Author's response to reviews

Title: A cross sectional survey of determinants of serum concentrations of polybrominated flame retardants among healthy pregnant women in an urban environment

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Author's response to reviews: see over
Response to Reviewer’s Comments

October 11, 2010

Reviewer's report

Title: A cross sectional survey of determinants of serum concentrations of polybrominated flame retardants among healthy pregnant women in an urban environment

Version: 1 Date: 28 June 2012

Reviewer: Ami Zota

Reviewer's report:

Horton et al., Predictors of PBDEs in New York City Pregnant Women

In this cross-sectional study, Horton and colleagues examine a rich dataset of a unique and important study population of diverse, urban pregnant women to examine predictors of serum PBDEs (mostly penta-BDEs). They find a variety of significant predictors including socioeconomic status (education, income), diet (such as processed meat), and use of electronics. The current manuscript, however, is lacking some key variables such as country of origin and years living in the US that would help to deconstruct their finding. Additionally, the discussion needs to be revised to include a more careful and robust discussion of the observed findings including possible explanations for some of the anomalous findings. For example, why would use of electronics (which is largely treated with deca-BDE) be associated with components of penta-BDE? Additionally, the discussion includes several important factual inaccuracies (see below) that need to be corrected.

Major Compulsory Revisions

Introduction

1. Discuss uniqueness of your cohort, and evidence suggesting non-white
populations may face higher exposures to PBDEs (see Windham et al., Zota et al. 2009, Stapleton et al. 2012)

We added a paragraph beginning on page 7 (beginning with “Recent studies suggest…”) to discuss higher exposures among non-White populations.

2. The authors should state that this is a unique opportunity to examine social determinants of PBDEs explicitly.

We added text on page 7 to emphasize the unique opportunity in this cohort to examine social, dietary and lifestyle determinates of PBDEs among a largely Dominican American population living in New York City.

3. They should also list housing characteristics in their list of important factors (See Rose et al. ES&T).

We added several sentences to the end of page 5 to discuss the influence of housing characteristics on PBDE body burden as discussed in Rose et al, (2010). In addition, we added a statement to the discussion of limitations, as we do not have data to evaluate housing characteristics in this cohort.

Methods
1. Do the authors have any data on country of origin and years lived in the United States? Given the CHAMACO study findings on the importance of these variables in determining PBDE exposure among Latina women, this is likely to be an important predictor of exposure in the present study population, and possible confounder for some of your observed findings.

We do not have information on country of origin and years lived in the United States.
We added a discussion of this limitation on page 26.

2. Did you consider examining interactions between race and diet? Did including sources of PBDEs in the model attenuate race or income coefficients?

We did examine interactions between individual PBDE congeners and ‘solid dairy’ and interactions between individual PBDE congeners and ‘processed meat’. Graphing the interactions suggested that among Hispanics, consumption of solid dairy items (> 10 servings per week) was associated with higher serum PBDE concentrations, while for Non Hispanic Whites, the trend was reversed (consumption of solid dairy was associated with lower serum PBDE concentrations). Interactions terms included in regression models were not significant. There were no suggested interactions between processed meat and PBDE congeners.

Including sources of PBDEs did not attenuate the race or income coefficients.

Results

3. Can you breakdown the Hispanic category into country of origin (Mexican-origin vs. Dominican)?

We cannot break down the Hispanic category. We asked Hispanic vs. Non-Hispanic.

4. Please include pre-pregnancy BMI in Table 1

We added pre-pregnancy BMI to Table 1.

5. Any information on housing characteristics (e.g., number of bedrooms, square footage, any proxies for air exchange or ventilation) [If not, this should be listed in limitations]
We did not query women about these housing characteristics. These limitations have been added to the discussion in the first paragraph on page 25.

Discussion
1. Last paragraph on page 24. The authors state, “para-Hydroxylated metabolites have not been detected in human serum [39]”. This statement is inaccurate and needs to be revised. 5-OH-BDE47 is as an example of a para-OH-BDE that has been measured in pregnant women (see Zota et al., 2011 and Qiu et al., 2009).

We removed the statement that PBDE metabolites had not yet been measured in pregnant women and added references for Zota et al., 2011 and Qui et al., 2009. Further we remarked that PBDE metabolite biomarkers were unavailable for the current study at this time.

2. If you do not have country of origin data, please address this in the study limitation section and discuss the potential implications for not having this covariate (for example, how it may have affected race/ethnicity findings).

We do not have country of origin data. We added a discussion of the limitation of lacking this data and the implications for house this may affect the race/ethnicity findings on page 25.

