Peer Reviewer Responses to Charge Questions for Exposure and Use Assessment and Human Health and Environmental Hazard Summary for Five PBT Chemicals

Exposure and Use Assessment Peer Review

Reviewer 1 - Exposure and Use Assessment Peer Review

Comments Relevant to All Chemicals

1. This information, when finalized will inform a technical support document to support document to support EPA's regulatory activities on PBTs. Please comment on the organization and structure of this document to inform this use. Do you have specific recommendations to improve clarity and presentation of this information?

Can you briefly summarize how these chemicals five were selected? Can you summarize the data showing that they are persistent and bioaccumulative?

Overall, the documents present a great deal of information. They appear to be comprehensive in their coverage of the available data. However, there is little in the way of discussion or interpretation. In some cases, the data are meaningless without additional explanation, such as units or the identity of the sampling matrix (e.g., "other"). This is especially critical for data poor chemicals, such as PIP, TTBP, and TCTP.

When will EPA actually evaluate the data and draw conclusions? Are these documents the sole basis for rulemaking, or will they be supplemented by additional analysis? The purpose of these reviews is still not entirely clear to me.

Please define all acronyms, especially in the supplemental report. There are a few instances of EndNote errors (Error: Reference Source Not Found) throughout the main document and supplement.

2. Please comment on the clarity of the descriptions of how the data were searched for, screened, and evaluated for inclusion in the exposure assessment.

The descriptions of the search strategies were quite detailed. They contain many elements of systematic review. I do not understand why TSCATS studies were removed from EndNote. In some cases, TSCATS may provide relevant information, such as physico-chemical properties. The supplemental document states that you will use TSCATS in the future, but does not explain how or why.

Please clarify what you mean by "backward searching," as in "These were: backward searches of frequently used sources…", on page 7 of the supplemental document.

3. Please identify any additional information and data sources that EPA should also consider.

Overall, the literature review was thorough. I cited a few additional references below.

4. Due to the large number of references identified during the literature search for Decabromodiphenyl ether, EPA used a prioritization approach to evaluate and extract exposure data for this chemical. Please comment on the prioritization approach that was used for Decabromodiphenyl ether (see section A.2.4 of the Supplemental Information for the Exposure

and Use Assessment document). Please comment on whether further characterization lower priority studies is expected to significantly affect the exposure characterization for Decabromodiphenyl ether. Please comment on the strengths/limitations associated with prioritizing use of studies/data sources with larger sample sizes versus smaller sample sizes.

See below under Decabrom.

5. EPA identified specific core exposure data: environmental monitoring, biomonitoring, estimated environmental concentrations, or estimated doses. Please comment on any additional core data that EPA should evaluate for each chemical.

As far as I can determine, EPA considered the appropriate data.

6. Please comment on the approach to consider read-across of data from similar chemical substances for Phenol, isopropylated, phosphate (3:1) (PIP (3:1)) and 2,4,6-Tris(tert-butyl) phenol (2,4,6 TTBP).

I'm not sure that "read-across" is the best way to describe considering data from surrogate chemicals. Due to the lack of exposure data on PIP and TTBP, the report considered data on surrogate chemicals, that is, chemicals with similar physico-chemical properties. In the case of PIP, usage patterns are similar to those of the surrogate (triphenyl phosphate). Therefore, the use of surrogate chemicals in this case is reasonable.

In the case of TTBP, the surrogate chemical (BHT) has quite different uses. Therefore, the use of surrogate data for TTBP, especially human biomonitoring data, seems inappropriate.

7. Please comment on whether EPA has appropriately captured the exposure scenarios. Please identify any existing exposure scenarios EPA may have missed. Please keep in mind the purpose of this document is to inform regulatory decisions under TSCA only.

Overall, the appropriate exposure scenarios are covered for most chemicals. I have some comments regarding decabrom and TCTP, below.

8. Please comment on whether inclusion of additional information on monitoring data would significantly enhance the exposure assessment for the intended purpose of this document. For example, characterization of sampling year vs. study year, characterization of free vs. particle bound chemicals in water and air, lipid normalization for biomonitoring data, and further characterization of studies that had incomplete reporting for their limits of detection. Please identify any specific chemicals for which this additional information would be helpful.

Characterization of the sampling year would be helpful in looking at trends and should definitely be included. The other kinds of information are always helpful for quantitative

exposure and risk assessment, although they probably are not needed for the current purpose.

9. Please comment on the reliability and relevance of the identified data sets for each chemical and on the strengths and weaknesses of individual data sets that will help to better inform future regulatory actions.

Overall, the data appear to be reliable and definitely are relevant. The limited amount of data for some chemicals (PIP, TTBP, etc.) is somewhat of concern.

Decabromodipheyl Ether (Decabrom)

1. This information, when finalized will inform a technical support document to support document to support EPA's regulatory activities on PBTs. Please comment on the organization and structure of this document to inform this use. Do you have specific recommendations to improve clarity and presentation of this information?

I thank the authors for their comprehensive review of the available exposure data on Decabrom. The document establishes that humans and biota are, in fact, exposed to Decabrom and that exposure is likely to continue for years to come.

It would be helpful if the Introduction did a better job of describing the organization of the decabrom chapter, which is much longer than the others. In many cases, my questions were answered as I read farther along. More importantly, I would like to see a little more in the way of discussion and conclusions.

Some specific comments:

- Page 22, last paragraph: "Use categories are drawn from CDR definitions laid out in Instructions for Reporting for the 2016 CDR (U.S. EPA, 2016c)..." Are you relying on CDR to identify uses? Many finished products are imported and, therefore, these uses might not be reported in the CDR.

- It appears that little or no decabrom is manufactured in the U.S., but finished products containing it may be imported. Would any regulations issued under TSCA 8(h) apply to imported products, or only to manufactured or importation of decabrom itself? Given that exposure appears to occur from imported finished products, would EPA regulations under TSCA 8(h) be able to reduce human exposure?

2. Please comment on the clarity of the descriptions of how the data were searched for, screened, and evaluated for inclusion in the exposure assessment.

The document appears to be quite comprehensive, but I identified several points that could be clarified:

- The log K_{ow} in section 4.1 is listed as 9.97, citing EU 2002. However, EU lists the log K_{ow} as 6.27 in Table 1.1. EU cited Watanabe and Tatsukawa, 1990, which was not available in Hero. However, McGregor and Nixon (1997) report a value of 6.26 (as cited in NRC 2000, p. 73), which is almost identical to the value reported by EU 2002.

- I'm a little confused. Figure 4-1 says that little decabrom is manufactured or imported into the U.S. However, the last paragraph on page 25 says that it "is"

(present tense) in a long list of articles. Do you know how much decabrom is present in imported articles?

- Section 4.4.9. "DecaBDE has also been found in children's products such as plastic play structures, and toys (EPA-HQ-OPPT-2016-0724)." Can the reference direct the reader to the specific document that refers to toys? Even so, was any data presented at the meeting? There are no data presented in the document. Were the concentrations of Decabrom or frequency of detection substantial? What is the potential for exposure from using these products or even having them present in the home?

- Figure 4-22. Please define the acronyms CTD and MMDB.

- Figures 4-24 and 4-25 Human (other). The numbers are meaningless if we do not know what the matrix is.

- Figure 4-35. Please convert the Hero ID numbers to literature citations.

- Figure 4-43. Please convert the Hero ID numbers to literature citations. Is ingestion due to ingestion of dust or food? Can you explain which sources/scenarios were included in each study?

- Section 4.8. What is the distinction between the 11 studies that "modeled" exposure and the 14 that "estimated" exposure? Why are the former reported as ng/kg-d, while the latter are reported as ng/d?

- Sections 4.8-4.10. Can you use consistent units? Mass/kg-d is preferred, especially because you are looking at adults, children, and infants.

- Page 68. Paragraph 5. "Only a subset of dust-monitoring studies considers potential indoor sources, which could contribute to levels reported in dust." Can you be more specific? How many? Which studies?

3. Please identify any additional information and data sources that EPA should also consider.

Section 4.5.11 and Figure 4-18. (Vegetation/Diet). Can you clarify in the text what matrix or matrices were studied? Were they grasses, trees, foodstuffs? Diet may be a significant source of exposure for hydrophobic compounds (Lorber 2008). If there is a lack of data on dietary exposure to Decabrom, this could be a significant data gap, which is worth mentioning in the document.

4. Due to the large number of references identified during the literature search for Decabromodiphenyl ether, EPA used a prioritization approach to evaluate and extract exposure

data for this chemical. Please comment on the prioritization approach that was used for Decabromodiphenyl ether (see section A.2.4 of the Supplemental Information for the Exposure and Use Assessment document). Please comment on whether further characterization lower priority studies is expected to significantly affect the exposure characterization for Decabromodiphenyl ether. Please comment on the strengths/limitations associated with prioritizing use of studies/data sources with larger sample sizes versus smaller sample sizes.

Can you clarify the first paragraph on page 18 of the supplemental document? It implies that you only applied the prioritization scheme only to the additional 13,000 articles identified in the chemical class (PBDE) search. Is this correct? Is so, this should have no effect on the data that you identified.

If I am incorrect, you still found an amazingly rick database. While I have worked on decabrom in the past, I was amazed at the size of the database. Given the number of references cited, it does not seem to have an adverse effect overall. However, it seems that there could be particular scenarios, such as data poor scenarios, where this process might eliminate relevant data. Exposure from food comes to mind. You might consider applying the prioritization scheme to subsets of data—by scenario, for example—if that is possible to do.

5. EPA identified specific core exposure data: environmental monitoring, biomonitoring, estimated environmental concentrations, or estimated doses. Please comment on any additional core data that EPA should evaluate for each chemical.

More detail and discussion on the exposure scenarios (section 4.8) and human biomonitoring sections would be justified. These sections are important because they provide information on total exposure and help to identify the key sources of exposure. Additional discussion of children's exposure would address some of the concerns expressed in the public comments.

6. Please comment on the approach to consider read-across of data from similar chemical substances for Phenol, isopropylated, phosphate (3:1) (PIP (3:1)) and 2,4,6-Tris(tert-butyl) phenol (2,4,6 TTBP).

Not applicable.

7. Please comment on whether EPA has appropriately captured the exposure scenarios. Please identify any existing exposure scenarios EPA may have missed. Please keep in mind the purpose of this document is to inform regulatory decisions under TSCA only.

The major exposure scenarios are included. However, I think the format could be clearer. Organizing by receptor (Eco, Consumer, etc.) is helpful, but the text format makes it difficult to identify specific scenarios such as diet and indoor dust. Perhaps a table, with receptors in rows and scenarios in columns, or a figure (mental model) would

be helpful. Figure 4-1 is helpful, but does not capture the details of the exposure scenarios.

8. Please comment on whether inclusion of additional information on monitoring data would significantly enhance the exposure assessment for the intended purpose of this document. For example, characterization of sampling year vs. study year, characterization of free vs. particle bound chemicals in water and air, lipid normalization for biomonitoring data, and further characterization of studies that had incomplete reporting for their limits of detection. Please identify any specific chemicals for which this additional information would be helpful.

Characterization of the sampling year would be helpful in looking at trends and should definitely be includes. Decabrom is a chemical that was not tested in many older studies of PBDEs, which lead to the false impression that exposure was low or non-existent. This point may bear discussion in the report. The other kinds of information are always helpful for quantitative risk assessment, although they probably are not needed for the current purpose.

9. Please comment on the reliability and relevance of the identified data sets for each chemical and on the strengths and weaknesses of individual data sets that will help to better inform future regulatory actions.

Overall, the database is quite rich. However, it would be helpful to identify data gaps. For example, there are limited data on dietary exposure (page 71, first paragraph). Data on time trends do not demonstrate any clear trends, but are the data adequate (e.g., Figure 4-35)?

Hexachlorbutadiene (HCBD)

1. This information, when finalized will inform a technical support document to support document to support EPA's regulatory activities on PBTs. Please comment on the organization and structure of this document to inform this use. Do you have specific recommendations to improve clarity and presentation of this information?

Figures 5-5 and 5-6, and below. Define the acronyms such as MMDB, IPCHEM, USGS, SE, GW, etc.

Page 104, Occupational scenarios. If HCBD is often a by-product during manufacture of other chlorinated solvents, are exposure to the other solvents the greater concern?

Page 105, paragraph 6. "…waste materials from production of tetrachloride, perchloroethylene, and trichloroethylene…" Do you mean "carbon tetrachloride"?

Page 106, paragraph 2. "Farrar (2001) described a study conducted by ICI (the chemical company) investigating the fate…" Change "the chemical company" to "Imperial Chemical Industries."

2. Please comment on the clarity of the descriptions of how the data were searched for, screened, and evaluated for inclusion in the exposure assessment.

This was clearly described and contains many elements of systematic review.

3. Please identify any additional information and data sources that EPA should also consider.

I was unable to identify any additional data sources.

4. Due to the large number of references identified during the literature search for Decabromodiphenyl ether, EPA used a prioritization approach to evaluate and extract exposure data for this chemical. Please comment on the prioritization approach that was used for Decabromodiphenyl ether (see section A.2.4 of the Supplemental Information for the Exposure and Use Assessment document). Please comment on whether further characterization lower priority studies is expected to significantly affect the exposure characterization for Decabromodiphenyl ether. Please comment on the strengths/limitations associated with prioritizing use of studies/data sources with larger sample sizes versus smaller sample sizes.

Not applicable.

5. EPA identified specific core exposure data: environmental monitoring, biomonitoring, estimated environmental concentrations, or estimated doses. Please comment on any additional core data that EPA should evaluate for each chemical.

I was not able to identify any additional core data to consider.

6. Please comment on the approach to consider read-across of data from similar chemical substances for Phenol, isopropylated, phosphate (3:1) (PIP (3:1)) and 2,4,6-Tris(tert-butyl) phenol (2,4,6 TTBP).

Not applicable.

7. Please comment on whether EPA has appropriately captured the exposure scenarios. Please identify any existing exposure scenarios EPA may have missed. Please keep in mind the purpose of this document is to inform regulatory decisions under TSCA only.

I am unable to identify any additional exposure scenarios.

8. Please comment on whether inclusion of additional information on monitoring data would significantly enhance the exposure assessment for the intended purpose of this document. For example, characterization of sampling year vs. study year, characterization of free vs. particle bound chemicals in water and air, lipid normalization for biomonitoring data, and further characterization of studies that had incomplete reporting for their limits of detection. Please identify any specific chemicals for which this additional information would be helpful.

Information on sampling year and geographical location should definitely be included. The other kinds of information are generally helpful, but might not be needed for this particular purpose.

9. Please comment on the reliability and relevance of the identified data sets for each chemical and on the strengths and weaknesses of individual data sets that will help to better inform future regulatory actions.

Overall, the data appear to be reliable.

Phenol Isopropylated Phosphate (PIP)

1. This information, when finalized will inform a technical support document to support document to support EPA's regulatory activities on PBTs. Please comment on the organization and structure of this document to inform this use. Do you have specific recommendations to improve clarity and presentation of this information?

For the most part, the data are presented clearly and in a logical fashion. However, the report lacks and discussion of the significance of the different data or conclusions. Some specific comments follow.

- Section 6.4.2. Can you explain when the isopropylation step occurs. Is it prior to the reaction of phosphorus oxychloride with phenol or after?
- Section 6.4.7. Can you be more specific? Is it used in polyurethane foam? Is the foam found in furniture, toys, etc.? Is it used in electronics? Is consumer exposure widespread? Is use in consumer products declining or increasing over time? Use of flame retardants in foam seems to be declining due to revision of California TB-117 and other standards. On the other hand, PIP is a component of FM550™, which is one of the major flame retardants used in polyurethane foam.
- Section 6.8. "Exposures were generally less than 2 ng/kg-d…" Does EPA have a reference dose for PIP?
- Page 127, first paragraph. Can you provide more details? What articles contain PIP? Is PIP commonly found in these article, or sporadically?

2. Please comment on the clarity of the descriptions of how the data were searched for, screened, and evaluated for inclusion in the exposure assessment.

The search strategy is described in detail. I don't understand why TSCATS data were excluded.

3. Please identify any additional information and data sources that EPA should also consider.

Section 6.1. The table lists the Log K_{ow} as 9.07, as estimated from EpiSuite. However, empirical values of around 5 are reported elsewhere (TSCATS 8HEQ-1179-0317; ChemID database). I do not understand why EPA uses modeled values when empirical values are available. In some cases, empirical values can differ greatly from the modeled values, often in ways that lead to underestimates of exposure or bioavailability. All of the physico-chemical values in this report should be re-evaluated.

The vapor pressure is listed as 2.1×10^{-8} mm Hg, based on EpiSuite. ChemID lists a modeled value of 3.5×10^{-7}, an order of magnitude lower. It does not appear that empirical values are available, but the difference between the modeled values illustrates the uncertainty in estimated values. These uncertainties have little effect on

the current evaluation, which is more qualitative in nature, but others may cite this document when conducting quantitative assessments.

The value for water solubility was calculated from water solubility and molecular weight. This does not make sense.

4. Due to the large number of references identified during the literature search for Decabromodiphenyl ether, EPA used a prioritization approach to evaluate and extract exposure data for this chemical. Please comment on the prioritization approach that was used for Decabromodiphenyl ether (see section A.2.4 of the Supplemental Information for the Exposure and Use Assessment document). Please comment on whether further characterization lower priority studies is expected to significantly affect the exposure characterization for Decabromodiphenyl ether. Please comment on the strengths/limitations associated with prioritizing use of studies/data sources with larger sample sizes versus smaller sample sizes.

