to perform laparoscopy for every woman, may have led to the underestimation of relative risks (49).

Several case-control studies have been performed on populations without accidental or occupational exposure. An Israeli study (50) reported that 2, 3, 7, 8-TCDD was detected in 8/44 (18%) of women with endometriosis, as compared with 1/35 (3%) of control women. The odds ratio associated with high blood 2, 3, 7, 8-TCDD levels was estimated at 7.6 (95%CI 0.87-169.7). However, the limitation of this study was that statistical power was lacking, and only 2, 3, 7, 8-TCDD but no other congeners/isomers were analyzed. In a Belgian study involving 42 cases and 27 controls with mechanical infertility (51), there were no significant differences in the blood levels of total TEQs, as determined by the chemical-activated luciferase gene expression (CALUX)-bioassay, or of one co-PCB (No. 118) or three non-coplanar PCBs (No. 138, 153 and 180). On the other hand, when a cut-off point of 100 pg-TEQ/g lipid was used, the odds ratio of endometriosis was elevated but not significantly (4.56; 95%CI 0.48-43.6). In a recent small case-control study (23 cases and 17 controls) performed in Belgium and Italy, there was no significant difference in the total TEQs in blood between cases and controls (52). Thus, at present it is not clear whether exposure to background levels of dioxins increases the risk of endometriosis. In the future, larger epidemiologic studies with sufficient statistical power will be required. For instance, if the true odds ratio is 2.3, an unmatched case-control study would require 99-282 women for both cases and controls, assuming that the prevalence of endometriosis among the source population is 10% and α and β are set to 0.05 (two-tailed) and 0.20, respectively (53).

Thyroid function

In animal experiments, exposure to PCDDs/PCDFs, and PCBs or their hydroxylated metabolites influences the hypothalamo-pituitary-thyroid axis by various mechanisms (54), although the direction of the effects may vary according to the animal species (55). In rats exposed to 2, 3, 7, 8-TCDD or PCBs, serum thyroxine (T4) decreased and secretion of thyroid stimulating hormone (TSH) from the pituitary increased. Exposure to 2, 3, 7, 8-TCDD or co-PCBs induced the enzyme T4-uridine diphosphoglucuronyl-transferase-1 (UDPGT-1) in the liver by an Ah-receptor-mediated mechanism and thereby increased hepatic glucuronidation and biliary excretion of T4 (56-58). It has also been shown that hydroxylated PCBs and PCDDs/PCDFs have higher affinity than T4 for the transthyretin (thyroxine-binding prealbumin), the major T4 transport protein in the plasma of rodents, which may lead to the inhibition of the T4 transportation to the brain (59). In fetal rats,

Table 3.   Effects of dioxin exposure on thyroid function in adults and infants

Population	No. of subjects	Mean exposure level (pg/g lipid)	T4	free T4	TSH	References
Adults						
BASF cohort (Germany)	138	1-553 (blood, 2,3,7,8-TCDD)				Ott, *et al*. (1994)
US (2,4,5-T exposed)	281	220 (blood, 2,3,7,8-TCDD)				Calvert, *et al*. (1999)
Yusho patients	16	222.4 (blood, TEQ)				Nagayama, *et al*. (2001)
US Air Force veterans	275	45.7 (blood, 2,3,7,8-TCDD)				Pavuk, *et al*. (2003)
Netherlands (pregnant women)	78	74.9 (milk, TEQ)				Koopman-Esseboom, *et al*. (1994)
Australia (2,4,5-T exposed)	37	2.6-8.1 (blood, 2,3,7,8-TCDD)				Johnson, *et al*. (2001)
Infants						
Netherlands (0-11 weeks)	15	37.5 (milk, TEQ)				Plium, *et al*. (1993)
Netherlands (2 weeks)	39	72.4 (milk, TEQ)				Koopman-Esseboom, *et al*. (1994)
Japan (1 year)	37	25.7 (milk, TEQ)				Nagayama, *et al*. (1996)
Japan (1 year)	337	13.1-29.5 (milk, TEQ)				Matsumura, *et al*. (2001)

range,   T4/TBG ratio.

T4 levels in the forebrain and cerebellum decreased following maternal exposure to PCBs, though T3 levels remained unchanged because of compensatory induction of type II 5'-deinodinase (60).

In humans, data about the association between exposure to dioxin-related compounds and thyroid function have been inconsistent for both adults and infants, though the blood levels of T4, free T4 and TSH are generally within the normal range even in heavily exposed subjects. Ott *et al*. (61) reported that serum T4 and thyroxine-binding globulin (TBG) levels significantly increased with increasing current TCDD concentrations in the blood among 138 members of the BASF cohort who had been heavily exposed to 2,4,5-T and 2,3,7,8-TCDD. Among 281 U.S. workers exposed to 2,4,5-T, there was also a significant increase in the free T4 index but no change in the serum TSH level (44). On the other hand, in 16 patients with Yusho, there was no association between total TEQ and serum concentrations of triiodothyronine (T3), T4, free T4 or TSH 27 years after the outbreak, despite extremely high TEQs in the blood (median=222.4 pg/g fat) (62). Pavuk *et al*. (63) reported that there was no difference in the serum T4 levels or T3% uptake between US Air Force veterans who had been heavily exposed to TCDD (median blood TEQ=45.7 pg/g fat) and control Air Force veterans. However, the serum levels of TSH were significantly higher in the exposed group.

