Published in final edited form as:

Int J Hyg Environ Health. 2007 October ; 210(5): 659–667.

Some evidence of effects of environmental chemicals on the endocrine system in children

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Abstract

Pollutant chemicals that are widespread in the environment can affect endocrine function in laboratory experiments and in wildlife. Although human beings are commonly exposed to such pollutant chemicals, the exposures are generally low and clear effects on endocrine function from such exposures have been difficult to demonstrate. Human data including both exposure to the chemical agent and the endocrine outcome are reviewed here, including age at weaning, age at puberty, anogenital distance, and sex ratio at birth, and the strength of the evidence discussed. Although endocrine disruption in humans by pollutant chemicals remains largely undemonstrated, the underlying science is sound and the potential for such effects is real.

Keywords

Endocrine disruptors; Environmental chemicals; Lactation; Thyroid function; Sex ratio; Puberty

Introduction

The notion that chemicals present in the environment, such as pesticides, could interfere with hormonal processes in vertebrates, especially those involving estrogens, goes back at least to the observation that dichlorodiphenyltrichloroethane (DDT) decreased hatchability of the eggs of pelagic birds (EPA, 1975). The mechanism of this effect was likely a combination of induction of enzymes that metabolized endogenous estrogens and occupancy of the estrogen receptor by very weak but persistent compounds. Some forms of DDT, other pesticides like methoxychlor and chlordane, and industrial chemicals like some polychlorinated biphenyls (PCBs) increase the wet weight of a virgin mouse uterus, which is the original bioassay for estrogenicity (Kupfer and Bulger, 1980). In addition, there is natural and pharmaceutical estrogen in the environment. Estrogens are excreted in the urine in amounts close to those administered or produced endogenously; thus, municipal sewage (Ternes et al., 1999) or runoff from feedlots in which animals are treated can contain significant amounts of estrogen.

Although estrogenicity is the most familiar of the hormone-like activities of exogenous chemicals, one form of dichlorodiphenyldichloroethene (DDE) is an antiandrogen (Kelce et al., 1995). Some pesticides and congeners of PCBs can occupy thyroid hormone receptors, and other agents produce symptoms such as infertility in chlordane (Cohn et al., 1978) and dibromochloropropane (Goldsmith et al., 1984) workers that are plausibly the result of

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interference with normal endocrine function, even if a hormonal basis is not established. Breast cancer is strongly related to hormone exposure, and has been studied extensively for an environmental hormonal etiology. So far, studies do not show any consistent relationship between body stores of DDT or PCBs and disease risk (Laden et al., 2001).

Secular downward trends in sperm counts have been associated with several environmental chemicals, and these studies have been reviewed recently (Hauser, 2006). Increased rates of testicular cancer, undescended testicles, and hypospadias all have been attributed to endocrine disruption by synthetic environmental agents. Hypospadias and undescended testes do not appear to be caused by DDT exposure specifically (Longnecker et al., 2002), but there are few studies available yet in which the outcome and the responsible chemical have been measured in the same people. Here we will review five areas related to the hypothesized endocrine disruption caused by environmental chemicals directly concerning children: the endocrine modulation of breastfeeding and weaning[BR1] ; thyroid function; sex ratio of births among heavily exposed persons; peripubertal growth and the onset of puberty in children; and anogenital distance, a measure adopted from animal studies in the laboratory measuring prenatal anti-androgen exposure.[BR2] For all these, there are reasonably good data that include measures of exposure and outcome, usually at an individual level. For a comprehensive discussion of endocrine disruptors see the World Health Organization review (International Programme on Chemical Safety, 2002).

Materials and methods

DDE and duration of lactation

Late in pregnancy, prolactin and estrogen are circulating at high levels; that causes increased surface area of the glands and ducts within the breast but impairs milk synthesis. Only when estrogen falls at term can prolactin act unopposedly to promote milk synthesis. Since older oral contraceptives with high estrogen doses, when used by nursing mothers, decreased milk volume and perhaps caused early weaning (Harlap, 1987), we thought that a weak but persistent estrogen like DDE might also interfere with milk synthesis, which would be observed as early weaning. This hypothesis was tested within the North Carolina Infant Feeding Study (Rogan et al., 1987).