Not applicable.

5. EPA identified specific core exposure data: environmental monitoring, biomonitoring, estimated environmental concentrations, or estimated doses. Please comment on any additional core data that EPA should evaluate for each chemical.

I cannot identify any additional core exposure data. However, EPA could consider performing additional exposure modeling of residential exposures. EPA could also try to identify whether there are any time trends in the use of PIP is polyurethane foam. In addition, it should be noted that PIP and other aryl phosphates are often used in combination with halogenated flame retardants, at least in applications involving polyurethane foam. Specifically, mixtures containing brominated phthalates, brominated benzoates, PIP, and triphenyl phosphate (TPP) (FM-550™) are commonly used as flame retardants in polyurethane foam. Exposure data on TPP and the brominated compounds have been reviewed recently (TERA 2015a; TERA 2015b; TERA 2016a; TERA 2016b).

6. Please comment on the approach to consider read-across of data from similar chemical substances for Phenol, isopropylated, phosphate (3:1) (PIP (3:1)) and 2,4,6-Tris(tert-butyl) phenol (2,4,6 TTBP).

I'm not sure that "read-across" is the best description of using data from surrogate chemicals. Due to the lack of exposure data on PIP, the report considered data on surrogate chemicals, that is, chemicals with similar physico-chemical properties. In the case of PIP, usage patterns are similar to those of the surrogate (triphenyl phosphate). Therefore, the use of surrogate chemicals in this case is reasonable. The logic behind the use of surrogate data and inferences obtained from surrogate data should be explained in the text.

7. Please comment on whether EPA has appropriately captured the exposure scenarios. Please identify any existing exposure scenarios EPA may have missed. Please keep in mind the purpose of this document is to inform regulatory decisions under TSCA only.

The exposure scenarios have been adequately captured and described. Additional details on indoor exposures (home, office, automobiles) would be helpful. This could include possible time trends in the use of PIP in furniture, automobiles, and electronics.

8. Please comment on whether inclusion of additional information on monitoring data would significantly enhance the exposure assessment for the intended purpose of this document. For example, characterization of sampling year vs. study year, characterization of free vs. particle bound chemicals in water and air, lipid normalization for biomonitoring data, and further characterization of studies that had incomplete reporting for their limits of detection. Please identify any specific chemicals for which this additional information would be helpful.

For PIP, limited biomonitoring data are available. Thus, this is a moot point.

9. Please comment on the reliability and relevance of the identified data sets for each chemical and on the strengths and weaknesses of individual data sets that will help to better inform future regulatory actions.

The primary weakness is the limited amount of data available. The role of data on surrogate chemicals should be clarified.

2,4,6-Tris-t-Butylphenol (TTBP)

1. This information, when finalized will inform a technical support document to support document to support EPA's regulatory activities on PBTs. Please comment on the organization and structure of this document to inform this use. Do you have specific recommendations to improve clarity and presentation of this information?

I would organize the use section (7.2) differently. The section begins with a discussion of regulations and their effect on uses. I would begin with the actual uses. Move the first paragraph farther down.

- Section 7.2, third paragraph. Can you be more specific on the use as an intermediate? Intermediate for what products or reactions?
- Page 129, third paragraph. By "gas" do you mean "gasoline"?
- Section 7.5. As explained in this section, the use patterns of TTBP are different from those of the surrogate (BHT). Therefore, the value of using surrogate biomonitoring data is uncertain.

2. Please comment on the clarity of the descriptions of how the data were searched for, screened, and evaluated for inclusion in the exposure assessment.

The literature search strategy was clearly described and includes many elements of systematic review.

3. Please identify any additional information and data sources that EPA should also consider.

I have not identified any additional data sources.

4. Due to the large number of references identified during the literature search for Decabromodiphenyl ether, EPA used a prioritization approach to evaluate and extract exposure data for this chemical. Please comment on the prioritization approach that was used for Decabromodiphenyl ether (see section A.2.4 of the Supplemental Information for the Exposure and Use Assessment document). Please comment on whether further characterization lower priority studies is expected to significantly affect the exposure characterization for Decabromodiphenyl ether. Please comment on the strengths/limitations associated with prioritizing use of studies/data sources with larger sample sizes versus smaller sample sizes.

Not applicable.

5. EPA identified specific core exposure data: environmental monitoring, biomonitoring, estimated environmental concentrations, or estimated doses. Please comment on any additional core data that EPA should evaluate for each chemical.

I have not identified any additional data sources.

6. Please comment on the approach to consider read-across of data from similar chemical substances for Phenol, isopropylated, phosphate (3:1) (PIP (3:1)) and 2,4,6-Tris(tert-butyl) phenol (2,4,6 TTBP).

I'm not sure that "read-across" is the best description of using data from surrogate chemicals. Due to the lack of exposure data on TTBP, the report considered data on a surrogate chemical (BHT), which has similar physico-chemical properties. However, the use patterns of BHT are quite different from TTBP. Therefore, the use of surrogate exposure data, especially human biomonitoring data, seems unjustified in this case.

7. Please comment on whether EPA has appropriately captured the exposure scenarios. Please identify any existing exposure scenarios EPA may have missed. Please keep in mind the purpose of this document is to inform regulatory decisions under TSCA only.

It appears that the relevant exposure scenarios have been captured.

8. Please comment on whether inclusion of additional information on monitoring data would significantly enhance the exposure assessment for the intended purpose of this document. For example, characterization of sampling year vs. study year, characterization of free vs. particle bound chemicals in water and air, lipid normalization for biomonitoring data, and further characterization of studies that had incomplete reporting for their limits of detection. Please identify any specific chemicals for which this additional information would be helpful.

Not applicable.

9. Please comment on the reliability and relevance of the identified data sets for each chemical and on the strengths and weaknesses of individual data sets that will help to better inform future regulatory actions.

The primary concern is the lack of available exposure data.

Pentachlorothiophenol (PCTP)

1. This information, when finalized will inform a technical support document to support document to support EPA's regulatory activities on PBTs. Please comment on the organization and structure of this document to inform this use. Do you have specific recommendations to improve clarity and presentation of this information?

Section 8.4. This section reports that PCTP is (current tense) used in rubber manufacturing and making golf balls. Are these current uses, considering that PCTP is no longer manufactured in significant quantities in the U.S. or many other countries?

Do you have any information on the types of rubber that may be manufactured using PCTP, such as tires or footwear?

The table on p. 146 suggests that PCTP is added in large amounts (15-20%) by weight. Is PCTP likely to be present in finished products, such as footwear, tires, or anything else to which the general population might be exposed?

Section 8.6.1. Please specify what "other" means. Given the limited amount of data available, additional details here could be critical in assessing whether human exposure is likely.

2. Please comment on the clarity of the descriptions of how the data were searched for, screened, and evaluated for inclusion in the exposure assessment.

The literature search strategy was clearly described and includes many elements of systematic review.

3. Please identify any additional information and data sources that EPA should also consider.

I have not identified any additional data sources.

4. Due to the large number of references identified during the literature search for Decabromodiphenyl ether, EPA used a prioritization approach to evaluate and extract exposure data for this chemical. Please comment on the prioritization approach that was used for Decabromodiphenyl ether (see section A.2.4 of the Supplemental Information for the Exposure and Use Assessment document). Please comment on whether further characterization lower priority studies is expected to significantly affect the exposure characterization for Decabromodiphenyl ether. Please comment on the strengths/limitations associated with prioritizing use of studies/data sources with larger sample sizes versus smaller sample sizes.

Not applicable.

5. EPA identified specific core exposure data: environmental monitoring, biomonitoring, estimated environmental concentrations, or estimated doses. Please comment on any additional core data that EPA should evaluate for each chemical.

I have not identified any additional data sources.

6. Please comment on the approach to consider read-across of data from similar chemical substances for Phenol, isopropylated, phosphate (3:1) (PIP (3:1)) and 2,4,6-Tris(tert-butyl) phenol (2,4,6 TTBP).

Not applicable.

7. Please comment on whether EPA has appropriately captured the exposure scenarios. Please identify any existing exposure scenarios EPA may have missed. Please keep in mind the purpose of this document is to inform regulatory decisions under TSCA only.

I am concerned about consumer exposures in products like footwear and crumb rubber, which is used in athletic fields, as mulch, and in playground surfaces (EPA 2016).

8. Please comment on whether inclusion of additional information on monitoring data would significantly enhance the exposure assessment for the intended purpose of this document. For example, characterization of sampling year vs. study year, characterization of free vs. particle bound chemicals in water and air, lipid normalization for biomonitoring data, and further characterization of studies that had incomplete reporting for their limits of detection. Please identify any specific chemicals for which this additional information would be helpful.

Not applicable due to the lack of biomonitoring data.

9. Please comment on the reliability and relevance of the identified data sets for each chemical and on the strengths and weaknesses of individual data sets that will help to better inform future regulatory actions.

References

EPA (2016) Federal Research Action Plan on Recycled Tire Crumb Used on Playing Fields and Playgrounds. Status Report. U.S. Environmental Protection Agency, Office of Research and Development, National Exposure Research Laboratory. EPA/600/R-16/364. https://www.epa.gov/sites/production/files/2016-12/documents/federal_research_action_plan_on_recycled_tire_crumb_used_on_playing_fields_and_playgrounds_status_report.pdf

Lorber M (2008) Exposure of Americans to polybrominated diphenyl ethers. Journal of exposure science & environmental epidemiology 18(1):2-19

NRC (2000) Toxicological Risks of Selected Flame Retardant Chemicals. National Research Council, National Academy Press, Washington, DC

TERA (2015a) Environmental Concentrations and Consumer Exposure Data for Selected Flame Retardants (TBB, TBPH, TBBPA, ATO). Toxicology Excellence for Risk Assessment (TERA), Cincinnati, OH; prepared for U.S. Consumer Product Safety Commission, Rockville, MD. Contract no. CPSC-D-12-0001. August 13, 2015. https://www.cpsc.gov/s3fs-public/Environmental%20Concentrations%20and%20Consumer%20Exposure%20Data%20for%20Selected%20Flame%20Retardants.pdf?wI1XZOItAFgOqb2mJ.jPBVtfdYlkYs_Z

TERA (2015b) Environmental Concentrations and Consumer Exposure Data for Selected Flame Retardants (TDCPP, TCPP, TEP, TPP). Toxicology Excellence for Risk Assessment, Cincinnati, OH. Prepared for U.S. Consumer Product Safety Commission, Rockville, MD. Contract no. CPSC-D-12-0001. June 26, 2015. https://www.cpsc.gov/s3fs-public/pdfs/CPSC%2520Staff%2520Statement%2520on%2520Toxicology%2520ExcellenceRiskAssessmentsReportExposureDataSelectedFlameRetardants.pdf

TERA (2016a) Flame Retardant Exposure Assessment. Toxicology Excellence for Risk Assessment, Cincinnati, OH. Prepared for U.S. Consumer Product Safety Commission, Rockville, MD. Contract no. CPSC-D-12-0001. September 28, 2016. https://www.cpsc.gov/s3fs-public/FR-exposure-assessment-contractor-report-18-09282016-with-cover.pdf?

TERA (2016b) Flame Retardant Exposure Assessment Database. Toxicology Excellence for Risk Assessment, Cincinnati, OH. Prepared for U.S. Consumer Product Safety Commission, Rockville, MD. Contract no. CPSC-D-12-0001. January 6, 2016. https://www.cpsc.gov/s3fs-public/Flame%20Retardant%20Assessment%20Database.pdf

Reviewer 2 - Exposure and Use Assessment Peer Review

Letter Peer Review Response

Exposure and Use Assessment Peer Review Charge Questions

1. This information, when finalized will inform a technical support document to support document to support EPA's regulatory activities on PBTs. Please comment on the organization and structure of this document to inform this use. Do you have specific recommendations to improve clarity and presentation of this information?

- In general, the information was presented in a clear and consistent manner both within and between each of the chemicals under review. There are a few points at which additional information could be added to improve clarity of the overall document that will be noted in subsequent responses.

2. Please comment on the clarity of the descriptions of how the data were searched for, screened, and evaluated for inclusion in the exposure assessment.

   - In general, the descriptions of how the data were searched, screened and evaluated were clear and consistent.
   - **Page 78** of the "Exposure and Use Assessment for Five PBT Chemicals_HERONet links" document correctly states that "Reports from manufacturers to the State of Washington's Department of Ecology under the Children's Safe Product Act indicate that HCBD was detected in 5 of 88 consumer products". Further the section states "No function was identified for four of the five products, while protective coating was identified as a function for the headwear product. Manufacture of these products may lead to occupational exposures," while the underlying reference indicates more descriptively "no function – contaminant". Recommend that the text be adjusted to reflect more descriptively that HCBD was a *contaminant* rather than an *unidentified function*.
   - **Page 94** of the "Exposure and Use Assessment for Five PBT Chemicals_HERONet links" document has an error that reads "Figure 5-24 to **Error! Reference source not found**." – presumably this is should read "Figure 5-24 to Figure 5-26".

3. Please identify any additional information and data sources that EPA should also consider.

- The comments raised by the SI Group (both of which are available in the docket) do not appear to have been reflected in the 2,4,6-TTBP section, especially as pertains to water solubility and the use of BHT as a surrogate. Particularly concerning is the discrepancy between the SI submitted experimental value (0.0629 mg/L) and the value utilized in the assessment (35 mg/L). Given the fundamental importance of water solubility to fate and transport, it is essential that the correct value be incorporated into the assessment and the relevant portions be updated. It appears that the most pertinent section would be **7.3 Characterization of Expected Environmental Partitioning**. Strongly recommend that EPA further investigate further.
- The concerns associated with BHT will be discussed under Charge Question 6.

4. Due to the large number of references identified during the literature search for Decabromodiphenyl ether, EPA used a prioritization approach to evaluate and extract exposure data for this chemical. Please comment on the prioritization approach that was used for Decabromodiphenyl ether (see section A.2.4 of the Supplemental Information for the Exposure and Use Assessment document). Please comment on whether further characterization lower priority studies is expected to significantly affect the exposure characterization for Decabromodiphenyl ether. Please comment on the strengths/limitations associated with prioritizing use of studies/data sources with larger sample sizes versus smaller sample sizes.

    - I do not think it would be appropriate for me to comment as to whether lower priority studies would be expected to significantly affect the exposure characterization of Decabromodiphenyl ether. A prioritization approach, such as the one described should result in similar results with both full dataset as the smaller prioritized dataset, if the results differ significantly, the approach should not be used. The prioritization approach described in Section A.2.4 and the underlying reference appears scientifically sound and robust.

5. EPA identified specific core exposure data: environmental monitoring, biomonitoring, estimated environmental concentrations, or estimated doses. Please comment on any additional core data that EPA should evaluate for each chemical.

    - These are the appropriate core exposure data. I would caution that environmental monitoring and biomonitoring *may* be biased due to well established concerns with selection bias (see NAS report on **Human Biomonitoring of Environmental Chemicals**, Chapter 4, https://www.nap.edu/catalog/11700/human-biomonitoring-for-environmental-chemicals). This may also skew the frequency of reporting metric, which may not necessarily informative. I recommend that a short caveat or disclaimer be incorporated into the assessment on this point.

6. Please comment on the approach to consider read-across of data from similar chemical substances for Phenol, isopropylated, phosphate (3:1) (PIP (3:1)) and 2,4,6-Tris(tert-butyl) phenol (2,4,6 TTBP).

- The use of TPP for a surrogate for PIP (3:1) is well supported but the relationship between the two is unclear, especially when presenting concentration ranges. For example, Figure 6.3 presents "Concentration of PIP (3:1) and TPP (ng/g) in indoor dust" and it is unclear which portion of the range of values is PIP (3:1) or TPP. In reviewing the underlying data, some report exclusively PIP (3:1) while others do not. Recommend that there be an expansion of the discussion to elucidate this more effectively and that figures be annotated to distinguish which data is being reported.
- The use of BHT as a surrogate for 2,4,6-TTBP is not appropriate for characterizing use and emissions (This concern was also raised in the SI comments). The uses of BHT are vastly different (I compared to EPA ChemView) and provide an inaccurate reflection upon 2,4,6-TTBP. Recommend that BHT not be used as surrogate for use and emissions and that this portion of the assessment be reassessed.

7. Please comment on whether EPA has appropriately captured the exposure scenarios. Please identify any existing exposure scenarios EPA may have missed. Please keep in mind the purpose of this document is to inform regulatory decisions under TSCA only.

- The exposure scenarios are appropriately captured and presented.

8. Please comment on whether inclusion of additional information on monitoring data would significantly enhance the exposure assessment for the intended purpose of this document. For example, characterization of sampling year vs. study year, characterization of free vs. particle bound chemicals in water and air, lipid normalization for biomonitoring data, and further characterization of studies that had incomplete reporting for their limits of detection. Please identify any specific chemicals for which this additional information would be helpful.

- One area of potential concern is the approach used on presenting the monitoring data from peer-reviewed literature and that as presented would cast a misleading and biased picture (pages 30-31, pages 79-80, pages 116-117, page 136, and pages 150-151). As noted, "EPA recognizes that the sampling dates, rather than the publication date, would be a better reflection of temporal trends" and reflecting the sampling date would be a recommended approach. More troubling is an inherent sampling bias towards chemicals identified for scrutiny within the peer review sources, to wit, researchers are reasonably going to investigate the chemicals in need of greatest concern. My recommendation would be to indicate that there may be a sampling bias in the data collection.

