Hypothesis/Commentary

Pharmacokinetic Variability and Modern Epidemiology—The Example of Dichlorodiphenyltrichloroethane, Body Mass Index, and Birth Cohort

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Background

Exposure misclassification is a serious concern in environmental epidemiology, as errors in the dependent variable (exposure) may dilute or magnify the effect size. Exposure biomarkers overcome many sources of bias in exposure assessment, but they have limitations that are often overlooked. One such factor is pharmacokinetic variability: It is much neglected, but is not easy to incorporate into epidemiology research. A single biomarker measurement has been considered robust for agents such as dichlorodiphenyltrichloroethane (DDT), because it accumulates in the body and levels change only slowly. Other carcinogenic halogenated hydrocarbon compounds (HHC), including dichlorodiphenyl dichloroethene (DDE), 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, polychlorobiphenyls (PCB), polybrominated biphenyls, hexachlorobenzene, hexachlorocyclohexane, and chlordane, behave the same. These lipophilic compounds or their residues are neutral, poorly metabolized, and have long elimination half-lives (~10 years). Because HHC biomarkers reflect long-term cumulative exposure, they logically fit an etiologic model for cancer and other chronic diseases hypothesized to have causal exposures that precede diagnosis (and sample collection) by a long latency period. In fact, >90 original investigations have been published on HHC as a factor in etiology and prognosis of cancer since 1976. Breast cancer has been most widely investigated, but research has also implicated HHCs in non–Hodkin's lymphoma (1) and testicular cancer (2), among others. HHC have also been studied in relation to noncancer effects, including fertility, fecundity, pregnancy outcomes, child growth, sexual maturation, neurologic development, diabetes, cardiovascular disease, and degenerative neurologic diseases (3-6).

In this commentary, we summarize recent evidence suggesting that pharmacokinetic variability may cause exposure misclassification when using a single HHC measurement. A few reports have addressed specific pharmacokinetic issues, signaling their importance, including windows of exposure, adiposity, race, and genetics. Pharmacokinetic variability deserves our attention for several reasons, among them the need to promote recognition of pharmacokinetic variability in biomarkers, the desire to understand its effect on disease models, and an appeal to consider ways to incorporate this knowledge into epidemiology. *Cancer Epidemiology Biomarkers & Prevention* has been an active forum for such exchanges, including many methodologic and etiologic reports on HHC measurements. We discussed pharmacokinetic variability in a letter to the journal in 1999 (7), which stimulated our further detailed investigation of HHC and body mass index (BMI; ref. 8). The 1999 letter was also generously cited in another *Cancer Epidemiology Biomarkers & Prevention* article (9), the report that prompts the current comment.

Assessing Pharmacokinetic Variability in Statistical Models

Associations of BMI with HHC Levels. Our foray into this arena began with an attempt to explain reported disparate correlations between DDE and BMI (7), and in particular the positive association seen by Schildkraut et al. (10). As noted (7), a positive correlation seemed intuitively correct, but in fact a negative correlation between DDE and BMI is dictated by simple pharmacokinetics. To recap this argument briefly, during uptake or absorption of DDT the pharmacokinetic model predicts an inverse relationship because DDT concentrations in low-BMI persons will be greater than in those with a high BMI (Figs. 1 and 2). For example, a low-BMI person with intake of 20 μg of DDT and 10 kg of adipose would have a DDE level of 2 μg/kg lipid, whereas someone with the same exposure and 20 kg adipose (high-BMI) would have 1 μg/kg DDE-lipid.[5] Thus,

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[5] This example assumes similar uptake regardless of BMI; the main DDT dietary sources are unlikely to be disproportionately consumed by high BMI persons enough to equalize the lipid-based concentration for lean and obese body sizes. In other words, even if caloric intake were entirely responsible for higher BMI, it would not be directly proportional to DDT intake (34, 35). If a high-BMI person in the example ingests twice as much of a single DDT source (e.g., milk), the net adipose concentration would still be the same or lower than in the low-BMI person.