The North Carolina Infant Feeding Study enrolled about 900 children in a prospective birth cohort study from central North Carolina (USA) between 1978 and 1982. At or near birth, samples of breast milk or colostrum, maternal serum, placenta, and cord blood were collected and analyzed for DDE, the most stable and persistent compound of the DDT family. The children were followed clinically and developmentally with periodic examinations and psychometric testing from birth until 5 years of age, and parents were surveyed by mail periodically after that. Information was gathered about how the child was fed and, if breastfed, when the child was weaned. Although the North Carolina study was primarily concerned with the possibility that PCBs and DDE in breast milk might produce detectable toxicity in the breastfed child, the process of lactation itself was also a focus.

Although such an effect had been hypothesized, the strength of the relationship was surprising—the women with the highest levels of DDE and PCBs (approx >5 parts per million (ppm) of fat basis in milk) breastfed less than 40% as long as women with the lowest levels (approx <2 ppm of fat basis in milk), unaccompanied by any increase in illness in the children (Rogan et al., 1987).

To replicate the association, we did a smaller study in the north central Mexico, in a region that had historically used DDT on cotton crops. The levels of DDE in breast milk in Mexico were several times higher than those in North Carolina, with a median >5 ppm of fat basis in

milk, compared with approximately 2 ppm in North Carolina. If data from both studies are compared, there was a very similar relationship between DDE concentration and weaning (Table 1). Although the study in Mexico was only of 230 women, for this purpose it was statistically about as powerful as the larger North Carolina study, because so many more of the women had higher levels of DDE in their milk (Gladden and Rogan, 1995).

Researchers in upstate New York (USA) had assembled a cohort of families who caught and ate fish from Lake Ontario, and were thus thought to have increased exposure to PCBs and DDT (McGuinness et al., 1999). Among 54 primiparous women, DDE in milk had no relation to breast feeding duration, but the levels found were substantially lower than in NC or Mexico. Unexpectedly, fish consumption was not associated with higher levels of DDE in milk.

Similarly, a Michigan (USA) anglers' cohort had been established in the mid-1970s to track families thought to have high exposures through Great Lakes fish consumption. Breast feeding histories and DDE levels at the time of delivery were estimated for 176 pregnancies among 91 mothers, and women with higher DDE levels had earlier weaning, at least among non-smokers (Karmaus et al., 2005). The strength of the effect was similar to what was seen in NC and Mexico, and no effect was seen for PCBs, similar to NC.

Also in Michigan (USA), after an episode of food contamination with polybrominated biphenyls (PBB), women with higher levels in their milk weaned earlier than those with lower levels, but they had been advised to do so by health authorities, and so the effect could not be interpreted to be attributable to the chemical (Weil et al., 1981). Of methodological interest was a study done decades later among women in this Michigan PBB cohort, which found no evidence of early weaning in interview data (Thomas et al., 2001). Thus it may be that time until weaning is not remembered by most women with sufficient precision for it to be used with confidence about lactations that occurred long in the past (Rogan and Weil, 2002). Promislow (Promislow et al., 2005) found, in a study of older woman who had kept a diary during lactation, that the degree of imprecision in recall of length of lactation was sufficient to attenuate associations with subsequent health status.

There is a resurgence of interest in DDT for malaria vector control. Unfortunately, the same parts of the world in which malaria is a problem are also places where prolonged breastfeeding may be life saving, and thus the decision poses a public health dilemma. Bouwman et al. showed that DDT and DDE are quite high in the milk of women living in homes in KwaZulu-Natal (South Africa) where DDT was sprayed for mosquito control. In their cross sectional data, the ages of the infants did not vary by the level of DDT/DDE in milk, which they considered evidence that DDT/DDE did not influence duration of lactation in KwaZulu-Natal (Bouwman et al., 1990). This design, however, does not allow study of women who have ceased lactating, and thus is not strong evidence that an effect on weaning did not occur. It might be possible, however, to do appropriate studies in Africa as DDT is used.