9. Please comment on the reliability and relevance of the identified data sets for each chemical and on the strengths and weaknesses of individual data sets that will help to better inform future regulatory actions.

- Academic research is essential in identifying challenges and concerns, but it does appear that is difficult to incorporate this information into regulatory decisions because of the diversity of sampling and analysis approaches due to the inconsistencies.

References

Reviewer 3 - Exposure and Use Assessment Peer Review

Exposure and Use Assessment Peer Review Charge Questions:

1. *Please comment on the organization and structure of this document to inform this use. Do you have specific recommendations to improve clarity and presentation of this information?*

In general:

It would also help for all compounds to know whether this was a liquid or solid at room temperature so boiling point and melting point information would also have been helpful.

The organization was reasonable, but some categories were redundant, creating inclusion of the same text in multiple locations, for example…….

"Manufacturing Process Various methods for HCBD synthesis have been described in two patents. HCBD can be directly synthesized through the chlorination of butadiene or butane or produced as a by-product of chlorinated hydrocarbon manufacturing, including perchloroethylene, trichloroethylene, and carbon tetrachloride. It appears that HCBD, generated as a by-product during the synthesis of other compounds of interest, may be recovered or recycled for commercial purposes" appears verbatim in both the report on the chemical EPA 17c and in the main text.

In the supplement:" This document describes the literature search strategy to support the exposure assessments for five persistent, bioaccumulative, and toxic (PBT) chemicals. The intent of the search is to assess the likely exposure of the general population, consumers, occupational populations, potentially exposed or susceptible subpopulations, and the environment to the conditions of use of PBT chemicals based on the criteria outlined in the Toxic Substances Control Act (TSCA) section 6(h) (OLRC, 2016). The conditions of use are defined as the circumstances under which a chemical substance is intended, known or reasonably foreseen to be manufactured, processed, distributed in commerce, used or disposed of.

Data sources in the peer-reviewed (open) and gray literature were considered as shown in Figure C-1. In addition to the primary searches of the peer-reviewed literature in Web of Science, PubMed, and Toxline, there were additional supplemental searches that were used to complement and/or evaluate the primary peer-reviewed search strategy. These were: backward searches of frequently used sources, a Google Scholar search of the top 100 results by chemical, and public comments and associated references cited in those comments submitted to the dockets by mid-January 2018." Is used for every chemical adding needlessly to the overall length of the document. Use the paragraphs once for all chemicals and note differences in each subsection.

Another example, statements like "Only studies or databases that reported measurements of the chemical of interest above the limit of detection were extracted and included in the "# of studies" count." appears twice in each section. Organization would help reduce this redundancy.

While a tradeoff exists between thoroughness and concise expression, I believe a more concise document (without duplication of text) better serves the reader.

The human health hazard document should be incorporated within the main document. It is difficult to judge the relevance of concentrations measured in compartments such as serum or

other non-human data without context, specifically health hazard summary. The hazard summary was brief enough that with removal of redundant text, the overall document size would increase only slightly.

There were too many abbreviations used before defined eg PECO and algorithm abbreviations eg DoCTER and PRISMA used without explanation. You cannot assume that every reader is as versed in the nomenclature as the document creators. Every abbreviation should be spelled out the first time it is used in a document section, eg each new chemical review should stand alone.

This document contains many conclusions based on logical extrapolations of the data found or speculation about industry practices. "PIP (3:1) is not reported to the Toxics Release Inventory and no release data over time were identified. However, the production and use of PIP (3:1) may have increased since the flame retardant pentabromodiphenylether was banned and phased out of production in 2013." These speculations may be useful but should be used cautiously as they may not agree with other data such as dust concentrations which were measured often over the last nine years. This caution is especially important since the document is built to have each section as a stand-alone assessment, or so it would seem as the text is often repeated. Repeating text is only useful if each section is meant to contain its own conclusion and there was no attempt to link conclusions from section to section.

PBDE 209: The organization was reasonable for PBDE 209. It had the greatest amount of literature cited among the PBTs and organization based on each possible exposure route allowed for evaluation of each source individually and as a whole. The graphs allowed for a comparison among all the studies for each matrix/contributor. The graphs were easy to understand and presented so that multiple studies could be normalized on a single page.

Placing all non-serum human data on one graph referred to as "other" does not allow anyone to evaluate one of the most significant exposure sources to children, specially breast milk. It also does not allow for the estimate of fetal dose through cord blood. It would also have been helpful to summarize the finding of each graph so that when a reader makes comparisons to; review papers, longitudinal studies, modeled values or across matrices, the summaries will allow the reader a quicker reference of what each plot described.

Hexachlorobutadiene (HCBD): The lifecycle diagram like that for PBDE209 uses a font which is far too small to read. It also appears from the display order that the primary use for HCBD is as an analytical standard. I am hard pressed to believe that more than grams/year across the entire country are used in analytical standards and that the use as a waste fuel in kilns should probably occupy the top spot (if it is indeed the single largest user of HCBD).

The legend fonts eg pg 82, 83, 84, 85…. are way too small to read.

Phenol, isopropylated, phosphate (3:1) As with the other lifecycle diagrams, the font is much too small.

2,4,6-Tris(tert-butyl) phenol (2,4,6 TTBP) I was glad to see in the lifecycle diagram that the principal use was listed in fuel additives and in lubrication. This seems appropriate and does not overemphasize its use in analytical standards.

Pentachlorothiophenol (PCTP) Not enough data to present any other way, no recommendations.

2. *Please comment on the clarity of the descriptions of how the data were searched for, screened, and evaluated for inclusion in the exposure assessment.*

In general

I recommend the paragraph (s) on search criteria from the supplement be included in the overall document. "The literature search strategy to support the exposure assessments for five persistent, bioaccumulative, and toxic (PBT) chemicals……"
It does not need to be included and can even be summarized but it would help the reader understand the criteria used without having to go into detail in the supplement.

Descriptions of each search and inclusion criteria were easy to follow and understand in the supplement. The descriptions of why things were not included, was much less so. There were instances where a search was limited without clear explanation as to why, eg top 100 Google scholar results returned were used. Did this include duplicate references? Is there a reason why only 100 were used? Did the authors stop at 100 references for the other search targets eg Medline? There was also declarative statement about not using TSCATS, without justification other than it may be considered later. Was this to immature a search target? I can certainly understand limiting inclusion of too many references for a compound such as PBDE 209 but no limits should have been used for compounds where very little data could be located such as PIP and TTBP.

I believe some of these criteria limited and shaped the conclusions that were drawn from the data and there was not enough feedback between categories to try to explain the data. Finally, there are multiple typos, and errors through each of the documents that need to be corrected, eg "Error! Reference source not found" and even our charge document "*a technical support document to support document to support EPA's regulatory activities on PBTs"*

PBDE 209: The lack of clear description of what data was included and excluded for 209 made it difficult to understand where some of the main document's conclusions were derived, especially in the face of contradictory data.

Hexachlorobutadiene (HCBD) There was no apparent information in the main document on how data was selected for this compound. The standard language was noted in the supplemental document, without exception to standard procedure.

Phenol, isopropylated, phosphate (3:1) There was little apparent information on how data for this compound was searched for in the main document, only a description the TPP was added as a search parameter.

2,4,6-Tris(tert-butyl) phenol (2,4,6 TTBP) There was information on the supplemental search in the main document describing the discovery of BHT as a surrogate/read across. I believe it was selected based on its prevalence in environmental monitoring studies, not a good inclusion criterion. There are different manufacturing, distribution and certainly routes of exposure. Noted in external comments was a significant contradiction in the solubility of this compound. This needs to be addressed. The observation in the external comments that incorporation of data from

outside the US as not necessarily transferable may be correct, but currently it is better than drawing conclusions without any data.

Pentachlorothiophenol (PCTP) I was glad the Pentachloro phenol was not used as a read across. Structurally almost identical but uses; environmental concentrations, exposure scenarios and toxicological endpoints are all completely different.

3. Please identify any additional information and data sources that EPA should also consider.

In general, but especially for PBDE 209: NHANES data should be included as well as toxicological equivalency factors examined, where applicable.

Overall significant differences in data should be explained when possible. Many of the data plotted demonstrate orders of magnitude differences in concentrations that should be equivalent. With other general comments offered "Generally consistent with the fate summary and physical-chemical properties of HCBD, higher concentrations were reported in ambient air, surface water, soil, and sediment. Lower concentrations were reported in drinking water, indoor air, and sludge/biosolids." it would not be difficult to offer comment on disparate data.

PBDE 209 studies should be included because uses of PBDEs are usually made as formulations of PBDE mixtures and it would be difficult to explain why some PBDEs might increase while others would fall. There was also no data on degradation products in the environment or biodegradation literature examined. This might explain some of the concentration rise and fall in soils, sediments and sludges. There was a lack of and toxicological

Hexachlorobutadiene (HCBD) The report often makes general statements without supporting evidence or even logic such as "Occupational exposures to HCBD at cement kilns and related incinerator facilities are expected to be minimal". There was no ranking on relative amounts potentially released, but I would assume that its use as a fuel would have a greater potential for release then an analytical standard which is generally tracked carefully from cradle to grave. The logic for chemical analysis losses imply errors in measurement and laboratories are required to dispose of all reagents, vials etc. in compliance with RCRA. If a general statement about minimal exposure is being made, one would assume that at least the logic behind a statement would also present.

There was conflicting data that needed to be explained "TRI data confirm the number of reporting facilities and the total domestic release quantities to all media have remained relatively constant since 2000" vs "HCBD is a highly regulated chemical. In tandem with increased regulation, releases of HCBD have declined over time."

The statement "Only studies or databases that reported measurements of the chemical of interest above the limit of detection were extracted and included in the "# of studies" count.", should include whether the LODs were normalized or did the study # increase with time as measurement sensitivities increased?

Statements like "Generally consistent with the fate summary and physical-chemical properties of HCBD, higher concentrations were reported in ambient air, surface water, soil, and sediment. Lower concentrations were reported in drinking water, indoor air, and sludge/biosolids." (and others with objective terms) need to be defined. What is "higher" and what is "Lower"

A single plot pg 86 displaying 12 orders of magnitude for sediment concentrations should be explained or at least commented upon. Data absence should be explained, eg why were no biomonitoring studies reported with detectable levels of HCBD in serum (blood). Did no one look for it or was it just not found?

Likewise, data that is remarkably consistent should also be recognized. Plot on pg 93 demonstrate consistent air concentration data but contradict the statement about decreasing concentrations.

Phenol, isopropylated, phosphate (3:1) There are multiple compounds including TPP that can act as surrogates for PIP in both usage and toxicity such as TBP, TCP etc. It is also worth including their metabolites (a hydroxyl substitution for one ligand) in any human health hazard assessment as the metabolites are more reactive than the parent compounds. This data should be included when available.

2,4,6-Tris(tert-butyl) phenol (2,4,6 TTBP) The authors should have included a more significant discussion on differences between TTBP and BHT in both manufacture and fate and transport through the environment. There was very little information about these differences which could have been described from more work/publications on BHT. Its inclusion as a read across or surrogate in environmental monitoring studies may lead to an overprediction in the environment.

Pentachlorothiophenol (PCTP) The physical properties of pentachloro phenol and PCTP are likely to be similar so fate and transport eg partitioning data is likely to be similar. PCP studies on the physical distribution could be included. PCP is not a surrogate for PCTP.

4. *Due to the large number of references identified during the literature search for Decabromodiphenyl ether, EPA used a prioritization approach to evaluate and extract exposure data for this chemical. Please comment on the prioritization approach that was used for Decabromodiphenyl ether (see section A.2.4 of the Supplemental Information for the Exposure and Use Assessment document).*

A.2.4. seemed to deal much more with the limited inclusion of references rather than their exclusion for too large a database generated by PBDE 209. As I understand the DoCTER algorithm, it uses a match between article title and abstract text to prioritize inclusion. It would appear to an outside observer that the title and abstract could match very well and not be on topic while a lesser match between title and abstract does not exclude the possibility that it is a good fit for inclusion. The example of PBDE as an expansion of the search terms is a natural for congener 209 but it is not clear that if 209 was not included in the set of congeners examined, that the article would be viewed as a lower priority fit.

What articles were not available as full text? Were they just not retrievable with the software tool employed or did the full text article not exist? How many articles does this represent? For example an excellent review could not be located either in the main body of the text nor in the supplements. Hakk, H. and Letcher, R.J., 2003. Metabolism in the toxicokinetics and fate of brominated flame retardants—a review. Environment International. Was it missed because it did not list PBDE 209 by name but included it in a broader class of compounds? The data in this review article on PBDE was well worth the secondary level of digging and it's absence demonstrates a potential flaw in the approach taken.

Another example worth noting, no real conclusion was drawn about whether the levels of 209 were increasing overall. Some paragraphs summarized that the concentrations of this PBDE peaked in about 2000 but continued to be manufactured through 2013. The decreasing concentrations in many of the media studied as manufacturers had removed the product from production and import, was noted but not explained with respect to contradictory data. Some of the data supported this observation eg birds and yet the temporal bird egg studies suggested the level were continuing to rise through 2005 when the studies ended. There is no clear attempt made to rectify contrary data such as this. All studies appear to be weighted equally, even when conclusions do not agree and without further clarification on how searches were carried out, the reader can draw no meaningful conclusions.

There was also a noticeable lack of data included from some professions and uses that were likely to produce higher levels of exposure. Both indoor airline air and vehicle air seemed to have exceedingly high concentrations but there was no data on flight attendants or cab drivers both who would spend significant amounts of time in these highly exposed environments. It may be that there were just no studies but the lack of data was also not discussed.

The authors did not discuss what a high end (not occupational) exposure was on the graph human (other). It is difficult to ascertain who these studies represent and why they are not studied more if it really is a non-occupational exposure.

In addition, PBDE 209 is not generally metabolized in rats but is in mice. This was mentioned no where in either the health supplement not the main body of the document. Its implications for human health could therefore not be addressed in either a projection of risk nor a vulnerable population assessment. The data was available but missed, again pointing out a flaw in the data inclusion approach. It would explain why studies were listed as other (in addition to human blood) as it may not have been found in human biomonitoring studies that analyzed urine.

> *Please comment on whether further characterization lower priority studies is expected to significantly affect the exposure characterization for Decabromodiphenyl ether. Please comment on the strengths/limitations associated with prioritizing use of studies/data sources with larger sample sizes versus smaller sample sizes.*

From A.2.4:" Few of the results added by including terms for chemical class are likely to be relevant to an exposure assessment of DecaBDE; therefore, the results of the title abstract screening of the DecaBDE search results were used to prioritize the results added by including chemical class search terms using…."

I do not agree as I believe removing compound class was especially detrimental in this case. I understand the hesitancy to deal with 13,000 references but this is one case where the compound class may produce some of the missing areas (eg metabolism biodegradation and life cycle), I have mentioned elsewhere. This observation was also made by one of the external commenters to this report. I also believe there needed to be more human intervention once the search algorithm was complete. There are many key documents that should be used as the "tracers" such as the ATSDR report or NHANES reports/papers to ensure all the key references are included. I do not know whether these studies/database/papers were reviewed carefully after the search. I understand the need to focus on work after 2000 and the difficulty with dealing with non-tabular data but there may have been significant studies given a lower priority score using these criteria that should have been included. Was the search rerun and dataset priority algorithm retrained for data after 1995 including data in graphical form and compared to the search used; to make sure nothing was missed? As illustrated above, you do not have to drill down very far to get to some extremely useful data that was missed using these algorithms.

Examples of additional articles that probably should have been included:

Hakk, H., Larsen, G., Bergman, Å. and Örn, U., 2002.,
Sørmo, E.G., Salmer, M.P., Jenssen, B.M., Hop, H., Bæk, K., Kovacs, K.M., Lydersen, C., Falk-Petersen, S., Gabrielsen, G.W., Lie, E. and Skaare, J.U., 2006. ,
McDonald, T.A., 2005.

There are many more and these may be part of the overall risk assessment/exposure prediction reported but I believe the search algorithm exclude them.

5. *EPA identified specific core exposure data: environmental monitoring, biomonitoring, estimated environmental concentrations, or estimated doses. Please comment on any additional core data that EPA should evaluate for each chemical.*

In general: Biodegradation, environmental degradation/transformation studies and other fate and transport studies should be included (if available). When studying any environmental contaminant (eg arsenic or DDT) you must consider no only the primary contaminant but also the converted forms created within the environment. It is the DMA III and MMA III that have higher toxicity than inorganic As (III or V) and DDE is much more persistent than DDT. These are two examples of how risk assessment for a compound cannot be complete without consideration of other contaminants that are derived from the original PBT. There were no significant environmental compound lifecycle studies described. This may be due to a lack of availability but if this is true, it is also worth mentioning.

For PBDE 209: As mentioned above, the biomonitoring studies described did not include NHANES data for PBDEs as near as I could ascertain, which is a gold standard for the exposure community when benchmarking biomonitoring results against a national sample. This data may have been included in other reports such as EPA17x but a direct reference to the database should be included (if used) as it represents the actual human exposure data.

Hexachlorobutadiene (HCBD) Difficult to find other data sources but also difficult to find what was specifically used and not used in drawing conclusions about the data. This is one example of where read across data should probably have been presented.

Phenol, isopropylated, phosphate (3:1) TPP was chosen as the read across for PIP. The selection is sound based on formulation and physical properties in environmental monitoring studies. From what is becoming more apparent, TPP would also be suitable in read across for human health data as well. It is recommended that as this report is updated, TPP be used as a surrogate for human health data reports on PIP if no studies are available for PIP. As mentioned above, metabolite data for all the OPFRs and OP esters should include metabolite data once available.

