ADVERSE HEALTH EFFECTS OF PCBs: INTERPRETING THE EPIDEMIOLOGICAL EVIDENCE

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Introduction

Although polychlorinated biphenyls (PCBs) have been in use for 75 years and dioxin / furan contamination has been known for several decades, current knowledge on their adverse impacts on human health is limited. For example, the U.S. EPA's risk assessment for noncarcinogenic effects of PCBs is based on animal studies carried out with industrial Aroclor products. Their congener compositions substantially differ from the weathered mixture that humans are exposed to. A recent critique has focused on the validity of epidemiological findings. Thus, the American Council on Science and Health concluded:[1] '…there is no conclusive evidence that background PCB levels in the general population, or even the very high levels to which some occupational groups were exposed, have resulted in acute effects, increased cancer risk, "endocrine disruption", or widespread intellectual deterioration in children exposed to PCBs *in utero*.'

Such controversy should inspire an assessment of the weaknesses associated with observational studies of PCB-exposed populations. Interpretation should take into account what can be reasonably demonstrated by such studies. These considerations may lead to improved study designs, and prudent decisions on preventive efforts should involve a cautious evaluation of the epidemiological data. This paper addresses some key issues in regard to exposure assessment, the temporal association between exposure and suspected outcomes, the possible impact of concomitant exposures, and the choice of appropriate outcome variables.

Exposure Assessment

Ideally, the exposure estimate should reflect the concentration of toxic agents at the vulnerable target. The main concern of the analytical chemist is to optimize the analytical quality, i.e., both precision and accuracy. While this issue is crucial, the validity of the results when applied in an epidemiological study must also consider specimen characteristics, e.g., whether a blood sample was taken from fasting subjects, or whether the sample reflects the maternal or the fetal circulation. Fortunately, when the result is expressed on a lipid basis, PCB concentrations are similar in maternal and cord serum (Figure 1, left). However, the correlation shows more scatter when one sample is assessed on a wet-weight basis (Figure 1, right).

Modern congener-specific analyses also allow determination of the non-*ortho*-chlorinated and mono-*ortho*-chlorinated PCBs that are associated with dioxin-like effects.[2] However, within a population with dietary exposure to PCBs from the same sources, the concentrations of different congeners generally show a very high degree of association with one another.[3] Thus, the total PCB concentration, which is mainly based on persistent di-*ortho* substituted PCBs, correlates very well

with the estimated weighted concentration of dioxin-equivalent concentrations of mono-*ortho*-substituted PCBs (Figure 2, left). Thus, such epidemiological studies are unlikely to enable separation of effects that may be attributed to individual PCBs or PCB congener groups.