3. Please address the finding with education and how it compares to other populations? What are potential reasons for this finding?

In our dataset, there is a nonlinear association between education status and serum PBDE concentration whereas PBDE levels appear highest among the high school/high school equivalent category and lower among mothers reporting less than high school education or greater than high school education. As race, income and socioeconomic
status are closely associated in this cohort, it is difficult to disentangle the effects of each predictor. However, Stapelton et al (2012) suggested that there were no differences between PBDE concentrations in house dust samples by race or education, suggesting differences in serum concentrations may not be solely driven by higher levels of PBDEs in dust from homes in lower socioeconomic strata.

4. Please address the finding between congeners of penta-BDE and electronics use. Why do you think you see an association between penta-BDE congeners and electronics, which are primarily treated with deca? While BDE-153 may be a breakdown product of BDE-209, I am less convinced that BDE-47 comes from deca?

This finding was unexpected and we do not know how to further explain this finding. We add text to page 25 to indicate that, due to the registered uses of PBDEs and literature on exposure patterns, we anticipated higher number of electronics would be associated with higher deca-PBDE (PBDE-209) measured in human serum.

We also ran 2 x 2 tables with detect/nondetect PBDE 209 and electronics and PBDE 209 and race/ethnicity. There were no associations between PBDE 209 and electronics in the home. We added a sentence to describe this finding on page 25.
a. Specifically, you need to substantiate the plausibility of this result. Have other studies found an association between penta-BDEs and electronics? If so, please discuss these studies in the discussion. Also, since you measured BDE-209, why don’t you see if those who used more electronics were more likely to have measured levels of BDE-209 (do a 2 by 2 table with <BDE-209 below and above LOD by high versus low electronic use).

No other studies we reviewed found an association between penta-PBDEs and electronics. Please see above response.

5. The section on “Levels and patterns of PBDE exposure” (page 18) needs to be revised to be more specific. For example, the statement, “levels of PBDE measured in the women enrolled in our urban cohort are slightly lower than those measured in these other studies conducted in North America (US and Canada)”.

Can you make this more specific since levels in your cohort are roughly six times lower than those in California pregnant women and two times lower than Mexican immigrant women and similar to what has been previously found in women in New York City. The word “slightly” is vague and inaccurate. It may be useful to directly compare your studies to findings of other Hispanic women (e.g. CHAMACOS) and then do a separate comparison to other cohorts of contemporary pregnant women (e.g. Zota et al. 2011; Stapleton et al. 2011) and then perhaps another with other New York City populations. These would make for the most relevant comparisons.
We considerably revised this section of the paper to compare our results to 1) pregnant women in NHANES, 2) Hispanic pregnant women in California, 3) Non-Hispanic Black pregnant women in North Caroline and 4) cord blood samples in NYC.

a. The authors go on to say, “Notably, the samples in the current study were collected several years later than those in the other North American cohorts.”
This is also not true. The present study population was sampled between 2009-2010. Zota et al. (2011)’s cohort was sampled between 2008-2009 and Stapleton et al. (EHP2011)’s cohort was sampled between 2008 -2010. Please revise and make the appropriate comparisons.

Please see response above.

b. The authors continue, “Further, the U.S populations represented in the National Health and Nutrition Examination Survey (NHANES) is a non-pregnant population.” This is also not true since NHANES does include pregnant women, and Woodruff et al. (2011) examined chemical exposures in US pregnant women from NHANES including PBDEs. It would be useful for the authors to compare their levels to NHANES pregnant women.

Please see response above.

6. The discussion and data on congener distribution seems overly long and unnecessary since it is not adding much to the literature. Can you make greater use of your BDE-209 data?

We shortened this section considerably. As discussed above, PBDE-209 was detected infrequently (< 20% of samples). We examined the association between detect/nondetect PBDE0-209 and electronics and did not see an association.
7. In the following sentence on page 21, “In one recent study of a largely Mexican immigrant population of pregnant women living in California, PBDEs concentrations increased with increasing years residing in the U.S. and with the number of pieces of stuffed furniture in the home [42].” You have cited the wrong article. This was not a finding by Zota et al. but from the CHAMACOS group (Bradman et al.)

We corrected this error.

8. On page 18, the authors say, “Consistent with other studies, the distribution of PBDEs in our cohort is log-normally distributed”. If this is true, why did the study authors use a gamma regression analysis instead of log-transforming PBDE concentrations and do multivariate regression analysis? Were the results different between the two methods?

We corrected this statement on page 18 to state “the distribution of PBDEs in our cohort is non-normally distributed”. Gamma and log logistic regression analysis allowed left-censoring to adjust for PBDE values less than the limit of detection and better fit the distribution of the data.