2,4,6-Tris(tert-butyl) phenol (2,4,6 TTBP) If any studies exist linking the two compounds such as a metabolism or degradation study of TTBP, that would have been a high priority document to target for supplemental searches and inclusion. As stated above the searches should also include degradation and metabolism studies for all PBTs. If none were located, that should be included in a statement.

Pentachlorothiophenol (PCTP) No real studies to comment on. As suggested above studies describing/quantifying PCP behavior one released may add value.

6. *Please comment on the approach to consider read-across of data from similar chemical substances for Phenol, isopropylated, phosphate (3:1) (PIP (3:1)) and 2,4,6-Tris(tert-butyl) phenol (2,4,6 TTBP).*

In general: This is a good practice, especially in the absence of data on the compound being characterized. It's value is only as good as the similarity of the target compound is to the surrogate. It must be evaluated on a case by case basis comparing not only at the physical properties of the surrogate but also the use and toxicity.

PBDE 209: I think this approach is most useful for the PBDE as they (PBDEs) usually travel in bunches and there are probably more studies available on multiple PBDE congeners that may or may not include 209. The body of existing literature on 209 makes a read across approach the least necessary for this compound but as previously mentioned, key data was not included when the compound class was not considered as a wole.

Hexachlorobutadiene (HCBD) Some of the data available is more than adequate for this compound but in other areas of the assessment read across data could have been helpful, if available. Perhaps another lesser chlorinated butadiene, if one is available with complimentary data for human biomonitoring data since there are none reported.

Phenol, isopropylated, phosphate (3:1) PIP is not reported under the TRI and as such it is a prime candidate for a read across with TPP. It is a good choice having similar structure and generally used in the same formulation. Metabolite data for the OPFRs but not pesticides may also be worth evaluating.

2,4,6-Tris(tert-butyl) phenol (2,4,6 TTBP) BHT is not a suitable alternative for TTBP. BHT was a food additive along with BHA and would not be introduced into the environment through any of the same pathways. I believe this was also observed by a commenter and I agree with their comment; however structural similarity should always be considered in the choice of a surrogate. While the physical properties are similar I do not believe BHT to be an environmental degradant it may actually be a metabolit,e although I do not see a phase one metabolic pathway. Difficult to determine how much of the environmental monitoring data came from BHT vs TTBP but as stated above, the use of BHT may lead to an overprediction of TTBP in the environment overall.

Pentachlorothiophenol (PCTP) See other comments on PCP vs PCTP. Similar physical characteristics but not appropriate for exposure assessment, environmental monitoring or human health risk from exposure models.

7. *Please comment on whether EPA has appropriately captured the exposure scenarios. Please identify any existing exposure scenarios EPA may have missed. Please keep in mind the purpose of this document is to inform regulatory decisions under TSCA only.*

In general: The exposure scenarios were generally comprehensive if not over protective. For example, while release of a chemical due to an abrasion of a plastic or other polymer may be the most likely scenario for release for some chemicals. The question remains without further study, whether the chemical is actually released from its matrix or whether smaller matrix compartments are created. Do you release PCTP after a toy is scraped on the ground or have you just made smaller pieces of toy?

Overall, the assessment for compartmentalization and distribution of PBT (eg soil vs air vs water) based on the physical properties of the compound (Kow, Koc etc.) is a logical approach but should be coupled with manufacturing and deployment practices. The document is very good in trying to couple this data (manufacturing use and release with fate of compound in the environment) but should note any studies that support the approach. They should also note places where literature reported studies contradict those assumptions, for example HCBD concentrations were expected to decrease based on manufacturing practices but did not in environmental monitoring studies.

PBDE209: The descriptions of possible exposure scenarios were described in detail for almost all of the possible exposure scenarios for 209 as a single chemical but its' use is always with other PBDEs with similar toxicological properties. They should be evaluated for total PBDE exposure in these scenarios, whenever possible.

Hexachlorobutadiene (HCBD) The modeled data used to estimate dose is the only means for estimating risk and again would benefit from read across data as comparison.

Phenol, isopropylated, phosphate (3:1) There is no TRI data for PIP so it is more difficult to determine what is released during manufacture. The compound is used in many products as both a plasticizer and flame retardant making a lack of TRI data even more difficult to speculate about distribution and subsequent risk. There appears to be no production data either although speculation on an increase of use as it becomes more widely substituted for other flame retardants. The hypothesis of increased use seems reasonable based on both replacement of flame retardants and its versatility as a plasticizer but the indoor dust (most available environmental marker) did not show significant increase with time. Another situation where data conflicting a conclusion are not pointed out, but should be.

2,4,6-Tris(tert-butyl) phenol (2,4,6 TTBP) BHT is not a suitable alternative for TTBP as much larger concentrations of BHT should be present and ingestion would be a primary route of exposure for BHT and perhaps nonexistent for TTBP. I am not convinced that measurements of BHT in the environment and the subsequent exposure pathways linked by interactions with the

environment, are valid. The description of occupational exposures by fuel processes a much more reasonable. As with HCBD, I do not believe use as an analytical standard, produces any significant amount of industrial release, nor presents a significant or even measurable risk.

Pentachlorothiophenol (PCTP) May offer a comment on whether golfers or those who work in the industry are at greater risk of exposure.

8. *Please comment on whether inclusion of additional information on monitoring data would significantly enhance the exposure assessment for the intended purpose of this document. For example, characterization of sampling year vs. study year, characterization of free vs. particle bound chemicals in water and air, lipid normalization for biomonitoring data, and further characterization of studies that had incomplete reporting for their limits of detection. Please identify any specific chemicals for which this additional information would be helpful.*

In general: As described above there needs to be assessment and comparison of contradictory data or data that seems to contradict the findings of another study. This report could use comparisons of; biomonitoring data to modeled data, to environmental sampling data, to fate and transport data. There should be a comparison of temporal studies to individual studies over the same temporal period. Free vs bound would help to understand both exposure pathway and bioavailability of the compound. I also recommend selected comparisons between affinity groups such as worker biomonitoring studies and environmental matrices specific to the manufacturing/processing area. These comparisons will help in creating the overall (30,000 ft view) rather than just a collection or individual studies targeting individual matrices. In addition, the EPA should consider GIS mapping of MAJOR release sites (eg electronics recycling for PBDE209) and their proximity to specific population centers to determine whether there are additional geographically created at-risk populations.

PBDE209: It would be difficult to believe that additional data for PBDE 209 could enhance the risk assessment but the inclusion of class specific studies on PBDEs to determine an overall PBDE exposure, could only help in assuring that all sources are covered. This could be accomplished using modeled exposures with assumptions that ratios of PBDEs in popular formulations of flame retardants be used to estimate a total PBDE exposure scenario. TEFs should be employed as well.

Hexachlorobutadiene (HCBD) See comment on read across for estimating risk in previous section. This is a compound that relies too heavily on modeled exposures and physical data because there is no close match read across nor are there a significant number of fate and transport studies. While more than for compounds such as PIP, TPP or PCTP, there are so many less than PBDE 209 that the uncertainty is much larger for this compound.

Phenol, isopropylated, phosphate (3:1) OP-esters have toxicity and release data that have been studied in pesticides for decades. It is NOT appropriate to use the pesticide data as read across to fill in missing data gaps in any health risk or in distribution. I believe it is appropriate to use any of the OPFRs and OP plasticizers in place of PIP, for either release or prediction of risk. It is also appropriate for substitution of most physical property driven metrics such as partitioning between air and water or free vs particle bound form.

2,4,6-Tris(tert-butyl) phenol (2,4,6 TTBP) It is difficult to determine whether additional studies would change any of the conclusions about TTBP as there were really not enough to draw any conclusions at all. By inference any additional data/studies are more than likely to

help. As proposed by an external commenter, the bulk of TTBP may be consumed in production and not available for secondary release. Additional data here is critical in determining whether this is true.

Pentachlorothiophenol (PCTP) Any additional information would be valuable. The conclusions suggested based on its physical properties (eg portioning within an organism) may be supported with PCP data. PCP is not a suitable surrogate for worker exposure, quantity in the environment not overall human health risk. Laboratory usage is not a reasonable predictor of potential risk because of the very low quantities used and the way it is used.

9. *Please comment on the reliability and relevance of the identified data sets for each chemical and on the strengths and weaknesses of individual data sets that will help to better inform future regulatory actions.*

In general: I did a random search on the quality of the papers used for this report, all seemed very reasonable from reliable sources and provide solid data for the report.

PBDE 209: The limits of the report are clearly driven by the availability of literature describing each PBT. For some PBTs there is an abundance of literature, while for others there is very little. It would be interesting however to change the inclusion (and exclusion) criteria in the search algorithms for compounds such as PBDE 209, to see how much it changes the result. I believe for the other PBTs it would make very little difference.

Hexachlorobutadiene (HCBD), relying on modeled data for estimating risk is inherently noisy and arguably unreliable. In the absence of other available data on levels of exposure, it may be the only way to estimate risk. Another difficulty on the reliability of data used is reflected in magnitude differences in much of the data presented. If your data varies by 12 orders of magnitude (see comment above) is the concentration "high" or "low" in the environmental media reported. Is the subsequent estimated dose, based on a model and a 12 order of magnitude spread in concentration, reliable?

Phenol, isopropylated, phosphate (3:1) PIP has very little available data for making this type of assessment, complicated by a lack of TRI data. It is a compound that favors a read across approach to substitute for actual measurement data. I recommend expanding the search parameters to include all OPFRs and plasticizers instead of using speculation on usage distribution or toxicity data, in the absence of peer review literature. While the modeled data seems reasonable it should not trump read across data for PIP. This is especially true in the absence of more toxicological data. Is 30 ng/day a lot for a stay at home toddler or not?

2,4,6-Tris(tert-butyl) phenol (2,4,6 TTBP) Overall I believe the only real challenge to reliability came from the use of BHT as a surrogate. Any conclusions draw from such sparse coverage in the literature should not carry significant confidence. The overall exposure estimates using seven anti oxidants as surrogates is not reasonable and will probably overestimate exposure to TTBP.

Pentachlorothiophenol (PCTP) Not really enough data sets to comment on or even make predictions on the reliability of the data used. The 2 studies used for the human biomonitoring both appear to be reasonable.

Comments not addressed elsewhere: It is difficult to determine whether tribal lifeways present a greater risk of exposure to any of these PBTs based on proximity to waste sites, manufacturing facilities or recycling facilities without significant GIS studies described above. Generally, those are well beyond the charge assigned here, with one possible exception. The greater reliance of subsistence fishing and hunting potentially make those who rely on hunting and fishing (including but not limited to tribal communities) a potential vulnerable subpopulation, based on exposure through ingestion. Without significant documentation this is too difficult to predict but PBDE209 is the most likely to present an increased risk because of the many pathways to game and was perhaps produced in far greater quantities than the other PBTs.

References:

Hakk, H., Larsen, G., Bergman, Å. and Örn, U., 2002. Binding of brominated diphenyl ethers to male rat carrier proteins. *Xenobiotica*, *32*(12), pp.1079-1091.

Sørmo, E.G., Salmer, M.P., Jenssen, B.M., Hop, H., Bæk, K., Kovacs, K.M., Lydersen, C., Falk-Petersen, S., Gabrielsen, G.W., Lie, E. and Skaare, J.U., 2006. Biomagnification of polybrominated diphenyl ether and hexabromocyclododecane flame retardants in the polar bear food chain in Svalbard, Norway. *Environmental Toxicology and Chemistry: An International Journal*, *25*(9), pp.2502-2511.

McDonald, T.A., 2005. Polybrominated diphenylether levels among United States residents: daily intake and risk of harm to the developing brain and reproductive organs. Integrated Environmental Assessment and Management: An International Journal, 1(4), pp.343-354.

Reviewer 4 - Exposure and Use Assessment Peer Review

TSCA Exposure and Use Assessment
Peer Review Charge Questions

First, the rank and file employees of the Agency have done as good a job as can be expected given the limited resources and flexibility that they have been allowed. The Agency teams that assembled the documents for inclusion in this report should be commended. There are however serious problems in making decisions about all of the chemicals under consideration. Many of the compounds have little if any data defining environmental fate, target biological receptor identification (organism, organ or gene), or long term toxicological effects. In the absence of much basic chemical and biological testing (in vitro or in vivo) there are serious questions about the hazards that these compounds may pose.

1. *This information, when finalized will inform a technical support document to support document to support EPA's regulatory activities on PBTs. Please comment on the organization and structure of this document to inform this use. Do you have specific recommendations to improve clarity and presentation of this information?*

   First, the rank and file employees of the Agency have done as good a job as can be expected given the limited resources and flexibility that they have been allowed. The Agency teams that assembled the documents for inclusion in this report should be commended. There are however serious problems in making decisions about any of the chemicals under consideration. Many of the compounds have little if any data defining environmental fate, target biological receptor identification (organism, organ or gene), or long term toxicological effects. In the absence of much basic chemical and biological testing (in vitro or in vivo) there are serious questions about the hazards that these compounds may pose. Section 3

   P18. Receptor: Change Who to "Which organisms (including humans)…"

   Section 4

   P.24 section 4.3: The statement that decaBDE is not likely to partition from water to air is misleading. A small FRACTION of DBDE is predicted to volatilize from water to air. That is fundamentally different than the compound being unlikely to partition into air. This holds true for release from soil to air and for sorption to biosolids, and to ANY other partitioning/leaching statements throughout this document.

   Any instances where parameters are estimates or were modeled must be noted. For instance, the first line of section 4.3 should explicitly state that the characterization is

based on estimated vapor pressure, Henry's law, and log Koa constants. To do otherwise is to mislead the citizens the Agency is charged to protect. This comment pertains to EACH chemical included in the assessment, although it will not be repeated in detail in my comments.

There are also many instances throughout the PBDE and other sections where referenced data ARE NOT in the information provided in the HERO data base or are selectively drawn from referenced data in a way that diminishes the calculated risks to humans and other biological receptors which mean that any or all receptors are likely to experience greater risk than those predicted in this assessment.

Statements regarding attachment to biosolids in wastewater treatment are true only to the extent that solids do NOT remain in the water column and that organic matter to which DBDE may sorb are not present.

DBDE mobility in groundwater and landfills is similarly most likely to be dependent on movement of dissolved organic matter (DOM) or dissolved inorganic solids (e.g. micro and nanoparticles). Data in table 4-17 demonstrate very clearly that landfill leachate may contain DBDE.

P.28: Where/how are DBDE containing materials recycled?? And in the absence of this information, the Agency can not defend statements that dismiss the potential for environmental or occupational exposures, aka inhalation of dusts or fugitive vapors from melting plastics.

Section 4.5
p.30 Table 4.3 demonstrates the presence of DBDE in all environmental matrices which supports the wording changes suggested (above) related to partitioning. The fact that NO studies were identified for drinking water (p.38) must be explicitly stated in Table 4.3. The zero in the column for Number of datasets is insufficient. The NO in the presence column must also be altered to language noting NO AVAILABLE STUDIES or some similar language.
P.34. The residential data from fig 4-5 should be moved to figure 4-4.
P.35. Are data in tables 4-6 and 4-7 for vapor phase or is that unknown??

Figs 4-24 and 4-25 should use different terminology than "other" to describe the sample types. Perhaps non-serum or other than serum…
Table 4-26 could benefit from inclusion of Rayne et al 2004 (ET&C) and Krahn et al 2007 Marine Pollut Bull

Section 4.7

P. 57. Data in table 4-35 do not support the statement about temporal variance versus variance among studies. More is needed in the table. Or the statement needs modification.

P. 60: No reference is provided for the reported USGS studies spanning the years 2004-2006. This citation needs to be included. AND the general class of invertebrates is FAR TOO broad to have any utility, these data must be parsed into meaningful taxonomic groups or trophic groups for reportage and consideration. The text and Figure presented allow no meaningful assessment of the manner in which the data were assembled or interpreted. INTERESTINGLY when trying to locate this study, a 2006 USGS study "PBDE contamination of soil from weathered outdoor computer scrap," was found (pubs.er.usgs.gov/publication/70193438). This should be reviewed and included, especially in view of the statements related to low/no exposures from end of life activities. Again, there are many studies of Aquatic Invertebrates and those results should be used in a meta-analysis to develop trends.

p.61. The implication of section 4.7.9 is that there are 2 studies addressing this topic. That is incorrect. There are numerous studies of decaBDE in eggs (located 25 from 2010-2018). The best approach would be to estimate of the NUMBER of studies demonstrating increases OR a meta analysis of trends over time in feeding guilds is essential.

Add the term DecaBDE to section 4.7.9. Also concentrations is a preferable term to replace level, which has multiple meanings.

Section 4.8

P.62: I would not say on average. You might be better served with the word median.

p.65: Furthermore, the purity issue raised by the NAS is poorly justified given the commercial formulations of PIP containing materials normally range from 65-95% (see European Environmental Agency, 2009 as referenced on p 125 of the document being reviewed) . The excluded study has a purity near the midpoint of this range.

4.10 p.68: Decabromobiphenyl and transformation products are released from melting or burning of plastics or polymer foams. This is a viable release route and should be noted in disposal and recycling sections.

4.11 P. 70: The absence of DBDE and known transformation products are required to suggest that DBDE has not been present in biotic or abiotic media. This must be stated explicitly in this document.

