CORRESPONDENCE

To the Editor: With great interest I read the recent article by Karmaus *et al.* in *Pediatric Research*, entitled "Early childhood determinants of organochlorine concentrations in school-aged children" (1). The authors investigated whether early childhood factors such as breast-feeding, parity, and maternal smoking during pregnancy contribute to the concentrations of several organochlorine compounds, including polychlorinated biphenyls (PCBs) and hexachlorobenzene (HCB), in children at approximately 7 years of age. They found a strong relationship between breast-feeding and the concentration of all organochlorine compounds investigated, whereas no systematic association was detected for birth order or maternal smoking. I have several concerns regarding these findings as well as the study design.

The study was conducted in the Federal State of Hessen, Germany, in 1994 and 1995. In the study population of 337 children, only 28 children (8%) were exposed to tobacco smoke during pregnancy (maternal smoking after 20 weeks of gestation). In contrast, the number of smoking mothers was estimated to be about 30% in the Perinatal Survey of the State of Hessen in 1996 (2). This significant difference in the number of smoking mothers is obviously the result of the restriction in the present study to parents who reported a consumption of 10 cigarettes per day or fewer. Parents smoking more than 10 cigarettes per day were excluded from the study design. Therefore, the study group presented by Karmaus *et al.* is not representative with regard to the influence of maternal smoking during pregnancy on organochlorine concentrations in the offspring.

The authors assert that neither maternal smoking during pregnancy nor passive smoking of children has any significant effect on organochlorine concentrations in children. Last year we could demonstrate a significant increase in the neonatal burden with PCBs and HCB in offspring of active and passive smoking mothers during pregnancy (3). Whereas these results were obtained from 80 full-term neonates born even in the State of Hessen in 1994–1995, we were recently able to confirm our findings in a large study group of 200 neonates born in 1998 (4). Having in mind the half-life of higher-chlorinated biphenyls, which are suggested between 3.3 and 5.6 years in humans (5), the prenatally increased body burden with PCBs and HCB due to maternal smoking during pregnancy should be vanished in 7- to 10-year-old children. Overall, the study presented by Karmaus *et al.* is not able to make reliable statements about maternal smoking during pregnancy and the later body burden with PCBs and HCB in the offspring.

The total PCB concentration (geometric mean) decreases from 0.43 $\mu\text{g/L}$ in 7-year-old children to 0.18 $\mu\text{g/L}$ in 10-year-old children in the study by Karmaus *et al.* This finding is inconsistent with all previous studies investigating the kinetics of PCBs in humans. The concentration of these organochlorine compounds in men increases steadily during lifetime, with the

lowest concentrations in children and the highest values in the elderly. Recently, the *Umweltbundesamt* has published actual reference values of PCBs in humans (6). Total PCB concentration was 1.3 $\mu\text{g/L}$ in 7- to 10-year-old children and 12.2 $\mu\text{g/L}$ in 56- to 65-year-old people. Furthermore, we were able to demonstrate actual reference values in neonates, which fit very well into the age-dependent reference values established by the *Umweltbundesamt* (7). The results obtained from Karmaus *et al.* need further critical discussion in face of these findings.

Last but not least, having again in mind the half-life of PCBs in humans (see above), it seems questionable that an increase of the body burden with PCBs during the 1st year of life due to breast-feeding will lead to a detectable elevation of these compounds 10 years later (8). The influence of breast-feeding on serum PCB concentrations should be investigated during the 1st year of life, thereby obtaining blood samples at different times up to 12 months of age. Such an investigation is currently under progress in our institution.

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DOI: 10.1203/01.PDR.0000060103.17338.B3

Response

To the Editor: We thank Dr. Gerd-Michael Lackmann for debating our findings. We will respond point-by-point to his questions.

First, we clearly stated that we excluded children who were exposed to higher environmental tobacco smoke (ETS) in their homes (1). Hence, we excluded mothers who currently smoked more than 10 cigarettes. However, we did not exclude children of mothers who smoked during pregnancy. A substantial proportion of mothers stopped smoking during the childhood of their offspring. The restriction in our study is comparable to stratification, focusing on the stratum of children without current ETS but who experienced smoking exposure *in utero*. Regarding current blood concentration of organochlorine compounds (OC) in chronically ETS exposed children, it is practically impossible to disentangle the effect of smoking exposure *in utero* and current ETS exposure, due to their collinearity.

Lackmann *et al.* apparently confuse the argument of representativeness and establishing “causal” associations. Representativeness addresses the question of whether we can generalize from our sample to the universe of all children, *e.g.* from non-smoking households. Even with a non-representative sample based on extreme groups, *e.g.* smoking and non-smoking mothers (2), we can make causal assumptions. Nevertheless, with extreme groups we also have to provide information concerning the extent to which samples were selected or represent the universe of extreme exposures. Lackmann *et al.* were not requested to provide information on the proportion of participation in studies (2, 3).

