

# 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 signaling, as evidenced in laboratory experiments and in wildlife with relatively high exposures. Although humans 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. Several instances in which there are data from humans on exposure to the chemical agent and the endocrine outcome are reviewed, including age at weaning, age at puberty, and sex ratio at birth, and the strength of the evidence is 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. *Pediatrics* 2003;112:247–252; endocrine disruptors, puberty, lactation, thyroid, child.

ABBREVIATIONS. DDT, dichlorodiphenyltrichloroethane, PCB, polychlorinated biphenyl; DDE, dichlorodiphenyldichloroethene; ppm, parts per million.

The most informative studies of the effects of environmental chemicals on the endocrine system in children concern 2 ubiquitous, persistent halogenated organic pollutant chemicals: dichlorodiphenyltrichloroethane (DDT) and its derivatives and polychlorinated biphenyls (PCBs) and chemicals similar to them. Although these agents have a variety of toxic effects, some of which might have an endocrine mechanism, the focus here is on several areas that are the most plausibly related to endocrine function: duration of lactation (age at weaning, not length of a feeding); growth, especially at puberty; sex ratio at birth among heavily exposed groups; and thyroid function. Much of the background material was originally prepared by the Committee on Environmental Health of the American Academy of Pediatrics for its *Handbook of Pediatric Environmental Health*,<sup>1</sup> but it appears here with more detailed references and at somewhat greater length. The potential for PCBs specifically to act as endocrine disrupters at background exposures has been reviewed recently.<sup>2</sup>

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## BACKGROUND

The idea that certain pesticides could interfere with hormonal processes in vertebrates probably goes back to the observation that DDT decreased hatchability of the eggs of pelagic birds.<sup>3</sup> 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 such as methoxychlor and chlordane, and industrial chemicals such as some PCBs have been proved to increase the wet weight of a virgin mouse uterus, which is the classic bioassay for estrogenicity.<sup>4</sup> Compounds of diverse structures can be potent estrogens; the best example of this structural heterogeneity is the stilbene diethylstilbestrol, which looks nothing like a 17 ketosteroid. Examples of synthetic environmental chemicals acting as estrogens or more generally disrupting hormonal events have been documented in wildlife. Male alligators in Florida were feminized by exposure to a spill of the pesticide dicofol,<sup>5</sup> and birds near the Great Lakes have failed to reproduce likely because of high body burdens of DDT.<sup>6</sup> In addition to synthetic chemicals, there are also many naturally occurring phytoestrogens in plants, mostly isoflavones, that are less potent than estradiol and more readily cleared than pesticides. Infants who are fed soy formula have high exposures to these compounds,<sup>7</sup> and there are some data suggestive of an estrogenlike effect on cholesterol synthesis in soy-fed infants.<sup>8</sup> Endogenous and pharmaceutical estrogens are excreted in the urine in amounts close to those administered synthetically or produced naturally. Human sewage<sup>9</sup> or runoff from feedlots in which animals are treated can contain significant amounts of estrogen.

Although estrogenicity is the most familiar of the hormonelike activities of exogenous chemicals, one form of dichlorodiphenyldichloroethene (DDE) is an antiandrogen.<sup>10</sup> Some pesticides and congeners of PCBs can occupy thyroid hormone receptors, and other agents produce symptoms such as infertility in chlordane<sup>11</sup> and dibromochloropropane<sup>12</sup> workers that are plausibly the result of interference with normal endocrine function, even if a hormonal basis is not established.

Secular trends in sperm counts and increased rates of testicular cancer, undescended testicles, and hypospadias all have been attributed to endocrine disruption by synthetic environmental agents, although no studies are available yet in which the outcome

and the responsible chemical has been measured in the same people. There are such studies on breast cancer, and these so far do not show any consistent relationship between body stores of DDT or PCBs and disease risk.<sup>13</sup>

Three areas related to the hypothesized endocrine disruption caused by environmental chemicals directly concerning children are discussed: the endocrine modulation of breastfeeding and weaning; peripubertal growth and the onset of puberty in children; and sex ratio of births among heavily exposed individuals. For all of these, there are reasonably good data that include measures of exposure and outcome, usually at an individual level. There are also good data concerning child development and PCBs and DDT; however, it is not clear that these effects are produced through an endocrine mechanism, and there are enough data to warrant a separate discussion.