PCBs, hypotonia and thyroid function

In the early studies of background exposures to PCBs, hypotonia at birth was related to prenatal exposure to PCBs (Rogan et al., 1986) or to a history of consuming PCB-contaminated fish (Jacobson et al., 1984), which was suggestive of an effect on thyroid hormone. PCBs have long been known to be toxic to the developing thyroid gland (Collins and Capen, 1980). Subsequently, hypotonia was shown to be accompanied by higher thyroid-stimulating hormone in one study (Koopman-Esseboom et al., 1994).

There are now data from several additional studies (Table 2, adapted from Longnecker, 2001). The level of PCB exposure in the Faroe Islands (Denmark) (Steuerwald et al., 2000), where the marine diet includes pilot whale consumption, was higher by an order of magnitude

than other studies. For all studies, PCB levels (median or mean) are reexpressed in terms of $\mu\text{g/l}$ serum, by the methods of Longnecker (Longnecker, 2001). Except for the study from Germany (Osius et al., 1999) of school children exposed to a toxic waste incineration plant, all other studies are from cohorts of infants or mothers with no particular exposures, from Holland (Koopman-Esseboom et al., 1994; Fiolet et al., 1997), North Carolina (Longnecker et al., 2000; Rogan et al., 1986), Taiwan (Wang et al., 2005), and Québec (Canada) (Takser et al., 2005). The combination of the highest exposures and the second largest sample size makes the Faroe Islands study the most useful. In general, associations between PCBs and a variety of measures of thyroid hormone status have been weak, inconsistent, or absent. Even if the association was causal, the effect from background exposure is unlikely to be clinically significant. For an extensive discussion of this topic, see the review by Hagmar (Hagmar, 2003).

Sex ratio

Perhaps because of the decreased redundancy of genetic information on the Y chromosome, the male is the more delicate of the species, with shorter life expectancy at all ages. Theoretically, a toxic exposure during pregnancy might selectively damage males, resulting in a greater ratio at birth of the hardier females. This would not necessarily involve a hormonal mechanism, but studies of sex ratio at birth have been a part of the discussion on endocrine disruption. Although there are some data on secular trends, the most relevant data from a toxicological perspective come from Seveso (Italy), where in 1976 a factory exploded, releasing perhaps 1 kg of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, one of the most toxic chemicals known. A variety of illnesses have been attributed to this exposure, but, besides the previously established association between chloracne and exposure, a clear pattern of severe toxicity has not emerged (Bertazzi et al., 1989). In 1996, however, Mocarelli (Mocarelli et al., 1996) observed that between 1977 and 1984, only 26 males and 46 females were born to the most exposed families, a sex ratio (SR) of 56. Human sex ratio at birth, conventionally expressed as the number of male live births per 100 female live births, is about 106, and is the same worldwide. This large effect was without mechanistic explanation.

There was information about the Yu-Cheng cohort of children born in Taiwan after exposure in 1979, when rice oil contaminated with PCBs and polychlorinated dibenzofurans (PCDF) was accidentally ingested by the parents. There was clearly more toxicity apparent among the exposed Taiwanese than among the residents of Seveso. However, a change in sex ratio of births 1978–1985 was not detected among Taiwanese families studied in which at least the mother had been exposed (Rogan et al., 1999). This posed a problem in interpretation until the publication of more detailed and longer term data from Seveso showing that the decrease in male births occurred specifically among families where the father was exposed—50 males and 81 females (SR = 62), were born in families in which the men had been exposed before 19 years of age (Mocarelli et al., 2000). However, rather than clarifying the issue, the detailed report also noted that the ratio of boys to girls had begun to decrease in the area before the exposure took place in 1976. Subsequently, Gomez determined the number and sex of offspring from exposed males in the Taiwan Yu-Cheng cohort, and found that men exposed before age 20 had 46% male children (SR = 85), while unexposed neighborhood control men had 54% male children (SR = 117) (Gomez et al., 2002). At this point, the very large departure from the expected 106 in the sex ratio of Seveso and Taiwan births remains unexplained, and although it would seem straightforward to replicate in the laboratory, no report is yet available of such an experimental study.

