Letter to the Editor


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The paper by Schildkraut et al. (1) offers an opportunity to comment on issues affecting body burden measures of persistent OCs.2 Our attention first was drawn to this question in recent studies of breast cancer where OCs were assessed (2–4). Similar to the report by Schildkraut et al. (1), several of these papers report a positive association between OC levels and BMI. At first glance, these positive associations are not entirely consistent with basic principles of pharmacology concerning body burdens of persistent lipophilic compounds.

As we have discussed, where recent exposures are substantial, absolute uptake of OCs (e.g., absorption of exogenous contaminants) exceeds elimination (5). Under these circumstances, the OC body burden will increase and be reflected in a higher serum OC concentration. Serum OCs are in passive pharmacodynamic equilibrium with the adipose reservoir of the individual. As a result, obese, high BMI women with a larger adipose reservoir should have lower levels, consistent with an inverse (negative) association of OC levels in blood or adipose tissue with BMI, when compared with similarly exposed thin, low BMI individuals. This relationship has been described (5). In other words, given similar mass absorption (mg of OCs), dilution by a larger adipose reservoir (kg) leads to lower levels (mg of OCs/kg adipose) in the body of obese persons (e.g., see Fig. 1 at t = −20 to 0 year). This also may explain many reports that males had higher levels than females (6, 7).

In their recent report of OC levels around 1980, Dorgan et al. (8) found negative associations of BMI with PCB but not DDT. Similarly, in our report (5), PBB (a source of recent exposure) levels in adipose showed this pattern, e.g., negative associations with BMI and female sex. However, DDE did not. In addition, in this study we also observed that during the elimination phase, if uncomplicated by further exposure/uptake, removal of both DDE and PBB were slower by about half in obese persons (upper versus lower quartile of BMI).

To explain these apparent inconsistencies, we used these parameters in a simple pharmacokinetic model (5). We found that only after ~15 years, or 1–2 half-lives after exposure ends, could a positive association with obesity be seen (see Fig. 1). Clearly, many factors, including underlying metabolism rates, ratio of continuing exposure to elimination, lactation, and weight gain or loss, may alter this model. Unfortunately, no longitudinal studies are available to elucidate such details.

Turning to the recent paper examining extremes of BMI with DDE levels, Schildkraut et al. (1) report significant positive associations of OCs with age, BMI, breast-feeding, and African-American ethnicity; nonsignificant positive associations with waist-to-hip ratio, rural residence, and fish intake; and negative associations with weight loss and weight gain. We suggest that these patterns are related to the pharmacokinetics of DDE in the study population. The present DDE (but not necessarily PCB) levels probably represent a long period of elimination exceeding intake, i.e., a long gap between the last significant exposures and measurements of DDE, as in Fig. 1. Differences between African-American and Caucasian women may also be attributable to pharmacokinetic differences between the two groups.

Recent data on population and individual half-lives of OCs (DDE, dieldrin, PBB, and TCDD) are remarkably similar (6–12 years; Ref. 9). Also, their contents in adipose tissue, serum, and breast milk are identical (1:1:1 on a lipid basis; 10, 11).

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2 The abbreviations used are: OC, organochlorine; BMI, body mass index; PCB, polychlorinated biphenyl; PBB, polybrominated biphenyl; DDE, bis(4-chlorophenyl)-1,1-dichloroethene.

3 Parenthetically, Schildkraut et al. (1) decided not to lipid-adjust their serum DDE concentrations because there was no correlation between serum lipids and serum concentrations. The purpose of lipid adjustment is to minimize intridual variability and to approximate most closely the adipose tissue concentrations, as demonstrated by Phillips et al. (10), whose authors found that this procedure afforded an average improvement in intridual variability of 10%.
However, associations between BMI, parity, lactation, absorption, metabolism, and levels of DDE, PCB, and PBB differ in various reports since 1970. These variations may be attributable largely to timing and duration of OC exposures relative to the time they are measured in the body, including whether (and when) the exposures have ceased. Therefore, the use of current OC body burden measurements in epidemiological studies may require a statistical approach that pays more attention to potentially important information on timing and duration of OC exposures as well as body mass.

If earlier, past peak concentration of OCs circulating in serum is important in disease causation, then BMI may be an important effect modulator (protective) when the study population has a positive OC-to-BMI relationship. Although the high BMI individuals comparatively have elevated OCs, it is the low BMI individuals who are likely to have had the highest concentrations one to two decades earlier.

References

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