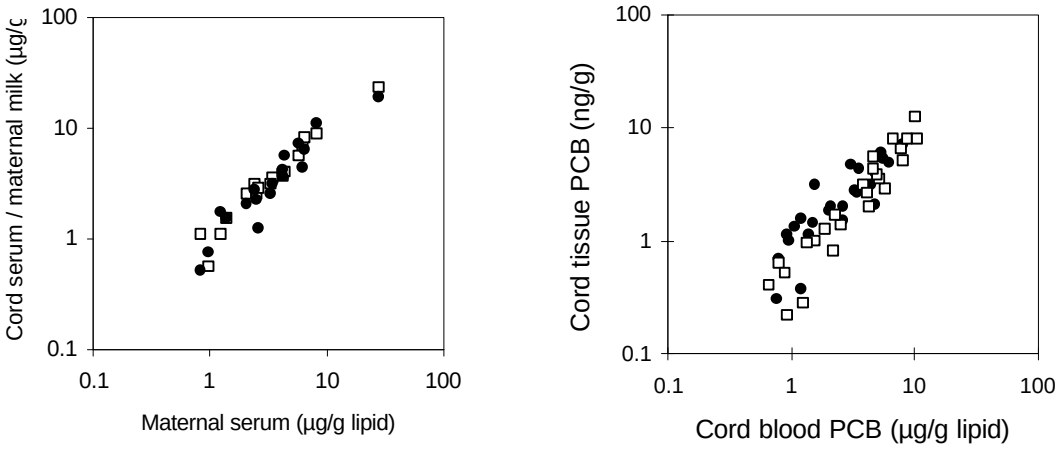

Figure 1. Total PCB concentration in paired samples of (left) maternal serum and cord serum (open squares) and maternal transitional milk (closed circles) (N = 18), and (right) in whole-blood (lipid-based) from the cord and in the cord tissue (wet weight) (N = 50). The total PCB concentration was calculated as the sum of congeners CB-138, CB-153, and CB-180 multiplied by 2.0. Serum and whole-blood concentrations are expressed in relation to the lipid content, while the cord tissue concentration is on a wet-weight basis due to the low lipid content that makes lipid assessment unreliable. The correlation coefficients were 0.97 for maternal and cord serum, 0.94 for maternal serum and milk (left), and 0.83 for cord blood and cord tissue (right). Two different laboratories analyzed cord tissue (open squares and filled circles), and a third analyzed cord blood. Data are from Faroese Cohorts 2 (left) and 1 (right).[4,5]

Temporal Connection between Exposure and Outcomes

The exposure estimate should also be representative in regard to the suspected time of toxic damage. Because weathered PCB congeners are generally highly persistent, a serum obtained today will probably show almost the same PCB concentration as one obtained last year. However, this assumption is true only if the subject maintained his or her body weight and did not substantially change dietary habits. In regard to studies of developmental toxicity, greater changes may occur due to the impact of postnatal exposure from breast-feeding. Thus, although a child is born with a PCB body burden similar to the mother's (Figure 1, left), the resulting serum-PCB concentration of the child after completion of the breast-feeding period may be different (Figure 2, right). If the child has not been breast-fed, the increased body size will result in a dilution of the PCB concentration in the body, while prolonged breast-feeding can lead to levels that exceed those of the mother. Such differences may allow epidemiological studies to determine the relative impact of prenatal and postnatal exposures.[6]

Interpreting exposure estimates in regard to time windows of vulnerability is of course of key importance in developmental toxicity studies. However, its relevance to cancer studies has not been properly emphasized. Thus, most studies of PCB-associated cancer have determined the subjects' exposure from a serum or tissue sample obtained at the time of diagnosis or up to a few years before. Not surprisingly, most of these studies have failed to document a significant effect of the serum PCB concentration. The absence of statistical significance may be due to exposure misclassification and does not necessarily indicate a lack of an effect.

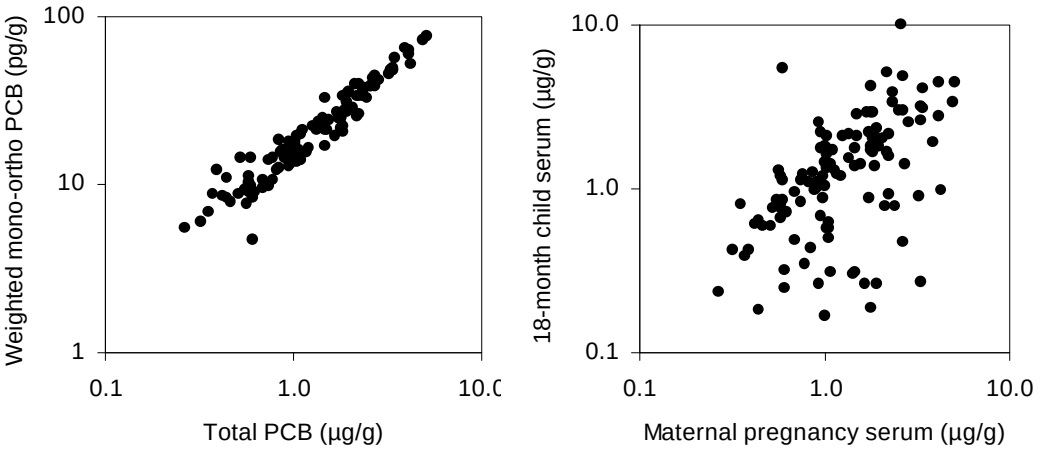

Figure 2. Total and dioxin-equivalent weighted mono-*ortho* PCB concentrations in maternal serum (N = 119) (left) and total PCB concentrations in maternal pregnancy serum and the child's serum at 18 months of age (N = 116) (right). The total PCB concentration was calculated as the sum of congeners CB-138, CB-153, and CB-180 multiplied by 2.0, while the concentrations mono-*ortho* congeners CB-105, CB-118, and CB-156 were added after multiplication by the dioxin toxicity equivalency factors.[2] All concentrations are expressed in relation to the lipid content. The correlation coefficients were 0.96 for analyses of maternal serum, and 0.53 for PCB in maternal and child serum samples. Data are from Faroese Cohort 3.[7]

