Chapter 4

Neurological condition in 18-month-old children perinatally exposed to polychlorinated biphenyls and dioxins

M. Huisman, C. Koopman-Esseboom, C.I. Lanting, C.G. van der Paauw, L.G.M.Th. Tuinstra, V. Fidler, N. Weisglas-Kuperus, P.J.J. Sauer, E.R. Boersma, B.C.L. Touwen. Early Human Development 1995;43:165-176.

Abstract

The neurological optimality of 418 Dutch children was evaluated at the age of 18 months, in order to determine whether prenatal and breast milk mediated exposure to polychlorinated biphenyls (PCBs) and dioxins affected neurological development. Half of the infants were breast-fed, the other half were formula-fed. PCB concentrations in cord and maternal plasma were used as a measure of prenatal exposure to PCBs. To measure postnatal exposure, PCB and dioxin congeners were determined in human milk and in formula milk.

After adjusting for covariates, transplacental PCB exposure was negatively related to the neurological condition at 18 months. Although greater amounts of PCBs and dioxins are transferred via nursing than via placental passage, an effect of lactational exposure to PCBs and dioxins could not be detected. We even found a beneficial effect of breast-feeding on the fluency of movements.

We conclude that transplacental PCB passage has a small negative effect on the neurological condition in 18-month-old toddlers.

Introduction

Polychlorinated biphenyls (PCBs) and dioxins are widespread toxic environmental pollutants. Until the late-1970s, PCBs were produced for use as fire retardants, plasticizers, dielectric fluids in capacitors and transformers, and hydraulic fluids. There is a total number of 209 possible PCB congeners, which all differ in their degree of chlorination and the position of the chlorine atom. PCBs can be divided into planar and non-planar PCBs. The planar PCBs resemble the dioxins to the largest extent. Dioxins are unwanted byproducts of thermal and industrial processes, consisting of 75 possible polychlorinated dibenzo-*p*-dioxin congeners and 135 possible polychlorinated dibenzofuran congeners. Due to a high persistency, they can be detected in food products of animal origin, human adipose tissue and blood [1]. Once entered into the food-chain,

these lipophilic compounds are bioconcentrated exposing human beings who continuously absorb very small doses. Substantially greater amounts of PCBs are transferred via nursing than as a result of placental passage in both animals [2,3] and humans [4,5]. Infant formulae contain only lipids of a vegetable origin with a negligible content of PCBs and dioxins. Since breast-fed children receive considerably more of these compounds compared to those formula-fed, controversy exists over whether breast-feeding should be encouraged.

Rogan *et al.* showed that higher levels of transplacental exposure to PCBs were associated with hypotonicity and hyporeflexia in neonates [6]. We partly confirmed these results in our study concerning neonates. The combination of a high prenatal and a high lactational exposure during the first 2 weeks after birth was associated with an increase in the prevalence of neonatal neurological non-optimality and a higher incidence of hypotonia [5].

So far, the effects of PCB exposure have been evaluated as regards mental and psychomotor development [7]. We now report on the relationship between prenatal exposure to PCBs and lactational exposure to PCBs and di xins and the neurological condition at 18 months.

Subjects and Methods

From June 1990 until June 1992, pregnant women were recruited for the study in Groningen and Rotterdam. The planned sample size was 100 breast-feeding and 100 formula-feeding mothers in each centre. The women were approached between the 32nd and 34th week of pregnancy and provisionally assigned, on the basis of their intention, to the formula-feeding or the breast-feeding group. Women suffering from serious illnesses or complications during pregnancy and delivery were excluded, as were mothers having an instrumental delivery. From the provisional breast-feeding group, only the mothers were included in the study who breast-fed their infants for at least 6 weeks. Formula milk from a single batch (Almiron M2; Nutricia N.V., The Netherlands) was used in the formula-feeding group. Approval was obtained from the ethics committees of the University Hospitals in both centres.

Social, obstetrical, and perinatal circumstances were recorded by means of a questionnaire with 72 representative items. The number of items that fulfilled predefined optimality criteria [8] was used as an obstetrical optimality score [9]. All newborns underwent a neurological examination according to Prechtl [10].