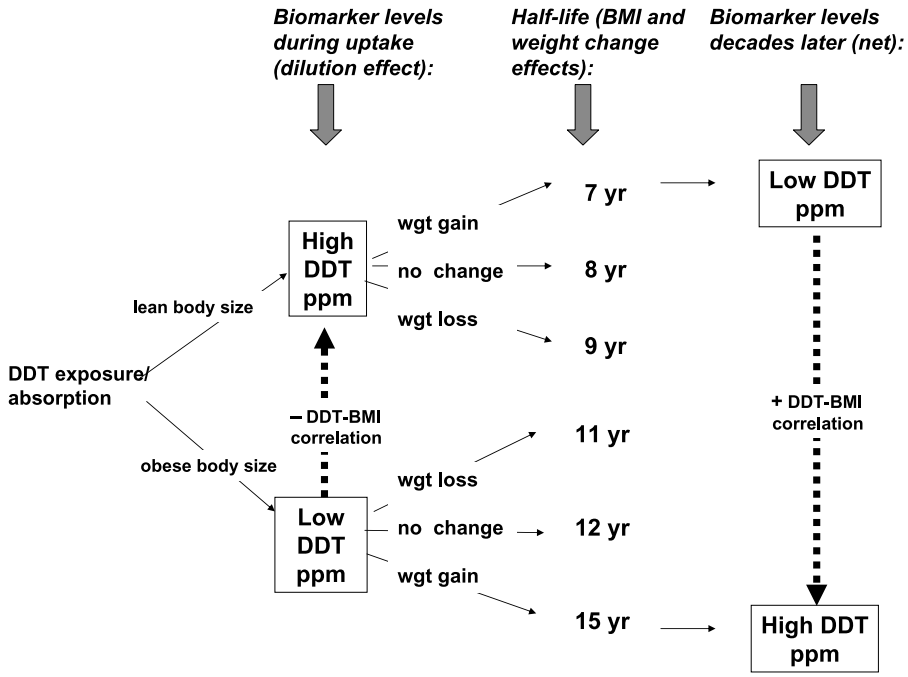

Figure 1. Summary of body size effects on DDT levels in lipids. Early effect is dilution (*Biomarker levels during uptake*). Subsequent postexposure effects on DDT levels decades later result from DDT half-life, including weight change alteration of elimination rate (*Biomarker levels decades later*); half-life estimates are based on those from Thomaseth and Salvan (12).

because of the greater lipid denominator in obese persons, with comparable uptake their concentrations should be lower than those of lean individuals. Hence, correlations of DDE with BMI would be negative (like those in ref. 9). This is shown in Fig. 2A, which is a vertical slice of Fig. 2B at one time point (e.g., 1962), simulating cross-sectional data collected in that year. The ''plot'' of 1962 cross-sectional data in Fig. 2A shows an inverse relationship between lipid concentrations of $DDT_{adipose}$ and BMI because $DDT_{adipose}$ decreases as BMI increases from low to high; the slope of the $DDT_{adipose}$-BMI relationship is −258 as estimated from $\Delta(DDT_{adipose}) / \Delta BMI = (5{,}160 - 2{,}060\ ng/g) / (23 - 35\ kg/m^2)$. If measurements were made in blood on a volume (wet) basis as in ref. 9, the slope would be $-1.8(DDT_{blood})$, assuming that blood serum is 0.7% lipid