Adolescent growth and sexual maturation

When Herman-Giddens (Herman-Giddens et al., 1997) published data showing that many US girls, especially black girls, had pubic or axillary hair and breast development before 7 years

of age, it was viewed by many as evidence that puberty was occurring younger than it had been at some unspecified time in the past. Although there is good evidence that age at menarche has been decreasing in white girls for decades (Tanner and Eveleth, 1975), there were no data on black girls or on the other stages of puberty to allow estimation of a secular trend.

There was interest in studying the onset of puberty among the children in the aforementioned North Carolina study. Beginning in 1992, 594 of the North Carolina children were successfully recontacted as they reached adolescence. Height, weight, and stage of pubertal development were assessed through annual mailed questionnaires for up to 5 years. The child or the parent provided the assessment of pubertal stage, using line drawings of the Tanner stages. These show characteristics of the pubic hair, penis, and scrotum in boys and pubic hair and breast in girls that range from 1 (prepubertal) to 5 (adult). There is good evidence that children can report their stage accurately using this instrument (Brooks-Gunn et al., 1987; Duke et al., 1980). The higher the prenatal exposure to DDE, the taller and heavier boys were at 14 years of age; those with the highest exposures (maternal concentration of DDE ≥ 4 ppm of fat) had an adjusted mean height of 6.3 cm and an adjusted mean body weight of 6.9 kg higher than those with the lowest exposures (0 – 1 ppm of fat). There was no effect on the ages at which pubertal stages were attained. Lactational exposures to DDE had no apparent effects, and neither did transplacental or lactational exposure to PCBs. Girls with the highest transplacental PCB exposures were heavier for their heights than other girls by an average of 5.4 kg, but differences were significant only if the analysis was restricted to white girls. Although there was some evidence that the girls with the highest PCB exposure reached the early stages of puberty sooner, the numbers were small, age at menarche appeared unaffected, and there was no previous hypothesis concerning individual stages of puberty. The conclusion was that prenatal exposures at background levels may impact body size at puberty (Gladden et al., 1999).

In a subsequent analysis, using follow-up data from 304 males, enrolled at birth between 1960 – 1965, who had been followed to adolescence in the US Perinatal Collaborative Project, Gladden (Gladden et al., 2004) did not see any effect of prenatal DDT exposure on growth at puberty, and so the large effect seen in North Carolina remains unconfirmed.

The North Carolina data are peculiarly well suited to this kind of study, because the observed associations all concerned prenatal exposure, which could be assessed because biologic samples were collected perinatally. There was no relationship seen with the larger but later exposure through breastfeeding. Adolescents' body burdens of these agents, however, appear to be primarily determined by how much they were breastfed (Niessen et al., 1984), and thus, a study using biologic samples collected at the time of puberty could not determine the prenatal effect.

Selevan et al. (Selevan et al., 2003) and Wu et al. (Wu et al., 2003) reported that, among adolescent black US girls participating in the 3rd National Health And Nutrition Examination Survey (NHANES III), those with the highest blood lead levels were less likely to have passed menarche. In these cross sectional data, the range of blood lead concentration in the girls was small, and later menarche was observed in the girls with blood leads of 3 $\mu\text{g}/\text{dl}$, around the US mean. This finding was unexpected and unanticipated from the familiar effects of lead. It is in the direction of being an artifact of mineralization of bone at menarche, with lead from soft tissue and thus blood being stored in bone in girls who have gone further into puberty, leaving girls who go into puberty later with higher blood leads longer. In another cross sectional study, den Hond et al. (2002) found several stages of puberty delayed in Belgian adolescents with higher PCB or dioxin levels. This finding, while it may represent causation, is consistent in direction with an artefact caused by dilution of the relatively fixed body burden of contaminants by the growth spurt in children achieving puberty.