A maternal blood sample was taken in the last month of pregnancy and cord blood was collected immediately after birth. Plasma samples were analyzed for four non-planar PCB congeners 118, 138, 153, and 180 only. Plasma has a relatively low fat content compared to human milk and a too large volume of blood would be needed to measure all the PCB and dioxin congeners, such as were analyzed in human milk. The

sum of the concentrations of the four PCB congeners 118, 138, 153, and 180 in plasma (i.e. $\Sigma PCB_{maternal}$ and ΣPCB_{cord}, respectively) was used as a measure of prenatal exposure to PCBs. Postnatal exposure to PCBs and dioxins via breast milk was reflected by the levels of these compounds in a 24-h sample taken in the second week after delivery. Contents of 17 2,3,7,8-substituted polychlorinated dibenzo-*p*-dioxins and dibenzofurans, three planar PCBs, and 23 non-planar PCB congeners were determined in breast milk fat as well as in the formula milk fat. In order to express the toxicity of the mixture of compounds in breast milk and in the artificial feeding, the toxic equivalency approach was used [11]. With this approach, the relative toxicity (TEQ) of each congener towards the most toxic dioxin congener was calculated. By adding up the TEQs of all congeners, the total TEQ value was obtained (in ng TEQ/kg milk fat). The sampling, analytical, and data processing procedures have previously been described [5].

At 18 months of age, the neurological condition was assessed using an age-specific neurological examination [12]. This technique focuses on the observation of motor functions (grasping, sitting, crawling, standing, and walking) in a standardized free field situation [13,14]. On the basis of this examination each toddler was classified as normal, mildly abnormal, or abnormal. The classification 'abnormal' implies the presence of an overt circumscript neurological syndrome, which usually leads to a handicap in daily life, such as cerebral palsy. 'Mildly abnormal' signifies the presence of mild signs which do not necessarily lead to a handicapping condition, e.g. slight asymmetries, or mild hypo-, and hypertonia. The neurological findings were also evaluated in terms of optimality [8]. A list of 57 neurological items was composed, for each of which an optimal range was defined (Appendix). By giving a point for each item meeting the criteria for optimality, the neurological optimality score was calculated by counting the number of optimal items. It must be emphasized that optimality is not identical with normality, and that a reduced optimality not always mean abnormal [8]. Special attention was given to the quality of movements in terms of fluency. Fluency of motility has been shown to be an indicator for the integrity of brain function in fetuses and prematures [15,16]. The quality of movements during prehension, sitting, crawling, standing, and walking was scored separately as a fluency cluster (Appendix). The neurological examinations were carried out in Groningen by M.H. and in Rotterdam by C.K E. after extensive training. The examiners were aware of the feeding status but not of the results of the chemical analyses of the plasma and milk samples.

Chi-square, Student's *t*-test, and the Mann-Whitney *U*-test were used to compare groups. The effect of PCB and dioxin exposure on the neurological condition was investigated by a multiple linear regression analysis. The dependent variables were the neurological optimality score and the fluency cluster score at 18 months. The distribution of the neurological optimality score was skew to the left. The highest possible score is 57. In order to achieve normality, the neurological optimality score was transformed into: $-log(57.5 - \textit{the neurological optimality score})$. The independent varia-

Table I
Characteristics of the study group.

Variable	Breast-fed	Formula-fed
Number of children	209	209
Neonatal neurological diagnosis		
normal	197 (94%)	197 (94%)
mildly abnormal	10 (5%)	10 (5%)
abnormal	2 (1%)	2 (1%)
Neurological diagnosis at 18 months		
normal	205 (98%)	203 (97%)
mildly abnormal	3 (1%)	6 (3%)
abnormal	1 (1%)	0 (0%)
Neurological optimality score at 18 months		
P_5, P_{50}, P_{95}	41, 48, 53*	40, 47, 52
Fluency cluster score		
mean ± SD	10.2 ± 1.6*	9.5 ± 1.7
PCB/dioxin exposure†		
P_5, P_{50}, P_{95}		
ΣPCB_{cord} in μg/L	0.20, 0.43, 0.99*	0.16, 0.34, 0.80
$\Sigma PCB_{maternal}$ in μg/L	1.1, 2.2, 4.0*	0.95, 1.9, 3.6
TEQ_{PCB} in ng TEQ/kg milk fat	17, 33, 61*	below detection limit
TEQ_{dioxin} in ng TEQ/kg milk fat	15, 29, 52*	below detection limit
Education		
mother, higher education‡	132 (63%)*	50 (24%)
father, higher education	130 (62%)*	64 (31%)
Duration of exclusive breast-feeding (weeks)		
P_5, P_{50}, P_{95}	6, 13, 31	0
Parity		
first-born	107 (51%)	94 (45%)
Gender		
male	118 (57%)	107 (51%)
Obstetrical optimality score		
P_5, P_{50}, P_{95}	59, 65, 69*	57, 64, 68
Birth weight (kg)		
mean ± SD	3.54 ± 0.46	3.49 ± 0.43
Maternal weight (kg)		
mean ± SD	64 ± 9	66 ± 11
Smoking		
mother, no smoking during pregnancy	175 (84%)*	135 (65%)
father, no smoking during pregnancy	126 (60%)	117 (56%)
Alcohol consumption during pregnancy		
mother, no alcohol consumption	131 (63%)*	171 (82%)