5.3
p.75 Are any of these data empirically derived? Leo and Hanish did great work, but their data are modeled estimates based on training sets of data that was available at the time. If these data are estimates, that should be explicitly stated and this uncertainty should be included in model estimates of exposures and risk. See comments for section 4 p. 24 related to language describing partitioning.

Volatilization can also be enhanced by wetting through rainfall or irrigation. Movement into groundwater can be through vapor phase transport in the vadose zone. The Koa is an important constant. What is the value used and is it an estimate or an empirically derived value??

p.76: There is a period missing in the second paragraph. Also, surely landfilling is an option for end of life disposal.

p. 77: Airborne releases could easily occur during extrusion processes.

5.4.5 P.78 Thermal degradation products should be noted.

5.4.7
P.79: How can 9 facilities report manufacture of HCBD when in 5.2 (p. 74) there is a statement that there is no intentional manufacture. Is the manufacture in 5.4.7 unintentional or not? It is an important distinction given the statement in 5.2.
Table 5-2: For Indoor dust reportage, the zero in the column for Number of datasets is insufficient. The NO in the presence column must also be altered to language noting NO AVAILABLE STUDIES or some similar language. To do otherwise is misleading that HCBD is not present in indoor dust. Same comment for matrices NOT monitored, but reported in Table 5-3 on p. 139.

Section 5.5.1 p.80: There is a discrepancy with section 5.4.6,which states that that HCBD was used to manufacture headware, underware, dolls and soft toys. How then can there no expected sources of HCBD??

Section 5.5.5 Figure 5-7 this figure demonstrates the significant problem using modeled data instead of empirical data. The modeled data underestimate by at least a factor of 5.

5.5.9 p.86: It seems additional data should be available.

5.6.1: P.88 This points to a SERIOUS data gap that must be closed to finalize any decision supporting the use/tolerance of HCBD.

5.6.2-5.7.7. pp89-102: Genus or Guilds or trophic levels must be defined for data in these tables to lump all species together in these tables in quite confusing and improper. Similar for sediments that may be fresh versus saltwater, alpine versus coastal, etc.

5.7.3; p. 94 There is an error in table identification for sediments.

5.7.7; p.106 : best to restate that Choudhry provides a review of data generated by others. Also there is no indication in Choudhry whether the air samples included particulate matter or not. There is no indication in the primary literature (Singh et al 1982) from which Choudhry derived the data that there was any discrimination of gases and particles. Singh did reference a 1982 EPA report that may provide that detail. These data would be strengthened by resampling with more modern equipment that can separate particles from gases and identify and quantify analytes more specifically.

Section 7.3
p.131: There are NO physical constants listed in the text. Placing the values in the text would be helpful, and designating which are measured and which are estimated is essential. See comments related to wording about partitioning behavior from Section 4 p.24.
What transformation products are likely to be released from contaminated environmental media?
Section 7.4.7
P.135: threshold for reporting is needed here. No reports, but what is the threshold quantity for reporting?? Also there is a duplication of wording in the title of this section.
Section 7.5 P.135: The statement about BHT transforming to TTBP is incorrect. TTBP would be far more likely to transform to BHT.
P.136 For Several matrices in table 7-2, presence is listed as NO when in fact there are NO studies related to the toxicant in question in that matrix. Thus the table is in ERROR the presence was NOT ASESSED or NO DATA was available. That must be included in table 7-2. Same comment for Table 7-3 on p. 139.
p.139: The statement that "only a small hand full of studies show 2,4,6TTBP detected" is HIGHLY misleading. ONLY ONE STUDY was identified wherein analyses were conducted to evaluate TTBP presence.
Section 7.9. detection limit of 2 ppm for TTBP is abysmal and renders this information virtually useless.
Section 7.10 p. 143: why not include inhalation from or dermal contact with fuel additives as a viable exposure scenario??

Section 8

p.146: Stating explicitly that PCNB is a CURRENT use fungicide is important. Please see comments about partitioning language in my comments from section 4.

p. 147: Language about small particles in subsurface environments is good and should be added to EACH section of the Agency's assessment. Also the inclusion of movement in soil vapors within the vadose zone should be added.

P.150: This table must explicitly note that NO STUDIES address this toxicant for 8 of the 9 matrices reported. The zero in one column is insufficient.

This dataset indicates that no uses can be justified until registrants provide data to support exposure and effects assessments.

2. *Please comment on the clarity of the descriptions of how the data were searched for, screened, and evaluated for inclusion in the exposure assessment.*

P.20 Modeled Chemistry and Modeled Environmental fate data are NOT quantitative. They are qualitative. This lack of specificity cascades into whether Modeling estimates can be considered quantitative.

P.21 The Physical-Chemical Data for DecaBDE include

1) a log Kow of 9.97. which includes a reference from EU, 2002 with a primary source of Watanabe and Tatsukwa, 1990. It MUST be noted that the EU document reports OTHER values and the 9.97 value is the least protective of the values reported. Thus a logKow closer to 6 is more likely to be appropriate and this cascades into any computed/modeled partitioning data.

2) a water solubility value from Chemicals Inspection and Testing Institute, that is nothing more than a list of parameters with no explanation of techniques for determining these parameters. More troubling is the fact that the reference included in HERO for these data does NOT have any mention of decaBDE. The reference quality provides NO confidence in data quality even for compounds that are not part of this assessment but that are included in the referenced material.

3. *Please identify any additional information and data sources that EPA should also consider.*

Guo et al. Environ. Sci. Technol. 2017, 51, 89−97 DOI: 10.1021/acs.est.6b06128 contains good sediment information and flux data in the great lakes.

The Agency should revisit the human monitoring data and should NOT limit the studies to long term studies. The literature is replete with data describing human serum DBDE concentrations most often reported in relation to concentrations to environmental exposures. This represents a serious omission.

4. *Due to the large number of references identified during the literature search for Decabromodiphenyl ether, EPA used a prioritization approach to evaluate and extract exposure data for this chemical. Please comment on the prioritization approach that was used for Decabromodiphenyl ether (see section A.2.4 of the Supplemental Information for the Exposure and Use Assessment document). Please comment on whether further characterization lower priority studies is expected to significantly affect the exposure characterization for Decabromodiphenyl ether. Please comment on the strengths/limitations associated with prioritizing use of studies/data sources with larger sample sizes versus smaller sample sizes.*

   Some prioritization was needed, and the approach taken made reasonable sense. However, the failure to consider toxic transformation products of DecaBDE (penta and other congeners) should be corrected especially for the drinking water studies.

5. *EPA identified specific core exposure data: environmental monitoring, biomonitoring, estimated environmental concentrations, or estimated doses. Please comment on any additional core data that EPA should evaluate for each chemical***.**

   The Agency should insure that data of this type are available for each compound under consideration.

6. *Please comment on the approach to consider read-across of data from similar chemical substances for Phenol, isopropylated, phosphate (3:1) (PIP (3:1)) and 2,4,6-Tris(tert-butyl) phenol (2,4,6 TTBP).*

   Read across techniques only make sense if the influences of structural differences within a class of toxicant is well understood. That is not the case for PIP and TTBP.

7. *Please comment on whether EPA has appropriately captured the exposure scenarios. Please identify any existing exposure scenarios EPA may have missed. Please keep in mind the purpose of this document is to inform regulatory decisions under TSCA only.*

   Section 4.6
   Monitoring Decachlorodiphenyl ether alone is not an appropriate tool. This is true for ALL biological exposure estimates where specific chemodynamic or toxicokinetic/dynamic models are not complete. Decachloro diphenyl ether is well known to degrade in the environment to toxic transformation products. Unless specific multigenerational studies of decacholordiphenyl ether depuration in eggs has been completed, exposure assessments must include decachlorodiphenyl ether AND known transformation products to be conservative.

Section 4.9 p.65: The input data for the risk assessment of Hays and Pyatt is significantly flawed in ways that would under predict exposures. For example one entire scenario uses data from 1974, when methodologies were unreliable for determining aqueous partitioning of hydrophobic compounds. Also the risk assessment cherry-picks approaches and literature values that benefit their sponsor's (an industry advocacy group) desired outcome of the assessment. The authors simultaneously use the Agency guideline approach when convenient to exclude information that would show increased exposure or more severe effect while deviating from the guideline approach to include a Reference dose RfD of 4 mg/kg/d, 400 times higher than the IRIS RfD, is not defensible. The study cited for using the 4 mg/kg/d was published by the National Academy of Sciences, a very prestigious and reputable source. The ACTUAL data they relied upon to develop the RfD was generated by the National Toxicology Program, another highly reputable organization. UNFORTUNATELY, the study cited reported adverse effects at the LOWEST decaBDE concentration tested. Thus settling on a NOEAL that is at the mid point between zero and the LOAEL is not reliable.

Section 6.1
It is IMPOSSIBLE to calculate a single value for physical constants of a mixture of this nature.
p. 111
The Log Kow seems unreasonably high given the logKow of triphenylphosphate (4.6), although this may also be a computed value. This logKow value for PIP needs to be determined experimentally to insure that it is not in error. In fact, all of these physical parameters are relatively simple to measure and that should be done rather than adding uncertainties by modeling easily measured parameters. See comments for section 4 p. 24 related to language describing partitioning.
P.116 Table 6-3: ONLY five of the reported matrices have any data. The format of the table is QUITE misleading indicating that PIP is not found in the untested matrices. The fact that no tests have been done DOES NOT suggest that the toxicant in question is not present! The zero in the column for Number of datasets is insufficient. The NO in the presence column must also be altered to language noting NO AVAILABLE STUDIES or some similar language. Same comment for Table 6-4 on p. 121.
p.118
figure 6.3: Concentrations in dust that approach 0.1% are troubling from a risk assessment perspective.
Section 6.6.3 and 6.6.4
P123: see comments for wildlife in previous sections.
Evaluating a single well written article (Larsson), the 95th centile concentrations of TPHP in dust was 7.5 ng/g. Figure 6.3 demonstrates that concentrations of PIP are more likely in the microgram/g range and the 95th centile would be in the mg/g range. Thus all of these exposure estimates are likely to be much lower than are actually occurring.

Section 6.9 P.125 To effectively place the data from the UK into context evaluation of similarities and differences in PIP presence/allowance in the UK and the US are needed.

8. *Please comment on whether inclusion of additional information on monitoring data would significantly enhance the exposure assessment for the intended purpose of this document. For example, characterization of sampling year vs. study year, characterization of free vs. particle bound chemicals in water and air, lipid normalization for biomonitoring data, and further characterization of studies that had incomplete reporting for their limits of detection. Please identify any specific chemicals for which this additional information would be helpful.*

Characterizing based on sampling year is surely essential. Standard procedures that include lipid normalization, organic carbon normalization, particle-liquid particle-gas concentrations also reduce uncertainty. After sufficient data are available, which they currently are not, particle verus "free" values could be very important for any subsequent risk assessment.

9. *Please comment on the reliability and relevance of the identified data sets for each chemical and on the strengths and weaknesses of individual data sets that will help to better inform future regulatory actions.*

P. 18

The Agencies Chemistry Dashboard includes many instances where little if any experimental data are provided for chemical characteristics or environmental fate and transport. Specifically, this is true to a LARGE extent for the 5 chemicals under review.

The worst case is phenol-isopropylated,phosphate (3:1), which has NO CHEMICAL OR ENVIRONMENTAL DATA and which has a single listed component that has NO measured chemical or environmental data.

Decabromodiphenylether has only melting point, boiling point and fish biotransformation half life. Pentachlorothiophenol has only a measured melting point. 2,4,6-tris-(tertbutyl)-phenol is a bit better with 5 measured chemical parameters and 2 environmental factors. Hexachlorobuta-1,3-diene, has 6 of 16 tabulated physical properties and 2 of 6 environmental properties.

Futher there are NO data describing chemical behavior in waters of differing pH or salinity. Thus there can be no data describing multimedia partitioning between water and other environmental compartments. Finally ranges of temperatures are not addressed in the tabulated parameters.

In summary, the BEST coverage of measured parameters for any chemical in this assessment is 38% of chemical characteristics and 33% of environmental characteristics. This lack of empirical data places significant uncertainty in ANY attempt to regulate by modeling effects from modelled characteristics and will require significant safety factors to mitigate these uncertainties. The two most likely and equally troubling reasons for the omission of these data are failure of the registrant (producer) to provide them, or insufficient resources being provided to the Agency to compile data from available sources. The omitted data should be obtained before finalizing any decisions that decrease restrictions on the chemicals being considered.

Section 4.7
P58: The study by Yu measured dusts, not soils. Granted the description of sampling out door dust was ambiguous, but the term DUST is used and SOIL is NOT. This study also provides good estimates of bioaccessibility in the (14-23% range), which should be included in the assessment.

Reviewer 5 - Exposure and Use Assessment Peer Review

Exposure and Use Assessment Peer Review Charge Questions:

Please provide a separate response to questions for each one of the 5 chemicals as appropriate:

1. This information, when finalized will inform a technical support document to support document to support EPA's regulatory activities on PBTs. Please comment on the organization and structure of this document to inform this use. Do you have specific recommendations to improve clarity and presentation of this information?

General response for all compounds (by section)

First of all, I appreciate all the effort that went into gathering the data and producing these documents. It is an impressive compilation of data. The following questions, comments and suggestions are an attempt to make the document more helpful.

I've attempted to provide comments in the order of their appearance in the document. However, I think the overall order of the various sections in this document should be changed. My overall suggestion to improve the clarity and presentation of the document is to reorder the sections as follows: 1) uses 2) lifecycle and potential routes of exposure 3) physical chemical properties 4) expected environmental distribution 5) summary of review articles 6) overview of existing exposure assessment 7) Compare and contrast reviews with data collected in this document. In addition, the cookie-cutter approach used to present the data is distracting when comparing chemicals that have considerable environmental monitoring data (decabromodiphenyl ether) with those that have almost none (2, 4, 6-TTBP). For example, there was only one set of biomonitoring data for 2,4,6-TTBP. Tables like 7-3 and Figures like 7-9 are not appropriate and should be eliminated. Finally, the environmental monitoring data would be much more instructive if studies that measured concentrations in multiple phases at the same time were included and summarized (e.g. sediment and pore water, soil and pore water, fish tissue and water, etc). I realize the number of these types of studies are limited but they would be very valuable in assessing distribution and exposure.

Physical chemical properties

Only one experimental value for each of the listed physical-chemical properties was presented for all five compounds. It would be more appropriate to present the range experimental values that are available or the justification for selecting just the one value. For decabromodipheyl ether as an example, I found several log Kow values that differed greatly from the 9.97 value presented in the table on page 21 of 190 including an EPA technical document (https://www.epa.gov/sites/production/files/2014-03/documents/ffrrofactsheet_contaminant_perchlorate_january2014_final_0.pdf) that listed a log Kow value of 6.265. Given that the decabromobiphenyl has an experimental log Kow value of 8.58 (Doucette and Andren, 1987) it is unlikely that the 9.97 value is correct and the Kow value may be high by several orders of magnitude.

It might be a good idea to include a couple of reference PBT chemicals (one or more of the "dirty dozen") that have a full set of physical chemical properties for comparison and perspective.

Most of the physical properties (e.g. aqueous solubility, vapor pressure) listed in the various tables for each compound are temperature dependent. The temperature at which the properties were measured or estimated should also be listed. Values for boiling point and melting point should also be included to determine the physical state of the compound at environmentally relevant temperatures. Values of pKa should be included for ionizable compounds like pentachlorothiophenol. This will have a large impact on the discussion in the environmental partitioning section for this compound.

For any PBT assessment, it would also be critical to include experimental or estimated values of persistence properties such as biodegradation, atmospheric oxidation, hydrolysis, etc. in this section. EPISuite includes predictive routines for some persistence properties.

Uses

The uses sections were generally well organized and presented. No specific recommendations for improvement or changes were identified.

Characterization of Environmental Partitioning

The environmental partitioning sections were generally not very instructive. For example, it was stated that "some fraction will partition out of air to water particulates or soil while some will remain in the vapor phase". Statements like this apply to all organic chemicals and are so vague that they are not useful. For persistent chemicals, a release to any media will result in chemical being found in all environmental phases with the concentrations in each phase a function of the physical-chemical properties of the chemicals. However, EPA notes that uses and processes for each of these five PBT chemicals are not expected to result in releases to all media. While this general statement may be true, it has little impact the longer term environmental distribution of persistent compounds. One simple suggestion might be to frame the discussion around a relatively simple Fugacity Level 1 or 2 calculation using appropriate environmental compartments that could be used to help the reader make a relative comparison between the expected environmental distribution of the chemicals. Addition of persistence properties would be needed for a Level 2 or higher modeling effort. A comparison to a well-studied reference PBT chemical (one or more of the so called "dirty dozen" chemicals for example) would also help put this partitioning discussion into perspective. Minor point, I would also recommend using the terms sorption or sorb instead of adsorption or adsorb unless you a referring to a specific type of chemical solid interaction mechanism.

Overview of lifecycle and potential sources of exposure

The presentation of these sections were generally clear and useful. No specific recommendations for improvements or changes were identified.

Environmental Monitoring

The purpose of including the frequency of detection tables for biomonitoring was unclear and these tables could be eliminated since they don't really provide much useful information. It's not clear that that analytical methods and limits of quantitation are comparable across the different studies and different animal species/tissues. In addition, publications showing detections are more frequently reported than non-detections.

Figures such as 4-2 (frequency of peer-reviewed publications) don't provide much useful information either and could be eliminated. The number of studies/publications tend to increase over time as a finding is reported, interest is generated and funding/regulatory agencies take notice.

