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Fecundability and Serum PBDE Concentrations in Women

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Harley et al. (2010) reported that as serum concentrations of BDE-47, BDE-99, BDE-100, and BDE-153 [polybrominated diphenyl ether (PBDE) congeners] increased, the time to achieve conception also increased (Harley et al. 2010). Although PBDE concentrations in serum were measured only near the end of the second trimester of pregnancy, the authors reported that the association with a longer time to achieve pregnancy was likely causal. This conclusion is inappropriate for the following reasons.

Although PBDEs are persistent, levels are not completely static, and it is not known how much these levels change in an individual over time, or how PBDE levels during the second trimester of pregnancy differ from those before pregnancy. Given that the interquartile ranges (IQRs) of BDE-47, BDE-100, and BDE-153 were quite small (all with the ratio of the 75th percentile to the 25th percentile being < 3.5) and that exposure measurements were taken only once near the end of the second trimester of pregnancy, even a small difference between the measured PBDE level and the actual levels prior to conception could have led to a relatively high degree of exposure measurement error, biasing the results.

Harley et al. (2010) assessed fecundity using the Cox proportional hazards model. There are two major assumptions of this model. First, there is a multiplicative relationship between the hazard function and the log-linear function of covariates. Harley et al. (2010) did not discuss a mode of action by which this could occur. The second assumption is that the impact of each covariate on hazard remains the same during the entire follow-up period, meaning that all covariates must affect risk in the same proportion over time to prevent a biased risk estimate. The authors did not demonstrate that this is likely the case, either for PBDEs or other covariates.

Many factors can affect when or if pregnancy occurs. Among those not evaluated by Harley et al. (2010) are the timing and frequency of sexual intercourse, the number of potential partners, the timing of ovulation, alcohol consumption (e.g., number of drinks per day), smoking (e.g., number of cigarettes per day), drug use and type, stress-related factors, and paternal factors such as health status, chemical exposures, and behavior

(e.g., Eggert et al. 2004). All of these factors could have confounded the reported associations.

The analysis of Harley et al. (2010) also suffers from selection bias—that is, they included only women who became pregnant. The authors explained that if PBDEs are associated with decreased fecundability, then exclusion of nonpregnant women who were trying to get pregnant would bias results toward the null. However, they neglected to discuss the possibility that if PBDEs are not associated with decreased fecundability, excluding these women would bias results away from the null. Because this is precisely the hypothesis being tested, making assumptions either way is inappropriate.

Harley et al. (2010) suggested that interviews conducted at the beginning of pregnancy led to a short recall time for time-to-pregnancy information. They cited several articles on recall of time to pregnancy and menstrual cycle characteristics, but they did not demonstrate whether these were applicable to their study subjects. Thus, recall bias could have led to errors in the outcome measure, leading to unreliable results.

Based on the foregoing limitations, we caution readers to consider that the conclusion reached by Harley et al. (2010)—that PBDEs are associated with decreased fecundability—is not based on robust data and therefore may be inappropriate.

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PBDE Concentrations in Women: Harley et al. Respond

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In our study (Harley et al. 2010), we found statistically significant associations between higher PBDE (polybrominated diphenyl ether) concentrations in women and longer time to achieve pregnancy. According to Goodman et al., we stated that the association of PBDEs and fecundability is likely causal. We never made this claim. As with all observational studies, associations do not guarantee causation. However, we believe this is a well-conducted study with a strong design to investigate the potential effects of PBDEs on time to pregnancy.

Goodman et al. argue that errors in the measurement of PBDE exposure or in recall of time to pregnancy could bias our results. We agree that little is known about the degree to which PBDE levels vary over time. However, we have no reason to believe that this variability would lead to differential misclassification with regard to the outcome. Similarly, women were blinded as to their PBDE levels, so we have no reason to believe that recall of time to pregnancy was biased. In both cases, measurement error would likely bias our results towards the null, making our results conservative.

Goodman et al. also questioned the appropriateness of our statistical model. The authors correctly point out that a key assumption of the discrete-time Cox proportional hazards model is that the hazard ratio [or, in this case, fecundability odds ratio (fOR)] be constant over the follow-up time. When this assumption is not met, the reported fOR represents a weighted average of the estimate in each month of trying to become pregnant,