† ΣPCB: sum of the levels of PCB 118, 138, 153, 180; TEQ_{PCB}: toxic equivalent for planar, mono-ortho, and di-ortho PCBs; TEQ_{dioxin}: toxic equivalent for dioxins; ‡ Higher level secondary school or professional/university training.
* Significantly different from the formula-fed group ($P \leq 0.05$).

bles in the regression analysis were the logarithmically transformed PCB and dioxin levels, social, perinatal and obstetrical variables from the obstetric optimality list, and the study centre. A *P*-value of 0.05 or less was considered significant.

Results

The study group consisted of 418 mother-infant pairs: 209 in the breast-feeding group and 209 in the formula-feeding group. On the basis of the neurological examination, 408 toddlers were classified as neurologically 'normal'. Nine children were categorized as 'mildly abnormal': mild hypertonia was found in six toddlers, one child showed non-fluent movements in several positions, one toddler had a poor variability of the motor functional repertoire, and in one case instability for the behavioural states was found during two independent sessions. One toddler had a hypertonic syndrome which was diagnosed as 'abnormal'. In the normal group, the median neurological optimality score was 48 (range: 34-55), whereas in the group classified as mildly abnormal or abnormal the median was found to be 42 (range: 38-45). Characteristics of the study group are presented in Table I. Three maternal blood samples were missing. No cord blood samples could be obtained from 36 mother-infant pairs. For the analysis of PCB 118 in cord plasma, nine samples were missing. In human milk, representative dioxin, planar and non-planar PCB congeners were available in 176, 194 and 195 milk samples, respectively.

Table II presents the results of the regression analysis for the neurological optimality score. Neither PCB nor dioxin exposure via breast milk were associated with the neurological optimality score. The final model included education of the father, parity, study centre, and smoking of the father during pregnancy, and ΣPCB_{cord}. The first three variables had about the same effect (regression coefficients $\beta \approx 0.15$). The children of less educated fathers scored lower than the children of well educated fathers; the first-born children had a higher score than the second- or third-born children. The model also included a significant ($P=0.011$) interaction between ΣPCB_{cord} and smoking of the father. To facilitate the interpretation of regression coefficients, we worked with $\log(\Sigma PCB_{cord})$ minus its minimal value log(0.08). With this definition, the regression coefficient of smoking of the father ($\beta=-0.402$, $P=0.002$) estimates the effect of smoking at the lowest ΣPCB_{cord} exposure. Similarly, the coefficient for ΣPCB_{cord} estimates the effect of ΣPCB_{cord} in the non-smoking-father group. This effect was negative ($\beta=-0.149$, $P=0.003$), in contrast to hardly any effect in the smoking-father group ($\beta=-0.051$, $P=0.404$). The children of non-smoking fathers had the highest adjusted neurological optimality score in the presence of a low ΣPCB_{cord} value. In case of a high ΣPCB_{cord} value, the optimality score was similar to that of children of smoking fathers. Nearly the same results are obtained if ΣPCB_{cord} is replaced by $\Sigma PCB_{maternal}$.

Table II
Regression analysis: neurological optimality score*.

Variable	Regression coefficient (standard error)	*P*-value (two-tailed)
Constant	−2.039 (0.094)	
Education of the father (0=low, 1=high)	0.135 (0.046)	0.004
Parity (0=first, 1=not first-born)	−0.159 (0.038)	0.000
Study centre (0=Groningen, 1=Rotterdam)	0.135 (0.038)	0.000
$Log(\Sigma PCB_{cord}/0.08)$	−0.149 (0.049)	0.003
Smoking of the father (0=no, 1=yes)	−0.402 (0.130)	0.002
$Log(\Sigma PCB_{cord}/0.08)$ x Smoking of the father	0.200 (0.078)	0.011

* transformation neurological optimality score into: −log(57.5 − neurological optimality score).
n=373, R^2 = 0.14

Table III
Regression analysis: fluency cluster score.