In most cases, exposure imprecision is likely non-differential, i.e., the coefficient of variation will be independent of the level of exposure. Such misclassification will lead to an underestimation of its true association with the outcomes. The dose-effect or dose-response relationships then become biased toward the null hypothesis: The greater the imprecision, the larger the bias. In addition, adjustment for confounders may further dilute the dose-association with the outcome. Sensitivity analysis may provide adjustment for the effects of the exposure misclassification, but it requires that the imprecision is known. Due to toxicokinetic factors and other preanalytical variation, laboratory reproducibility alone will substantially underestimate the total imprecision of PCB exposure biomarkers. Thus, if laboratory imprecision is used for such adjustment, the association with outcome parameters will remain biased.

Concomitant Exposures

PCBs occur in the environment with other lipophilic and persistent pollutants. As with correlations between PCB congeners themselves, other contaminant concentrations are often closely associated with those of the PCBs. However, the contaminant profile will vary geographically, it will depend on the trophic level of the diet, and will change with time. In human studies, much attention has been paid to chlorinated dibenzo-*p*-dioxins and associated furans, chlorinated pesticides, and methylmercury. Concomitant exposure to such compounds can increase the apparent PCB-associated risk, unless adjustment for the concomitant exposures is carried out. However, if the concomitant exposures are highly associated with PCB, this confounding is difficult to resolve.

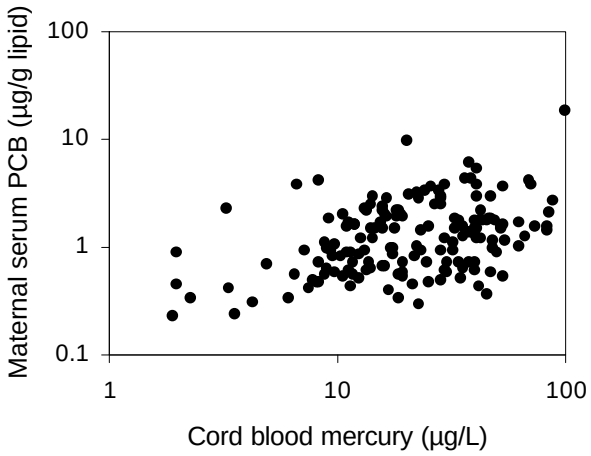

Figure 3. Total PCB concentration in maternal pregnancy serum and the mercury concentration in cord blood (N = 182). The total PCB concentration was calculated as in Figure 1. The correlation coefficient was 0.43. Data are from Faroese Cohort 2.[4]

In some cases, adjustment for this confounding effect is possible; e.g., in regard to methylmercury when the association between mercury and PCB concentrations is not close (Figure 3). In a study of Faroese birth cohort 1, the neuropsychological test results suggested PCB-associated deficits.[5] However, this association disappeared when adjusted for the mercury exposure level. On the other hand, when the children were separated into three groups according to the mercury exposure tertiles, a PCB effect appeared most clearly in the group with the highest concomitant methylmercury exposures.[5]

Outcome Indicators

Effect parameters must be chosen with careful attention to the *a priori* hypotheses. An insensitive outcome test may lead to underestimation of the true effect, and non-specific effect measures are often subject to confounding. Among additional considerations, all tests should be appropriate for the age and culture, they should be conducted by highly skilled professional examiners and should employ feasible, modern technology.

