DISPOSITION OF PEER REVIEW COMMENTS FOR TOXICOLOGICAL PROFILE FOR POLYBROMINATED DIPHENYL ETHERS (PBDEs)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

March 2015

Peer reviewers for the third pre-public comment draft of the Toxicological Profile for Polybrominated Diphenyl Ethers (PBDEs) were:

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Review comments provided by Reviewer #1:

GENERAL COMMENTS

Reviewer 1 made several editorial suggestions throughout the review of "The Profile." Unless otherwise noted, all grammatical/language/stylistic suggestions from Reviewer 1 were incorporated into "The Profile," and will not be discussed individually.

COMMENT: Regarding the question of whether there are any data relevant to child health and developmental effects that have not been discussed in the profile, the Reviewer commented, "Although the report provides an extensive review of the neurobehavioral and neurotoxicity literature for both humans and model mammalian species, it would be useful to specifically address the potential for PBDEs to be linked to the etiology of some childhood behavioral problems, such as Attention Deficit and Hyperactivity Disorder and Autism Spectrum Disorder. These will be particularly important points for discussion in the Public Health Statement. With regard to the potential link to autism, please refer to the mini-review by Anne Messer (2010) published in Physiology and Behavior 100:245-249. While I recognize that these links between pre-natal or peri-natal PBDE exposure and childhood behavioral problems are speculative, it would be prudent to directly address these issues in the Review."

RESPONSE: *The potential link between Attention Deficit and Hyperactivity Disorder (ADHD) and PBDEs, reported in the study by Gascon et al. (2011) and already mentioned in Sections 2.2, 3.2.2.6, and 3.7, is now discussed in Chapter 1 as well (How can PBDEs Affect Children). Since the link between PBDE exposure and Autism Spectrum Disorder (ASD) is speculative at this point, the potential link and need for targeted research is now included in Section 3.12.2 (Identification of Data Needs) under the heading "Epidemiological and Human Dosimetry Studies). The potential link to ASD was not included in Chapter 1 at this time due to a lack of experimental evidence.*

COMMENT: One convention used by the authors that I took exception to throughout the document was use of the word, "levels", when the word, "concentration" is more appropriate. I corrected this in many places, but at some point I ceased to bother.

RESPONSE: *This change has been applied throughout the document where applicable.*

COMMENT: Some sections used incorrect sentence structure, particularly in places where a semi-colon was used, followed by the word, "however".

RESPONSE: *Existing sentence structure adheres to the grammatical rules of usage for a semicolon, which indicate that a semicolon should be used to link two independent clauses connected by a conjunctive adverb. Statements utilizing this particular sentence structure were not revised unless such a revision would improve clarity.*

CHAPTER 1. PUBLIC HEALTH STATEMENT

COMMENT: Regarding the question of whether scientific terms used are too technical or require additional explanation, the Reviewer commented, "Individuals with a post-secondary level of education

should be able to understand the technical language used in this chapter. The only exception is the lack of explanation of "monoBDEs" in the section on, "What Recommendations…." (page 8)."

RESPONSE: *Text was added to provide more descriptive information on monoBDE.*

COMMENT: Page 3, lines 6-7: As acknowledged later in the Review, there is evidence that toddlers accumulate higher concentrations of PBDEs than juveniles and adults, and this is probably due to their direct contact with PBDE treated materials in the home, and/or ingestion of contaminated dust. This should be stated in this paragraph. This information is provided later in Chapter 1 in the section on, "How Can PBDEs Affect Children?".

RESPONSE: *This section is for general exposure information. Increased exposure risks in children are addressed in "How Can PBDEs Affect Children?"*

COMMENT: Page 4: Somewhere in this section of the Chapter, it should be stated that many of the endocrine effects of PBDEs, such as thyroid disruption are not caused by the parent compound, but by metabolites.

RESPONSE: *In response to this comment, the second statement of the "How PBDEs Can Affect Your Health?" section was revised to state: "The majority of information regarding toxicity of PBDEs and their breakdown products (metabolites) is from animal studies . . ."*

CHAPTER 2. RELEVANCE TO PUBLIC HEALTH

COMMENT: Page 11: This section of the Chapter includes a statement that, "Body burden data have consistently shown that residents of North America have higher levels of PBDEs in blood than people residing in Europe…..". Here, and elsewhere in the chapter, it should be explained that exposures in Europe are probably lower and involve a different PBDE congener profile than in North America because of the production and use of the pentBDE commercial formulation in the USA. Also, data are presented in the Chapter on the concentrations of PBDEs in populations in Asian countries, where it is likely that there has been a different exposure pattern relative to North America. This should also be discussed in the section in Chapter 3 on Oral Exposure (i.e. 3.4.2.2) related to Human Studies.

RESPONSE: *Text was revised to read: "Body burden data have consistently shown the residents of North America have higher concentrations of PBDEs in blood than people residing in Europe, likely due to differences in past production and use of commercial formulas," and data regarding detection of PBDEs in China were added to the following paragraph.*

COMMENT: Page 13 (bottom) – define hypospadias

RESPONSE: *In response to this comment, hypospadias is now defined as "abnormal location of the urinary tract opening" in the text.*

COMMENT: Page 21 (bottom) – define pre-pregnancy menstrual length

RESPONSE: *In response to this comment, the text was revised to read: "Increased length of menstrual periods (prior to pregnancy) . . .".*

COMMENT: In the Chapter, the argument is made that humans are likely to be less sensitive to the effects of PBDEs than in rodent studies. This point of view is mainly based upon differences between rats and humans in thyroid hormone homeostasis and the affinities of T3 and T4 with thyroid transport proteins. A different approach was used by McDonald, TA (Integrated Environmental Assessment and Management, 1:343-354) to show that a fraction of the population in the USA may be at risk for the neurodevelopmental effects that have been observed in rodents. A more conservative view would be to extrapolate the thresholds for effects on rodents to humans.

RESPONSE: *This argument regarding sensitivity of humans to PBDE-induced effects is not discussed in Chapter 2. It is discussed in Chapter 3 (Section 3.5.3 Animal-to-human extrapolation; Section 3.7 Children's susceptibility), but is limited to a potential decreased sensitivity in humans for effects of PBDEs on circulating thyroid hormone levels. Chapter 3 was thoroughly reviewed and edited to ensure that it was not stated, or implied, that there was evidence for decreased sensitivity for other effects associated with PBDE exposure. As for extrapolation of the thresholds for effects, default uncertainty factors of 3 (for inhalation studies with dosimetric adjustments) and 10 (for oral studies) were applied for animal-to-human extrapolation, using the conservative default assumption that humans are more sensitive than animals.*

CHAPTER 3. HEALTH EFFECTS

COMMENT: In 3.2.3 (Dermal Exposure) and 3.5.1 (Pharmacokinetic mechanisms – absorption) sections, what does "occluded" mean?

RESPONSE: *In occluded dermal studies, the application area is covered during the exposure period. This is a standard experimental practice, so it does not require a definition in Chapter 3 (which is written for a technical audience).*

COMMENT: In Section 3.4.2.2 (distribution, oral exposure), the overview should point out the importance of the location where the studies were carried out (e.g. Asia, Europe or North America) because the patterns of exposure to congeners from commercial mixtures were different.

RESPONSE: *The following statement was added: "In evaluation of these studies, the location where the study was performed (e.g., Asia, Europe or North America) is very important, as the patterns of exposure to various congeners were different due to different usage patterns of commercial mixtures (see Section 6.5, General Population and Occupational Exposure, for more information)."*

COMMENT: In Section 3.4.4.2 (elimination oral exposure), what is meant by apparent in the following sentence: "Apparent half-lives of PBDE congeners in blood of PBDE-exposed workers during non-exposed vacation periods ….." ?

RESPONSE: *Studies calculating half-lives in workers had to add assumptions regarding non-occupational exposures to PBDEs (assuming the same exposure for all workers). These half-lives are therefore referred to as "apparent."*

COMMENT: In Section 3.5.1. (pharmacokinetics mechanisms), dermal absorption efficiencies are reported. Is there no data on the mechanisms of absorption?

RESPONSE: *There are no available data regarding specific mechanisms of absorption for PBDEs. This is now clearly stated in the text.*

COMMENT: For Section 3.5.2 – are there any studies of AhR mediated responses for metabolites of PBDEs?

RESPONSE: *Review of the literature search only identified two studies:*

- *Hamers T, JH Kamstra, et al. (2006). Tox Sci 92(1):157-173, which evaluated AhR-mediated responses with 6OH-BDE-47 (DR-CALUX); this information from this study was added to Section 3.5.2.*
- *Su et al. (2012); Environ Sci Technol 46(19):10781-10788, which evaluated activation of AhR by 34 PBDE metabolites in the H4IIE*-luc *rat hepatoma transactivation bioassay ; this study was already included in Section 3.5.2.*

COMMENT: For Section 3.5.2 – p. 182 line 30. What are receptor proteins? Does this refer to receptors?

RESPONSE: *The term "protein" has been replaced with "subunit" (PBDE binding to receptor subunits* THR-α *and* THR-β *was measured in vitro).*

COMMENT: For Section 3.5.2 – p. 184 line 21. Was the recombinant yeast assay by Nakari and Pessala (2005) with human ER α?

RESPONSE: *Nikari and Pessala (2005) reported that the assays used human estrogen receptor (hER); no information was provided regarding whether or a not a specific subunit (e.g., α) was used. This information was added to the profile.*

COMMENT: In the section on mechanisms of immunotoxicity (page 191), data are reviewed on the immunotoxic effects of chlorinated DPEs. It should be pointed out that the studies with these compounds may not be relevant to PBDEs because of the considerable difference in the molecular size of brominated and chlorinated analogues, which may influence receptor-mediated effects, or the toxicokinetics of exposure. Also, identify the species for this study.