Discretionary Revisions
1. Why did you choose an 80% cutoff, that seems high?

We changed this in the text to read a 50% cutoff. The next highest detection frequency was PBDE-28 (45%). We could not run gamma regression models on outcomes with less than 50% detection frequency.

2. Table 1 is redundant and has been shown in many other publications. I would
remove this and use the space to further examine the data.

We removed Table 1.

3. Page 4: reference 7, is this appropriate reference?

We corrected this inaccurate reference.

Level of interest: An article of limited interest
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I declare that I have no competing interests

REVIEWER 2

Reviewer's report
Title: A cross sectional survey of determinants of serum concentrations of polybrominated flame retardants among healthy pregnant women in an urban environment
Version: 1 Date: 29 June 2012
Reviewer: Pierre Ayotte
Reviewer's report:
This is a very well written paper that presents interesting information on sources of exposure to PBDEs in a group of pregnant women from New York City.

My only major criticism is the lack of information on the recruitment process and the participation rate. The authors need to provide information on women who were solicited but did not agree to participate. The reader needs to know if these women are different from those who were enrolled.

We agree with the reviewer that this would be useful information. Unfortunately, this information is not available.
The statistical analyses are appropriate. It is somewhat disappointing that so little variance could be explained for serum PBDEs 47, 99 and 100 levels. Important sources of exposure remain to be identified and characterized for these congeners. PBDE 153 appears to be a food-chain contaminant for which exposure can be better predicted. Exposure to these PBDEs will likely decrease because their use is restricted but what about replacement products?

We do not have biomarkers of potential replacement products in this study.

Minor corrections:
1) P. 7, line 4: synaptogenesis

We made this correction.

2) P. 21, line 11: ...college education, being classified as obese prior to pregnancy and less weight gain prior to pregnancy...

We made this correction.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests:
I declare that I have no competing interests

REVIEWER 3
Title: A cross sectional survey of determinants of serum concentrations of polybrominated flame retardants among healthy pregnant women in an urban environment
Version: 1 Date: 5 July 2012
Reviewer: Alicia Fraser
Reviewer’s report:
Review of “A cross sectional survey of determinants of serum concentrations of polybrominated flame retardants among healthy pregnant women in an urban environment.”
Overall, while I find the paper’s topic and findings to be of some interest, there are serious deficiencies with the manuscript which require attention before a decision regarding publication could be made. I have made an effort to make comments as detailed as possible and to divide them appropriately between
those that are major and those that are minor. However, the sheer number of
errors in this paper, whether minor or major, brings me to question the level of
attention paid to this manuscript by the authors. The multitude of grammatical
errors, typos, and lack of clarity and attention to detail, in general, is surprising.
Nevertheless, the study’s findings are relevant to the field and would be of some
interest if the manuscript is revised sufficiently.

Major Compulsory Revisions:
1. Needs a thorough grammatical cleaning. Listed under Minor Essential
Revisions are some, but not all, of the items to be addressed. While many of
these are minor issues, taken together, they represent a more significant issue.

We addressed grammatical issues.

2. If removal of the woman with extremely high PBDE concentrations made no
difference in the regression results, then why was she removed? This should be
explained better or else she should not be removed.

Subject was not removed. Results, tables, figures and conclusions have been revised to
present updated analyses including this subject.

3. Methods, Exposure questionnaire data, 2nd paragraph: In the description of
how various diet items were examined, the authors need to give more detail. Did
the questionnaire include anything about serving size? If not, this needs to be
identified as a weakness in the discussion. How were items summed? Again,
was serving size considered or just serving frequency? For dairy, was fat content
considered in summing items?

We expanded the description of how various diet items were collected and examined.
We queried mothers about whether or not she consumed a particular food item (y/n)
and the frequency of consuming one serving size of the food item. Food items were
then examined individually and as groups generated from summing the frequencies of
consuming one serving size of all items in a group.

4. Methods, Exposure questionnaire data, 3rd paragraph: Please give more
detail on how cut-points were chosen for dietary categories. When you say that
you selected the cut-points in an attempt to have equally sized levels, do you
mean that you created true tertiles? If not, how did you make the determinations?
Did you inspect histograms? I understand wanting to have evenly sized levels,
but 5 servings/week seems high for a “low” category. Did you try other
cut-points? Did you get different results?

We present the dietary category by ‘true’ tertiles. We also examined quartiles and
dichotomous variables cut either at the median or as yes/no variables. In final analyses,
we used the category that provided the most information without compromising power.