In a Dutch study of pregnant women with no known accidental or occupational exposure (mean PCDDs/PCDFs/co-PCB TEQ in the breast milk=74.9 pg TEQ/g lipid), serum levels of T4 and T3 significantly decreased as the dioxin levels in the breast milk increased (64). In contrast, among Australian men exposed to very low levels of 2,4,5-T (mean serum 2,3,7,8-TCDD=2.6-8.1 ppt), serum levels of TSH (Spearman r=-0.4) but not T4 were significantly and negatively correlated

with TCDD (65).

In infants, two studies, one conducted in the Netherlands (at 2 weeks of age) (64) and the other in Japan (at 1 year of age) (66), found that decreased serum T4 levels were related to high TEQ levels in breast milk. In contrast, there were increased blood levels of total T4, T4/TBG ratio and TSH among infants (aged 11 weeks) with high PCDDs/PCDFs TEQs in another Dutch study (67). In another Japanese study, there were no differences in the blood levels of T4, T3, free T4 or TSH between breast-fed and bottle-fed infants aged 1 year (68). The reason for the discrepancy among these studies remains unknown; however, the decreased T4 and the increased TSH levels in the blood of infants reported by Koopmann-Esseboom *et al*. (64) were consistent with those of experimental studies on rats (56,57). Since thyroid hormones are essential for normal brain development during fetal and neonatal periods, some researchers proposed the decreased serum T4 levels observed among pregnant women (64) and infants (64,66) as one of the possible mechanisms linking exposure to PCBs/dioxins and impaired neurodevelopment of children, as discussed below.

Neurodevelopment of infants

The association between exposure to PCDDs/PCDFs/PCBs and neurodevelopment of infants has been reported mainly in relation to non-dioxin-like PCBs (69). An impairment of neuropsychological development was reported among Taiwanese children born to mothers who had been accidentally exposed to high levels of PCBs and other thermally degraded substances, including PCDFs, through contaminated rice oil (70). Animal experiments also showed that PCBs have direct toxic effects on neurotransmission and neural network formation that are not mediated

Table 4.   Effects on growth and neurodevelopment associated with exposure to PCBs and/or PCDDs/PCDFs/co-PCBs

Cohort	No. of subjects	Age	Exposure variables	Effects	References
North Carolina	912	0 m	Prenatal total PCBs exposure (Breast milk(0 w) total PCBs)	Birth weight Head circumference NBAS tonicity NBAS reflexes	Rogan, *et al.*(1986)
	802	6 m 12 m	Prenatal total PCBs exposure	Bayley Scales psychomotor Bayley Scales psychomotor	Gladen, *et al.*(1988)
	676	18 m	Prenatal total PCBs exposure	Bayley Scales mental Bayley Scales psychomotor	Rogan, *et al.*(1991)
	670	24 m	Prenatal total PCBs exposure	Bayley Scales mental Bayley Scales psychomotor	
Netherlands	207	0 m 0-3 m 3-42 m	Cord PCBs, maternal PCBs Cord PCBs, maternal PCBs Cord PCBs, maternal PCBs	birth weight growth rate growth rate	Patandin, *et al.*(1998)
	209	0 m	Breast milk PCBs(2 w) Breast milk total TEQ(2 w)	Prechtl neurological optimality score (hypotonic)	Huisman, *et al.*(1995a)
	207	3 m 7 m 18 m	Maternal plasma PCBs Breast milk total PCBs-dioxins TEQ (postnatal exposure) Perinatal PCBs, total TEQs Postnatal PCBs, total TEQs	Bayley Scales psychomotor Bayley Scales psychomotor Bayley Scales mental, psychomotor Bayley Scales mental, psychomotor	Koopman -Esseboom, *et al.*(1996)
	418	18 m	Cord PCBs, maternal PCBs	Prechtl Neurological Optimality score	Huisman, *et al.*(1995b)
	395	42 m	Maternal plasma PCBs	Kaufman Assessment Battery for Children Overall cognitive Sequential Simultaneous	Patandin, *et al.*(1999)
	394	42 m	Maternal plasma PCBs Cord plasma PCBs 42 mo. plasma PCBs	Towen/Hampel Neurological condition	Lanting, *et al.*(1999)
Germany	171	7 m	Breast milk(2,4 w) PCB 138,153,180	Bayley Scales mental motor Fagan visual recognition memory	Winneke, *et al.*(1998)
	171	30 m 42 m	Breast milk(2 w) PCB 138,153,180 (prenatal exposure) Breast milk(2w) PCB 138,153,180 Milk PCBs x duration of breast-feeding 42 mo. plasma PCBs	Bayley Scales mental Bayley Scales motor Kaufman mental development Kaufman mental development Kaufman mental development	Walcowiak, *et al.*(2000)

by Ah-R (71). Cohort studies have also been conducted on children born to mothers who had consumed PCBs-contaminated fishes from Lake Michigan (72) and Lake Ontario (73), and contaminated whale meat and blubber from the Faroe Islands (74). However, these studies on accidental (70) or environmental exposure (72-74) were excluded from this review because the exposure levels of PCBs in such studies may be higher than the levels in the general population.