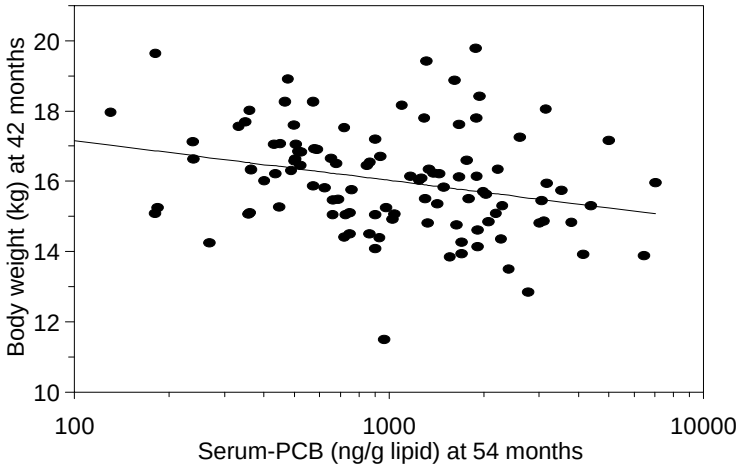

Figure 4. Total PCB concentration in serum collected from Faroese Cohort 2 children at age 54 months in regard to the most recently assessed body weight (at 42 months). The body weight has been adjusted for sex, birth weight, and maternal smoking during pregnancy, while the serum-PCB concentration has been adjusted to an average ponderal index.[6]

The PCB-associated adverse effects that have attracted most attention are postnatal growth, neurobehavioral development, immune function, and cancer. One complication in human studies of postnatal growth is that breast-fed children in general show smaller increases in height and weight as compared to children who are bottle-fed. Although the extent of this effect appears to vary for unknown reasons, the significance of PCB exposure from breast-milk has only recently been determined. A prospective study of the Faroese Cohort 2 replicated the inverse association of body weight and height with duration of breast-feeding, but this effect was fully accounted for by the calculated amounts of methylmercury or PCB transferred to the infant through human milk.[6] In addition, the confounder-adjusted body weight at 42 months was negatively associated with the child's PCB concentration in the serum (obtained with a delay of 12 months) (Fig. 4).

The available evidence documents that subtle neurobehavioral effects may occur as a result of both prenatal PCB exposure and transfer via breast-milk.[8] Although immunotoxic effects provide the basis for the U.S.EPA's evaluation of non-carcinogenic risks due to PCB exposure, too little is known about effects in humans on clinically relevant immunological parameters. While previous studies have suggested some adverse effects, increasing evidence now indicates that antibody responses to childhood vaccinations may be adversely affected by developmental PCB exposures.[7] This new information may very well lead to lower exposure limits.

Conclusions

Epidemiological studies are crucial to risk assessment, but offer only incomplete insight due to the limitations of observational studies, which depend, e.g., on study opportunities. Often the follow-

up is too short, or the exposure estimates do not reflect the long induction time of the health outcomes under study. These problems tend to cause an underestimation of the true effects caused by PCBs. On the other hand, confounding from concomitant exposures to other toxic substances may be difficult to control for and may therefore cause an overestimation of the effects. Due to the high correlation of PCB congeners, such population studies are unlikely to reflect toxicity differences between congeners. Still, the associations found appropriately reflect the prevalent exposures to pollutant mixtures, where PCBs constitute a major part.

In designing future studies, populations should be identified, where exposures cover a wide interval and are only weakly related to socioeconomic and other confounders. Preferably, more than one exposure variable should be obtained, and they should reflect the time period of greatest relevance for the outcome variables chosen. Because of high correlations between congener concentrations, analytical efforts should focus on the most prevalent lipophilic contaminants, while detailed population exposure profiles may be characterized from analysis of pool samples. Joint studies or meta-analyses of comparable cohorts may enable comparison of outcomes related to different exposure profiles. Although the potential effects have been insufficiently studied so far, accumulating evidence suggests that clinically important deficits in neurobehavioral and immune function may occur at widely prevalent exposure levels.

While more insight is being gathered, prudent prevention should be based on cautious interpretation of the available documentation, rather than a harsh and unfounded critique like the one quoted in the Introduction. The absence of statistically significant associations by no means indicates that an effect is not present. Emphasis should be placed on confidence intervals rather than p values. In addition, the likely underestimation due to imprecise exposure assessment and insensitive outcome variables should be taken into account. Because the PCBs are highly persistent, the exposures will remain and will continue to provide challenges to risk assessment.

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