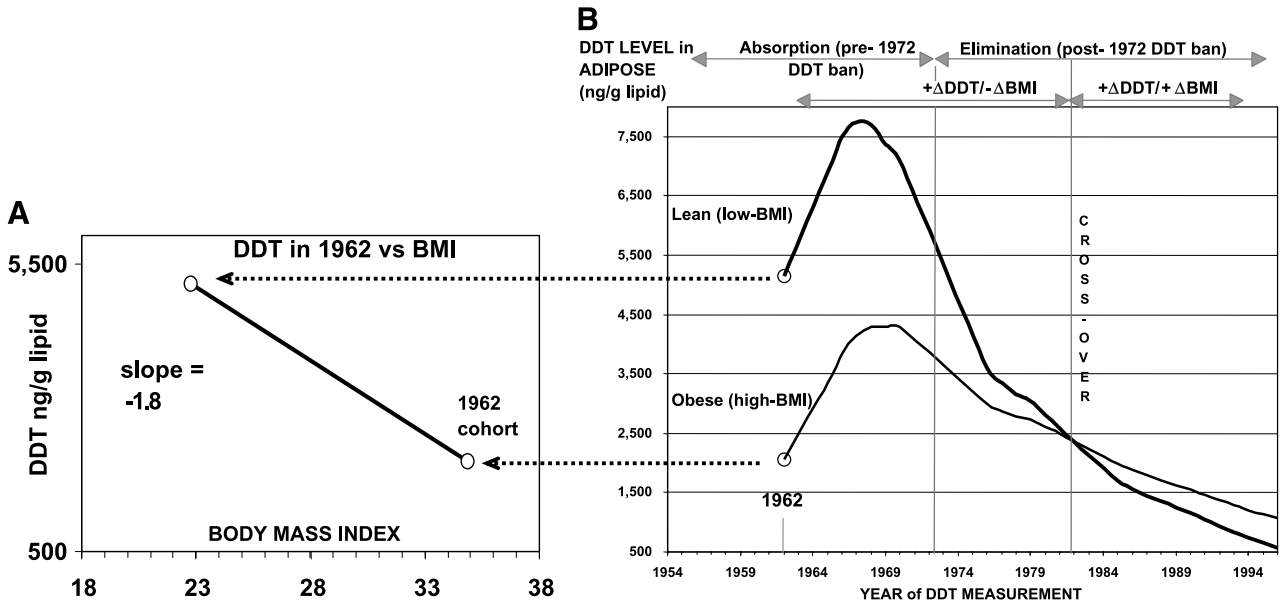

Figure 2. A. *Left,* the expected relationship between DDT and BMI in a cross-section of Fig. 1B at 1962 (slope = −1.8) **B.** *Right,* single birth-cohort model of DDT with two extremes of BMI where first exposure starts in 1962 (modified from ref. 8). DDT levels in adipose lipids for a lean BMI ($\sim 23\ kg/m^2$) are in the upper DDT curve. Levels for an obese BMI ($\sim 35\ kg/m^2$) are in the lower curve.

(blood, milk, and adipose concentrations are identical if based on lipid content).

This reasoning is at odds with the reported positive correlation between HHC and BMI such as those in ref. 10. We proposed an explanation—that BMI altered HHC pharmacokinetics during the elimination phase after a cessation of substantial exposure (7). In North America, this phase began around 1970 for DDT as HHCs were removed from the diet and the physical environment. A marked secular decline was seen in blood, milk, and adipose HHC concentrations in North America and elsewhere at a rate almost exactly the average elimination HHC half-life of ~10 years (11). However, the average clearance rate encompasses extremes that depend on total body fat depot. The HHC half-life is longer in obese than in lean individuals, so that obese persons were predicted to eliminate DDE more slowly as shown by longitudinal data (7, 12, 13). As a result, after two or more half-lives, DDT levels among lean and obese persons converge (post-1982; Fig. 2B). After this crossover point, the body burden becomes greater in high- versus low-BMI individuals, and the DDT-BMI correlation flips from negative to positive. As seen in Fig. 2B, correlations between BMI and DDT would become positive after 1982; for example, in 1996, $\Delta DDT/\Delta BMI = (1{,}060 - 575\ ng/g) / (35 - 23\ kg/m^2) = +40$ for adipose-lipid basis and +0.3 for blood-wet basis. More recently, we recognized that weight change (or BMI change) profoundly alters these relationships, as elegantly shown using longitudinal data of tetrachlorodibenzo-*p*-dioxin and body size measurements (12). Weight gain subsequent to exposure shortens the HCC half-life by diluting the body burden (yielding an inverse HHC–weight gain correlation), whereas BMI lengthens elimination time and increases half-life (Fig. 1, *right side*; ref. 8). Weight gain is not included in the Fig. 2 models; during elimination, weight gain would lower the curve whereas weight loss would increase it (see Fig. 6 in ref. 12). As cohorts age, especially cohorts of children and older women, weight gain or BMI increase is likely to be a significant determinant of HHC concentrations. Weight gain during growth accounts for inverse correlations of age with HHC and shorter half-life among children (14).