#### DDE AND DURATION OF LACTATION IN NORTH CAROLINA AND MEXICO

Very high levels of prolactin during pregnancy are accompanied by very high levels of circulating estrogen, which result in increased duct surface area within the breast but usually not in full milk synthesis. Only when estrogen levels fall at term can prolactin act unopposed to promote milk synthesis. Old-style, high-dose oral contraceptives given to lactating women were associated with decreased milk volume and perhaps early weaning.<sup>14</sup> It was thought that the presence of a weak but persistent estrogen-like DDE might interfere with milk synthesis, which would be observed as early weaning. This is because a child who is fussing or not gaining weight while being breastfed is often given supplemental formula or food, and supplementation decreases sucking vigor and, thus, further decreases supply. This hypothesis was tested within the North Carolina Infant Feeding Study.<sup>15</sup>

The North Carolina Infant Feeding Study was a 900-child, prospective birth cohort study of children from central North Carolina enrolled 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 (approximately >5 parts per million [ppm] of fat

basis in milk) breastfed <40% as long as women with the lowest levels (approximately <2 ppm of fat basis in milk), unaccompanied by any increase in illness in the children.<sup>15</sup> To replicate the association, a smaller study was conducted in the north central part of Mexico, in a region that had historically used DDT on cotton crops. The levels of DDE and PCBs in breast milk were several times higher than those in North Carolina, with a median of >5 ppm of fat basis in milk, compared with approximately 2 ppm in North Carolina. When data from all of the women were used, 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 approximately as powerful as the larger North Carolina study, because so many more of the women had higher levels of DDE in their milk.<sup>16</sup>

Studies such as these are subject to a peculiar form of bias. The concentration of DDE (and PCBs) decreases over the course of lactation. The rate of this decrease was ~20% for each 6 months of lactation.<sup>17</sup> This occurs because the chemical is transferred to the child, making the concentration in the mother's fat lower. Supposing that there are 2 kinds of breastfeeding women, those who naturally breastfeed for a long time and those who do not for reasons completely unrelated to DDE, when these women have children and nurse them, the long-term breastfeeder will end up with a lower concentration of DDE and PCBs at the time she weans than will the short-term breastfeeder. If the women are then observed in second and later lactations, they will likely proceed to breastfeed in a manner similar to what they did with their first pregnancy. If DDE is measured in their milk, even if it is measured very early in lactation, then the women with lower levels will breastfeed longer, but this will be an effect rather than a cause. The simplest way to avoid being misled by this bias is to study the phenomenon among first lactations. In the North Carolina data, the relationship was very similar when examined in women who were pregnant for the first time, but in Mexico, it was not. Although a statistical simulation that showed that it was improbable that the bias would have produced an effect as large as was seen in Mexico was performed, it was nonetheless not a completely clean

**TABLE 1.** Median Age at Weaning and DDE Concentration in Breast Milk, Mexico and North Carolina

DDE (ppm)	Mexico		North Carolina	
	N (%)	Median Age (Months)	Median Age (Months)	N (%)
0-2.4	29 (13)	7.5	7.6	392 (52)
2.5-4.9	59 (26)	5.0	6.0	282 (38)
5.0-7.4	66 (29)	3.0	3.5	45 (6)
7.5-9.9	33 (14)	3.5	2.2	18 (2)
10.0-12.4	21 (9)	4.0	2.8	9 (1)
12.5+	21 (9)	3.0	7.7	6 (1)
Total	229			752
Median DDE (ppm)	5		2	

ppm indicates parts per million.

confirmation of the previous result. There has not yet been another study specifically addressing this question. In Michigan, after an episode of food contamination with polybrominated biphenyls, 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.<sup>18</sup>

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 the decision poses a public health dilemma.<sup>19</sup>

#### PCBs, HYPOTONIA, AND THYROID FUNCTION

In the early studies of background exposures to PCBs, hypotonia at birth was related to prenatal exposure to PCBs<sup>20</sup> or to a history of consuming PCB-contaminated fish,<sup>21</sup> which was suggestive of an effect on thyroid hormone. PCBs have long been known to be toxic to the developing thyroid gland.<sup>22</sup> Subsequently, hypotonia was shown to be accompanied by higher thyroid-stimulating hormone in 1 study,<sup>23</sup> and now there are data from 5 additional studies (Table 2).<sup>24</sup> The level of PCB exposure in the Faeroe Islands<sup>25</sup> was higher than in studies from Holland,<sup>23,26</sup> North Carolina,<sup>27</sup> and Germany.<sup>28</sup> The combination of the highest exposures and the second largest sample size makes the Faeroe 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. The hypothesis has a very reasonable basis in laboratory evidence, though, and is probably worth additional innovative study.

#### SEX RATIO

Perhaps because of the decreased redundancy of genetic information on the Y chromosome, the male human is the more delicate of species, with shorter life expectancy at all ages. Theoretically, a toxic exposure during pregnancy might selectively damage male fetuses, resulting in a greater ratio at birth of the hardier female infants. 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 toxicologic 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 a clear pattern of severe toxicity has not emerged.<sup>29</sup> In 1996, however, Mocarelli et al<sup>30</sup> observed that between 1977 and 1984, 48 girls but only 26 boys were born to the most exposed families. This was a very large effect on a very stable number, and without obvious mechanistic explanation. There was information about the children who were born in Taiwan after the exposure there to PCBs and polychlorinated dibenzofurans, and there was clearly more toxicity apparent among the exposed Taiwanese than among