RESPONSE: *The following statement was added following the discussion of the study by Howie et al (1990): "However, these findings may or may not be relevant to immunotoxic activities of PBDEs because of the considerable difference in the molecular size of brominated and chlorinated analogues, which may influence receptor-mediated effects, as wells as potential toxicokinetic differences." Also, the text now indicates that this study was conducted in mice.*

COMMENT: In Section 3.8.1, pg 209 lines 18-22, Could high ratios also indicate metabolic debromination over time?

RESPONSE: *That is correct. The statement has been revised to reflect that possibility.*

COMMENT: In Section 3.8.2, second paragraph regarding use of T4 levels as a biomarker of effect is unclear and contradictory. A similar issue is in section 3.12.2 (data needs for biomarkers of exposure and effect).

RESPONSE: *Section 3.8.2 (Biomarkers Used to Characterize Effects Caused by PBDEs) has been thoroughly revised. The relevant portion of Section 3.12.2 has also been revised accordingly.*

COMMENT: Regarding the question whether the Reviewer agrees with the identified data needs, the Reviewer commented, "The data needs are identified appropriately, and justification is provided for why these data are needed. As discussed later, there is an additional data gap which should be recognized, which is information on the concentrations of PBDEs in agricultural soils to which municipal biosolids have been applied, and on the potential for uptake into crops."

RESPONSE: *This comment is addressed below with comments for Chapter 6, as it is a data gap for Potential for Human Exposure, rather than a data gap for assessing potential health effects of exposure.*

CHAPTER 5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

COMMENT: Regarding the question whether the Reviewer is aware of any information that is wrong or missing, the reviewer commented, "The Review seems to accept that regulatory action to stop the importation and use of PBDEs in the USA has taken effects with 100% compliance. It would be useful to have data that tests whether this is the case. It is not clear whether the production of PBDEs has been terminated in all Asian countries, for instance, so these compounds may still be available commercially and are being imported in various products manufactured in Asian countries."

RESPONSE: *Recent data to determine the concentration of PBDEs in recent (2013–2015) U.S. imports were not located. An evaluation of international compliance with regulations aimed at PBDE manufacture and trade could not be made at this time.*

CHAPTER 6. POTENTIAL FOR HUMAN EXPOSURE

COMMENT: In general, the Review provides accurate information on the release and transport of PBDEs in various environmental compartments. There is also a discussion of the potential exposure of populations with potentially high exposure. One population that has not been considered, however, is the Inuit populations of Alaska that are potentially exposed to PBDEs through consumption of "country foods" that are contaminated through atmospheric transport.

RESPONSE: *Data are presented in this chapter for Native American arctic residents exposure to PBDEs based on food consumption (Jaret 2000). Additional data evaluating PBDE concentrations in adult Canadian Inuit blood was added to this section of the profile, from Laird et al. (2013), to further address Inuit population exposure concerns.*

COMMENT: Section 6.2.3 Soil: While information is provided on the concentrations of PBDEs in biosolids, there are no data provided on PBDEs in agricultural soils to which biosolids have been applied, or on the potential for uptake into crops. This should be recognized as a data gap.

RESPONSE: *A new entry was added to Section 6.3.1 to address the application of biosolids to agricultural soils (Hale et al. 2012). The lack of data evaluating the potential for uptake into crops was also added to address this comment.*

COMMENT: Section 6.3.1 Transport and partition: The statements that there is little volatilization of PBDEs from soil or water, is inconsistent with the presence of these compounds in the atmosphere and their long-range transport to polar (i.e. Arctic) regions. Obviously, volatilization to the atmosphere is occurring.

RESPONSE: *Section 6.3.1 was revised to address this. Specifically, the terms 'not important' and 'not expected' were removed.*

COMMENT: Section 6.4.3 Sediment and Soil: I strongly disagree with the statement made at the end of this section that the data on PBDEs in sediment cores indicates that there are, "…yet unknown sources of PBDEs produced in nature". Vertical mixing of sediment cores has been noted before, and it is probably due to blurring of the core horizons through the burrowing activity of benthic organisms. There is no evidence that I know of that PBDEs can be produced through natural processes.

RESPONSE: *Section 6.4.3 was revised with the expanded list of potential sources of PBDEs in the core samples. The sentence noting "…yet unknown sources of PBDEs produced in nature PBDE from nature" was also revised.*

CHAPTER 7. ANALYTICAL METHODS

COMMENT: Regarding the question whether methods for measuring key metabolites were discussed, the Reviewer commented, "Little information is provided on methods for the analysis of the bioactive metabolites of PBDEs, including hydroxy- and methoxy-derivatives. See Malmberg, T et al. (2005) Environ. Sci. Technol. 39:5342-5348 for a study of the identification of PBDE metabolites in exposed rats."

RESPONSE: *A summary of the suggested study from Malmberg et al. (2005) was added to Section 7.1.*

CHAPTER 9. REFERENCES

COMMENT: There are a few additional references that could be added, and these have been identified above.

RESPONSE: *Responses regarding additional references can be found in previous sections.*

Review comments provided by Reviewer #2:

GENERAL COMMENTS

Reviewer 2 made several editorial suggestions throughout the review of "The Profile". Unless otherwise noted, all grammatical/language/stylistic suggestions from Reviewer 2 were incorporated into "The Profile", and will not be discussed individually.

CHAPTER 1. PUBLIC HEALTH STATEMENT

COMMENT: P1, L.10 Have the EPA actually LOOKED for PBDEs in any of the 1,699 NPL sites? If so, how many? Given the ubiquity of these contaminants, I do not find it credible that they have not been found. I also do not understand the focus on these NPL sites as sources of exposure. They may have some relevance, but everything we know about exposure to PBDEs suggests it is ubiquitous and occurs in the home, the workplace, transportation microenvironments and via food

RESPONSE: *Chapter 1 states that the total number of NPL sites evaluated for PBDEs is not known. NPL site information is limited; the actual number of sites tested for PBDEs specifically is not readily available. The other sources of PBDE exposure are discussed in the section "How might I be exposed to PBDEs?" of Chapter 1. Please note that biphenyl (CASRN 92-52-4) and monoBDE (CASRN 101-55-3) have been detected at 26 and 23 unique sites, respectively, but were not included in this entry since they are not polybrominated compounds.*

COMMENT: P1, L.33-34 My understanding is that the EU ban on Penta and Octa-BDE came into force in 2004 and not 2003. Deca-BDE was severely restricted but not completely banned in 2008, so some rephrasing is called for here.

RESPONSE: *This section was revised to more clearly identify the effective date of the EU penta- and octaBDE ban and the restricted use directive for decaBDE.*

COMMENT: P4, L,4 suggest heading reworded thus "HOW CAN PBDEs AFFECT MY HEALTH?"

RESPONSE: *The headings in this chapter are standardized headings for ATSDR profiles. ATSDR will consider the suggestion during the next revision of the ATSDR profile format*

COMMENT: P6, L8, the statement that "In most cases.." begs the obvious question of in what cases will the benefits of breastfeeding not outweigh the risks. I would suggest rephrasing this to say something like "The available evidence suggests that any risks from exposure to PBDEs from mother's milk are outweighed by the benefits of breastfeeding."

RESPONSE: *The statement was revised to read: "In general, however, any risks from exposures in mother's milk are outweighed by the benefits of breastfeeding." The exact wording from the Reviewer was not used because it implies that there are specific studies (i.e., evidence) indicating that risks from exposure to PBDEs specifically are outweighed by benefits of breastfeeding; however, these particular data do not exist.*

COMMENT: P7, L2, some lay explanation of what a concentration of 7.9 pg/g (or ng/kg) represents would be sensible. Perhaps a factually correct analogy along the lines of "1 grain of birch pollen in a kg of food" would be appropriate.

RESPONSE: *This sentence was revised for simplicity (in Chapter 1), as follows: "The concentrations of PBDEs in foods from the United States have been measured. Fish, meat, and dairy products had the highest levels of PBDEs (Schecter et al. 2006). Reducing intakes of these food items may reduce exposure."*

COMMENT: P7, I would also suggest that regular vacuuming to reduce dust levels would likely reduce exposure

RESPONSE: *In response to this comment, and a comment by Reviewer 3, the following statement has been added to the "How Can Families Reduce the Risk of Exposure to PBDEs?": "Additionally, PBDE exposure may be decreased by regular vacuuming and cleaning of air ducts and filters to reduce indoor dust levels."*

COMMENT: P7, L21-22, are the "tests" referred to looking at health effects or exposure? This needs clarification. Moreover, I suspect in either case (but certainly in the case of testing for whether exposure has occurred), tests can be effective some time after exposure has occurred. This will be less true for BDE-209, but this distinction is not made.

RESPONSE: *The section title clearly indicates that the tests are to determine exposure to PBDEs. For determination of a suspected, <u>acute exposure to high levels</u> of PBDEs, tests need to be conducted within days because PBDEs and their metabolites either leave the body or are distributed to body fat fairly rapidly. This distinction is now made in the text.*

COMMENT: P8, L15-19, I do not understand the reference to "mono-PBDEs"

RESPONSE: *Section 2.1 and 4.1 of the profile describe monoBDE in more detail. MonoBDE is the monobrominated structure(s) or diphenyl ether with one bromine substituent (i.e., one bromine atom attached to the molecule). A description of monoBDE will be added to for improved clarity.*

CHAPTER 2. RELEVANCE TO PUBLIC HEALTH

COMMENT: P11, L.26-27, the situation is more nuanced than stated. In the US, I suspect that diet is more important than implied here especially for the lower brominated PBDEs (see e.g. Wu N, Herrmann T, Paepke O, Tickner J, Hale R, Harvey E, La Guardia M, McClean MD, Webster TF. Human exposure to PBDEs: associations of PBDE body burdens with food consumption and house dust concentrations. Environ Sci Technol 2007;41: 1584–9.). Moreover, while it is true that for the UK population indoor dust is a relatively minor, though appreciable exposure pathway for Σtri-hexa-BDEs, it is far more important for BDE-209, and for some individuals may be the overwhelming vector of exposure as opposed to diet as stated here. (S. Harrad, C. Ibarra, M. A. Abdallah, R. Boon, H. Neels, A. Covaci "Concentrations of brominated flame retardants in dust from United Kingdom cars, homes, and offices: Causes of variability and implications for human exposure", *Environment International*, 34, 1170–1175 (2008)).