Therefore, BMI, weight change, and time since peak exposure are key factors in pharmacokinetic variability of a single HHC biomarker. For a single measurement, some idea of how pharmacokinetic variability may affect accuracy can be gathered from crude and adjusted associations of HHC with BMI and weight gain. For example, in two breast cancer cohorts of older women (ref. 8 and unpublished data from ref. 15), both DDE and PCB were positively associated with BMI, but negatively associated with weight gain in multivariate linear regression models. However, crude correlations of DDE with both BMI and weight gain were positive, whereas PCB was negatively correlated with both. Of the 16 studies listed in Table 1 of ref. 8, 10 had positive DDE-BMI correlations, 3 had essentially zero correlations, and 3 had negative correlations. The mean interval between DDT ban (1972) and blood collection was 17 years (median 21 years), 15 years (median 15 years), and 1.7 years (median 4 years), respectively. For PCBs (8), 10 of the 16 cohorts had negative correlations with BMI, suggesting ongoing or recent exposure. Presumably, the direction of these correlations would be reconciled if estimates were adjusted for both BMI and weight gain and other characteristics such as age and lactation.

Timing of Exposure and HHC Levels—Onset of Exposure. A new wrinkle arose in this argument with the noteworthy report from Perry et al. (9), which found that the magnitude of the negative slope for DDT versus BMI varied by year of birth independent of age. First, the strong negative association between DDT residues and BMI indicates that exposure was recent and/or ongoing. Second, the negative correlation was larger with earlier birth year (older cohorts had a greater negative DDT-BMI slope, age-adjusted). These novel findings provide an opportunity to revisit HHC pharmacokinetic variability. Our original model can be said to predict DDT body burden for a single birth cohort (i.e., 1962 in Fig. 2). When this model is adapted to depict DDT levels in sequential birth cohorts (Fig. 3), the observed DDT-BMI relationships in successive cohorts behave just like those reported by Perry et al. (9). That is, later birth cohorts (i.e., younger individuals) have smaller negative slopes ($\Delta DDT/\Delta BMI$) in their first 10 to 20 years of exposure. Younger cohorts have lower DDT concentrations during peak exposure periods because their accumulation time (duration) is shorter (Fig. 3B). During the exposure period, distances between DDT curves for lean and obese persons are smaller for later birth cohorts (equivalent to smaller negative slopes, Fig. 3A). In Perry et al., the largest negative DDT-BMI slope was observed for the oldest cohort (−2.82); it became successively smaller in younger cohorts (−1.24, −1.16, and −1.03 for DDT in ng/g lipid versus BMI in kg/m^2). In Fig. 3A, for the first year of DDT exposure for the 1962, 1965, and 1967 cohorts, the model-estimated slopes for blood are −1.8, −1.5, −0.8, respectively (using 0.7% serum lipid to extrapolate to serum wet basis, which is the unit reported in ref. 9).