the residents of Seveso. However, a change in sex ratio was not detected among families studied in which at least the mother had been exposed.<sup>31</sup> This posed a problem in interpretation until the publication of more detailed data from Seveso showing that the decrease in male births occurred specifically among families in which the father was exposed: 50 boys and 81 girls were born in families in which the men had been exposed before 19 years of age.<sup>32</sup> However, rather than clarify the issue, the detailed report noted that the ratio of boys to girls had begun to decrease in the area before the exposure took place in 1976. At this point, the very large departure in the sex ratio of Seveso births remains unexplained, and although it would seem straightforward to replicate in the laboratory, no report is yet available of such an experimental study. Because data on fathers' exposures in Taiwan were unavailable, the failure to replicate the Seveso finding could have been attributable to a large number of families with only maternal exposure in the Taiwan study.

#### ADOLESCENT GROWTH AND SEXUAL MATURATION

When Herman-Giddens et al<sup>33</sup> published data showing that many 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,<sup>34</sup> there was no data on black girls or on the other stages of puberty to allow estimation of a secular trend. There was interest in onset of puberty among the children in the North Carolina study, and 594 of them were recontacted as they reached adolescence. Height, weight, and stage of pubertal development were assessed through annual mailed questionnaires. The child or the parent provided the assessment of pubertal stage, using line drawings of the 5 Tanner stages. These show characteristics of the pubic hair, penis, and scrotum in boys and pubic hair and breast in girls that range from 0 (prepubertal) to 5 (adult). There is good evidence that children can report their stage accurately using this instrument.<sup>35,36</sup> It was found that 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  $\geq 4$  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 when 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 seemed unaffected, and there was no previous

TABLE 2. Summary of Epidemiologic Data on Associations Between Levels of PCBs and Measures of Thyroid Hormone Economy From the Dietary Exposure Studies<sup>24</sup>

Country	Population and Year Specimens Collected	Reference	Mean Age (Years)	n	Measure of Association With PCBs							
					Total Triiodothyronine	Free Triiodothyronine	Total Thyroxine	Free Thyroxine	Thyroid-Stimulating Hormone	Radioiodine Triiodothyronine Update		
Children												
Rotterdam, Netherlands	105 mother-infant pairs; 1990-1992	23*	0	78	NS	NM	NS	NM	$r = 0.38†$			NM
Netherlands	93 mother-infant pairs; 1993	26	0	93	NM	NM	NS	NM	NM			NM
North Carolina	160 infants with samples available (from cohort of 900); 1978-1982	27	0	160	NM	NM	$r = 0.07$	NM	$r = -0.12$	$r = -0.08$		NM
Faeroe Islands, Denmark	182 infant-mother pairs; 1994-1995	25	0	182	NM	NS	NS	NS	$r = -0.04$			$r = -0.21†$
Hessen, Germany	320 school children 7-10 years of age; 1994-1995	28	8	296	NM	$\beta = -0.25†$	NM	‡	$\beta = 7.13§$			NM
Mothers												
Rotterdam, Netherlands	105 mother-infant pairs; 1990-1992	23	29	78	$r = -0.36†$	NM	NS	NM	NS			NM
Faeroe Islands, Denmark	182 infants and mothers, 1994-1995	25	28	182	NM	NS	NS	NS	$r = -0.13$			NS

NS indicates association not statistically significant; NM, not measured;  $r$ , correlation coefficient;  $\beta$ , regression coefficient.

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

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

‡ Nonlinear association (no strong evidence of any association).

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

Adapted with permission from Longnecker MP. Endocrine and other human health effects of environmental and dietary exposure to polychlorinated biphenyls (PCBs). In: Robertson LW, Hansen LG, eds. *Recent Advances in the Environmental Toxicology and Health Effects of PCBs*. Lexington, KY: University of Kentucky Press; 2001:114.

hypothesis concerning individual stages of puberty. The conclusion was that prenatal exposures at background levels may have an impact on body size at puberty.

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 biological samples were collected perinatally. There was no relationship seen with the larger but later exposure through breastfeeding. Adolescents' body burdens of these agents, however, seemed to be primarily determined by how much they were breastfed<sup>37</sup>; thus, a study done at the time of puberty using biological samples from the child could not determine the prenatal effect. There are several studies ongoing that will have the data to allow replication of the North Carolina findings, but none have appeared so far.

In Taiwan, male adolescents 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.<sup>38</sup> This is a complicated effect, not obviously an estrogenic one, and its mechanism is not known.

## CONCLUSIONS

What role, if any, environmental chemicals play in morbidity attributable to endocrine disruption is unclear. Many studies of breast cancer, endometriosis, testicular cancer, and other plausible end points are under way. Right now, environmental endocrine disruption in humans is much more speculation than demonstrated fact. In 1996, Congress enacted legislation requiring the Environmental Protection Agency to screen and test chemicals in food and water for estrogenic and possibly other hormonal activity. 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.

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