Variable	Regression coefficient (standard error)	*P*-value (two-tailed)
Constant	8.539 (0.356)	
Type of feeding (0=breast-feeding, 1=formula-feeding)	−0.450 (0.177)	0.012
$Log(\Sigma PCB_{cord})$	−0.295 (0.175)	0.093
Parity (0=first, 1=not first-born)	−0.394 (0.168)	0.020
Education of the father (0=low, 1=high)	1.352 (0.293)	0.000
Study centre (0=Groningen, 1=Rotterdam)	1.628 (0.336)	0.000
Education of the father x Study centre	−1.072 (0.388)	0.006

n=373, R^2 = 0.15

The size of the estimated prenatal PCB effect on the neurological optimality score is elucidated in the following example. A first-born toddler living in Groningen with a highly educated non-smoking father has an estimated neurological optimality score of 49.9 in case of a ΣPCB_{cord} value at the 5th percentile (i.e. 0.18) and a score of 47.9 in case of a ΣPCB_{cord} value at the 95th percentile (i.e. 0.86). Thus, the difference is only two points.

The fluency cluster score was neither related to the ΣPCB_{cord} and $\Sigma PCB_{maternal}$ concentrations nor to the PCB and dioxin levels in breast milk. Breast-fed children had a higher fluency cluster score compared to formula-fed children ($P=0.01$; Table III).

Discussion

Prenatal PCB exposure had a small negative effect on the neurological condition of 18 month-old toddlers whose fathers did not smoke. Such an effect seemed to be blurred in children of fathers who smoked. No effect of lactational exposure to PCBs and dioxins through breast milk on the neurological condition could be detected. In contrast, breast-fed children had a higher fluency cluster score compared to formula-fed children.

A negative effect of prenatal PCB exposure on psychomotor development was found by Rogan and Gladen [7,17] in North Carolina. They followed 802 children from birth through to 5 years of age by means of the Bayley - and McCarthy Scales. At 6, 12, 18, and 24 months of age, a significant relation between prenatal PCB exposure and a lower psychomotor performance was found, but at 3, 4, and 5 years of age, no effect of prenatal PCB exposure could be detected. PCB exposure via breast milk had no influence. Levels of PCB exposure in the USA are comparable to those in the Netherlands. It is important to realize that developmental tests and the developmental neurological examination measure different aspects of brain function. The Bayley - and the McCarthy Scales measure developmental levels at different ages quantitatively. The developmental neurological examination gives a qualitative appraisal of brain integrity, in which developmental age levels are unimportant.

In our study of newborns, we found that the combination of a high prenatal and high lactational exposure to PCBs and dioxins during the first 2 weeks after birth was associated with an increase in the prevalence of neurological non-optimality [5]. At 18 months, neurological differences could only be attributed to prenatal PCB exposure. It is difficult to relate the functions of the central nervous system in the neonatal period directly with those at 18 months, as they are generated by quite different brains. From the early stages of pregnancy until many years after birth, large morphological changes take place in the central nervous system, such as outgrowth and retraction of dendrites and axones, myelination, and synapse reorganisation. The effects of these maturational changes are reflected in the functional development of the child.

A possible explanation for the role of smoking of the father on the neurological condition at 18 months is a passive smoking effect. We prefer, however, to view this variable as a proxy variable of characteristics of the relevant environment. Smoking behaviour of the mother was not significantly related to the neurological optimality score, but we recorded the smoking behaviour of the mother only during pregnancy. It is possible that mothers temporarily stop smoking because of their pregnancy, whereas it is far less likely that fathers do.

The difference between the two study centres is probably due to difference between the two observers. We also found differences between the two centres/observers in our study of neonates [5]. The regression analysis adjusts for these effects. Nevertheless, the issue of the reliability of methods of assessment of neurological condition in healthy young children needs further attention.

The neurochemical mechanisms responsible for the neurotoxic effects of PCBs are not well understood. In animals, PCBs and dioxins have been found to affect dopamine [18-20] and thyroid hormonal metabolism [21,22]. In a subgroup of this study [23] and in another study concerning neonates [24], thyroid hormone status was not related to the neonatal neurological status [25,26].

An effect of lactational exposure to PCBs and dioxins could not be detected at 18 months. Despite the fact that greater amounts of PCBs and dioxins are transferred via nursing than via placental passage, we found indications of a beneficial effect of breast-feeding. These results support the findings of Rogan and Gladen [27], who reported that cognitive development in breast-fed children from 2 through to 5 years of age was slightly better than in formula-fed children. In the present study, a beneficial effect was found on the fluency of complex movement patterns. The fluency of movements is an indication of the quality of brain function rather than of the level of development. This aspect of the quality of movements can be regarded as a reflection of the differentiation of cortex and basal ganglia function; cortical networks develop largely after birth, and also during the period of lactation.

