Organochlorine chemicals and children's health

The organochlorine chemicals (OCs) are a large, environmentally important family of synthetic organic compounds that include dichlorodiphenyltrichloroethane (DDT) and polychlorinated biphenyls (PCBs), as well as halogenated dioxins and furans. Persistence, bioaccumulation, and lipid solubility are the hallmarks of these compounds, and since publication of Carson's Silent Spring[1] in 1962, they have come to be recognized as the archetypal persistent organic pollutants (POPS). Twelve OCs are now subject to an international ban on their production, under the terms of the 2000 Stockholm Convention.[2]

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OCs are toxic. In adults, exposures to OCs have been linked to cancer,[3-5] cardiovascular disease,[6,7] endocrine alterations,[8,9] and curtailed lactation.[10] In children, 2 important characteristics of the OCs are (1) their capacity for intergenerational transfer across the placenta and through breast milk, and (2) their capacity to cause fetal toxicity. An unresolved question is whether this fetal toxicity reflects low-dose exposure during early windows of exquisite sensitivity or is the result of cumulative exposure.

In utero exposures to OCs have been linked to reductions in intelligence and behavior. The evidence for this developmental neurotoxicity is strongest and most consistent following in utero exposure to PCBs,[11,12] and cognitive and psychomotor decrements have been observed in investigations undertaken in North America, Asia, and Europe.[13-18] Prospective epidemiologic studies of PCB-exposed children followed from birth through 11 years suggest that these neurodevelopmental effects are persistent at least to that age.[19]

OCs can profoundly affect growth, and exposures in utero appear especially toxic.[20,21] Thus, early exposures to PCBs and related compounds are associated with lower birth weight and decreased body size.[13,22,23] Elevated maternal levels of dichlorodiphenyldichloroethylene (DDE) and PCB have been associated with preterm birth and smaller size newborns[8,24]; DDE is the major metabolite of DDT.

OCs are toxic to reproductive development. There are many experimental reports of premature and delayed puberty and of disruption of estrus in females exposed to OCs in utero.[25-27] The human evidence here appears to follow the experimental data and suggests that intense exposures to antiestrogenic OCs delay puberty, whereas casual exposures to DDE, PCB, or polybrominated biphenyl (PBB) lead to earlier development. Thus, girls in Michigan with higher perinatal exposures to PBB had earlier ages at menarche.[28] DDE has been associated with higher weight and height in boys during puberty, whereas PCB levels have been associated with increased weight in girls.[29] Exposure to hexachlorobenzene has been associated with undescended testes.[30]

Now comes the report in this issue of the Journal by Karmaus et al,[31] who find that DDE levels measured at 8 years of age are related to *delayed* growth throughout early childhood. Thus, girls with higher DDE levels at age 8 exhibited consistently shorter stature than their peers from 1 month through 9 years of age. Average growth was slower, by more than 1.0 cm each year, among girls in the highest versus the lowest half of DDE exposures at 8 of 10 observation points from birth to 10 years of age. The height difference between the upper and lower half of DDE levels was 2 to 3 cm annually until 8 years of age, a decrement that represented 3% to 5% of the higher growth curve. At ages 9 and 10 years, the trends were similar, but smaller and not significant. By this age, many girls have passed their peak growth period, and perhaps by then, the shorter girls have caught up with the less exposed; "catchup" is a well-known phenomenon. Boys in the oldest age groups exhibited a similar, though not significant, trend. It is possible that their growth may become affected at later ages (ie, beyond 10 years of age) because boys mature later. Boys may be less susceptible to growth arrest associated with DDE. Boys also have less body fat, which may in turn be linked to reduced DDE levels and increased height. No independent effect on growth was seen in this study for PCBs in either girls or boys.

BMI	Body mass index
DDE	Dichlorodiphenyldichloroethylene
DDT	Dichlorodiphenyltrichloroethane
OC	Organochlorine chemicals
PBB	Polybrominated biphenyl
PCB	Polychlorinated biphenyl
POPS	Persistent organic pollutants

A strength of the findings of Karmaus et al[31] lies in the dose-response relationships he observes between higher DDE levels and lower height. Although the levels of OCs in these children at age 8 appear to be extremely low, 0.3 μg/L whole blood (median), equivalent to 0.6 μg/L in serum, levels in utero and at

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early ages were likely to have been several times higher. Thus, the perinatal exposures of the children examined by Winneke et al[17] may have been comparable to exposures seen in previously published studies of child development.

Two unresolved questions in the report by Karmaus et al[31] are (1) the relative importance on growth retardation of in utero exposures to OCs versus postnatal exposures via lactation, and (2) the possibly confounding effects of body mass index (BMI) and of BMI change as children grow.

