Effects of perinatal PCB and dioxin exposure and early feeding mode on child development
Lanting, Caren Ingeborg

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We studied the relationships between prenatal exposure to PCBs and postnatal exposure to PCBs and dioxins on the one hand, and the neurological and cognitive development at 42 months on the other. In order to be able to detect small negative effects of PCB and dioxin exposure, we followed a large group of children (n=418) at low risk of developmental deficit from birth. For each mother/infant pair, a wide range of social, obstetrical, nutritional, and perinatal conditions was recorded and in the statistical analyses, if necessary, adjustments were made for differences.

Breast milk not only is a source of toxic substances such as PCBs and dioxins, but it also contains components that are considered to be essential for optimal child development. In order to solve this controversy, the early type of feeding was explored in addition to the effects of lactational exposure to PCBs and dioxins. We found a beneficial effect of breast-feeding on neurological development at 42 months and at nine years of age. Our findings are in accordance with several other studies which have also shown a positive relationship between breast-feeding and brain development. Furthermore, in the present study no effects of lactational exposure to PCBs and dioxins could be detected, although plasma PCB levels of breast-fed 42-month-olds were 4½ times as high as those among formula-fed children. In all, despite the contamination of human milk with PCBs and dioxins, breast-feeding is the most optimal feeding method during the first period of life.

Prenatal exposure to PCBs was negatively associated with cognitive abilities at 42 months, but not with neurological development at that age. Both the cognitive and the neurological development are parameters of brain integrity. But they reflect different functions of the brain and they are assessed in a basically different manner. Cognitive tests, including the Kaufman Assessment Battery for Children, measure children’s abilities in a quantitative way, whereas the neurological examination measures functioning in a qualitative fashion. More importantly, in our age group the neurological examination might not have enough discriminating power to discern differences in motor behaviour due to perinatal exposure to PCBs and dioxins. At 42 months the so called ‘higher’ functions, that is the more complex motor skills which are cortically mediated, have not yet developed. Long-term follow-up and similar research in areas where the environmental PCB and/or dioxin exposure is
higher than that in the Dutch setting, such as in Eastern Europe and areas in the former Soviet Union or in communities with a high fish consumption, might shed light on this problem.

The finding that perinatal exposure to PCBs and dioxins was unrelated to the neurological development at 42 months does not prove that neurological development is not affected. Previous results concerning the same cohort in the second week after birth showed an adverse effect of the combination of high prenatal and high lactational exposure on the neurological condition. And at 18 months of age an adverse association between prenatal PCB exposure and neurological optimality was observed. Maturation of the brain is an ongoing process with its highest intensity during the first two decades of life. The maturation is reflected in the functional development of the child. Results found at a certain age can not easily be extrapolated to other ages as the neurological outcome at different ages is generated by a ‘different brain’. Therefore, on the basis of our findings adverse effects of PCB and dioxin exposure on the neurological development beyond the age of 42 months - an age at which the sensorimotor functions are still rather ‘simple’, so to say - can not be refuted. The same way of reasoning applies to the cognitive development. The finding of an association between prenatal PCB exposure and cognitive development in 42-month-olds does not imply that PCB-related cognitive differences may be found at later ages.

The way in which exposure to a mixture of PCBs and dioxins leads to alterations in brain development is unclear. Four mechanisms are suggested. Firstly, dioxins and dioxin-like planar PCBs have been found to exert their toxic effects by interaction with the arylhydrocarbon (Ah) receptor. Secondly, some PCBs have been found to influence brain dopamine concentrations but other neurotransmitter systems (serotonergic, noradrenergic) might also be affected. Thirdly, hormonal alterations may be involved. In rats several hydroxylated PCB metabolites were found to accumulate in fetal plasma and brain and to cause reductions in fetal plasma and brain thyroid hormone levels. PCB exposure has also been related to a slightly decreased plasma thyroid hormone level in human neonates. Adequate levels of thyroid hormone are essential for normal brain development. Fourthly, our data indicate an adverse relationship between environmental PCB exposure and human breast milk volume and fat content. Breast milk contains substances which are considered to be essential for optimal brain development like long-chain polyunsaturated fatty acids, and any substance suppressing lactation in a quantitative or a qualitative manner is a potential hazard for infant growth and development.