Therefore, an important implication of Perry et al. (9) is that birth cohort can be a surrogate for onset of exposure. Within a population, the resulting correlation between HHC and BMI differs by exposure onset, which reflects both intensity and duration. Duration of exposure may be captured by ''birth cohort''; in Fig. 3B, it is the window between birth date (or onset date if exposure begins after birth) and sample donation. Intensity (concentration) is cumulative exposure during the window; that is, $\Sigma_{\Delta t}$uptake − $\Sigma_{\Delta t}$elimination. In Fig. 2, intensity was derived from reported levels of dietary and ambient DDT contamination in the United States, which peaked around 1965 (8). During a long interval of exposure involving uptake and elimination, weight gain will differ for each birth cohort, and this will alter correlations of HHC with BMI at the time of HHC measurement for different cohorts. Weight gain surely would be greatest for the oldest cohort. Although weight loss reduces HHC levels and shortens half-life, only a small proportion of individuals lose weight over time (8, 12). However, weight loss may pose a serious problem for HHC measurement near the time of diagnosis for some cancers (16, 17). In the Fig. 2 models, environmental DDT contamination was known to change over time. A likely peak occurred around 1965 to 1970 (8), because DDT use had declined before it was banned in 1972. Because the model in Fig. 2 fits the Perry et al. (9)

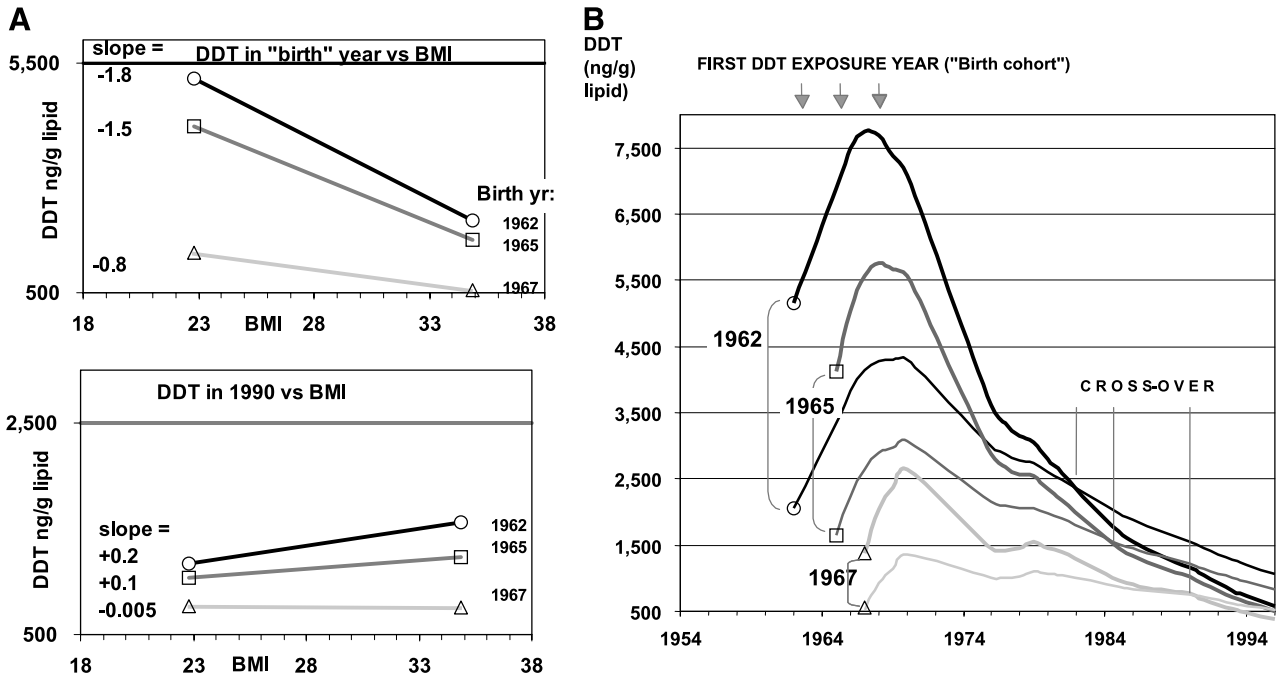

Figure 3. A. *Left bottom,* expected relationships between DDT and BMI in the 1962, 1965, and 1967 birth cohorts shown in Fig. 2B. *Left top,* in 1970, before crossover, the graphs all have negative slopes (−1.8, −1.5, −0.8). *Left bottom,* in 1990, after crossover, the same three cohorts in the DDT-BMI graphs have zero or positive slopes (+0.2, +0.1, −0.005). Models assume no weight change. **B.** *Right,* models for DDT levels in six cohorts, 1962, 1965, 1967, each with a low- and high-BMI DDT curve.