RESPONSE: *The paragraph was revised to (1) clarify the nuances in the Lorber (2008) and EPA (2010) summary to specify the source of exposure calculations presented and (2) note the congener differences between dust and food exposure.*

CHAPTER 3. HEALTH EFFECTS

Section 3.1. INTRODUCTION

COMMENT: P. 44, L. 23, I am not convinced that there is sufficient evidence to state that levels in humans continue to increase. I suggest amending this to say that PBDEs remain present in human tissues

RESPONSE: *The term "at levels that continue to increase" was deleted from the sentence in the profile because there is insufficient evidence supporting the hypothesis that the levels of PBDEs will continue to increase in the future, as PBDEs (continue to) migrate from products into the indoor and outdoor environments.*

COMMENT: P.45, L.6 why is it not thought that effects of multiple congeners may occur in a **more-**than-additive way? Especially pertinent, given P208, L23-24.

RESPONSE: *Current data are insufficient to determine if multiple PBDE congeners interact in a non-additive, less-than-additive, or more-than-additive way. The text was modified accordingly. The statement referred to by the Reviewer pertains to a single study evaluating the potential interaction between PCBs and PBDEs, rather than interactions between individual PBDE congeners.*

Section 3.2. DISCUSSION OF HEALTH EFFECTS

COMMENT: P142, L.31 Evidence to support the assertion that dermal absorption is likely to be low should be provided. To my knowledge such empirical evidence does not exist. The statement may well turn out to be correct, but at this point in time, I do not feel we can say this with any real certainty.

RESPONSE: *The statement in question was revised to indicate that it was based on* in vitro *dermal absorption assays (Hughes et al. 2002; Roper et al. 2006).*

Section 3.4. TOXICOKINETICS

COMMENT: Section 3.4.1.2 P.150- While the in vivo animals study database is described satisfactorily; there is no mention of the increasing number of in vitro bioaccessibility studies being conducted that examine gut absorption of PBDEs from dust and food. Examples include:

- M. Abdallah, E. Tilston, S. Harrad, C. Collins. "*In vitro* assessment of the bioaccessibility of brominated flame retardants in indoor dust using a colon extended model of the human gastrointestinal tract", *Journal of Environmental Monitoring*, 14, 3276-3283 (2012).
- Y. Yu, J. Li, X. Zhang, Z. Yu, T. Van de Wiele, S. Han, M. Wu, G. Sheng and J. Fu, J. Agric. Food Chem., 2010, 58, 301–308.
- P. Lepom, M. Berndt, A. Duffek and E. Warmbrunn-Suckrow, Organohalogen Compd., 2010, 72, 122–124.

RESPONSE: *The suggested studies were added to Section 3.5.1, Pharmacokinetic Mechanisms.*

COMMENT: P156, L30-33, it is worth highlighting that the omission of higher brominated PBDEs from earlier human biomonitoring studies stemmed from an inability to accurately measure such PBDEs as BDE-209 at that time.

RESPONSE: *The following statement was added to Section 3.4.2. Distribution: "Additionally, higher brominated PBDEs (e.g., decaBDE; BDE 209) were often omitted from early human biomonitoring due to the inability to accurately measure them at that time."*

COMMENT: P.157, L.8 more details are needed about the Carrizzo et al, 2007 study. Specifically, was the observed difference statistically significant and if so at what level? Also, did the study adequately control for differences between the two groups in exposures via other pathways like dust and food.

RESPONSE: *The differences were statistically significant ($p<0.05$) with increases ~5-fold. The study did not control for potential differences in other PBDE exposure pathways, such as ingestion of contaminated dusts or food. These details are now included in Section 3.4.2, Distribution.*

COMMENT: P.189, L.34-P190, L.2. While the statement that the pattern in human tissues differs from that in the commercial formulations is correct, the example given isn't the best in my view, unless a direct comparator is given – i.e. the % that BDE-47 comprises of the congeners measured in the Darnerud et al study in say the Penta-BDE formulation

RESPONSE: *This statement has been clarified by indicating that predominant congeners in commercial mixtures were penta-, octa-, and/or decaBDE.*

Section 3.7. CHILDREN'S SUSCEPTIBILITY

COMMENT: P.200, 1st para, while the pathways of toddler exposure to PBDEs are similar to adults, the greater hand-to-mouth behaviour of toddlers likely renders them more susceptible to exposure via hand contact with dust and PBDE-treated materials. Moreover, toddlers are more exposed than adults relative to their body weight via the diet, because they consume more calories normalised to their body weight, and because their diet is more likely higher in animal fats than adult. Some acknowledgement of these aspects is needed.

RESPONSE: *The following statement was added to Section 3.7. Children's Susceptibility: "However, exposure from these sources may be greater in young children due to: (1) greater hand-to-mouth behavior, increasing the risk of ingestion of contaminated dust and/or residues from PBDE-treated materials; and (2) increased exposure relative to their body weight via diet due to increased caloric intake normalized to body weight and a higher general intake of animal fats."*

Section 3.8. BIOMARKERS OF EXPOSURE AND EFFECT

COMMENT: Section 3.8.1, P206- on biomarker of exposure provides an adequate summary of such biomarkers, although of course it is not just maternal serum but male serum also that can be used as a biomarker of exposure.

RESPONSE: *The first sentence indicates that PBDEs can be measured in the adipose tissue, serum, and breast milk of the general population. The next statement, which specifically mentions maternal serum, refers to measuring maternal body burdens. Therefore, "male" serum was not added to this list.*

COMMENT: P206, L.20-22, the lack of correlation between PBDEs in indoor dust and hair may simply reflect fact that exposure via dust was not significant for the subjects involved, as opposed to being an indication that hair was not a good monitor of exposure.

RESPONSE: *The following statement was added to Section 3.8.1. Biomarkers Used to Identify or Quantify Exposure to PBDEs: "It is not clear if the lack of correlation between PBDE concentrations in indoor dust and hair reported by Zheng et al. (2011) indicates that hair is a poor monitor of exposure or if exposure via dust was not significant for the Chinese subjects involved in the study. Other potential exposure sources, including outdoor dust for individuals living near an e-waste area or ingestion of contaminated food, were not controlled for in this study."*

Section 3.10. POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

COMMENT: P211, L12-14, see earlier comment about P6, L8 [The statement that "In most cases.." begs the obvious question of in what cases will the benefits of breastfeeding not outweigh the risks. I would suggest rephrasing this to say something like "The available evidence suggests that any risks from exposure to PBDEs from mother's milk are outweighed by the benefits of breastfeeding."]

RESPONSE: *Please refer to response for earlier comment about P6, L8.*

Section 3.11. METHODS FOR REDUCING TOXIC EFFECTS

COMMENT: Section 3.11.2 on reducing body burden describes what little is known about this. My view is that the evidence base is too thin to make any real recommendations, especially in view of the concerns that reduced caloric intake would remobilise PBDEs internally with consequent potential for health effects. The section omits mention of a small body of work that indicates that Olestra may enhance excretion of contaminants like PCBs and DDT. See Jandacek, R. et al Journal of nutritional biochemistry 04/2014; 25(4):483-8. In extreme cases, this may be an approach worth considering.

RESPONSE: *In response to this comment, and a similar comment by Reviewer 3, this paper is discussed in Section 3.11.*

Section 3.12. ADEQUACY OF THE DATABASE

COMMENT: P226, L29, clarify that exposure had increased in the 25 years leading up to the study cited. As the study in question was published in 1998, this is NOT the same as increasing over the past 25 years leading up to the current report.

RESPONSE: *To avoid confusion, the sentence in question was revised to read: "Breast milk monitoring programs would provide time-trend data that would verify whether regulatory action to limit the use of PBDEs is reversing the previous trend of an exponential increase in PBDE concentrations in breast milk." This was an editorial suggestion made by Reviewer 1.*

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

COMMENT: Overall, this chapter is fit-for-purpose and covers the main relevant studies and information available. However, it does not include reference to or make apparent use of a paper that reports the relative abundance of individual congeners to various commercial formulations (La Guardia MJ, Hale RC, Harvey E. Detailed polybrominated diphenyl ether (PBDE) congener composition of the widely used penta-, octa-, and deca-PBDE technical flame-retardant mixtures. Environ Sci Technol 2006;40: 6247–54.)

RESPONSE: *A summary of the La Guardia et al. (2006) study was added to Section 4.1 of the profile to identify this source as a reference of PBDE congeners in various commercial formulations.*

COMMENT: Data does exist for vapor pressures of BDE-209 – see Fu and Suuberg. Environmental Toxicology and Chemistry, Vol. 30, No. 10, pp. 2216–2219, 2011. I recommend that a search is made to verify whether there exist data for other physicochemical properties of this congener

RESPONSE: *Since decabromodiphenyl ether (decaBDE) and BDE 209 are the same compound, the physical chemical property data are reported for decabromodiphenyl ether in Table 4-3 only; these were obtained using a literature search.*

COMMENT: I also recommend that data are included for the octanol-air partition coefficient K_{OA}

RESPONSE: *Octanol-air partition coefficient K_{OA} data were added to Table 4-4.*

CHAPTER 5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

COMMENT: P253, L18 as mentioned earlier, the EU ban (Directive 76/769/EEC) on Penta and Octa-BDE did not come into force until 15th August 2004, rather than 2003 as indicated. Moreover, Deca-BDE is banned in electrical and electronic applications in the EU since July 2008, but its use in other applications such as textiles is still not banned.

RESPONSE: *This section was revised to more clearly identify the effective date of the EU penta- and octaBDE ban and the restricted use directive for decaBDE.*

COMMENT: P255, L14. While it is true that the main use of Penta-BDE was in FPUF, it was also applied in printed circuit boards in PCs (see S. Hazrati, S. Harrad "Causes of Variability in Concentrations of Polychlorinated Biphenyls and Polybrominated Diphenyl Ethers in Indoor Air", Environmental Science and Technology, 40, 7584–7589 (2006). And related news article Betts, K. Environmental Science and Technology, 40, 7452 (2006).