Note: All figure captions should provide enough information that they "stand alone" and do not need any additional explanation in text. Units should be better defined. For example, are all solids concentrations expressed on a dry weight basis? Might not be important for indoor dust but it could be depending on the relative humidity during collection. Notation of dry or wet (fresh) weight is critical for sediments and soils. Biological tissues are often expressed on a fresh weight basis but this is not indicated in the figures.

Commercial vs residential in figure caption. It might be better to just combine all commercial and residential studies into one large bar with ranges since the reader has no idea about the sample location or if the analytical methods used are comparable without looking a every single reference.

While I found figures like 4-3 to be interesting and illustrative of the wide range of concentrations that have been reported, comparison between different studies and investigators can be tenuous if different analytical methods were used. Rather than expressing the information by individual studies, it might be more informative to combine the studies to better examine the different types of sample locations (e.g. commercial vs residential, residential vs vehicle, background vs near facility, particulate vs dissolved, etc.). This would likely show that given the variability between studies, there's no significant differences between the variables in question. The distinction between background and near facility also should be better defined. How close or how far away from the nearest facility were the samples collected? Overall, the impression from the figures is that there is little difference between background and near facilities in the range of reported concentration.

Frequency graphs like 4-21 can be eliminated. Newer analytical techniques (e.g. LC/MSMS) often allow detection at much lower levels than many previously used methods.

Trends in Monitoring Data.

The trends sections not useful given the large inter-study variability. I would suggest eliminating this section unless the study was specifically designed to look at changes over time and the analytical procedures used were identical or shown to yield comparable results. It's likely that

the studies were collecting and analyzing samples that were expected to have the contaminant of interest unless the study was specifically designed as a survey to assess how widespread the distribution of the contamination was.

Overview of Existing Exposure Assessments

Table 4-5 No data for vegetation despite levels in dairy, meat and poultry. How is DecaBDE getting in to those organisms? Diet? Suggests need for additional information on plant uptake and transfer to plant eating organisms.

Summary of Review articles

The articles summarized in this section provide a concise review of essentially the entire document. It might be worth considering moving this section to the front or just after the Overview of Lifecycle and Potential Sources of Exposure section. The data provided in the rest of the document could be used to support or refute the conclusions reached in the reviews.

Specific comments by chemical.

Decabromodiphenyl ether (DecaBDE) (CASRN 1163-19-5)

Pg 21 The aqueous solubility values listed is likely too high based on literature log Kow values. The pointer for the value is incorrect and shows a bromobenzene and chlorotoluene.

I found several log Kow values that greatly differed from the 9.97 value presented in the table on page 21 of 190 including an EPA technical document (https://www.epa.gov/sites/production/files/2014-03/documents/ffrrofactsheet_contaminant_perchlorate_january2014_final_0.pdf) that listed a log Kow value of 6.265. Given that the decabromobiphenyl has an experimental log Kow value of 8.58 (Doucette and Andren, 1987) it is unlikely that the 9.97 value is correct and the Kow value may be high by several orders of magnitude.

Pg 24. Environmental partitioning section: Refer to general comments section. Suggest using Level 1 or 2 fugacity type model to depict interphase distribution.

Unless a specific mechanism is implied, sorption is preferred over adsorption.

Need to provide additional information on how background and near facility samples are defined in terms of distance from facility.

The soil and sediment data should be organic carbon normalized. Can't really compare soil and sediment concentrations without this normalization.

Pg 25 of 19 Be careful not to equate the magnitude of partition coefficients to phase transfer kinetics. While they can be related, it's often more a function of the environmental conditions.

Vapor pressure is a temperature dependent, pure chemical equilibrium property. While it is often related to a tendency to volatilize you cannot state that "volatilization of DecaBDE from solid waste is not likely due to its vapor pressure". Volatilization from any environmental phase is related to the air/specific phase partition coefficient.

Pg 27 of 190 It was stated that "The quantity of DecaBDE in these articles is unknown; however, it may be substantial." What is meant by substantial? 50%?

Figures 4-3 and 4-4. It is difficult to determine from captions how they are different. Might be best to combine the information in Figures 4-3, 4-4 and 4-5 to show the potential differences between commercial, residential and vehicle.

Figure 4.7 Should define background locations and add information on location instead of study authors. Generally, not enough information in figure captions and text to understand data

presented. Is it appropriate to express dissolved and particulate concentration on same graph with same units?

Figure 4.8 Shouldn't particulate concentrations be expressed as mass per mass unless particle density was used to convert to volume? Without reading references and evaluating the models used, the figure is not very useful. Are the modeling approaches the same?

Figure 4.9 It would be useful to add a line on the graph (or value in the caption) showing the aqueous solubility value. Are these filtered (dissolved) samples? I don't see any modeled data even though it's listed in the figure legend.

Figure 4.10 Are these surface soils?

Figure 4.11 Why not combine Figures 4-10 and 4-11 or better explain how the near facility data is different between the two graphs.

Figure 4.12 Are these surface sediments? Any information with respect to sediment depth? Comparison between sediments (and soils) best done with organic carbon normalized values, at least for neutral compounds.

Figure 4.13 No difference between background and near facility sites suggests global transport of contaminants. However, without defining the criteria used to define background locations and near facility locations I'm not sure the figure provides any useful evidence one way or the other.

Figure 4.15 Need more information in figure captions. What type of facilities, how far from facilities? Dry weight basis?

Figure 4.16 Why influent/effluent? Shouldn't this be a unitless fraction? Would be helpful to add line showing aqueous solubility.

Figure 4.17 Filtered samples?

Figure 4.18 Fresh or dry weight? What types of vegetation? Again, need to define background and near facility.

Table 4.4 should be eliminated. See general comments for justification.

Figure 4.21 should be eliminated. See general comments for justification.

Figure 4.22 Same or comparable analytical methods?

Figure 4.24 ng/g of what? Grams of tissue? Fresh weight?

Figure 4.26 Figure not needed to describe results of a single study. Describe in text if this data is actually necessary.

Figure 4.28 Fresh or dry weight basis?

Pg 56 of 190
Temporal trends section likely not be useful if analytical methods and limits of detection are different between studies.

Figure 4-38. Are all samples surface sediments? Any studies showing core data as a function of depth? Dated cores?

Figure 4-40 Difficult to justify looking a trends over such a short period of time. Graph should be eliminated

Figure 4-41 Same lake? Figure captions should stand alone and not require any explanation in text.

Hexachlorobutadiene (HCBD) (CASRN 87-68-3)

Table 5-1 If not used since 1970 why show table? Implies current use rather than production as a by-product?

75 of 190 Environmental Partitioning section should be rewritten as discussed in general comments section for this and all subsequent chemicals in the document.

It was stated that HCBD in indoor air is not likely to adsorb to dust or other particles due to its log KOA. Everything sorbs to some extent. Consider what was said in the same section referring to the water environment.

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This statement belongs in the expected environmental partitioning section: “HCBD is an organic compound. It is a clear, colorless, oily liquid with a mild turpentine-like odor. It does not naturally occur. HCBD is poorly soluble in water. When released to the environment, it is expected to volatilize quickly. Further, its vapor pressure indicates that it will evaporate from surfaces.” Don’t equate equilibrium properties like vapor pressure with rates. Evaporation rates are generally expressed relative to ethyl acetate in industrial hygiene applications.

Figure 5-2 could be eliminated as suggested in general comments.

Indoor dust. All compounds sorb to some extent. Might be minor but avoid saying no sorption.

Figure 5-5 All using same analytical technique? Unlikely, given the spread of dates.

Pg 94-190 bookmark error reference source not found

Phenol, Isopropylated, Phosphate (3:1)-PIP (3:1)

Pg 110 Should emphasize that all physical-chemical properties are estimated.

2, 4, 6-Tris(tert-butyl) Phenol (2, 4, 6-TTBP)

pg 127 of 190 Should include pKa. Not likely to be environmentally relevant but phenols are ionizable.

Log Kow reference pointer is incorrect.

Pg 135 Statement made that 2,4,6-TTBP was detected in relatively few monitoring studies. This is probably due to the fact that is wasn't looked for in many studies.

Is BHT a reasonable surrogate for environmental fate? By what criteria? There are programs that attempt to quantify chemical structure similarity.

Frequency of detection tables? How were they generated?

Figure 7.2 Should be eliminated as discussed in general comments, especially given that only one or two studies were conducted per year..

Pg 139. Biomonitoring section: Can't identify it if it's not looked for.

Table 7.3 Should be eliminated as discussed in the general section. Especially important when there is only one study. I don't think it's necessary to follow exact same format for each chemical given the large differences in the number of studies.

Pentachlorothiophenol (PCTP) (CASRN 133-49-3)
Only estimated physical-chemical properties are reported. This should be emphasized.
No pKa value is presented. The chemical structure itself and estimated value in reference listed below indicate that PCTP will likely be negatively charged in aqueous, soil and sediment phases. Pentachlorophenol has a pKa value of about 4.75. Without considering pKa, the characterization of expected environmental partitioning is incorrect and should be redone. Aqueous solubility, log Kow, log Koc all depend on the form (neutral or negative).

Thermochemical Parameters and pKa Values for Chlorinated Congeners of Thiophenol
Mohammednoor Altarawneh, Tajwar Dar, and Bogdan Z. Dlugogorski *Journal of Chemical & Engineering Data* **2012** *57* (6), 1834-1842 DOI: 10.1021/je3003173

2. Please comment on the clarity of the descriptions of how the data were searched for, screened, and evaluated for inclusion in the exposure assessment.

General comment applying to all chemicals evaluated. The literature search strategy was adequately described. However, there is no need to repeat this information for all five chemicals. Just explain the general procedure for the collection and organization of the literature data for the first chemical and mention only differences or unique cases for all the other compounds.

3. Please identify any additional information and data sources that EPA should also consider.

See general comments. Addition of persistence properties and trophic magnification factors (TMF) would help the reader understand the persistence and bioaccumulation potentials. Biomonitoring data are helpful in this regard but even highly water soluble and degradable chemicals like pharmaceuticals are being reported in fish and plants.

4. Due to the large number of references identified during the literature search for Decabromodiphenyl ether, EPA used a prioritization approach to evaluate and extract exposure data for this chemical. Please comment on the prioritization approach that was used for Decabromodiphenyl ether (see section A.2.4 of the Supplemental Information for the Exposure and Use Assessment document). Please comment on whether further characterization lower priority studies is expected to significantly affect the exposure characterization for Decabromodiphenyl ether. Please comment on the strengths/limitations associated with prioritizing use of studies/data sources with larger sample sizes versus smaller sample sizes.

General comment applying to all chemicals evaluated. Given the variability in the methods and studies the prioritization approach was reasonable. The large difference between the amount of available data between the chemicals makes any comparison more difficult.

5. PA identified specific core exposure data: environmental monitoring, biomonitoring, estimated environmental concentrations, or estimated doses. Please comment on any additional core data that EPA should evaluate for each chemical.

General comment applying to all chemicals evaluated. As mentioned previously, additional information of persistence properties and trophic magnification factors (TMF) should be added.

6. Please comment on the approach to consider read-across of data from similar chemical substances for Phenol, isopropylated, phosphate (3:1) (PIP (3:1)) and 2,4,6-Tris(tert-butyl) phenol (2,4,6 TTBP).

General comment applying to all chemicals evaluated. Read across is acceptable if there is a documented approach for showing how the structures are determined to be "similar". This was not done in this document. Regardless, there is really no good substitute for actual experimental data.

7. Please comment on whether EPA has appropriately captured the exposure scenarios. Please identify any existing exposure scenarios EPA may have missed. Please keep in mind the purpose of this document is to inform regulatory decisions under TSCA only.

General comment applying to all chemicals evaluated. Exposure scenarios were reasonable but should be better tied to estimated distribution within the environment or to the environmental monitoring data that has been collected. Potentially unique exposures to special subpopulations described in several of the comments that were received should also be evaluated.

8. Please comment on whether inclusion of additional information on monitoring data would significantly enhance the exposure assessment for the intended purpose of this document. For example, characterization of sampling year vs. study year, characterization of free vs. particle bound chemicals in water and air, lipid normalization for biomonitoring data, and further characterization of studies that had incomplete reporting for their limits of detection. Please identify any specific chemicals for which this additional information would be helpful.

General comment applying to all chemicals evaluated. As mentioned in responses to the previous charge questions, additional information on analytical methods and quantitation limits are necessary to enable an accurate comparison between studies. Organic carbon normalized sorption data are needed to adequately compare concentrations between soils and sediments for the neutral forms of hydrophobic chemicals. Difference between freely dissolved and particle concentrations would also enable better intra-study comparisons. For pentachlorothiophenol, the pKa of the chemical and the pH of the environmental compartments were the samples were collected are needed to properly evaluate the data and resulting exposures.

9. Please comment on the reliability and relevance of the identified data sets for each chemical and on the strengths and weaknesses of individual data sets that will help to better inform future regulatory actions.

General comments

Except for partitioning and persistence properties, it seems like a reasonably systematic search and compilation of the available data for each chemical was conducted. However, without a thorough reading of every reference it's impossible to determine if the concentrations reported by the various studies are truly compatible. Were the analytical methods (sample size, extraction, instrument) the same? Unlikely. This greatly limits the usefulness of the figures the compare concentrations and trends between studies.

Reviewer 6 - Exposure and Use Assessment Peer Review

Exposure and Use Assessment of Five Persistent, Bioaccumulative and Toxic Chemicals

EPA Document # EPA-740-R1-8002 June 2018

Exposure and Use Assessment Peer Review Charge Questions:

1. This information, when finalized will inform a technical support document to support document to support EPA's regulatory activities on PBTs. Please comment on the organization and structure of this document to inform this use. Do you have specific recommendations to improve clarity and presentation of this information?

For simplicity, I will use the term "the document" thorough-out to mean the EPA Exposure and Use Assessment document.

I have provided separate detailed responses for the 5 PBT chemicals below with respect to specific aspects of their presentations (e.g. missing references, etc.) in the document. However, answers to most of the EPA charge questions are consistent between chemicals as most of these questions focus on the acquisition and presentation of the data.

Structure: My experience is that Executive Summaries provide an overview of the major conclusions of the study at hand. Here, the Executive Summary describes the rationale for the document and how the information in the document was obtained (i.e. methods), but not the findings or conclusions. As an alternative, I would suggest summaries of the major findings for each chemical.

The document presents considerable data in regards to monitoring results for DecaBDE. For the other 4 chemicals the data are sparse and insufficient to adequately assess exposure. Use data are more complete.

Unfortunately, much of the data returned by the searches are not described adequately in the document (i.e. most studies are listed in the figures by only author and date – parameters which are of limited use to actually evaluate their significance). Chemical use and subsequent human and ecological exposure will differ substantially by country. Thus co-mingling data from other countries without categorizing it limits its utility. To illustrate, use of chemicals, regulations and industrial hygiene differ between China and the U.S. Likewise, products may be manufactured and disposed of (e.g. electronics and e-wastes in Asia) in one region but used in another (e.g. North America or Europe). This complicates the melding of monitoring data from different countries.

The authors repeatedly note that use of sample collection date would be more pertinent than date of publication. However, the document continues to use date of publication in the many figures. Of course, in some cases, sampling dates may not be provided in the publication or be more difficult to extract, nonetheless it is critical.

2. Please comment on the clarity of the descriptions of how the data were searched for, screened, and evaluated for inclusion in the exposure assessment.

The document adequately describes how data were searched for, screened and evaluated for inclusion. That being said, the process appears to have overlooked or screened out important data. The adequacy of the data acquisition processes is best evaluated by the final output. As you will see from my comments below, I did not conclude that the document adequately defines "whether exposure to each identified PBT is likely, under the conditions of use".

3. Please identify any additional information and data sources that EPA should also consider.

Please see below my specific comments for the 5 PBT chemicals under review. There is a considerable number of published works that should be considered.

4. Due to the large number of references identified during the literature search for Decabromodiphenyl ether, EPA used a prioritization approach to evaluate and extract exposure data for this chemical. Please comment on the prioritization approach that was used for Decabromodiphenyl ether (see section A.2.4 of the Supplemental Information for the Exposure and Use Assessment document). Please comment on whether further characterization lower priority studies is expected to significantly affect the exposure characterization for Decabromodiphenyl ether. Please comment on the strengths/limitations associated with prioritizing use of studies/data sources with larger sample sizes versus smaller sample sizes.