The Michigan angler cohort whose members were exposed to DDE and PCBs by the consumption of contaminated fish from Lake Michigan in the 1970s was recontacted in the year 2000, and 151 of the 213 female offspring who were between ages 20 – 50 reported their recalled age at menarche. Their perinatal exposure was constructed from the analysis done earlier on their mothers' serum. A 15 µg/l increase in DDE in maternal serum was associated with experiencing menarche one year earlier. Controlling for BMI attenuated the effect. There was no effect of PCB exposure on age at menarche (Vasiliu et al., 2004).

The other Michigan cohort, with PBB exposure in the mid-1970's, was also followed-up for occurrence of menarche in the offspring. 328 daughters aged 5 – 24 in 1997 gave information on menarche, and their perinatal exposure was reconstructed from earlier study of their mothers. Among breast-fed girls, those with higher prenatal exposure to PBB reached menarche at 11.6 years, whereas those with lower PBB exposure did so at 12.2 years. Girls who had been formula fed reached menarche at 12.7 years and their PBB exposure had no effect (Blanck et al., 2000).

The Akwesasne Mohawk nation is a sovereign Native American territory that spans the St. Lawrence River, and includes part of Quebec and Ontario (Canada), and western New York State (USA). Because of a combination of heavy industrialization in the area and traditional diet that includes local fish and game, the Akwesasne are thought to have increased exposure to persistent organic pollutants and heavy metals. In a cross sectional study of 138 adolescent girls, those with higher concentrations of 4 PCB congeners or lower blood lead concentrations had earlier menarche (Denham et al., 2005). The other compounds measured, including mirex, hexachlorobenzene (HCB), mercury, and DDE, did not show effects. These findings are consistent with the NHANES analysis showing later puberty with higher blood lead, and partially with North Carolina, which showed no effect of DDE and a suggestion of an effect of PCBs limited to the stages of puberty before menarche.

China has used DDT relatively recently and there is thus potential for higher exposures there. Ouyang et al. (Ouyang et al., 2005) studied 466 newly married female Chinese textile workers ages 20 – 34 in 1996 – 1998. They asked the women about age at menarche and cycle length and measured concurrent serum DDT and DDE. They found that women in the highest quartile of total DDT/DDE reported menarche 1.1 years earlier than those in the bottom quartile. Women with higher exposures also reported more short cycles.

There are two case control studies of girls with precocious puberty and organochlorine exposure, one from Belgium and one from China, and one of precocious thelarche (isolated early breast development) and phthalates from Puerto Rico. In the Belgian 1989–2000 study (Krstevska-Konstantinova et al., 2001), of 145 patients with precocious puberty, 28% were immigrants. Organochlorines were measured in a substudy of 41 (15 natives and 26 immigrants); the immigrant girls had median DDE concentrations above 1 ng/ml, while control Belgian girls had no detectable DDE. There was no particular country of origin or other characteristic of the immigrant girls, and they more often had no other features to their condition other than accelerated puberty. None of the 7 other organochlorine compounds measured differed in cases and controls.

In China, 79 girls with precocious puberty and 42 controls had DDE, 4-nonylphenol, and diethylhexyl phthalate (DEHP) measured in serum (Lu et al., 2006). Levels of all three chemicals were higher in cases, and there was a positive correlation between 4-nonylphenol concentrations and uterine volume and bone density and DDE concentrations and uterine volume.

In Puerto Rico, 41 girls with early thelarche had much higher levels of 4 phthalates than 35 control girls (Colón et al., 2000); however, a commentary 3 years later pointed out that the

results were consistent with contamination of the serum samples in the lab (McKee and Toxicology Research Task Group, 2004), where phthalate containing equipment is common. No studies confirming or refuting this study have appeared, despite the very strong apparent effect.