RESPONSE: *Hazrati and Harrad (2006) and Betts (2006) were added and the summary was updated based on these new references.*

COMMENT: P257, L.3 Leaching from landfill of PBDEs is more of an issue than indicated here – see W.A. Stubbings, S. Harrad, "Extent and mechanisms of brominated flame retardant emissions from waste soft furnishings and fabrics: A critical review", *Environment International*, 71, 164-175 (2014) for an overview, plus:

- Danon-Schaffer, M.N.; Mahecha-Botero, A.; Grace, J.R.; Ikonomou, M.G., 2013a. Mass balance evaluation of polybrominated diphenyl ethers in landfill leachate and potential for transfer from e-waste. Science of the Total Environment, 461-462, 290-301.
- Danon-Schaffer, M.N.; Mahecha-Botero, A.; Grace, J.R.; Ikonomou, M. G., 2013b. Transfer of PBDEs from e-waste to aqueous media. Science of the Total Environment, 447, 458-471.
- Danon-Schaffer, M.N.; Mahecha-Botero, A., 2010. Influence of chemical degradation kinetic parameters on the total debromination of PBDEs in a landfill system. Organohalogen Compounds, 72, 47-50.
- Daso, A.P.; Fatoki, O.S.; Odendaal, J. P.; Olujimi, O.O., 2013. Polybrominated diphenyl ethers (PBDEs) and 2,2',4,4',5,5'-hexabromobiphenyl (BB-153) in landfill leachate in Cape Town, South Africa. Environmental Monitoring & Assessment, 185, 431-439.
- Kwan, C.S.; Takada, H.; Mizukawa, K.; Torii, M.; Koike, T.; Yamashita, R.; Rinawati; Saha, M.; Santiago, E.C., 2013. PBDEs in leachates from municipal solid waste dumping sites in tropical Asian countries: phase distribution and debromination. Environmental Science and Pollution Research, 20, 4188-4204.
- Li, B.; Danon-Schaffer, M.N.; Li, L.Y.; Ikonomou, M.G.; Grace, J. R., 2012. Occurrence of PFCs and PBDEs in Landfill Leachates from Across Canada. Water, Air, & Soil Pollution, 223, 365-3372.
- Odusanya, D.O.; Okonkwo, J.O.; Botha, B., 2009. Polybrominated diphenyl ethers (PBDEs) in leachates from selected landfill sites in South Africa. Waste Management, 29, 96-102.
- Oliaei, F.; Weber, R.; Watson, A., 2010. PBDE contamination in Minnesota landfills, waste water treatment plants and sediments as PBDE sources and reservoirs. Organohalogen Compounds, 72, 1346-1349.

RESPONSE: *This section on PBDE in leachate was expanded to discuss the mass balance studies and detection of PBDEs in leachate. Several of the sources listed above were referenced.*

CHAPTER 6. POTENTIAL FOR HUMAN EXPOSURE

COMMENT: As mentioned earlier, the significance of the opening statement depends on how many such sites have been tested for PBDEs. Notwithstanding this, this section as a whole provides an appropriately thorough summary of the relevant information pertaining to the environmental fate, behaviour, degradation and levels of PBDEs.

RESPONSE: *The total number of NPL sites evaluated for PBDEs is not known. NPL site information is limited; the actual number of sites tested for PBDEs specifically is not readily available.*

COMMENT: P259, L32-34, while not incorrect, this statement should emphasise that – at least for the UK study, cited, dust is the most important exposure pathway for BDE-209 in the UK.

RESPONSE: *This sentence was revised to present dust exposure as the most important pathway for BDE 209 in the United Kingdom.*

COMMENT: P260, L1-3, clarify that the PBDEs referred to here do not include BDE-209. Also, while age-stratified biomonitoring indeed shows that levels are higher in young children than adults, I am not convinced by the assertion here that they gradually decrease over time (I presume by "time", "age" is meant?)

RESPONSE: *The sentence was revised to change "over time" to "at older ages."*

COMMENT: P267, L1-4, see above comments and papers addressing PBDEs in landfill leachate.

RESPONSE: *The additions were added to this section (Section 6.2.2) as well.*

COMMENT: P267, L29-32, these data are for indoor air, data for North American outdoor air could also be cited Strandberg, B.; Dodder, N. G.; Basu, I.; Hites, R. A. Environ. Sci. Technol. 2001, 35, 1078-1083

RESPONSE: *This reference, Strandberg et al. (2001), was added to the profile.*

COMMENT: L268, L8-9 while true at background soil contamination levels, volatilisation from soil to air will likely occur at high contamination levels, especially if the organic carbon content of the soil is low.

RESPONSE: *Section 6.3.1 of the profile was revised to account for PBDEs being found in air as noted in the monitoring section (Section 6.4.1) and as described in this comment.*

COMMENT: Section 6.4.2, some recent data on concentrations of individual PBDE congeners in UK lake water is available, together with citations of other relevant studies. C. Yang, S. Harrad, M. A-E. Abdallah, J. Desborough, N. L. Rose, S. D. Turner, T. A. Davidson, B. Goldsmith. "Polybrominated diphenyl ethers (PBDEs) in English freshwater lakes, 2008–2012" Chemosphere, 110, 41–47 (2014).

RESPONSE: *Section 6.4.2 was revised to include a summary of Yang et al. (2014).*

COMMENT: Section 6.4.3, wherever possible, it is good practice to report concentrations on a congener-specific basis, at least for major congeners such as 47, 99 and 209. The sources, exposure pathways and effects of these congeners are very different, so knowledge of their relative concentrations is very pertinent.

RESPONSE: *Congener-specific information was added to Section 6.4.3 when suitable information was available in references.*

COMMENT: P283, L6, the presence of PBDEs in sediment core slices dated prior to their production may indicate natural sources, but it is unlikely that they have been mis-identified. Their presence in such deep core slices may also be due to in-core migration of PBDEs.

RESPONSE: *This entry was edited to include migration of PBDEs and the hypothesis about 'unknown sources of PBDEs produced in nature' was removed.*

COMMENT: P283, L19, again it is important to differentiate between Penta and Octa-BDE congeners and BDE-209. Concentrations in dust of the latter are similar in the UK and USA/Canada (S. Harrad, C. Ibarra, M. Diamond, L. Melymuk, M. Robson, J. Douwes, L. Roosens, A. C. Dirtu, A. Covaci "Polybrominated diphenyl ethers in domestic indoor dust from Canada, New Zealand, United Kingdom and United States", Environment International, 34, 232-238 (2008).) A comprehensive meta-analysis of available data on PBDEs in indoor air and dust and its relationship with human body burdens is available (S. Harrad et al "Indoor Contamination with Hexabromocyclododecanes, Polybrominated Diphenyl Ethers and Perfluoroalkyl Compounds: An Important Exposure Pathway for People?" Environmental Science and Technology, 44, 3221–3231 (2010)

RESPONSE: *The two references identified in this comment were added to the profile. The section was revised to better differentiate the congeners and trends found in dust.*

COMMENT: P284, L.33 and ensuing paragraph "VEGAN" not vegetarian, an important distinction as it allowed the study authors to infer that while plant-based foods WERE a source of exposure, meat, fish and dairy products were more important.

RESPONSE: *The suggested revision was made.*

COMMENT: P307, L32-33. It is crucial when commenting on temporal trends in contamination that the time period over which these are observed is specified. PBDEs may have risen for the 20 years prior to 2005 for example, but since then may have levelled off or even started to decline

RESPONSE: *The suggested revisions were made.*

COMMENT: P.321, L. 34 "vegan" NOT "vegetarian"

RESPONSE: *The suggested revision was made.*

COMMENT: Section 6.8.1. The data gaps identified are correct. However, there are some important omissions in my view. Firstly, more data is needed on the human bioavailability of PBDEs from external matrices such as dust and food. Another data gap not mentioned is better characterisation of the quantity of dust ingested by humans, in particular young children. Present exposure factors on which dust exposure estimates are based, are in my view insufficiently robust. Given the importance assigned to dust ingestion as an exposure pathway to Americans, this is an important data gap.

RESPONSE: *The suggested revisions were made.*

COMMENT: I agree with the need for more data on relevant physicochemical properties of relevant PBDE congeners. I would highlight Kow as being especially important. The data gaps are especially stark for BDE-209. The same applies to the data gap for PBDE environmental fate. I would highlight here the need for better data on degradation via OH radical reaction and photolysis.

RESPONSE: *The suggested revisions were made.*

CHAPTER 7. ANALYTICAL METHODS

COMMENT: Overall, this chapter is the weakest in this assessment. It requires substantial updating by review of RECENT literature on the topic.

RESPONSE: *A number of additions and revisions were made to Chapter 7 of the profile based on this and other comments.*

COMMENT: 329, L23-25. NO lab will today use FID or ECD for PBDE analysis, nor will these have been used for many years! Remove this sentence, and any other references to these techniques other than in a historical context e.g. P334, L7, reference is made to a WHO monograph dating from 1994!

RESPONSE: *The suggested revisions were made*

COMMENT: P330, para beginning L13. One recent way in which problems with the determination of BDE-209 have been overcome is use of LC-MS/MS – see M. A. Abdallah, S. Harrad, A. Covaci "Isotope Dilution Method for Determination of Polybrominated Diphenyl Ethers using Liquid Chromatography Coupled to Negative Ionization Atmospheric Pressure Photoionization Tandem Mass Spectrometry: Validation and Application to House Dust", Analytical Chemistry, 81, 7460–7467 (2009).