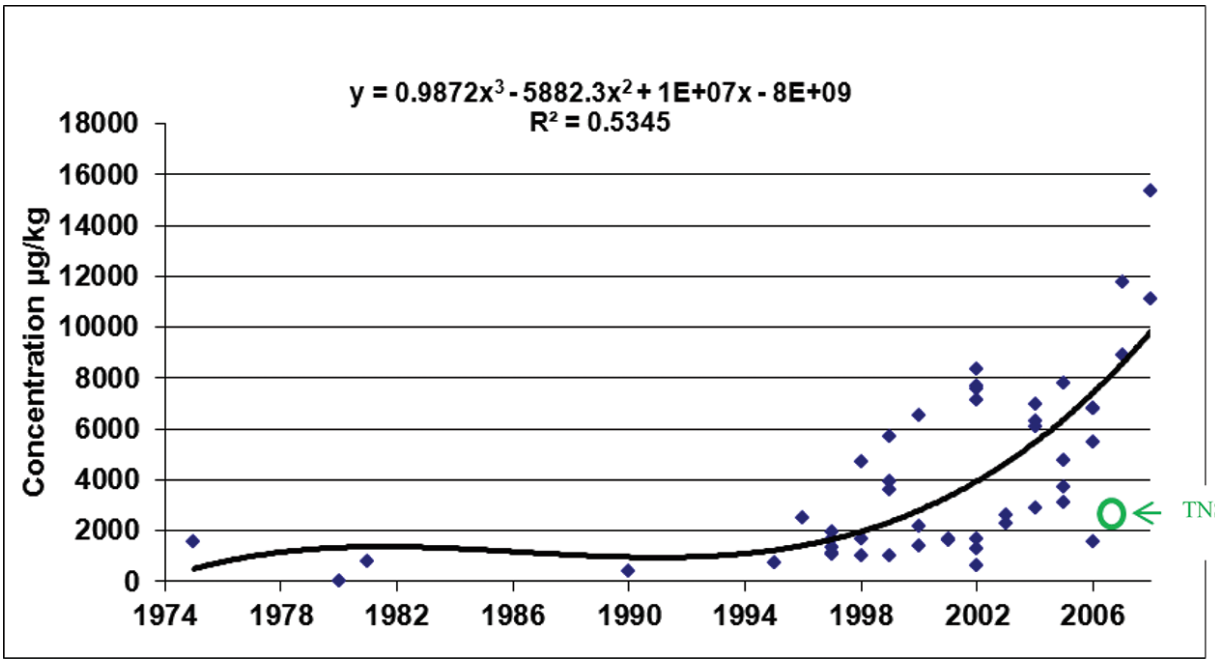
As the stated goal is to assess use, occurrence and exposure to 5 PBT chemicals, studies that describe North American (or better U.S.) samples should be specifically identified and prioritized. To illustrate, manufacture, regulation and use of DecaBDE differed(s) considerably between countries (e.g. U.S. versus China or Sweden). Inclusion in the document of foreign studies (e.g. related to e-waste sites) is interesting and potentially useful, but is less germane than U.S. studies. To illustrate: Swedish breast milk studies were among the first to graphically illustrate the rise of PBDEs in humans. However, it was later found that PBDE levels in U.S. citizens were considerably higher due to much greater use here (N. American demand was 95% of global PentaBDE use). Also regulatory restrictions and disposal practices between countries varied considerably.

Resultant exposure trajectories would therefore also differ. The document authors felt that considerable DecaBDE data exist, so they could be more exclusionary with respect to which studies to include (see below prioritization scheme). However if one excluded non-North American studies the available pool would be far smaller. *"EPA prioritized the following studies with the following criteria: Sample size of >10; Study published after 2000; – Quantitative data was available in a table, rather than graph or chart."* Studies using larger sample sizes are likely to be more representative of environmental distribution of DecaBDE, as well as other chemicals of concern. Hence, from that basis they are, in theory, preferred. However, other metrics that may be harder to assess, such as data quality, should be drivers as well. A focus on more recent (since 2000) works is appropriate in regards to current/recent use and exposure. Also analytical techniques for the measurement of chemicals such as DecaBDE (BDE209) have improved. For instance, its low volatility and potential for degradation in a GC injector resulted in inaccuracies in its measurement in early studies.

Obviously it is easier to extract tabular data accurately from tables versus figures. However, most journals encourage authors to present data in graphical versus tabular form, as it is more readily assimilated by readers. Indeed the document itself uses figures extensively to present data. Thus reliance on information obtained from available tabular data is not optimal. Upon further evaluation of the data presented in this document it is clear some useful studies were not included.

To illustrate: "4.7.5. Biosolids: No studies were identified that could be extracted temporally". Please see Hale et al. 2012. This study clearly shows trends in DecaBDE in

U.S. sewage sludges, albeit mostly in a graphical form. "TNSS" is from the EPA Targeted National Sewage Sludge Survey, which provides considerable DecaBDE data on levels in US wastewater sludges.



5. EPA identified specific core exposure data: environmental monitoring, biomonitoring, estimated environmental concentrations, or estimated doses. Please comment on any additional core data that EPA should evaluate for each chemical.

As noted above, my research group at VIMS previously published on time trends of DecaBDE in U.S. biosolids.

Also I did not see ANY discussion of metabolism/biotransformation of DecaBDE in humans. The CDC states (https://www.cdc.gov/biomonitoring/PBDEs_BiomonitoringSummary.html) "The metabolism and elimination of PBDEs in humans are not well characterized. One occupational study indicated that decaBDE has an elimination half-life of 11-18 days and the octaBDEs have half-lives ranging between 37-91 days (Thuresson et al., 2006). In animals, PBDE elimination occurs primarily through fecal excretion with decaBDE being more rapidly eliminated than the other less brominated PBDEs (Gill et al., 2004; Hardy, 2002)." Note that the document does mention metabolism products in regards to PCTP.

Obviously clearance (and associated variables) affects the disposition of DecaBDE in the human body. Resulting metabolites were not captured in the document discussion.

6. Please comment on the approach to consider read-across of data from similar chemical substances for Phenol, isopropylated, phosphate (3:1) (PIP (3:1)) and 2,4,6-Tris(tert-butyl) phenol (2,4,6 TTBP).

I see this approach as problematic. For PIP, TTBP and PCTP available data are limited. Clearly, more monitoring, fate and other data are needed. Analytical procedures for PIP have only begun to be validated by the scientific community. In the case of PIP it appears the read-across rationale is that PIP and TPP are both phosphate esters and both are/were present in some (but not all) commercial mixtures and products. However, the environmental properties and behavior of these two are quite different, e.g. water solubilities. At a minimum, a table of properties should contain data for both for ready comparison. Once released to the environment, the fate of TPP and PIP will deviate. Hence, it is not reasonable to expect they will parallel each other in downstream environmental compartments and resultant exposure. Bioavailability, bioaccumulation and biotransformation will also differ.

In the case of 2,4,6 TTBP, BHT is suggested as a surrogate. In this case their uses differ substantially as well. Hence, I question the applicability of the "read-across" of monitoring data for these as well. We just need more data on the actual targeted chemicals.

7. Please comment on whether EPA has appropriately captured the exposure scenarios. Please identify any existing exposure scenarios EPA may have missed. Please keep in mind the purpose of this document is to inform regulatory decisions under TSCA only.

A major use of DecaBDE is/was as a polymer additive. As such, its release is in part is controlled by the fate and stability of the polymer matrix. Many of these polymers are/were components in long-lived products, such as electronics casings. Most studies referenced in the document have focused on the presence of DecaBDE in materials associated with manufacture (either of the PBT chemical itself or of polymer products), product usage (indoor dust and air) or following intentional disposal (e.g. solid waste leachates).

Other release/exposure paths are wear, weathering (note recent concerns over secondary "microplastics": fragments of larger plastics) and unintentional destruction of products, e.g. accidental fires. House and wildfires are two examples where massive amounts of polymeric and other products are destroyed, likely releasing the percent by weight loadings of the additives to the surrounding environment.

Car and other vehicular fires will also liberate these chemicals, which may be present at percent by weight levels in products burned or partially burned. Verisk estimated that 4.5 million homes are at high or extreme risk to wildfire (https://www.verisk.com/insurance/visualize/key-findings-from-the-2017-verisk-wildfire-risk-analysis/?utm_source=Social&utm_medium=Twitter&utm_campaign=VeriskSM&utm_content=842017). A substantial portion of these PBTs may be chemically altered, e.g. the formation of halogenated dioxins and furans. A search of the document for the term "fire" only revealed 5 ioccurrences. Most of these usages were related to descriptions of the purpose of flame retardants, not the role of fire in releasing DecaBDE (or other PBTs). Fig. 4-3 does include data from Shen et al, who investigated flame retardants associated with fire stations, but there is nothing in the document discussion regarding this pathway.

8. Please comment on whether inclusion of additional information on monitoring data would significantly enhance the exposure assessment for the intended purpose of this document. For example, characterization of sampling year vs. study year, characterization of free vs. particle bound chemicals in water and air, lipid normalization for biomonitoring data, and further characterization of studies that had incomplete reporting for their limits of detection. Please identify any specific chemicals for which this additional information would be helpful.

Inclusion and discussion of such additional information (as well as geographical location and date of sampling) for all chemicals is absolutely necessary to understand/assess the data. The basis of many types of data (e.g. tissue date in biomonitoring studies, particulate/vapor/dissolved phases) are not indicated, let alone normalized to.

Detection limit data are essential when one is characterizing studies as to frequency of detection. In some cases in the document method detection limits (MDLs) appear to be confused with actual detections in environmental compartments. In most cases detection limits have improved/decreased over the years as methods and instrumentation have improved. This complicates data comparisons. With the exception of DecaBDE, monitoring studies presented for the other PBT chemicals are very limited.

9. Please comment on the reliability and relevance of the identified data sets for each chemical and on the strengths and weaknesses of individual data sets that will help to better inform future regulatory actions.

This would require in-depth reading all the studies cited, which is beyond the scope of the review. I do note in my comments below that there appears to be some disconnects/mistakes between the matrices discussed in the paper and the data actually presented in the document. I restate the view that the document should prioritize U.S. studies and to clearly identify which these are. Foreign studies may not reflect U.S. conditions, use and exposure. Older studies reflect at best past conditions of use and exposure. In some cases the methods used to determine concentrations in the past may be poorer than current approaches. Also in the past, quality control was less of a priority than in modern studies where good laboratory practices are more commonly adhered to.

Detailed comments on each of the PBT chemical discussions follow:

4.1 Decabromodiphenyl ether (DecaBDE)

DecaBDE is actually a mixture of several brominated diphenyl ethers. The dominant congener is the fully brominated BDE-209. However, commercial mixtures contain varying amounts of predominantly nona-BDEs. This should be explained in the document early. For details please see La Guardia et al. 2006. This is important as physical and pharmacological properties change with degree and location of bromination. For example, the bioaccumulation of congeners increases from deca to the tetras.

Also geographical use patterns are critical. In 1999, North America accounted for 44% of global decaBDE usage, but 97.5% of pentaBDE demand (see Hale et al. 2003).

p. 16. DecaBDE scored high for hazard, high for persistence, and high for bioaccumulation on the 2014 update. I am uncertain why DecaBDE would score high for bioaccumulation as studies indicate low/modest accumulation. It has an extreme Kow/Koc and thus a tendency to sorb to solids. This translates in low water concentrations and associated bioavailability.

Note that for the five PBT chemicals found in air and water, no distinction was made during data presentation for chemical bound to particulate matter versus free chemical in air/water. This approach is quite problematic as phase associations affects fate and effects.

p. 21. Table 4.1 Water solubility (1992 reference) is listed as 0.02 mg/l. (ATSDR 2015 suggests <0.01 mg/L). Note that physical property values for mixtures are nonsensical as they will vary by component and cannot be simply averaged.

p. 22. Document states "Additive flame retardants are relatively unattached to the polymer matrix and may readily migrate from products to the surrounding environment during manufacture, normal use, and disposal (Verslycke et al., 2005)." But I saw no discussion of flame retardant association/presence in polymers in the referenced Verslycke et al (2005) paper.

The dosage of DecaBDE additive in polymers should be discussed. DecaBDE may be present at > 10% by weight of the polymer. Such substantial levels have tremendous implications in terms of routes for DecaBDE release/transport to the environment. That is, "loss" of polymer to the environment relocates considerable DecaBDE with it. DecaBDE release then becomes an issue when the polymer deteriorates. The type and use of polymer will also control fate and exposure to the DecaBDE additive. This likely contributed to the disconnect in the original VCCEP DecaBDE report wherein the industry sponsor's consultant originally modeled and predicted lower blood levels in workers receiving occupational exposure than later were found in ordinary citizens. The latter exposures were from contaminated indoor dust exposure, in turn derived from DecaBDE in household products.

The document text states: “End of use for products containing PBDEs include disposal in landfills as well as recycling (USGS, 2006) or incineration. But I see no mention of the word “incineration” in Verslycke et al. (2005).

4.2. Use section. The temporal (and geographic) use of DecaBDE will affect its release and exposure characteristics. New use/manufacture of DecaBDE was to be voluntarily phased out by Dec 21, 2013 and likely decreased before that as manufacturing wound down. There is no mention of this here. In addition, some DecaBDE use appears to have occurred in 2015 (https://www.epa.gov/sites/production/files/2017-08/documents/decabde_-_use_information_-_8-7-17-clean.pdf). This is later mentioned on p.26 of the document.

There are published data on production by global region of DecaBDE. These show substantial production in Asia, as well as North America and Europe. This is a starting point for expected release and thus environmental distribution in the world. Fundamentally, we should be most concerned with the U.S./N. America production, use and exposure. This issue is true for the other PBT chemicals under review.

4.3. Characterization of Expected Environmental Partitioning p. 24. A citation is needed as to long range, particulate bound DecaBDE transport. Remote sites? Burning of trash (e.g. Farrar et al, 2004) and federal facilities may be large local sources in remote areas. We found high PBDE levels in Antarctica associated with the McMurdo research facility (Hale et al. 2008). Again a “high” (erroneous) water solubility for DecaBDE of 0.02 mg/L is quoted.

p. 25. Landfill leachate of decaBDE? Document states “If” released to the indoor environment? It definitely is released.

p. 27. DecaBDE was also used in liquid or paste (latex) back-coatings of textiles. This is discussed later (4.4.6)

4.4.3 Imported articles. The quantity of DecaBDE in these articles is unknown; however, it may be substantial.

p. 32. Fig 4-3. Indoor Dust. Concentration values start on the x-axis at 10^{-6}, but lowest values start >0.01? This makes evaluation of values presented more difficult. Same for **Fig 4-4 (p. 33) & Fig 4-5.** Also providing only the authors and publication dates in figures give no context for the characteristics of the samples portrayed. Many of these samples are not from North America, so their applicability and interpretation may be questionable to the U.S. situation. The figure should include the country of origin at a minimum. U.S. or N. American studies should be grouped together as these are most pertinent to American exposure. Why are residential dust sample results split into **Fig 4-3, 4-4 and 4-5**?

Fig. 4-6. Indoor air. Again, identifying countries of origin are critical. Which are U.S. studies? Are these vapor, particulate or whole air samples? This makes a big difference.

Fig. 4-7. Same questions as for Fig 4-6. “Particulate” is noted for one of the samples, but the rest? What type of “facilities”?

Fig 4-8. What does “modeled” mean? Requires some discussion of parameters used to model.

Fig 4-9. What is a “facility”? Could be anything. Countries of origin? Urban/rural sites…

Fig 4-10. Again “near facility”? Background? Countries?

Fig 4-11. Same above questions. Also why separate into a different figure 1979 to 2013 data? Better to separate US/N. American data from foreign data.

Fig 4-12. Are these dry weight concentrations? Sieved as to size? Country of sample origin?

Fig 4-13. What is a “facility”? Vague. What country of origin?

Fig 4-14 to 4-17. Same questions.

Fig 4-15. Sludge/biosolids. Missing the EPA Targeted National Sewage Sludge Survey EPA-822-R-08-014, wherein 74 wastewater treatment facilities were sampled for PBDEs, including decaBDE (BDE-209) collected in 2006-2007.

Fig 4-17. There are other leachate papers out there that are likely more germane than these two S. African & Asian studies. For example: Li et al. 2012.

Fig 4-18. Same questions as to need to identify site location and what the expression “near facility” means. Note, my group published a paper that examined BDE-209 in (U.S.) sludge-amended soil and in corn that is not cited. It is missing from Fig 4-10 (Hale et al, 2012).

4.5.5 Drinking water. No studies? “DecaBDE is not expected to be present or at extremely low levels in drinking water.” But that is a big “if”, even though it possesses low water solubility. If present, even at parts per trillion levels, then cumulative exposure may be substantial due to volumes consumed.

4.5.6. Soil. Fig 4-10. Same comment as above related to the lack of information content by depicting only “authors & years”.

Fig 4-21. Frequency of Detection has limited value in lieu of quantitation limits. Also true for other tables. Detection limits have improved substantially as methods have improved over the years.

Fig 4-22. As discussed for the above tables, at a minimum the country of sample origin should be noted. “Consumer” here apparently means fish consumer (gleaned this from the reference), but not evident from the figure caption. What does “high-end” mean? Term is vague.

Why does **Fig 4-23** provide data for one study versus being included in **Fig 4-22**?

Fig 4-24. What does "Other" mean here? I assume "other tissue". Country and tissue type should be added. Are these concentrations all on a wet weight basis?

Fig 4-25. "occupational"? Does that mean flame retardant manufacturing, plastics manufacturing or?

Fig 4-26 and 4-27. There are additional studies available, such as Stapleton et al (2008).

Fig-4-28. Aquatic invertebrates. The La Guardia et al study cited included sites that were not "background"; i.e. included sites that were downstream from discharges from likely DecaBDE sources, to wit: "The bivalve Corbicula fluminea, gastropod Elimia proxima and surficial sediments were collected in July 2009, from the Yadkin River, downstream of a North Carolina WWTP outfall. This treatment facility was constructed in 1968 to service a local textile mill. This WWTP was upgraded in 2003 to allow treatment of up to 16 million liters per day. According to their National Pollutant Discharge Elimination System (NPDES) permit this facility is owned and operated by a local textile manufacturer and treats ~92% industrial process wastewater and ~8% domestic sewage."

4.6.4. DecaBDE is highly sorbed to sediments, hence tends to exhibit low bioavailability to organisms exposed via the water column. Previous work has also shown that fish are capable of debrominating DecaBDE (e.g. La Guardia, et al. 2007).