There is not much information on long-term effects of human
exposure to PCB and dioxin. Exposure to these substances starts at conception. Each of the developing organs is equally subjected to these substances during critical or ‘sensitive’ periods of rapid growth and development in which the establishment of tissues and organs is achieved. Theoretically, exposure to PCBs and dioxins during early life can influence long-term outcome in three ways: (i) direct damage; (ii) induction, deletion, or impaired development of a somatic structure resulting from exposure during a critical period; or (iii) physiological ‘setting’ by exposure at a critical period, with long-term consequences for function. The term ‘programming’ has been applied to the latter two processes. PCBs and their hydroxylated metabolites have been found to exert oestrogenic activity. Early exposure might ‘imprint’ adult reproductive functioning. In female rats, translactational exposure to PCBs delayed puberty, and resulted in decreased uterine response to oestrogen, in impairment of fertility, and in irregular cycle patterns. Also, as testosterone secreted by the fetal testis at a critical period ‘programs’ development of the male genitalia, fetal exposure to anti-androgenic compounds like PCBs might disrupt genital tract development. Indeed high levels of perinatal PCB exposure were related to a shorter penis in 11 to 14-year-old boys born to accidentally exposed women.

Furthermore, perinatal PCB and/or dioxin exposure might ‘program’ hepatic enzyme activity, thus permanently modifying endocrine and metabolic feedback systems. Induction of hepatic microsomal mono-oxygenase activity is probably the most common effect observed in adult and perinatal animals following exposure to persistent halogenated compounds. Hepatic microsomal enzymes have a key-role in the metabolism of endogenous substances, such as steroid hormones. The ‘programmability’ of hepatic enzyme activity is illustrated by the fact that lifelong change in the activity of cytochrome P-450 dependent monoxygenase has been found in neonatal rats after a single dose of phenobarbitone. Long-term follow-up of subjects with known levels of perinatal PCB exposure is recommended.

An approach in which chronic exposure of large adult populations is addressed might also be of interest. A recent study suggested a relationship between exposure to PCBs and an increased risk on non-Hodgkin lymphoma. It also has been suggested that PCBs promote the development of mammary carcinoma through the oestrogenic activity of these compounds. Higher levels of PCBs were found in fat samples from women with breast cancer as compared to controls. In addition, more subtle effects of chronic exposure have been found on metabolic systems. In animal experiment, administration of tetrachlorodibenzo-p-dioxin (TCDD) led to a down-regulation of low-density-lipoprotein (LDL) receptors on the
plasma membrane of the hepatocyte 33. Human patients with genetic defects in their LDL receptors (i.e. familial hypercholesterolaemia) show high levels of serum cholesterol in terms of LDL, which is a well-known marker of risk on cardiovascular disease. Also, TCDD has been found to cause a decline of glucose uptake activities by adipose tissue and pancreas 34, 35 and a decrease in serum insulin levels 36 in rodents. It seems therefore possible that environmental exposure to organohalogens, whether or not superimposed on genetic and lifestyle factors, adversely influences the risk on adult morbidity such as cancer, vascular degenerative disease, and diabetes mellitus.

The presently encountered levels of environmental exposure to PCBs and dioxins in The Netherlands belong to the highest in the world. The reported effect of prenatal PCB exposure on cognitive development is small and of no clinical relevance. Yet this effect seems to be caused by exposure to substances which entered the environment as a direct result of human actions. On a population basis even such a minor decrease in cognitive abilities may have a noticeable effect. As food is the most important source of exposure 37, long-term dietary measures (viz less full-cream milk products and beef, and the use of vegetables oils instead of fish-oils) can be used to maintain low individual PCB and dioxin levels. But major effects can only be expected of a decline in environmental levels. Since PCBs and dioxins are transported by long-range atmospheric deposition, efforts should be made world-wide to detect sources and to further diminish the output of these hazardous substances.

References


General discussion & conclusions