RESPONSE: *The reference identified in this comment was added to the profile.*

COMMENT: Section 7.2, P, 334. Mention should be made of passive air sampling techniques – e.g those used in:

- M. A.-E. Abdallah, S. Harrad Modification and calibration of a passive air sampler for monitoring vapor and particulate phase brominated flame retardants in indoor air: application to car interiors. Environmental Science and Technology 44, 3059–3065 (2010).
- S. Hazrati, S. Harrad "Calibration of polyurethane foam (PUF) disk passive air samplers for quantitative measurement of Polychlorinated Biphenyls (PCBs) and Polybrominated Diphenyl Ethers (PBDEs): Factors Influencing Sampling Rates", Chemosphere, 67, 448-455 (2007).
- S. Harrad, S. Hunter "Concentrations of Polybrominated Diphenyl Ethers in Air and Soil on a Rural-Urban Transect Across a Major UK Conurbation", Environmental Science and Technology, 40: 4548-4553 (2006).
- S. Harrad, S. Hazrati, C. Ibarra "Concentrations of Polybrominated Diphenyl Ethers in Indoor Air and Dust and Polychlorinated Biphenyls in Indoor Air in Birmingham, United Kingdom: Implications for Human Exposure", Environmental Science and Technology., 40: 4633-4638 (2006).

RESPONSE: *Three of the references identified in this comment were added to the profile. The section was revised to better describe passive air sampling.*

COMMENT: P334, L.23, note that detection limits in water are lower than this. Those cited in C. Yang, S. Harrad, M. A-E. Abdallah, J. Desborough, N. L. Rose, S. D. Turner, T. A. Davidson, B. Goldsmith. "Polybrominated diphenyl ethers (PBDEs) in English freshwater lakes, 2008–2012" Chemosphere, 110, 41–47 (2014), are 0.2 to 1.4 pg/L

RESPONSE: *The reference identified in this comment was added to the profile. The section was revised to note the lower detection limits.*

COMMENT: Table 7-2 is quite out-dated in its coverage. As a rule of thumb, it should be possible to cite papers for each matrix published since 2008 with any problems. While the ELISA method for dust is worthy of note, citation of the far more commonly used GC-MS based methods for this matrix is required, e.g. S. Harrad, S. Hazrati, C. Ibarra "Concentrations of Polybrominated Diphenyl Ethers in Indoor Air and Dust and Polychlorinated Biphenyls in Indoor Air in Birmingham, United Kingdom: Implications for Human Exposure", Environmental Science and Technology., 40: 4633-4638 (2006).

RESPONSE: *Nine additional references were added to Table 7-2 based on this comment.*

COMMENT: Likewise for water, the Yang et al, 2014 reference above would be more appropriate, with any of the various more recent papers on PBDEs in sediments also more suitable.

RESPONSE: *The suggested revision was made.*

COMMENT: P337, L10, as highlighted above for water, the detection limits cited here are outdated and far too high. They must be replaced with figures from recent papers.

RESPONSE: *References were added to the profile based on this comment and the section was revised to note the lower detection limits.*

COMMENT: P337, L15, while true in 2000, it is no longer the case that improved methods are required for any of the PBDEs listed. Methods for BDE-209 have taken longer to finalise, but they are now satisfactory. I suggest deleting that sentence.

RESPONSE: *The suggested revision was made.*

COMMENT: P338, L11. It is no longer correct to say that "only 30-40 congener standards are available". It is now something like 60-70. As these comprise essentially all of those that are environmentally relevant, I am not sure that synthesising more standards is a pressing research gap.

RESPONSE: *The suggested revision was made.*

COMMENT: P338, L17. I am not sure I would agree with this statement. Those more qualified to comment on the toxicological/epidemiological database can confirm or deny this, but I recommend a thorough verification of this statement.

RESPONSE: *The statement has been verified.*

COMMENT: P338, L21-23. More recent papers than e.g. those dating from 1976 and 1978 etc are needed here.

RESPONSE: *The suggested revision was made.*

COMMENT: The statement on P338, L26 is incorrect. See section 3.4.3. of the document under review for example.

RESPONSE: *The suggested revision was made.*

CHAPTER 9. REFERENCES

COMMENT: Regarding the question of whether there are additional references that provide new data or if there are better studies than those already in the text, the Reviewer commented: "Overall, the reference list is comprehensive and up-to-date. However, I have identified at various points above, additional references. I also urge substantial updating of the references used as the basis for Chapter 7"

RESPONSE: *Responses regarding additional references can be found in previous sections.*

Review comments provided by Reviewer #3:

GENERAL COMMENTS

Reviewer 3 made several editorial suggestions throughout the review of "The Profile". Unless otherwise noted, all grammatical/language/stylistic suggestions from Reviewer 3 were incorporated into "The Profile", and will not be discussed individually.

COMMENT: Throughout the document, and especially in the detailed Health Effects Chapter, it would also be useful to specify the specific tetra-, penta- or octa- congeners used in toxicological studies, for example, for tetra- , specify 2,2',4,4'-tetrabromodiphenyl ether (BDE 47) if this was the specific congener used for a given study. This is especially important when summarizing key studies used to support an MRL. Furthermore, IF tetra- always specifies 47 and penta- always specifies 99, this needs to be clarified, but I do not believe that this is the case. Including congener specific data are of added human relevance since BDE 47 and BDE 99 are some of the most abundant PBDEs retained in humans.
RESPONSE: *The MRL summaries in Chapter 2 and the MRL worksheets in the Appendix were thoroughly reviewed and edited to ensure that specific test compounds/mixtures were identified. These details were not added throughout the text of Chapter 3, as studies were often grouped together for discussion in a way that would make it laborious to write and read if specific test compound/mixture information were added throughout. In order to provide the reader with this specific information, the Levels of Significant Exposure (LSE) tables were edited to include specific test compound/mixture information for each study.*

COMMENT: Since congener specific data are available, it would be useful to list or highlight the relative toxic potency of the non-decaBDEs (tetra-, penta-, octa-) for toxicological endpoints of concern.

RESPONSE: *In most instances, available studies cannot be directly compared in order to make these determinations for each toxicological end point of concern. One exception is the series of neurodevelopmental studies in mice following a single postnatal exposure to various PBDE congeners on PND 10. For these studies, the relative toxic potency could potentially be evaluated based on the effective dose that caused decreased spontaneous activity and/or impaired habituation at 2–6 months of age; however, in most cases, the lowest dose administered was the effective dose (BDE 153, BDE 183, BDE 203, BDE 206). Therefore, relative potency cannot be adequately evaluated.*

CHAPTER 1. PUBLIC HEALTH STATEMENT

COMMENT: Page 2, under "How might I be exposed to PBDEs". Consider including some of the content from page 320, lines 16-18 and Page 321, lines 17-20, which summarize key aspects of exposure.

RESPONSE: *The "How Might I be Exposed" section of has been revised to more clearly reflect the summary data reported later in the profile.*

COMMENT: Page 3, line 11. Include breast milk as a major source of exposure to PBDEs in nursing infants.

RESPONSE: *This point is now clearly stated.*

COMMENT: Page 3, line 15. Include residential and work place (office) dust as a source of PBDEs.

RESPONSE: *This point is now clearly stated.*

COMMENT: Page 3, line 24. Include Feo et al., 2013, Gross et al, 2015 and Erratico et al., 2011, 20012, 2013, which focus on metabolism in humans (more on Gross et al. 2015 is given below)

RESPONSE: *These citations have been added as requested.*

COMMENT: Page 7, line 2. Clarify units as pg/g wet weight or pg/g lipid weight.

RESPONSE: *Units are now reported as pg/g wet weight.*

COMMENT: Page 7, line 6. Include inhalation as a route of exposure to contaminated dust.

RESPONSE: *Inhalation was not added in this section because the sentence in question ("Ingestion and dermal contact with indoor dust containing PBDEs is the major exposure pathway to residents of the United States") refers to the major exposure pathways. Inhalation exposure is not considered a major exposure pathway.*

COMMENT: Page 7, line 13. Perhaps include cleaning air ducts, air filters, and vacuuming, all to reduce dust indoors.

RESPONSE: *In response to this comment, and a comment by Reviewer 2, the following statement has been added to the "How Can Families Reduce the Risk of Exposure to PBDEs?" on pg 7: "Additionally, PBDE exposure may be decreased by regular vacuuming and cleaning of air ducts and filters to reduce indoor dust levels."*

COMMENT: Page 7, line 18. Delete "urine". To the best of my knowledge, PBDEs and their breakdown products have not yet been detected in human urine. They have been detected in urine from animals given higher doses of PBDES.

RESPONSE: *In response to this comment, urine has been deleted from the list of substances that can be used to evaluate exposure to PBDEs in humans.*

COMMENT: Page 7, lines 21 and 22. This sentence is not entirely accurate and should be deleted. Humans are chronically exposed to environmental sources of PBDEs, which are persistent in humans. Thus, analysis of blood and breast milk is a good means to assess the magnitude of the chronic exposure and resulting body burden of PBDEs. Time sensitivity for analysis may only be necessary for assessing the rare case of an acute, high occupational exposure.

RESPONSE: *The sentence has been edited to read: "Because PBDEs and their metabolites either leave the body or are distributed to body fat fairly rapidly, the tests need to be conducted within days if an acute, high-level exposure is suspected."*

CHAPTER 2. RELEVANCE TO PUBLIC HEALTH

COMMENT: Page 29, lines 14. Consistent with "a different mode of action and" the high absorption efficiencies…

RESPONSE: *There is no clear evidence that decaBDE exerts toxic effects via a different mode of action than lower brominated PBDEs (see Section 3.5.2, Mechanisms of Toxicity). Therefore, the suggested text "a different mode of action" regarding rationale for deriving of separate MRLs for decaBDE was not added to the document.*

COMMENT: Page 30, line 2-3. Can unpublished studies be included in this document?