findings, it suggests that some similarities exist for historical patterns of DDT contamination in China. DDT use was banned in China in 1983 (18) or 1984 (9), and the Perry et al. birth cohorts were measured 13 to 14 years afterward (9). A model like Fig. 2 for PCBs is more uncertain because of continuing exposures, but it is similar, with lower $PCB_{adipose}$ concentrations and later crossover. Other exposure scenarios, such as sporadic or steady environmental contamination, would require a different model; the basis for such models can be found in examples in ref. 19.

The birth cohort models provide other interesting dimensions of pharmacokinetic variability. First, the crossover point for high- versus low-BMI curves is later for cohorts who are younger or who have lower exposure. In Fig. 3B, obese and lean pharmacokinetic curves from younger birth cohorts converge at later points in time compared with older cohorts. Here, the DDT curves for obese and lean in the 1962 cohort crossover in 1982. Successive cohorts (1965, 1967) crossover in 1984 and 1990. In general, low- and high-BMI DDT curves converge ~20 years after birth for the three cohorts; this is also 17 to 25 years after DDT dietary contamination peaked in 1965 (Fig. 3B). Decades later, in the 1990 cross-section (Fig. 3A, bottom), DDT-BMI slopes are +0.2, +0.1, and −0.005 for the three sample cohorts, respectively (blood serum wet basis). Second, relative to our Figs. 2 and 3, the crossovers in the Perry cohorts are likely to occur earlier than 20 years postexposure because of the relatively low BMI of their women (mean BMI 20 kg/m^2, mean age 25 years, mean DDE 28 ng/g; ref. 9) compared with those used in Figs. 2 and 3 (23 kg/m^2 for low BMI; 35 kg/m^2 for high BMI). If the model in Fig. 2B is modified to depict lower BMIs (26 and 30 kg/m^2), these DDT curves cross the low-BMI (23 kg/m^2) curve earlier than the transition shown at 1982 for BMI 35 kg/m^2 (not shown). The DDT graphs for BMIs of 26 and 30 kg/m^2 cross that for BMI 23 kg/m^2 in 1968 and 1976, respectively (not shown). Indeed, this observation explains the strong positive correlation of DDE with BMI found in an older Shanghai cohort (mean BMI 23, mean age 49 years, mean DDE 34 ng/g). They were recruited at the same time as the Perry cohorts (1996-1998; ref. 18), but their exposure duration was longer. Which specific variables are most important and their relative contribution to variance might be further clarified by constructing models for these two populations (9, 18) that included BMI, weight gain, age, birth cohort, and possibly historical DDT levels in China. In summary, a cohort effect on crossover is partly responsible for the large variance (and small correlation coefficients) seen for DDT-BMI relationships in cross-sectional studies where birth dates vary and where great heterogeneity exists in BMI and weight gain over time among cohorts (see examples in Table 1 of ref. 8).

Future Directions

Is it possible to reduce misclassification by incorporating appropriate covariates into statistical analyses? For cross-sectional studies with a single biomarker of exposure, risk models might be improved by including known and suspected pharmacokinetic factors and environmental

exposure information. Longitudinal data on both biomarkers and covariates would be ideal, even if only available for a subset. Misclassification from neglecting pharmacokinetics may be less important for cancers with shorter latency such as lymphoma (1).