In our study, we did not identify an effect of ETS in children on OC concentration. Additionally we have several concerns regarding the findings in Lackmann *et al.* (2) suggesting that maternal smoking is related to higher OC concentrations in cord blood. Our major concerns are rooted in Table 1 (2). According to the data, birth weight is substantially higher (≥ 400 g) and gestational age is longer (if only slightly) in the offspring of *actively* smoking mothers, contrary to present understandings of the effects of maternal smoking on fetal growth and gestational age. Current evidence suggests that on average, smoking during pregnancy is associated with a *decrease* in mean birth weight of approximately 200 g (4) and an increased risk of pre-term delivery (5). We would expect a finding so contrary to conventional thinking to be discussed within the body of the article, yet there is no mention of it in the text. This leads us to believe that there may have been a typographical error in the generation of the table.

Under the assumption that the information in the two studies is correct as printed, the reported values are not controlled for possible confounders such as maternal age, sex of the offspring, birth weight, and gestational age. In the first report, according to Table 1 (2), maternal age is oldest, gestational age is oldest, and birth weight is highest in the group of actively smoking mothers. Each of these factors would, by itself, tend to increase the *in utero* exposure of the fetus to both PCB and HCB; each may confound an association between maternal smoking and neonatal PCB and HCB concentrations. In particular, Lackmann reported in the second publication that the sum of PCB is highly correlated with maternal age ($r = 0.52$, $p = 0.0001$) (2, 3). We need to learn whether the maternal smoking effect is sustained once the confounders are taken into consideration.

Additionally, serum concentrations were not lipid-adjusted; with the vast differences reported in birth weight, this could have

a sizable impact on the findings, as PCBs and HCB are lipophilic compounds. Cigarette smoking has been shown to elevate blood lipids in adult women (6, 7). If a similar effect can be detected in the newborns of smoking mothers, failing to report lipid-based organochlorine concentrations could produce a spurious association between cigarette smoking and organochlorine concentrations. The lipid concentration in newborn capillary blood (1-6 days after birth) varies widely (340–890 mg lipids/100 ml) (8). If the blood of a newborn born to a smoking mother, *e.g.* contains a higher proportion of lipids, then the blood concentration of organochlorines might also be higher. One might not be able to attribute this finding to an effect of maternal smoking on organochlorine concentration, but rather to an effect of smoking on lipids. According to a publication of Flesch-Janys and colleagues (9), smoking exposure might induce an increase in the enzymatic *degradation* of organochlorines.

There is a decay in PCB during childhood. Lackmann *et al.* suggested that owing to their half-life, a higher OC-concentration due to smoking might have declined until age 7–10 years. However, in our sample, the effect of breast-feeding did not vanish. Hence, either there is only a spurious association between maternal smoking and OC concentration in cord blood, or, the effect is so small compared to breast-feeding that it could not be detected.

We did not state that the total PCB concentration decreased in 7- to 10-year-old children. A decrease can only be determined in longitudinal studies. However, controlling for body-mass, breast-feeding, etc. (1), we detected a lower concentration in older children. There is no firm conclusion supporting a linear increase of OC with age. A hockey-stick type of association may be a more appropriate description: The levels are higher after breast-feeding, decline until age 10 and increase thereafter. Lackmann *et al.* refer to data provided by the Federal Environmental Office in Germany, not mentioning that the data in children are predominately based on our study (10). Additionally, we did a follow-up in the same children two years later and found that, also highly correlated, the concentrations of different PCB congeners declined in this age group.

Lackmann *et al.* doubt that breast-feeding can lead to an increase of OC approximately 6–10 years after breast-feeding. Longnecker and Rogan, in their editorial, provide evidence from five other studies that increased OC concentrations at different ages in childhood may be due to breast-feeding (11). We agree that an optimal study would follow up children during breast-feeding to monitor the increase of OC. However, collection of blood samples in children is a challenge and burden, and a continuous monitoring would not contribute significantly to the understanding of exposure and OC metabolism. We also were surprised by the strength of the association between breast-feeding and OC levels in the children and assumed that *in utero* exposure would be more important (12). The dogma, however, of whether smoking may contribute to OC levels is of minor importance; sufficiently adverse effects are related to smoking during pregnancy to warrant banning it anyway. We suggest that research needs a more important perspective. A significant question is

whether prenatal or postnatal OC exposure is more detrimental to the child's development.

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DOI: 10.1203/01.PDR.0000060104.17338.7D