RESPONSE: *According to ATSDR policy, unpublished studies can be included if they go through an internal peer-review process. All unpublished studies included in this Profile were peer-reviewed.*

COMMENT: Page 36, line 18 and page 37, line 3. It would be useful to define a "minimal LOAEL"

RESPONSE: *An effect is considered a minimal LOAEL if the magnitude of the change is below the threshold for identifying a clearly adverse effect, but the effect was considered an early indication of an effect. This distinction is now made clear in Section 2.3 and the MRL worksheets:*

- *Intermediate oral MRL for lower BDEs: "The change in testosterone is considered a minimal LOAEL because it is unclear if the magnitude of change represents a biologically adverse effect; however, this statistically significant reduction in serum testosterone is considered an early indication of damage to the male reproductive system, considering the additional effects observed at ≥0.03 mg/kg/day (histological lesions in testes, sperm effects)."*
- *Intermediate oral MRL for decaBDEs: "The change in glucose is considered a minimal LOAEL because it is unclear if the magnitude of change represents a biologically adverse effect; however, the increase in serum glucose is considered to be part of a spectrum of effects indicative of altered insulin homeostasis and toxicity to the pancreas, including decreased serum insulin and morphological changes in pancreatic islet cells observed at ≥1 mg/kg/day following decaBDE exposure."*

COMMENT: Page 36, line 19. Specify that this study was for 2,2',4,4'-tetrabromodiphenyl ether (BDE 47), the most abundant congener retained in humans.

RESPONSE: *Congener-specific information was added throughout the MRL section of Chapter 2. However, BDE 47 was not identified as the "most abundant congener retained in humans." BDE 47 was reported as the congener with the highest concentration in breast adipose tissue (She et al. 2000) and in serum of office workers (Sjodin et al, 1999b); however, in computer disassembly plant workers and computer technicians, BDE 183 and BDE 153 have the highest concentrations, respectively (Hagmar et al. 2000; Sjodin et al. 1999b). According to recent studies, the U.S. population is estimated to have the highest intakes of BDE 47, BDE 99, and BDE 209, although the relative intakes between those three congeners vary between studies (Harrad et al., 2004; Lorber 2008, Wong et al. 2013).*

COMMENT: Page 37, line 8. Specify 2,2',4,4'-tetrabromodiphenyl ether (BDE 47)

RESPONSE: *Congener-specific information was added throughout the MRL section of Chapter 2.*

COMMENT: Page 37, line 23. Specify BDE 99, 2,2'4,4',5-pentabromodiphenyl ether. It should also be noted that the toxic response (decrease in serum testosterone) was the same adverse response used to support the MRL with BDE 47 (Zhang et al., 2013b).

RESPONSE: *Congener-specific information was added throughout the MRL section of Chapter 2. The text was edited to highlight that the decrease in serum testosterone observed following exposure to BDE 99 was the same adverse response observed following exposure to BDE 47.*

COMMENT: Page 37, lines 24-26. It is important state that these studies, which did not observe dose-related decreases in serum testosterone, used commercial mixtures (DE-71, Stoker et al 2005) or other environmentally relevant mixtures (Ernest et al. 2012) . These negative studies indicate that the mixtures that were studied are much less active than the specific congeners, BDE 47 and BDE 99. It is also important to note that these congeners are also some of the most abundant specific congeners retained in humans.

RESPONSE: *The text was revised to indicate that studies that did not observe altered serum testosterone levels used commercial or environmentally-relevant mixtures. Additionally, the following statement was added: "These data suggest that the individual congeners BDE 47 and BDE 99, which have been identified as two of the most abundant congeners for human exposure (Harrad et al., 2004; Lorber 2008; Wong et al. 2013), may have a greater capacity to alter serum testosterone levels than PBDE mixtures."*

COMMENT: Page 42, line 27. Clarify the wording for these gender specific doses. Also, is there any justification for using different doses for each gender?

RESPONSE: *In this study, rats and mice were fed decaBDE at dietary concentrations of 0, 25,000, or 50,000 ppm. Based on weight and food consumption differences, calculated doses in mg/kg/day differed between the sexes and species. Based on the ATSDR guidelines, all oral doses are reported as mg/kg/day throughout the document. The presentation of the different dose groups was revised for clarification: "In this study, F344 rats and B6C3F1 mice (50/sex/group per species) were administered a commercial decaBDE product (94–97% pure) in the diet for 103 weeks (NTP 1986). Calculated dietary doses based on body weight and food intake were 0, 1,120, or 2,240 mg/kg/day for male rats; 0, 1,200, or 2,550 mg/kg/day for female rats; 0, 3,200, or 6,650 mg/kg/day for male mice; and 0, 3,760, or 7,780 mg/kg/day for female mice."*

CHAPTER 3. HEALTH EFFECTS

Section 3.2. DISCUSSION OF HEALTH EFFECTS

COMMENT: Page 57, lines 1-4. Consider moving this to the cardiovascular section, bottom of 1.55.

RESPONSE: *The information from these lines (no relationship between stroke and serum BDE 47; Lee et al. 2012) was deleted from the hematological section and presented with the data regarding the lack of*

relationship between atherosclerosis and serum BDE 47 from the same study population in Sweden (Lind et al. 2012).

COMMENT: Page 65, lines 16-18. Can raw data be requested from the Van der ven et al., 2008b study? The studies are limited by only reporting BMD/BMDLRD10%. Throughout the document, this limitation is given.

RESPONSE: *As doses evaluated in these studies (Van der ven et al. 2008a, 2008b) are several orders of magnitude higher than the points of departure (PODs) used for MRL derivation, retrieval and review of raw data from these studies were not considered critical for identification of critical effect and POD.*

COMMENT: Page 67, lines 1-3. This clearly illustrates the unique sensitivity of mink relative to the more common studies conducted in rats and mice. This is also the case for other adverse effects of PBDEs. It might be appropriate to discuss mink as a relevant model to predict human risk.

RESPONSE: *The effects discussed here, elevated liver weight and induction of hepatic enzymes, were not used as a basis of a NOAEL/LOAEL determination for hepatic effects, as they are consistent with an adaptive response. From this single, low-dose study, it appears that this adaptive response may be induced at lower doses in mink, compared with rats and mice. However, this does not indicate that mink are more sensitive to adverse effects of PBDE exposure. Additionally, available evidence does not clearly support that mink are more susceptible to adverse effects following exposure to lower-brominated PBDE because critical effects considered for the intermediate oral MRL occur at doses of 0.001–0.03 mg/kg/day, which are lower than the lowest LOAEL identified in this study (0.06 mg/kg/day).*

COMMENT: Page 71, line 10-12. Perhaps include hepatic porphyria and markers of hepatic oxidative stress is this summary after "liver enlargement…"

RESPONSE: *Hepatic porphyria and markers of hepatic oxidative stress were added as adverse liver effects in animals in the summary statement, as suggested.*

COMMENT: Page 78, line 2. As association of BDE 153 (but not other congeners) was observed with the risk of diabetes and metabolic syndrome. Did the study by Lim et al (2008) assess associations with other classes of POPs, which may be co-related to levels of BDE 153?

RESPONSE: *Lim et al (2008) also assessed PBB 153. The statistical analysis did not control for levels of other PBDEs or PBB 153. However, the study authors indicate that the pattern of increased risk differed from PBDE 153, with similar increases in risk of disease with exposure to the 25th–50th, 50–75th , and >75th percentiles. Data on other POPs from this, and other epidemiological studies, were not included within the scope of this profile.*

COMMENT: Page 81, line 4. Another case of sensitivity of mink.

RESPONSE: *Please see the response above.*

COMMENT: Page 86, line 23. Why is "Body Weight Effects" located here in the document? I may be better placed earlier in the Health Effects chapter, perhaps after lethality.

RESPONSE: *The headings in this chapter are in a standardized order for ATSDR profiles. ATSDR will consider the suggestion during the next revision of the ATSDR profile format.*

COMMENT: Page 88, line 28. Clarify whole-body growth rates. For example, what does 1.57% mean? Are these daily % gain in body weight?

RESPONSE: ***The s****tudy authors define whole-body growth rates as "average growth rate after 90 day;" this clarification has been added to the text. It is likely that these are daily percent gain in body weight, but it is not explicitly clear in the study report.*

COMMENT: Page 89, lines 22-26. May state that body weight loss is a relatively sensitive response observed in PBDE exposed mink.

RESPONSE: *Please see the response above.*

COMMENT: Page 90, lines 25. "…significantly elevated serum insulin…" Also, it should be stated that this adverse response associated with exposure to deca-BDE warrants further investigations. Zhang et al., 2013a is a recent study.

RESPONSE: *Serum insulin levels were significant decreased in this study; "decreased" was added to the text. The suggestion for further investigation into the potential link between decaBDE and elevated glucose/reduced insulin was added to Section 3.12.2, Identification of Data Need.*

COMMENT: Page 93, line 14. Check on "doses up to 0.015 mg/kg/day" in the study by Daubie et al 2011. The dose seems very low relative to the other discussed before or after this study (lines 12-19).

RESPONSE: *The dose reporting for Daubie et al. (2011) is accurate.*

COMMENT: Page 98, line 21. Specify the penta BDE 99. Also specify if 0.015 mg/kg/d was the highest dose used in this study.

RESPONSE: *Please see response under General Comments regarding addition of congener-specific information throughout Chapter 3. The text now specifies that the 0.015 mg/kg/day dose was the highest dose tested.*

COMMENT: Page 98, line 25. Specify, BDE 47.

RESPONSE: *Please see response under General Comments regarding addition of congener-specific information throughout Chapter 3.*

COMMENT: Page 101, line 14. Confirm "several studies". It looks like there were only 2 studies.

RESPONSE: *The first line of this paragraph was revised to reflect that only two studies demonstrated reproductive effects in men associated with exposure to PBDEs.*

COMMENT: Page 101, line 16. Note that the study was limited to only 10 participants.

RESPONSE: *The text was revised to emphasize the small number of participants in the study.*

COMMENT: Page 104, lines 26-30. For this summary, it is important to specify the specific doses of BDE 47 and BDE 99 that were associated with these sensitive adverse responses.