For a single HHC measurement, joint consideration of the effects of birth cohort (or other quantifiable exposure source and timing), weight gain, and BMI within a study population is a start. Birth cohort, independent of weight gain and BMI, is possibly a surrogate for onset of exposure, which can then be used to compute exposure duration and intensity. Weight change and BMI are possible surrogates for individual differences in absorption and excretion. Additional information on diet, residence, metabolizing enzymes, lactation history, occupation, disease states such as thyroid disease or diabetes, or medication use may further sharpen the exposure estimates. Medications that alter lipid metabolism or their uptake might also affect HHC levels. Statistical methods would also benefit from more precise pharmacokinetics; these might be improvements on the simple first-order kinetics used in Fig. 2 such as nonlinear models having time-transfer functions to accommodate temporal changes (12). The utility of such an approach could be evaluated from existing studies; at least 90 investigations of HHC in relation to breast cancer and other cancers exist. Most of these studies were undertaken after 1995 and in developed countries, where use of many HHC had been banned decades earlier: Much of the interindividual differences could be due to pharmacokinetic variability. Some study populations, such as breast cancer, could be most useful as they are limited to one sex, older age, etc. These uniform characteristics make them amenable to pooling data, which might provide more power to examine effects and interactions among birth date, BMI, and weight gain. Additional insight can be drawn from data on HHC and body size among women who have been studied at other ages where effects of BMI on HHC are strong (20-24) but often neglected (23, 25). To some extent, proper adjustments for BMI may mitigate differences in HHC levels seen by sex in various populations. It might be helpful to know which factors have the greatest effect within a cohort. For example, age is less important than duration of exposure as an HHC predictor in occupational cohorts. BMI may be more important during absorption phase, and weight gain during the elimination phase, of exposure. There may be a need to look for ways to handle HHCs, such as PCBs, where there are both ongoing and long past exposure- and congener-specific half-lives.

Even better, sequential biological measures and other key information could be obtained longitudinally to capture important secular trends that contribute to pharmacokinetic variability in biomarkers. Several published studies on breast cancer have measurements of HHC at more than one time point (13, 26), which could be used to test models constructed with a single HHC measurement in blood or other tissue (or vice versa).

In future studies that use a single blood draw, models for past and future HHC levels could be constructed to inform the accuracy and precision of single HHC measurements. A second biological specimen, some distance in time apart from first, would be a useful even if it were obtained only in a representative subset. In chronic disease research, repeat samples on a small subgroup of a cohort over multiple years could be used to examine trends in a number of biomarkers over time, such as markers of susceptibility, biological effect, nutrients, and lipids. A repeat questionnaire could collect additional relevant data such as lifetime BMI, lactation, specific determinants of exposure, and temporal trends of the organochlorine exposure sources. The ideal timing of repeat biospecimens would be a key consideration; for example, to assess half-life, the optimal interval between measurements is one half-life (27). Thus, for HHC, an interval of at least 5 years might be required to evaluate half-life, whereas shorter intervals may be useful for effects of chemotherapy or weight loss (28-30). Investigations of pregnancy involve a shorter exposure interval than chronic disease research, requiring somewhat different pharmacokinetic considerations. For example, weight gain is strongly related to birth outcomes and to HCC levels (20) as well as to serum lipids (31).

Meanwhile, there is no better way to estimate HHC exposures from environmental (nonpoint) sources than to measure residues in biological samples. It is key to understand limitations and how best to use the data and what covariates must be considered. At the same time, similar approaches can be taken to consider limitations in other types of exposure data. Examples abound in nutritional epidemiology, where much research is done to supplement or validate misclassification of standard food-frequency questionnaires. Moreover, the basic pharmacokinetic principles are identical for other exposure biomarkers that have a significant body compartment, including lead (bone mineral) or dilution effect (urinary creatinine). With these measurements, there is acknowledged variability arising from genetic differences, sex, age, race, bone density, and BMI among other factors (32). Finally, a more critical problem arises when there is mutual confounding, such as where BMI is related both to HHC level and outcome (cancer, diabetes, birthweight, child growth, endometriosis) or diet (animal fat intake). Here, even if the confounding cannot be resolved, the limitations can be understood and design changes can be made to improve later studies. Thus, at the very least, pharmacokinetic variability issues should be appreciated even if they cannot be resolved (33).

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