In Taiwan, adolescent males who were exposed in utero to high levels of PCBs or polychlorinated dibenzofurans had normal progression through the Tanner stages but smaller penises than controls. Puberty in girls was unaffected, as far as could be determined (Guo et al., 1993). This is a complicated effect, not obviously an estrogenic one, and its mechanism is not known.

There is not yet a consistent set of findings for the organic compounds and onset of puberty or aspects of it in humans, although there are some suggestive findings. The studies are more consistent for lead; however, the direction of the association is consistent with reverse causality, in that the increased bone mass of girls entering puberty earlier may absorb some lead, leaving girls who mature later with higher blood lead concentrations. Prospective study might be able to separate these effects.

Anogenital distance

Newborn rats have no visible scrotum, and the distance from the anus to the base of the genital tubercle, called the anogenital distance (AGD), is almost twice as long in males as females. AGD decreases if the pup is exposed to anti-androgenic chemicals (such as some phthalates) or testosterone deficiency in utero. In Mexico, Salazar-Martinez (Salazar-Martinez et al., 2004) developed a method for reproducible evaluation of AGD in human newborns and showed that the distance from the anus to the base of the scrotum was longer than the distance from the anus to the posterior fourchette. Using these methods in a subsequent study of male infants with relatively high levels of DDE exposure, they saw no effect (Longnecker et al., 2007). Swan (Swan et al., 2005) showed that US boys (from the first Study for Future Families) with higher prenatal exposure to several phthalates had shorter anogenital index, defined as AGD/body weight. There were no associated genital anomalies in either study, and the prognostic importance of AGD or AG index is not yet established.

Discussion

What role, if any, environmental chemicals play in morbidity attributable to endocrine disruption is unclear. Many studies are underway of breast cancer, endometriosis, testicular cancer, and other plausible end points. Right now, environmental endocrine disruption in humans is more hypothetical than demonstrated fact. However, the inconsistency seen in the current literature is less evidence of no effect than a consequence of the broadness of the topic and the difficulty in studying it, especially with available epidemiologic tools. Of course, by the time epidemiology can demonstrate effects, people have been exposed and affected, so it is in some sense too late. In 1996, the US Congress enacted two pieces of legislation requiring the US Environmental Protection Agency to screen and test chemicals in food (Food Quality Protection Act (FQPA) of 1996) and water (Safe Water Drinking Act (SWDA) Amendments of 1996) for estrogenic and possibly other hormonal activity (Harding et al., 2006). Most likely, such testing would serve to pick out agents for more intense study. It would not replace more traditional tests for general toxicity and carcinogenicity. Chemicals are not currently tested specifically for their ability to mimic, disrupt, or otherwise act as hormone agonists or antagonists, except on a research basis. However, the detailed studies of general toxicity, carcinogenicity, and reproduction that new chemicals undergo would be likely to identify potent endocrine toxicity.

Abbreviations

DDT, dichlorodiphenyltrichloroethane; DDE, dichlorodiphenyldichloroethene; PCBs, polychlorinated biphenyls; PBBs, polybrominated biphenyls; PCDF, polychlorinated dibenzofurans; HCB, hexachlorobenzene.

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Table 1

Median age at weaning and DDE concentration in breast milk, Mexico (1988 – 89) and North Carolina (1978 – 82) (Rogan et al., 1987; Gladen and Rogan, 1995).

DDE (ppm)	Mexico		North Carolina	
	n	Median age (months)	n	Median age (months)
0 – 2.4	29	7.5	392	7.6
2.5 – 4.9	59	5.0	282	6.0
5.0 – 7.4	66	3.0	45	3.5
7.5 – 9.9	33	3.5	18	2.2
10.0 – 12.4	21	4.0	9	2.8
≥12.5	21	3.0	6	7.7
Total	229	5.0	752	6.2

Summary of epidemiologic data on associations between levels of PCBs and measures of thyroid hormone economy from the dietary exposure studies, sorted by size of study and by children versus adults.