RESPONSE: *The requested dose information was added (≥0.06 mg/kg/day pentaBDE, ≥0.14 mg/kg/day tetraBDE).*

COMMENT: Page 107, line 1-13. A reduction in serum testosterone is a sensitive response with BDE 47, observed at a dose of 0.001 mg/kg/d. There appears to be a lack of a consistent response with other PBDEs, such a penta- (99?) and deca BDE. It is very important to clarify and highlight if this response is specific for BDE 47, especially since this response is used as a basis for establishing an MRL (see page 36). This is very important to clarify since tetra and penta BDEs do not seem to produce a consistent response for this toxic endpoint.

RESPONSE: *The consistency, or lack thereof, in this response was discussed in the previous draft. Revisions to the text have been made for further clarification in the revised Section 2.3 and MRL Worksheet for the Oral Intermediate Duration MRL for lower-brominated PBDEs. The revised text states:*

> *No other study evaluated serum testosterone levels following exposure to BDE 47. However, as observed with exposure to BDE 47, acute exposure to 0.06 or 1.2 mg/kg of 2,2',4,4',5-pentaBDE (BDE 99) also led to a significant 40–45% decrease in serum testosterone levels in rats (Alonso et al. 2010). No other studies evaluated this end point following exposure to single congeners. Other studies evaluating serum testosterone levels after intermediate-duration exposure to lower-brominated PBDEs mixtures (DE-71, dietary PBDE mixture described above) did not report exposure-related decreases (Becker et al. 2012; Ernest et al. 2012; Stoker et al. 2005). These data suggest that the individual congeners, BDE 47 and BDE 99, which have been identified as two of the most abundant congeners for human exposure (Harrad et al., 2004; Lorber 2008, Wong et al. 2013), may have a greater capacity to alter serum testosterone levels than PBDE mixtures.*

COMMENT: Page 123, lines 4-10. The only deficit observed in these studies was a decrease in general sociability in female offspring. Since this response is in contrast to all other results which are negative, it is important to define general sociability and clarify whether the response was dose dependent.

RESPONSE: *The behavioral evaluations were only conducted at one dose level (0.03 mg/kg/day). In response to this comment, the differences between general sociability, social novelty, and barrier social interaction tests are clearly defined in Section 3.2.2.6, Developmental Effects.*

Section 3.4. TOXICOKINETICS

COMMENT: Page 147, line 27. If possible, insert Tables 3-6 here is possible, before Section 3.4 Toxicokinetics

RESPONSE: *ATSDR guidance dictates that tables and figures are inserted into the document on the page following call-out.*

COMMENT: Page 164, Line 2. Include a new sentence such as: Feo et al. 2013 and Gross et al. 2015 characterized the in vitro metabolism of BDE 47 and BDE 100 by pooled human liver microsomes and recombinant human CYPs. While these studies found a number of hydroxylated BDE metabolites, no brominated phenols were detected by the methods utilized by these investigators. A new publication by Gross et al., 2015 should be included in the discussion regarding human metabolism of PBDEs.

Gross, M.; Butryn, D.; McGarrigle, B.; Aga, D.; Olson, J.R. Primary Role of Cytochrome P450 2B6 in the Oxidative Metabolism of 2,2',4,4',6-pentabromodiphenyl ether (BDE-100) to Hydroxylated BDEs. Chemical Research in Toxicology. 01/28/15. DOI: 10.1021/tx500446c

And a related paper by Simpson et al 2015

Simpson S., Gross, M., Olson, J., Zurek, E., and Aga, D. Identification of Polybrominated Diphenyl Ether Metabolites based on Calculated Boiling Points from COSMO-RS, Experimental Retention Times, and Mass Spectral Fragmentation Patterns. Analytical Chemistry, Jan 7, 2015, DOI: 10.1021/ac504107b

Page 164, line 40 insert discussion on the metabolism of BDE 100 primarily by human CYP2B6:

> BDE 100 (2,2′,4,4′,6-pentabromodiphenyl ether), one of the most abundant PBDE congeners found in humans, was metabolized by recombinant human P450s and pooled human liver microsomes (Gross et al., 2015). As with BDE 47 and BDE 99, human CYP2B6 was found to be the predominant enzyme responsible for nearly all formation of six mono-OH-pentaBDE and two di-OH-pentaBDE metabolites. Four metabolites were identified as 3-hydroxy-2,2′,4,4′,6-pentabromodiphenyl ether (3-OH-BDE-100), 5′-hydroxy-2,2′,4,4′,6-pentabromodiphenyl ether (5′-OHBDE-100), 6′-hydroxy-2,2′,4,4′,6-pentabromodiphenyl ether (6′-OH-BDE-100), and 4′-hydroxy-2,2′,4,5′,6-pentabromodiphenyl ether (4′-OH-BDE-103) through use of reference standards **(see Figure 3-XX).** The two remaining mono-OH-pentaBDE metabolites were hypothesized using mass spectral fragmentation characteristics of derivatized OH-BDEs, which allowed prediction of an ortho-OH-pentaBDE and a para-OH-pentaBDE positional isomer. Additional information based on theoretical boiling point calculations using COnductor-like Screening MOdel for Realistic Solvents (COSMO-RS) and experimental chromatographic retention times were used to identify the hypothesized metabolites as 2′-hydroxy-2,3′,4,4′,6-pentabromodiphenyl ether (2′-OHBDE-119) and 4-hydroxy-2,2′,4′,5,6-pentabromodiphenyl ether (4-OH-BDE-91), respectively (Simpson et al. 2015). Kinetic studies of BDE-100 metabolism using P450 2B6 and HLMs revealed Km values ranging from 4.9 to 7.0 μM and 6−10 μM, respectively, suggesting a high affinity toward the formation of OH-BDEs. Compared to the metabolism of 2,2′,4,4′-tetrabromodiphenyl ether (BDE-47) and 2,2′,4,4′,5-pentabromodiphenyl ether (BDE-99) reported in previous studies, BDE-100 appears to be more slowly metabolized by P450s due to the presence of a third ortho-substituted bromine atom.

RESPONSE: *Data from the recently published paper by Gross et al. (2015), and companion paper Simpson et al. (2015), were incorporated in Section 3.4.3, Metabolism, as indicated by the Reviewer.*

COMMENT: Page 167. A new figure can be included for BDE 100. Figure 3-XX Structures and general metabolic scheme for hydroxylated metabolites of BDE 100 produced by human liver microsomes and human CYP2B6. (see fig 1 in Gross et al. 2015)

RESPONSE: *Figure 1 from the recently published paper by Gross et al. (2015) was incorporated in Section 3.4.3 Metabolism as indicated by the Reviewer.*

COMMENT: Page 167, line 4. Delete Feo et al. 2013 from cited refs. Insert a sentence such as: Feo et al. 2013 and Gross et al. 2015 characterized the in vitro metabolism of BDE 47 and BDE 100 by pooled human liver microsomes and recombinant human CYPs. While these studies found a number of hydroxylated BDE metabolites, no brominated phenols were detected by the methods utilized by these investigators.

RESPONSE: *Newly published data were added as suggested by the Reviewer.*

COMMENT: Page 167, line 5. Insert the following new sentence. " It is important to note that all studies consistently identified CYP2B6 as the primary human CYP responsible for the formation of hydroxylated metabolites of BDE 47, BDE 99, and BDE 100 (Erratico et al. 2012, 2013; Feo et al. 2013; Gross et al. 2015)."

RESPONSE: *Newly published data were added as suggested by the Reviewer.*

Section 3.5. MECHANISMS OF ACTION

COMMENT: Page 175, line 6. "… BDE 47, BDE 99, and BDE 100 produced multiple metabolites via hydroxylation (Erratico et al. 2012, 2013; Feo et al. 2013; Gross et al. 2015), and ether bond cleavage (Erratico et al. 2012, 2013)."

RESPONSE: *Newly published data were added as suggested by the Reviewer.*

COMMENT: Page 175, lines 15- 17. Delete the last sentence and replace with: "While rat studies provide evidence for metabolic oxidative debromination of BDE 47, 99, 100, 154, and 209, studies with human liver microsomes only found evidence supporting the oxidative debromination of BDE 47."

RESPONSE: *Revisions were made as suggested by the Reviewer.*

COMMENT: Page 179, lines 8-25. This paragraph seems out of place. Consider moving up earlier in this section.

RESPONSE: *This paragraph was moved up in this section. It is now before the paragraph that begins: "As discussed in the introduction," which is followed by AhR-mediated properties of PBDEs*

COMMENT: Page 183, line 24. A summary paragraph would help to pull this section together.

RESPONSE: *A summary paragraph for Mechanisms of Endocrine Disruption was added.*

COMMENT: Page 185, line 9. Insert : "In contrast to BDE-47, which was without activity, BDE-49, 6-OH-BDE-47 and 4'-OH-BDE-49 have been reported to be potent modulators of ryanodine receptors type 1 and 2, which regulate essential aspects of Ca2+ signaling (Kim et al. 2011c; Pessah et al. 2010)" Pessah, I. N., Cherednichenko, G., and Lein, P. J. (2010). Minding the calcium store: Ryanodine receptor activation as a convergent mechanism of PCB toxicity. Pharmacol Ther 125(2), 260-85.

RESPONSE: *Data regarding modulation of ryanodine receptors by BDE-49, 6-OH-BDE-47 and 4'-OH-BDE-49 have been added to the paragraph regarding disruption of calcium homeostatic mechanism and intracellular signaling events in the Mechanisms of Neurotoxicity Section of Section 3.5.2.*

COMMENT: Page 185, line 13. Consider inserting, "In addition, several mechanistic studies have shown that monohydroxylated metabolites of BDE‐47 are more potent than the parent BDE‐47 in disrupting Ca2+ homeostasis, modulating γ-aminobutyric acid (GABA) and α4β2 nicotinic acetylcholine (nACh) receptor function, altering spontaneous activity and cell viability in cultured cortical neurons, and competing with thyroxine (T4) for binding to human transthyretin (TTR) (Dingemans et al. 2008, 2010a, 2010b, 2011; Hamers et al. 2008; Hendriks et al. 2010; Kim et al. 2011c). Together, these studies suggest that bioactivation by oxidative metabolism contributes to the neurotoxic potential of PBDEs." [Break for new paragraph]

Hendriks, H. S., Antunes Fernandes, E. C., Bergman, A., van den Berg, M., and Westerink, R. H. (2010). PCB-47, PBDE-47, and 6-OH-PBDE-47 differentially modulate human GABAA and alpha4beta2 nicotinic acetylcholine receptors. Toxicol Sci 118(2), 635-42.