Advantageous effects of breast-feeding on brain development are well documented [28-30], but the mechanism behind such beneficial effects remains unclear. Besides the socio-behavioural aspect of breast-feeding, the composition of human milk might be responsible. Maternal hormones like the thyroid stimulating hormone and other biological active peptides reach the infant via breast milk. Long-chain polyunsaturated fatty acids seem to be essential for development of the brain [31-33]. They are present in breast milk, but are not in general added to term-infant formula milks.

In conclusion, transplacental PCB exposure is negatively related to the neurological condition in children at 18 months. No effect of postnatal exposure to PCBs and dioxins via breast milk could be detected. Despite the contamination of human milk with PCBs and dioxins, a beneficial effect of breast-feeding on the fluency of movements was found. This effect on the quality of brain function during development has not been reported before.

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Appendix

Criteria for the 57 items of the neurological optimality score at 18 months.

Item	Criteria for optimality
Prehension	
1. mode of grasping	pincer grasp present in left and right hand
2. posture arm/shoulder	normal, variable posture
3. quality of arm/shoulder movements*	smooth
4. posture hands/fingers	normal, variable posture
5. adjustment hand-opening	good
6. associated movements (hindering)	absent or if present they do not hinder
7. quality of hand mobility*	smooth
Sitting	
8. sitting (up)	can sit (up) without help
9. posture head/trunk/legs/feet/toes	normal, variable posture (head: centred and well-adapted posture)
10. trunk rotation, spontaneous*	trunk rotation present
11. trunk rotation, elicited*	trunk rotation >45°
12. fluency of trunk movements*	smooth
13. acceleration/deceleration*	smooth
Crawling	
14. symmetry of movements*	no asymmetry
15. posture head	centred and well-adapted
16. coordination of arm-leg movements	coordinated arm-leg movements
17. variability in speed	variable speed
18. fluency of trunk movements*	non-fluent/smooth
Standing	
19. standing up/free	can stand up without help with object in both hands/stands free
20. variability in standing up	various ways of standing up
21. posture head/arms/trunk/legs posture feet/toes	normal, variable and well-adapted
22. distance between feet	medium
23. balance without movements	no correction movements visible
24. balance with movements	no or small correction movements in the arms
25. trunk rotation, spontaneous*	trunk rotation present
26. trunk rotation, elicited	trunk rotation present
27. fluency of trunk movements*	non-fluent/smooth
28. reaction to push against shoulders	good balance

Walking		
29.	ability to walk	able to walk without help
30.	fluency of trunk movements*	non-fluent/smooth
31.	fluency of leg movements	non-fluent/smooth
32.	reciprocal arm swing*	present
33.	posture head/arms/trunk/legs/feet/toes	normal, variable and well-adapted posture
34.	gait width	medium
35.	balance during walking	good balance, no correction movements needed
36.	abduction shoulders	no abduction of the shoulders
37.	walking on tiptoe*	no walking on tiptoe involuntarily
38.	variability of speed	variable speed
39.	manoeuvrability	changing direction in wide and sharp turns
40.	ability to avoid objects	avoids obstacles adequately or steps on objects sometimes
Head		
41.	eyes, position	symmetrical and centred position
42.	eyes, movements	smooth, symmetrical movements
43.	nystagmus (spont./direct)	no nystagmoid movements
44.	optokinetic nystagmus	symmetrical present horizontally and vertically
45.	pupils size and shape/reaction to light, (in)direct	round, medium sized pupils/immediate reaction
46.	visual fields	visual fields apparently intact
47.	visual acuity	visual acuity apparently intact
48.	hearing acuity	quick and adequate reaction to sounds
49.	facial expression/symmetry	normal alert and symmetrical facial mobility
50.	drooling, continuous	absent
51.	speech/language	normal, age-adequate speech and language development
Manipulative examination		
52.	resistance against passive movements	moderate resistance
53.	active muscle power	adequate for age
54.	range of movements	medium range
55.	tendon reflexes	normal intensity
56.	reflex thresholds	medium threshold
57.	footsole response	no movements or plantar flexion of big toe

* Included in the fluency cluster score.
For descriptive details of the items see: Hempel MS [12].

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