Lactational exposures, while not so toxic gram-for-gram as exposures in utero, are responsible for a significant proportion of the organochlorine body burden in young children, and the quantities of OCs transferred from mother to infant in lactation far exceed those transferred across the placenta. At young ages, breast-fed babies may have several times the OC level of nonbreast-fed infants, and this difference remains discernible until late childhood.[32-35] In earlier data presented by Karmaus et al,[36] breast-fed children had 50% higher OC levels at age *7* years than children who were bottle-fed. In fact, most children in this study were breast-fed, and there was a strong positive correlation of OC levels at 8 years of age with breast-feeding; a very high proportion of the children in the upper quartile of DDE exposures appear to have been breast-fed.

In their earlier report of these children, Karmaus et al[36] observed an inverse association between OC levels and BMI. This association was mainly because of lower OC levels at *7* years of age among children in the topmost quartile of BMI. For this reason, the height reductions observed in children who had simultaneously the lowest BMI and highest DDE levels may be caused, at least in part, by a variation in BMI. Does this imply that DDE in breastmilk or in the diets of young children overcomes the positive effect of breast-feeding on growth? Or do bottle-fed baby girls become fatter, have lower DDE levels, and grow more? Although the authors do adjust for BMI, lactation, and other potentially confounding variables, it is possible that statistical adjustment cannot completely separate the strong, common contributions of in utero and lactational exposures, gender, birth weight, and BMI to both DDE levels and growth. It would be helpful to study this question more closely, either in a prospective study, by stratifying on the duration of lactation or by removing the nonbreast-fed babies from the model. Controlling for breast milk DDE levels, if they were available, might also help clarify the issue.

In addition, it may be useful to more closely examine the abundant literature on the relationship of early body size on development. For example, if we assume that only pre or very early postnatal OC exposures alter development, it would be predicted that early overnutrition would lead to exactly the same results seen here: higher childhood BMI, lower DDE, and greater height. Several recent reports have attempted to elucidate relationships among fetal, childhood, adolescent and adult body sizes. For example, in a recent Swedish study, children whose BMI increased during childhood (2-8 years of age) were approximately 3 cm taller at 8 years than children whose BMI decreased.[37] Just as in the current report by Karmaus et al,[31] no height differential was evident in those children, either at birth or in later adolescence. Also similar to the Swedish data,[37] in the current study, the girls with higher BMI were taller. It would be helpful to study *weight gain* in the new dataset, to establish parallels with the Swedish data.

Another possible pathway to the association seen by Karmaus et al between reduced childhood height and DDE level could be through intrauterine growth retardation.[8] Reduced birth weight associated with higher in utero exposure to DDE could lead to smaller body size in childhood,[38] which in turn would result in higher OC levels at 8 years of age.

Why do Karmaus et al[31] see an effect of DDE, but not of PCB, on growth? If BMI alone were responsible for the findings, the same association should be seen for PCBs. The explanation may be that the PCB levels seen among 8-year-olds in this cohort reflect childhood exposures from nonmaternal sources, most likely fish consumption. Three observations support this hypothesis. First, the trends for PCBs with BMI and lactation are somewhat different than those for DDE. Second, the inverse association of BMI with PCB is stronger than that for DDE, suggesting more current exposure to PCB.[33,39] And third, nonbreast-fed children had PCB levels that were two thirds those of breast-fed children.

Serious gaps exist in current understanding of the mechanisms by which OCs modulate growth and development. A better mechanistic understanding for these observations might enable us to better comprehend the implications to health and to resolve the results of apparent conflicting studies. For example, the inverse association of DDE with height seen in the data of Karmaus et al[31] contrasts with previous findings on the effect of DDE on body size in adolescence,[29] but it is consistent with negative effects of OCs on growth in other studies. A likely biologic mechanism for the findings of Karmaus et al is that DDE is antiandrogenic,[40,41] and that androgens may control growth factors key to body size. If this hypothesis is true, we need to look at DDE/androgen/growth models in epidemiologic studies, such as those that are investigating racial/ethnic differences in androgens and development as they relate to the onset of puberty,[42-44] cardiovascular disease,[45] and breast cancer.[46] PCDD/DFs, PCBs, and PBBs may all affect neuroendocrine function through thyroid, Ah, and hormone receptors. These mechanisms have been explored, but there is a need to consolidate the experimental and human data into a unified mechanistic basis for future epidemiologic research. Such research

may also help to clarify the speculation that the in utero milieu may influence later disease risk.[47-49] For the future, it will be important to separate the effects of in utero from lactational exposure. Better understanding of the source and timing of exposures will clarify research findings and guide public health policy.

Our long experience with human exposure to OCs, particularly to DDT, has found few acute health effects. But meticulous studies such as this report by Karmaus[31] that have carefully measured exposures have documented a series of subclinical deleterious effects. As in the case of children exposed to levels of lead that were insufficient to cause acute toxicity, the individual deficits may be difficult to discern.[50] The population effects are, however, enormous, and have profound effects on societal productivity and even on the sustainability of the human species.

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