RESPONSE: *Data from Hendriks et al. (2010) were added to the paragraphs on cholinergic and gabaergic function. The above statement was modified and added to the overview paragraph at the beginning of the section on Mechanisms of Neurotoxicity to inform the reader that available data indicated that bioactivation by oxidative metabolism contributes to the neurotoxic potential of PBDEs. It was not added in the paragraph suggested by the Reviewer, as that paragraph was limited to discussing effects on calcium homeostasis.*

COMMENT: Page 189, line 10. Include Staskal el al. 2006b in the references cited at the end of this sentence.

RESPONSE: *The citation was added.*

COMMENT: Page 189, lines 29-32. This concluding sentence is not clearly and does not seem to be correct as written.

RESPONSE: *This statement and the one preceding it were removed from the document. They were unclear, and did not provide information or citations directly related to the issue at hand (potential differences the effects of PBDEs on circulating thyroid hormone levels.)*

Section 3.6. TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

COMMENT: While the toxicological profile must follow a specific format, it would be beneficial to eliminate sections which a very redundant:

- Page 191, lines 26-33. This paragraph is redundant and exactly as written on page 181.
- Page 192, lines 1-9. Redundant and exactly as written on page 181.
- Page 192, lines 11-34. Redundant and exactly as written on page 182.
- Page 193. The entire page is redundant and exactly as written on page 182 and 183.
- Page 194. The entire page is redundant and exactly as written on pages 186 and 187.
- Page 195, lines 1-10. Redundant and exactly as written on page 187.
- Page 195, lines 21-34. Redundant and exactly as written on page 180.
- Page 196, line 1-22. Redundant and exactly as written on page 180.

RESPONSE: *The redundant paragraphs have been removed. The end of the second paragraph in Section 3.6. now reads: "Since these effects could be mediated by the neuroendocrine axis, several studies have tested PBDEs and their metabolites in in vitro endocrine disruption screens and in vivo gene expression assays. These studies, and their results, are summarized in Section 3.5.2 (Mechanisms of Toxicity) in the subsections on Mechanisms of Endocrine Disruption (thyroid hormone assays; anti-estrogenic, -androgenic, -progestagenic, and -glucocortogenic assays) and Mechanisms of Reproductive Toxicity (steroidogenesis assays). While results are not always consistent between studies, the data collectively indicate that there is a potential for some PBDEs to disrupt thyroid and other endocrine system functions in humans.*

Section 3.11. METHODS FOR REDUCING TOXIC EFFECTS

COMMENT: Page 215, line 3. The following study can also be included in this section: Jandacek et al. 2014 recently conducted a pilot study in participants from Anniston, AL, who had elevated PCB levels. Although PBDEs were not measured, this study demonstrated that olestra, a non-absorbable lipid, can safely reduce body burdens of PCBs

Jandacek, R, Heubi, JE, Buckley, DD, Khoury, JC, Turner, WE, Sjodin, A, Olson, JR, Shelton, C, Helms, K, Bailey, TD, Carter, S, Tso, P, Pavuk, M. Reduction of the Body Burden of PCBs and DDE by Dietary Intervention in a Randomized Trial. (2014) Journal of Nutritional Biochemistry, 25: 483-488. doi: 10.1016/j.jnutbio.2014.01.002

RESPONSE: *In response to this comment, and a similar comment by Reviewer 2, this paper is discussed in Section 3.11*

Section 3.12. ADEQUACY OF THE DATABASE

COMMENT: Page 223, line 15. Include dose and duration of exposure to deca.

RESPONSE: *Dose (up to 100 mg/kg/day) and duration (60 days prior to mating through postnatal day 21) information was added.*

COMMENT: Page 226, lines 18- 20. This is an important limitation, perhaps include another sentence.

Human studies limited to assessing serum or breast milk levels of PBDEs need to assess other POPs since responses may be co-dependent on other persistent lipophilic agents such as PCBs, PCDDs, and /or PCDFs.

RESPONSE: *Since this paragraph is identifying studies that would be useful for the current assessment, the above comment was addressed by adding the following statement: "Studies that assess PBDE concentrations in serum or breast milk along with concentrations of other POPs, such as PCBs, PCDDs, and /or PCDFs, would be useful to evaluate responses that may be co-dependent on other persistent lipophilic agents."*

CHAPTER 6. POTENTIAL FOR HUMAN EXPOSURE

COMMENT: Page 284, line 9. Define ball clay.

RESPONSE: *A definition was added to this term.*

COMMENT: Page 293, line 12 to page 294, line 9. Delete this entire section. It is repeated from the text on pages 292-293.

RESPONSE: *The suggested revision was made.*

COMMENT: Page 294, lines 21-27. Temporal trends in the levels of PBDEs in fish and other environmental media are very relevant to the potential for human exposure. Perhaps a figure or table can be constructed with temporal data that is relevant to the potential for current and future human exposures.

RESPONSE: *The suggested additional figure was added.*

COMMENT: Page 304, table 6-9. Are there more recent data on PBDE levels in marine animals? The most recent study is cited is from 2002. This is relevant to the issue of temporal trends in PBDE levels.

RESPONSE: *Studies from 2009 and 2012 were added to the section based on this comment.*

COMMENT: Page 305, line 1-2. This statement needs to be revised since it refers to trends in PBDE levels that are more than 12 years old.

RESPONSE: *The suggested revision was made.*

COMMENT: Page 305, line 5. This refers to the PBDE levels in seal blubber collected in 1998. It would be very useful if more recent data were available to document more current trends in levels. Hopefully levels are beginning to decline, with the reduction and elimination of production of PBDEs.

RESPONSE: *New studies evaluating seal blubber were added to the profile based on this comment.*

COMMENT: Page 309-312, Tables 6-10, 11, 12. Make sure all studies discussed in the text are included in tables that summarize PBDE levels in human blood, adipose tissue and breast milk. For example, the recent study by Rawn et al 2014 (page 308, lines 26-31) is not included in Table 6-10.

RESPONSE: *Several studies were added to Tables 6-10 and 6-12 from the text. Not all studies described in the text were entered, since several studies were confirmation of existing studies or did not have data that met the table format.*

COMMENT: Page 314, lines 17-18. Check if this sentence should read "…levels in cord blood, 0-2 year olds, 2-6 year olds, …"

RESPONSE: *This entry was confirmed; the age of 2 was included in both groups.*

COMMENT: Page 317, table 6-13. Clarify whether the levels in units of ng/g lipid wt. or wet wt. Also, define the column with the heading "nursing" what is being quantified? Months of nursing??

RESPONSE: *The unit lipid weight was added, and the unit 'week' was added to the table heading.*

COMMENT: Page 320, lines 1-12. Perhaps include a heading for this concluding paragraph. This is an important concluding paragraph, perhaps it can be expanded a bit to include age dependent data on PBDE levels which can support our understanding of the primary current sources of human exposure.

RESPONSE: *A new heading was added, "Biomonitoring historical trends and future projections." The Toms et al. (2009) reference summary was added to this section.*

COMMENT: Page 324, lines 7-11. These levels in toys from China a very high. Further studies are needed to confirm and extend these findings. Perhaps highlight this study elsewhere—see comments below.

RESPONSE: *This concern was added to the profile under the 'Bioavailability from Environmental Media' and 'Exposures of Children' sections.*

COMMENT: Page 326, lines 8-9. " …does not appear to be significant for commercial mixtures of PBDEs…"

RESPONSE: *The suggested revision was made.*

COMMENT: Page 326, line 20. Need data on the bioavailability of PBDEs from highly contaminated toys (Chen et al. 2009).

RESPONSE: *The reference identified in this comment was added to the profile. The section was revised to the bioavailability data need.*

COMMENT: Page 327, line 22. Delete this line in bold, it is stated above in lines 19-20.

RESPONSE: *The suggested revision was made.*

COMMENT: Page 327, line 25. "formula" delete? Baby formula in the US is not an important source of exposure for infants. Breast milk is clearly the main source for infants

RESPONSE: *The suggested revision was made.*

COMMENT: Page 327, line 30. Here is another place to highlight the need to identify other potential sources of exposure in infants and children, such as toys from China (Chen et al. 2009).

RESPONSE: *The suggested revision was made.*

CHAPTER 7. ANALYTICAL METHODS

COMMENT: Page 329, line 16. Replace "very" with "**relatively**"

RESPONSE: *The suggested revision was made.*

COMMENT: Page 329, lines 14-19, please review and edit the entire paragraph . last sentence is especially not clear. What points? What two classes of compounds?

RESPONSE: *Revisions were made to clarify this section and the last line was deleted.*

COMMENT: Page 329, line 21. Are there any more current reviews?

RESPONSE: *A review from Stapleton (2006) was added to this section.*

CHAPTER 8. REGULATIONS AND ADVISORIES

COMMENT: Page 341, line 11, 28, 33, 34. There is very little reference to monoBDEs in the entire document but they are mentioned at least 4 times on this page. Perhaps indicate why they are the focus of regulations.

RESPONSE: *A description of monoBDE was added to this section for clarity concerning the structure, as indicated in previous comments about Sections 2.1 and 4.1. Rationale for the regulatory focus on monoBDE was not added.*

CHAPTER 9. REFERENCES

COMMENT: Regarding the question of whether there are additional references that provide new data or if there are better studies than those already in the text, the Reviewer commented: "I have suggested the possibility of additional references in previous sections and will not duplicate that here."

RESPONSE: *Responses regarding additional references can be found in previous sections.*