5. In statistical methods, the authors need to describe how determinations of significance were made for predictors. Table 4 has a footnote that suggests an alpha=0.1 was used, but it’s unclear.

The footnote has been corrected to read alpha < 0.20. We added text to the section to better describe the analytical approach (page 14).

6. Also, in stat methods, please explain that values <lod were substituted with lod/sqrt 2.

On page 14, we revised the description of the statistical approach. Values less than LOD were not substituted with LOD/SQRT 2. Rather, we used left censored observations for values < LOD and a parametric generalized gamma distribution for the regression.

7. Table 4 does not show “prediction models”. It shows no regression results except for the ** symbol for p<0.1. Please re-label the table for accuracy. Something such as, “Median and interquartile ranges of lipid-adjusted PBDE concentrations (ng/g lipid) in maternal blood collected upon delivery by demographic, dietary, and lifestyle characteristics.” The table should also make it clear which group is the reference group for regression analyses if these are to be shown or alluded to with the **.

The text in the first paragraph on page 18 (beginning on page 17) was revised to more accurately state that ‘...four characteristics were associated with maternal PBDE-47 concentrations...’ . In the statistic analysis section, we describe that table 3 reflects the results of univariate comparisons of PBDE concentrations across groups, the table presents median and interquartile ranges of lipid-adjusted PBDE concentrations.

8. Results, “Single predictor models”: This section needs more detail and the description needs to match the data presented in the table. When the authors say that something is associated with PBDE concentrations, they need to say how large the association is and in what direction. These data are not presented in the table or text.

We re-organized the results section to clarify the descriptive analyses from the univariate associations and the regression models. In particular, we added text to clarify the direction of the association.

9. The presentation and description of Table 5 needs work. It’s unclear to me why, for example, the text states that having a college education is associated with increased PBDE-47 in maternal serum, but not having a high school
education or a graduate education. How were determinations made as to what was a predictor and what wasn’t? Please give an example of how to interpret the Beta estimates.

We converted the Table 4 (revised Table 5) to display the mean ratio rather than the coefficients regression models as they are easier to understand.

10. The discussion is very long considering how few results are presented. It needs to be shortened and made more directly related to the results presented in the current study.

We shortened the discussion and focused on the results from the current paper.

11. In general, the authors need to explain why predictors of PBDE body burdens may be different in pregnant women compared to non-pregnant women. They make a strong case for the importance of understanding exposure in pregnant women, but not why exposure studies of non-pregnant women are not generalizable to pregnant women.

To our knowledge, there are currently no studies reported PBDE levels among urban minority populations, pregnant or non-pregnant. We believe this makes a contribution to the literature.

12. The conclusion in the abstract is not wholly supported by study results or discussion. Women can modify diet, reduce use of electronics, wash hands more frequently. While none of these may eliminate exposure, I don’t think the statement that “there may be little women can do at the level of the individual to limit exposure” is supported by the study...or at least the way it is written. On the contrary, the study finds associations between specific foods and electronics use and PBDE body burdens. Please revise the conclusion to match the study’s findings. The statement in the conclusion of the body of the paper is more accurate and I would suggest a version of it, “While maternal education and reporting of household electronics predicted exposure...we did not observe a single predictor or a consistent pattern of predictors representing a significant source of exposure for any individual congener.” (the statement in the abstract also appears in the body of the paper conclusion, but it is in context there, and so does not present the same issue).

We revised the conclusion on the abstract to read:

Sources of PBDEs in this urban cohort are ubiquitous and diverse. We did not observe a single predictor or a consistent pattern of several predictors representing a significant source of exposure. Lifestyle modifications, including reduced consumption of processed meat and high fat dairy products and reduction of the number of electronics
in the home may reduce PBDE body burdens.

13. Table 1: About.com should not be used as a reference. There are plenty of legitimate sources to cite for the chemical structures. Please find something more appropriate.

We removed Table 1.

Minor Essential Revisions:
1. Grammar, spelling, typos, clarity, etc:
   a. Background, first line: should be “diphenyl” ethers and not “diethyl” ethers.

   We corrected this mistake.

   b. Background, 3rd sentence: legislation has not addressed the “use and exposure of these compounds.” Perhaps it has addressed exposure “to” these compounds, but I suggest something like, “addressed the production, sale, and use of these compounds.”

   We made this change as suggested.

   c. Background, 1st paragraph: comma after “In 2003”. Please review paper for similar instances where commas are lacking. There are too many to list individually here.

   d. Background, 1st paragraph: DDE should be spelled out at first use.