Table 2

Country	Population and years specimens collected	Reference	Mean age (years)	comparable PCB levels µg/l@@	Measure of association with PCBs						
					n	Total triiodothyronine (TT ₃)	Free triiodothyronine (FT ₃)	Total thyroxine (TT ₄)	Free thyroxine (FT ₄)	Thyroid-stimulating hormone (TSH)	Radioiodine triiodothyronine uptake (RT ₃ U)
Children											
Rotterdam, Netherlands	105 infant-mother pairs; 1990–1992		0	3.4	78	NS	NM	NS	NM	$r = 0.38^{\dagger}$	NM
Netherlands	93 infant-mother pairs; 1993		0	2.1	93	NM	NM	NS	NM	NM	NM
Taiwan	118 infant-mother pairs (from 430 mothers); 2000–2001		0	Not estimable	118	Females: $r = 0.227^{\$}$ Males: NS	NM	Females: $r = 0.282^{\$}$ Males: NS	Females: $r = 0.247^{\$}$ Males: $r = -0.302^{\dagger\dagger\dagger}$	Females: $r = -0.264^{\dagger\dagger\dagger}$ $r = -0.320^{\dagger\dagger\dagger}$ Males: $r = -0.239^{\$}$	Females: NS Males: $r = -0.237^{\$}$
North Carolina	160 infants w/ samples (from cohort of 900); 1978–1982		0	3.6	160	NM	NM	$r = 0.07$	$r = -0.12$	$r = -0.08$	NM
Faeroe Islands, Denmark	182 infant-mother pairs; 1994–1995		0	14.2	182	NM	NS	NS	NS	$r = -0.04$	$r = -0.21^{\dagger}$
Hessen, Germany	320 school children 1994–1995		8	0.8	296	NM	$\beta = -0.25^{\dagger}$	NM	$\neq$	$\beta = 7.13^{\dagger\dagger}$	NM
Mothers											
Rotterdam, Netherlands	105 infant-mother pairs; 1990–1992		29	3.4	78	$r = -0.36^{\dagger}$	NM	NS	NM	NS	NM
Québec, Canada	101 mother - cord bloods; 1999–2001		27	0.4	101	+ $F = 9.6^c$ $F = 11.2^d$ $F = 8.6^e$ $F = 7.7^f$	NM	NM	NS	++ $F = 4.6$	NM
Faeroe Islands, Denmark	182 infant-mother pairs 1994–1995		28	14.2	182	NM	NS	NS	NS	$r = -0.13$	NS

NS indicates association not statistically significant; NM, not measured; r , correlation coefficient; β , regression coefficient; F , Type 3 F -value

* Results shown are for nonplanar PCB TEQ, but results were described as being similar for nonplanar PCBs.

Adapted and expanded with permission from Longnecker

@@ comparable PCB levels, reexpressed in terms of µg/L serum, by the methods of Longnecker

Nonlinear association (no strong evidence of any association).

+ Association with total PCBs^c, PCB-138^d, and PCB180^f statistically significant ($P < .01$); association with mono-ortho coplanar PCBs (sum of PCB-105,-118 and -156) not statistically significant.

++ Association with PCB-180 statistically significant ($P < .01$); association with other PCBs not statistically significant.

* Association statistically significant ($P < .05$).

*+ Association with PCB 118 only statistically significant ($P < .05$); association with other PCBs nonlinear and not statistically significant.

^{†††} Association with non-*ortho* PCBs statistically significant ($P < .05$); association with other PCBs not statistically significant.

^{††††} Association with mono-*ortho*^a and non-*ortho*^b PCBs statistically significant ($P < .05$); association with other PCBs not statistically significant.

^{†††††} Association with PCB-180 (adjusted for total lipid concentration) statistically significant ($P < .05$); association with other PCBs not statistically significant.

[§] Association with mono-*ortho* PCBs statistically significant ($P < .1$); association with other PCBs not statistically significant.

^{§§} Association with PCB-138,-153,-180 statistically significant ($P < .1$); association with other PCBs not statistically significant.