Several longitudinal studies in the U.S.(75-78), the Netherlands (79-84) and Germany (85,86) investigated the effects of background exposure to PCBs or dioxins on mental and psychomotor development of infants (Table 4). In North Carolina, U.S., approximately 900 pairs of mothers and infants were initially enrolled, and total PCBs in breast milk (0 week) was measured

as an index of prenatal exposure. The median total PCB concentration in the breast milk at birth was reported to be 1,770 ng/g lipid (75). However, this value may be overestimated because of the old analytical method used (69). No PCDDs/PCDFs congeners/isomers in breast milk were analyzed. There was no association between prenatal PCBs exposure and weight or head circumference at birth. However, high exposure was associated with hypotonicity and hyporeflexia, as assessed by the Neonatal Behavioral Assessment Scale (NBAS)(76). The Bayley Psychomotor Scales were decreased at 6, 12 and 24 months in relation to high transplacental exposure, but not postnatal exposure through breast milk (77,78). No effects on mental development were observed.

In the Netherlands cohort, approximately 400 mother-

infant pairs, 200 each in Groningen and Rotterdam, were enrolled (79). Umbilical cord plasma and maternal plasma PCBs (No. 118, 138, 153 and 180) were measured as an index of prenatal exposure, and PCDDs/PCDFs/PCBs content in breast milk (at 2 weeks) multiplied by the number of weeks of breast-feeding was used as an index of lactational exposure to these substances. The median total PCBs concentration in cord plasma, maternal plasma and breast milk was $0.40\mu g/l$, $2.04\mu g/l$ and $391.5 ng/g$ lipid, respectively, and the median total PCDDs/PCDFs/co-PCBs in breast milk was $64.8 pg$ TEQ/g lipid. Prenatal PCBs exposure was inversely associated with birth weight and growth rate during 0-3 months (change in weight, length and head circumference) (79). There were also negative effects on motor and cognitive development, as assessed by Bayley Psychomotor Scales at 3 and 7 months (80) and Kaufman Assessment Battery for Children at 42 months (81), respectively, mainly in relation to prenatal PCBs and partly in relation to postnatal PCDDs/PCDFs/co-PCBs exposure. On the other hand, breast-feeding itself had a positive effect on the Bayley Psychomotor Scales at 7 months. The Prechtl Neurological Optimality Score at 0 month decreased as the combined pre-and early neonatal exposure (both dioxin-like and non-dioxin-like PCBs, and PCDDs/PCDFs/co-PCBs-TEQ in breast milk at 2 weeks) increased (82). The same score at 18 months decreased as the prenatal PCBs exposure (cord and maternal PCBs) increased (83). At 42 months, there was no significant association between PCBs or PCDDs/PCDFs/co-PCBs exposure and neurological condition as assessed by the Towen/Hempel method (84). There was no significant relationship between the serum thyroid hormone levels and the mental or psychomotor development at any age (80).

In Dusseldorf, Germany, 171 healthy mother-infant pairs were initially recruited (85). The sum of the levels of three non-dioxin-like PCBs (No. 138, 153 and 180) in breast milk (at 2 weeks) were used as an index of prenatal exposure, and milk PCBs multiplied by duration of breast-feeding and plasma levels of PCBs in infants were used as an index of postnatal exposure. The median total PCBs concentration in cord plasma and breast milk was $0.39\mu g/l$ and $404 ng/g$ lipid, respectively. No PCDDs/PCDFs concentrations in cord plasma or breast milk were analyzed. A negative association was observed between prenatal exposure and neurodevelopment, as assessed by the Bayley Mental/Motor Scales of Infant Development at 30 months and the Kaufman Assessment Battery for Children (simultaneous and sequential information

processing) at 42 months, after adjustment for various potential confounders, including smoking, alcohol drinking and parental education (86). There was also an inverse association between postnatal PCBs exposure and Kaufman Assessment Battery for Children at 42 months. On the other hand, a good home environment compensated for the adverse effects of PCBs exposure.

In summary, inhibitory effects on motor and mental development of infants have been observed in relation to background exposure to PCBs/dioxins, especially trans-placental PCBs, although there are some inconsistencies in the exposure media and outcome variables. The lack of significant association between serum thyroid hormone levels and mental/motor development (80) suggests the involvement of non-thyroid-mediated mechanisms. At all events, efforts should be made to further decrease exposure levels among women of reproductive age as much as possible, by reducing the release of PCDDs/ PCDFs/ PCBs into the environment. In the future, longitudinal studies of the neurodevelopment of infants should be performed on fish-eating populations such as the Japanese, because fish is a major source of exposure to dioxin-like and non-dioxin-like PCBs.

ACKNOWLEDGEMENTS

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