   We spelled out dichlorodiphenyltrichloroethylene for DDT.

   e. Background, 2nd paragraph, 1st sentence: the phrase “body burden of exposure” is strange...suggest “body burden of PBDEs in humans.” The phrase “body burden of exposure” is used incorrectly in this way throughout the paper and should be revised as appropriate.

   We made this change as suggested on page 4, page 6 and page 18.

   f. Background, 2nd paragraph, 2nd sentence: “Like the POPs” should be “Like other POPs”.

   We made this change as suggested.

   g. Background, 2nd paragraph, 3rd sentence: comma after “Consequently”.


We made this change as suggested.

h. Background, 3rd paragraph, 1st sentence: “body burden exposure to PBDEs in the general public” should read “PBDE body burdens in the general public.”

We made this change as suggested.

i. Background, 3rd paragraph: correct spelling of “synaptogenesis “.

We misspelling was corrected.

j. Methods, 1st paragraph: CDC should be spelled out at first use (and it should be CDC “were” not CDC “was”)

We made these changes as suggested.

k. Methods, 1st paragraph: sentence beginning with “Aliquots...” needs work towards the end where it gets confusing.

We rewrote these sentences to clarify the methodologies.

l. Methods, 1st paragraph: next to last sentence is a run-on. Please put a period after “participants” and begin the next sentence with “However,”.

We made these changes as suggested.

m. Methods, 1st paragraph, last sentence: Tables need to be numbered in sequence. Table 3 comes out of order here since Table 2 hasn’t been introduced.

We corrected this error.

n. Methods, Exposure questionnaire data, 4th paragraph: “crumpling” should be “crumbling”.

We made this change as suggested.

o. Results, 3rd paragraph: 2nd sentence is confusing. Please revise the phrase “in small, low range”.

We changed this to read simply “low concentrations”.

p. Discussion, 1st sentence: Run-on sentence...place period after “neurotoxicants”, remove “thus”, and begin new sentence with “Understanding”.
We made these changes as suggested.

q. Discussion, 2nd paragraph: Sentence that begins, “These trends were anticipated...” should probably end with “in Europe” in order to make sense.

We made this change as suggested.

r. Discussion, 3rd paragraph: Last sentence is meaningless as written. Revise thus, “This may be due to a higher proportion of foreign-born participants in our cohort.”

We modify this statement to reflect that perhaps our cohort has a higher proportion of foreign-born participants and not that we do not have data on country of origin.

s. Discussion, predictors/sources of exposure: Please revise the sentence that includes the phrase, “being classified as obese prior to pregnancy less weight gain predicted...” as it is unclear.

We revised this sentence to read “being classified as obese prior to pregnancy and gaining less weight during pregnancy predicted higher cord blood concentrations.”

2. Background, 2nd paragraph: last sentence is confusing. It seems to come out of nowhere and it’s unclear why you’re comparing diet to these other factors. Could use a little more context and clarity.

We modified the statement and moved it to the beginning of the paragraph for clarity.

3. It’s confusing that the size of the cohort is given as 315 at the end of the Background section and then as 316 two sentences later in the beginning of Methods. I realize that you explain the missing woman at the end of Methods, but this should come earlier if you’re going to use two different numbers like that. I would suggest using 316 in the Background, as well, to avoid the confusion.

The correct number is 315. This is used consistently throughout the text.

4. In Results, there are two sections devoted to prediction models. One is called, “Single predictor models” and the other is “Gamma regression models.” This is confusing because the methods seem to suggest that all of the prediction models used a gamma distribution. Please, re-label these sections for clarity.

We clarified this description on the text.
5. Discussion, 2nd paragraph: I’m not sure I understand why it’s relevant that the NHANES population is a non-pregnant population. You could compare your results to young women in the NHANES study because it is given by sex and age.

We revised the discussion and this comment is no longer included in the text.

6. Discussion, 2nd paragraph: Sentence that begins, “These trends were anticipated...” should probably end with “in Europe” in order to make more sense.

We made this suggested change.

Discretionary Revisions
1. Background, 2nd paragraph: in discussion of dermal absorption, you may want to read and reference Watkins, et al (2012) paper in ES&T and/or Watkins, et al (2011) paper in EHP. While data may be scarce on dermal absorption, these papers deal directly with the issue and present results of dermal absorption and contribution to body burdens of PBDEs.

We added this reference to the background section.

2. Did you have any vegetarians in your study and did you consider a comparison of body burdens between vegetarians and meat-eaters? This would be good to add.

Only 15 subjects in the study reported eating a vegetarian diet. Inclusion of this characteristics into our final model was not independently predictive of any PBDE congener and did not influence our other findings.

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Needs some language corrections before being published
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests:
I declare that I have no competing interests.