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Fecundability and Serum PBDE Concentrations in Women

doi:10.1289/ehp.1002283

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.

The views and opinions expressed in this letter are those of the authors and not necessarily those of their respective employers.

J.E.G. received an honorarium for incidental expenses related to her contribution in drafting and reviewing this correspondence. J.A.B., H.S., M.H., and T.S. are employed by specialty chemical manufacturers whose product lines include brominated flame retardants. G.T.J., C.H., Y.Z., R.V.L., and R.D.H. declare no actual or potential competing financial interests.

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PBDE Concentrations in Women: Harley et al. Respond

doi:10.1289/ehp.1002283R

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,

and may be biased for the exposure effect at a specific time. We tested the proportionality assumption by examining the odds of becoming pregnant in each discrete month when no contraception was used. Although the magnitude of the association was slightly less in the first month of follow-up compared with later months, we found that higher PBDE concentration was associated with decreased fecundability in every month.

Goodman et al. were also concerned about uncontrolled confounding. Although it is true that many factors affect the timing of pregnancy, confounding is present only when these factors are associated with the exposure as well as the outcome. We have no reason to believe that the factors mentioned by Goodman et al. would be associated with PBDE levels, other than by chance. We did evaluate many of the factors they listed (i.e., frequency of intercourse, alcohol consumption, smoking, and drug use) and reported that they did not confound our results. Although we agree that one can never control for all possible confounding factors in an observational study—this is an inherent limitation of epidemiology—we have taken care to minimize confounding as much as possible.

Finally, Goodman et al. argue that limiting the study to pregnant women could bias results away from the null. We cannot think of a circumstance in which this would be true. The inherent selection bias of retrospective studies in pregnant populations is that infertile couples are excluded and subfertile couples are underrepresented. Thus, if there is a true association between PBDEs and time to pregnancy, then limiting the study to the most fertile couples will reduce statistical power and lead to an underestimation of the effect. However, if there is no association between PBDEs and time to pregnancy, then we would expect the fOR to be 1.0 among all women. Overrepresenting the most fertile couples would continue to show a null effect. We fail to see how excluding subfertile women would bias findings away from the null or show a spurious association.

Time-to-pregnancy studies are methodologically complicated, and both prospective and retrospective studies have their limitations. For a detailed discussion of the biases in retrospective study designs, as well as a discussion of how to minimize them, see Joffe et al. (2005). A strength of our study is that we undertook multiple sensitivity analyses to investigate the extent that our findings changed when inclusion criteria or details of the analytic methods were altered. Our findings remained largely unchanged in all these sensitivity analyses. In summary, the limitations pointed out by Goodman et al. would serve to underestimate our estimate of effect, not inflate it. However, since this is the first study of PBDE exposure and time to pregnancy, our findings need to be replicated in other populations.

The authors declare they have no competing financial interests.

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Probabilistic Modeling of Dietary Arsenic Exposure

doi:10.1289/ehp.1002328

We read with interest the article "Probabilistic Modeling of Dietary Arsenic Exposure and Dose and Evaluation with 2003–2004 NHANES Data," by Xue et al. (2010). We are concerned that the article misrepresented our earlier article on a similar topic (Petito Boyce et al. 2008) and that, by doing so, Xue et al. failed to appreciate the consistency of their estimates of arsenic intake from food and water with ours. Specifically, Xue et al. (2010) stated, "A recent publication [i.e., Petito Boyce et al. (2008)] concluded that typical and high-end background exposures to iAs [inorganic arsenic] in the U.S. population do not present elevated risks of carcinogenicity." However, they then seemed to call into question our conclusion and to suggest that our analysis either underestimated or failed to include consideration of dietary intake of iAs, citing work by others indicating that iAs intake from food has been estimated to be on the order of several micrograms per day. This suggestion does not accurately reflect our analysis. In fact, our estimates of background exposures to iAs include dietary intake estimates similar to those noted by Xue et al. (2010), and both studies used some of the same data sources.

In our study (Petito Boyce et al. 2008), we conducted a probabilistic analysis using Monte Carlo analysis with Crystal Ball software, incorporating 10,000 iterations, whereas Xue et al. (2010) used the SHEDS model. Table 1 demonstrates the remarkable similarity between the iAs intake estimates from dietary and drinking water sources reported by Xue et al. (2010) and our 2008 intake estimates (Petito Boyce et al. 2008). Our analysis also included estimates of iAs intake from soil, as well as total iAs intake.

A key element of our conclusion (Petito Boyce et al. 2008) regarding the lack of carcinogenic risk was the use of a margin-of-exposure model for iAs, which was applied using an epidemiologically derived no observable adverse effect level. We chose this model based on an analysis of arsenic's mode of action, from which we concluded that all plausible modes of action were supportive of a nonlinear dose response. Our conclusion was not based on a lower iAs intake estimate, as implied by Xue et al. (2010).

We believe that the analysis by Xue et al. (2010) is important and provides additional understanding of the significance of background exposures to iAs, particularly via ingestion of food. However, by not providing an accurate representation of our work, the authors missed an opportunity to provide additional support for their overall conclusions.

S.M.C. receives private industry funding for some of his arsenic research. M.E. is the chair of the Organic Arsenical Products Task Force, an organization consisting of the producers of organic arsenic products (Drexel Chemical Co, and Luxembourg Industries Ltd.); she is also an employee of Luxembourg Industries Ltd. C.P.B., A.S.L., S.N.S., and B.D.B. are employed by Gradient, an environmental consulting firm, which receives some financial support on arsenic issues from industrial organizations.

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Table 1. Comparison of iAs intake estimates.

Study	iAs intake from food (µg/kg/day)			iAs intake from drinking water (µg/kg/day)		
	Mean	50th percentile	95th percentile	Mean	50th percentile	95th percentile
Petito Boyce et al. 2008	0.061	0.048	0.14	0.034	0.001	0.12
Xue et al. 2010	0.05	0.02	0.19	0.025	0.002	0.11

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Xue J, Zartarian V, Wang S-W, Liu SV, Georgopoulos P. 2010. Probabilistic modeling of dietary arsenic exposure and dose and evaluation with 2003–2004 NHANES data. Environ Health Perspect 118:345–350.

Dietary Arsenic Exposure: Xue et al. Respond

doi:10.1289/ehp.1002328R

In our article (Xue et al. 2010), we cited Petito Boyce et al. (2008) based on their major conclusion stated at the end of their abstract that, "typical and high-end background exposures to inorganic arsenic in U.S. populations do not present elevated risks of carcinogenicity." We agree with Petito Boyce et al. that we "missed an opportunity to provide additional support for" our overall conclusions, and very much appreciate that they have offered this detailed comparison showing the agreement between our modeling results.

Our discussion of Petito Boyce et al. (2008)'s conclusions was intended to bolster the need to develop a more comprehensive analysis of the sources of inorganic arsenic exposure, not to suggest that their exposure analysis was incomplete or inaccurate.

The authors declare that they have no competing financial interests.

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