Fig 4-31. Terrestrial invertebrates. The Yin study sited appears to use an aquatic snail, not a terrestrial invertebrate. Here it appears the concentrations are on a lipid basis, not wet weight? Neither is an N. American study. The following study included US terrestrial invertebrates: Gaylor et al**.** 2014.

Fig 4-32. Terrestrial-feeding birds (i.e. raptors) appear to have anomalously high BDE-209 levels compared to other organisms, especially aquatic species. Figures should indicate tissue type sampled. Country of origin (prioritize/separate US samplings, then North American, Europe/developed Asian countries…). Missing some U.S. references, including two from my lab alone: Chen et al. 2008 and Potter et al. 2009.

Fig. 4-33. Misses pertinent N. American references, e.g. Christensen et al. 2005. Should indicate species, location and tissue sampled in Figure as well as concentration basis (pipid, wet weight?).

Fig. 4-34. Country, species and tissues sampled?

Fig 4-35. Indoor dust. Levels is be linked to the types and condition (including age) of DecaBDE-containing materials. As DecaBDE may be >10% by weight of these, small losses of fragments may heavily influence measured DecaBDE levels since methods do not differentiate polymer-associated versus unassociated residues.

4.7.3 Soils.

Fig. 4-37. One study from China. How pertinent is this? This was meant to be a seasonal study versus a longer time period.

Fig 4.7.5. Biosolids (temporal). The document states: "No studies were identified that could be extracted temporally." However, note our previous study on DecaBDE (BDE-209) in Chicago sludges. Hale et al. 2012.

4.7.6. Use, handling, disposal and hence exposure to DecaBDE differs by country. This longitudinal study is for Swedish mothers. This crucial information is not mentioned in the document. The northern Europeans used less and restricted PBDE due to environmental concerns compared to the U.S. Also in thiscited article are data for breast milk (not discussed in the document).

4.7.8. Noteworthy are the very low DecaBDE levels reported in fish, most < 1 ng/g. Were these values on a wet weight basis?

4.7.9. Bird data presented are from Spain and Sweden. Important as use and hence exposure will vary geographically.

4.9. Overview of Existing Exposure Assessments. p. 65.

I served on the original VCCEP DecaBDE panel selected by EPA. When the industry presentation draft was first provided to the panel it contained no indoor dust data, as papers indicating high PBDE burdens in indoor dust were just published. Measured PBDEs burdens in non-occupationally-exposed people soon showed higher PBDE levels than the modeled occupationally-exposed individuals. First data on human PBDE burdens came from Sweden. However later, breast milk data for North Americans were found to 40-fold higher than Swedish counterparts. Hence, I am leery of exposure modeling of infant burdens based on milk levels of Swedish mothers. Also BDE-209 is a relatively short half-life in humans. So consideration of DecaBDE metabolism should be part of the assessment. Circa 2000 the analytical methods for BDE-209 were often poor/still being improved.

4.10. Representative Exposure Scenarios. p. 68

A substantial reduction in release rate (except for manufacturing-related) is uncertain as significant release may occur during weathering and after discard of DecaBDE-containing products that contain percent levels of this additive. Release from aging products may increase as they deteriorate/lose integrity. The release in homes may decrease due to product replacement, but that from landfills and other discarded materials repositories may increase. See: Chen et al. 2013..

While the EPA TRI notes substantial past release via the air, I expect in reality that release to land predominate. The TRI focuses on manufacturing, not ultimate product fate/disposal. Most decaBDE ends up in products. It does not then just disappear.

Accumulation of DecaBDE in fish and fish-eating birds is small, compared to terrestrial feeding birds. This is likely a clue to mechanism/route of exposure to wildlife and humans.

This brings into question the "representative exposure scenarios" described on pg. 69 as these seem to heavily weight transfers to air as the initial point of release step.

4.11.4. Human Biomonitoring p. 72

The document states: "The highest levels of PBDEs in human biological samples were detected at e-waste recycling sites in South China, East China and South Korea." This is consistent with my previously expressed view that identification of geographical locations of samples is critical and that some countries differ substantially from the U.S. in terms of use, disposal and thus exposure to DecaBDE.

5. Hexachlorobutadiene (HCBD) Pp. 73.

The comments from Dianne C. Barton, Chair National Tribal Toxics Council appear to be based on the premise that we are evaluating HBCD (hexabromocyclododecane, a brominated flame retardant) instead of HCBD. However, some of her general comments on flame retardants are pertinent to DecaBDE. Also points regarding exposure to subpopulations are also valid in general.

As is the case for all 5 PBT chemicals under review, discussions/data on degradation/metabolism/half-life are absent from the document. These parameters will affect HCBD distribution and exposure…and ultimately toxicity.

Again , presentation of data by author & date only, without characterizing context (sampling location, date of sampling, sample characteristics (lipid, dry or wet weight basis, tissue type, etc) limits value and the ability to interpret. For example some high values in soils and sediments. This is true for all 5 chemicals under review.

Fig 5-9 Soil and 5-10 Sediment. Details? Again only study authors & date of publication with concentration are not very illuminating.

5.5.2. Indoor Air. Crump study indicating very high HCBD was from UK residences located on an old landfill. Was classified in the document as residential (as in houses) or other (as over landfill)?

Fig. 5.5.8. Sludge/Biosolids. Only one study on wastewater sludge affected by an industrial source? And it is from China. Applicability to the U.S. situation?

Fig 5.5.9. Influent/Effluent. Only one source for influent/effluent? What is influent and what are effluent data? Expect orders of maginitude differences between influent (high) and treated effluent (low).

5.5.10. Landfill Leachate. How many studies were found for landfill leachate? None? Somewhat surprising no HCBD was detected. Note the Crump study (5.5.2. Indoor Air) was done in homes over an old landfill and HCBD was detected?

5.5.11 Vegetation/Diet. Only one 1975 study? This is >40 years old. This is very old. Where was this work done? What type of samples?

5.5.12.1. Seawater. Again the same old 1975 study?

5.6.1 Human blood (serum). No data? This contradicts the statement on pg.106 “HCBD has also been detected in human urine, blood, and tissues. One study reported occupational exposures of 1.6-12.2 mg/m3 and urine levels of up to 20 mg/L.”

5.6.2. Aquatic invertebrates. Again, critical to include country. Most are not N. America data. Also data that are 18 years old may not be that applicable to the current situation. Same for **Fig 5-17: fish data.**

5.6.4. Aquatic mammals. One data set from circa 2000?

5.6.5 Terrestrial invertebrates. All data are very old: 1975-1987.

5.6.6. Birds. How accurate are the data from early the 1970s, as analytical methods were often poor in that era. Also study is from the UK zone, i.e. not U.S.

5.6.7. Terrestrial mammals. How accurate are these old analytical data from 40 years ago.

5.7.3 Sediments: "error message-ref sources not found"? On a positive note, this section is one of the only that put U.S. samples in context with other geographical locations. That is: *"US sediments reported higher concentrations of HCBD than sediment concentrations from The Netherlands, Germany, Belgium, France, Malta, Spain, and Denmark. The latter group of seven countries are part of the European Union and subject to different regulations than the US, which may contribute to the differences observed."* This is a "needed context and interpretation" comment I have made repeatedly above.

Again, how accurate/comparable were the analytical methods over this extended year range ? QC, quantitation limits and methods have improved substantially over time. I expect most studies before the mid-1990s did not emply mass spectrometry-based methods.

Due to the limited data available I find the separate discussion of, for example aquatic invertebrate data 5.7.5 (temporal range), redundant with the earlier discussion of aquatic invertebrate concentration data.

5.7.4. Influent/Effluents. Same concerns as mentioned above: combining influent and effluent data in single bars? They are quite different in character. Are these dissolved, whole (includes particulates)?

Fig 5-28. Aquatic invertebrates. Almost all of these data are older than 7 years and not N. American.

Fig. 5-29. Aquatic invertebrates. So little US data. Not sure how pertinent EU data are here.

5.7.7. Aquatic mammals. I do not view data spanning one year to be representative of a time range.

5.8 Modeled Intake/dose data. Earlier data and discussion suggest that HCBD is predominantly airborne and thus inhalation will be major exposure source, not dermal exposure as may be construed by Fig 5-33.

5.9. Overview of Existing Exposure Assessments. The document states: "An assessment by Euro Chlor (2002) of risks to marine (North Sea) ecological receptors also identified food as being a potentially significant source of HCBD." **However, e**arlier discussion suggests that airborne will be the most significant exposure route. In fact on p. 104 the document states: *"However, potential for human exposure remains. Based on its physical-chemical properties, inhalation is likely the primary exposure route although ingestion and dermal exposure are possible."*

Likewise, the document now agrees with my previous statements: *"In addition, the majority of these monitoring studies is older and represents conditions when HCBD was likely released to the environment in higher amounts."*

5.10. Representative Exposure Scenarios. I expect it should, but does the available data really show decreases over time?

5.11. Summary of Review Articles. A review article from 1975 is probably of little relevance due to changes in use/release as well as unreliability of analytical methods. "HCBD was predominantly found to be in sediment and biota. HCBD has been measured in urban air below 0.5 μg/m3 and below 1 pg/m3 in remote areas." This quote seems at odds with the view that HCBD is predominantly airborne due to volatility.

"As part of an extensive indoor monitoring program conducted by ICI, indoor air in a small number of properties was shown to have HCBD levels greater than 0.6 ppb (24 hour time-weighted average, the proposed toxicity benchmark), but the vast majority of properties in the vicinity of the quarries were shown to be much lower." Is this consistent with the previous indoor air section?

6. Phenol, Isopropylated, Phosphate (3:1)-PIP (3:1). p. 106.

6.1. Chemistry and Physical-Chemical Properties

Water solubility: 2.6 × 10-5 mg/L Estimated using EPISuite v 4.11 (U.S. EPA, 2012)]

But estimate reported in UK EA, 2009d water solubility is 0.12 mg/L. This reference states: "Annex B considers the available data for all aryl phosphates and estimates that the water solubility of tris(isopropylphenyl) phosphate would be around 0.12 mg/l. This value is used in the risk assessment, although this estimate is somewhat uncertain." The UK report mentions a value of "around 2.6×10-5 mg/l for tris(isopropylphenyl) phosphate using the Syracuse Research Corporation WSKOW version 1.30 software". The value in Table 6.1 is 2.6 ×10-5. This represents a substantial margin for error in estimating behavior.

https://biomonitoring.ca.gov/sites/default/files/downloads/031612NhArPvers3.pdf

6.4.4. Processing: Incorporation into Articles. p. 114. "Releases of additives from rubber manufacturing are possible to water, air, and land. Water releases are expected to be most prevalent. "If the water solubility is so low, I would expect low water releases (except associated with product fragments).

6.4.5. Industrial Use: Hydraulic Fluid / Lubricants and Greases. Hydraulic systems commonly leak, so this may be a substantial avenue for release to the environment.

Fig 6-2. Clearly available data (especially in the U.S.) are insufficient to characterize exposure and environmental distribution in the U.S. TPP and PIP have not been commonly analyzed in environmental samples. While these chemicals have been utilized for decades, they have only recently been recognized as contaminants of emerging concern. PIP also likely is used as a mixture of isomers so detection inaccuracies increase. Thus the lack of detection to date should not be construed as a lack of presence. Nor should an apparent increased detection frequency be construed as increasing environmental levels. TPP and PIP exhibit considerably different physical properties, different concentrations in products in which they may co-exist, so I do not support using TPP as a proxy for PIP in environmental matrices. Certainly the data presented for PIP should not be co-mingled with that for TPP, it should be clearly delineated as which are data for PIP and which are for TPP. The properties of TPP should also be provided in an initial table for comparison (e.g. **6.1 Chemistry and Physical-Chemical Properties**).

Figure 6-3. Indoor dust. What data are for TPP versus PIP? Which are U.S. data? What is the bioavailability of PIP in the dust? Presence within microplastics may limit its mobility/bioavailability.

Figure 6-4. Indoor air. Particulate, vapor phase or both?

6.5.3. Ambient Air. Only two studies are cited. Salamova is for outdoor arctic air (particulate phase) and Xu is for (indoor stationary air and personal ambient air in Norway). These details are critical, yet are not revealed in the text of figure. How pertinent to the U.S.?

6.5.4. Soil. Only two studies are cited. Both are denoted as "near facility", but no further details are provided. David & Seiber is for US air base soil, while Matsukami et al is for N. Vietnamese e-waste-impacted soil. Thus the former contamination is likely hydraulic fluid-related, the latter likely polymer-associated. Bioavailabilities will likely differ drastically.

6.5.5. Sediment.

The Muenhor et al study cited here is about dust, not sediment. Plus sampling was in Thailand: *Organophosphorus flame retardants (PFRs) and phthalates in floor and road dust from a manual e-waste dismantling facility and adjacent communities in Thailand.* This makes me concerned about how many other citations are incorrectly assigned with respect to media, etc? The Matsukami et al study concerns e-waste in North Vietnam.

A U.S. paper on phosphate esters in the U.S. Great Lakes was missed (Cao et al. 2017).

We recently published a study that included TPP in Chinese sediments associated with e-waste. Huiru et al 2019. We are only now working on analytical methods for PIP.

6.5.6. Other. The document states: "EPA did not identify any studies with extractable PIP (3:1) nor TPP data in surface water, drinking water, wastewater treatment plants influent or effluent, or landfill leachate." Sorption to solids would not eliminate PIP from wastewater influent. Leaching studies appear to be critical.

6.6.1. Human blood (serum)

Only one study is listed and participants were from the Canary Islands, Spain. At least in this case it is noted that data are for TPP, not PIP.

6.6.2. Human (other). Only two studies cited. Neither from N. America. Cequier et al is for urine from Norway and Fromme et al for Germany.

The following includes data for human urine from the U.S.: Hoffman, et al. 2015.

6.6.2.1. Dermal Wipes. The above Hoffman et al study should be included in this section. The Larsson et al study cited in the document is for Sweden, Sugeng et al for the Netherlands and Xu et al for Norway.

6.6.4. Terrestrial mammals. The only study depicted in the figure is for domestic cats. This detail is important as most readers will assume wildlife and outdoor exposure.

6.6. Biomonitoring. Again TPP and PIP exhibit different properties. Hence using TPP as a proxy may be very misleading.

Figure 6-12. "Concentration of TPP (ng/g), a surrogate for PIP (3:1), in birds for background locations in 2015." All tissue data should indicate the basis (i.e. wet, dry or lipid weight corrected).

6.10. Representative Exposure Scenarios. Pg. 126. Since PIP appears to be used in hydraulic fluids common in military equipment, the military should be mentioned specifically:

Occupational: Use of PIP (3:1) in hydraulic fluids, lubricating oils, and grease results in full hand immersion, splashing, or spraying during handling. Dermal exposure to workers who use these products is possible. Inhalation and dermal exposure to mist from spray application of these products is also possible.

Ecological: releases to the environment to soils and water may occur as a result of usage of hydraulic fluids (e.g. at military and flight facilities)

7. 2, 4, 6-Tris(tert-butyl) Phenol (2, 4, 6-TTBP). p. 127.

The information here on TTBP is quite sparse. A discussion of biotransformation/metabolism, photodegradation?The contributed memo from the SI Group was useful. I agree with some of their suggestions and concerns.

The water solubility in Table 7-1 is listed as 35 mg/l. The SI Group suggests 0.0629 mg/L, a difference of over 3 orders of magnitude. This requires investigation as it will control fate and exposure.

7.5. Environmental Monitoring

"BHT and 2,4,6 TTBP are structurally similar, have similar physical-chemical properties" Suggest a side by side table of properties of both to allow facile comparisons, e.g. in 7.1. Chemistry and Physical-Chemical Properties. That being said, different uses will result in different distributions in the environment, except perhaps if they are susceptible to long range transport (i.e. long distance from sources). This is also stated in the SI Group memo.

Table 7-2. Summary of 2,4,6 TTBP and BHT Monitoring Data from Peer-Reviewed Literature. The data here are very sparse. Which are for BHT and which TTBP?

7.5.1. Indoor Dust. A single study from China. Which data are for TTBP? Applicable to the U.S.?

7.5.3. Ambient Air. A single study from japan. Which data are for TTBP? Applicable to the U.S.?

7.5.4. Surface Water. Data from Spain and Italy. Which data are for TTBP? Applicable to the U.S.?

7.5.5 Sediment. Three Japanese studies. Not sure how applicable such data are to the U.S. situation.

If BHT is included, then depiction of studies should separate them (e.g. include a column denoting this).

7.5.7. Other. The document states: "EPA did not identify any studies with extractable 2,4,6 TTBP nor BHT data in drinking water or landfill leachate. EPA did not identify any studies with detectable levels of 2,4,6 TTBP nor BHT in soil, sludge/biosolids, or vegetation/diet." Did not the cited Calderón-Preciado paper discuss vegetation levels? If these chemicals sorb to solids then they should be concentrated in biosolids if present in wastewater influent.

TTBP has a substantial water solubility (35 mg/L) as stated in Table 7.1. This seems at odds with the document statements related to drinking water sorption to solids and unlikely presence in landfill leachates.

Fig 7.9. Fish. The SI Group notes a mistake in citing a USGS database here. Rather it is to the EPA National Lake Fish Study, wherein TTBP was not detected. However, I note that MDL listed is extremely high (111 ug/kg-wet weight basis), so it is possible TTBP was more widely distributed.

7.7. Trends in Monitoring Data. 7.7.2. Fish. Fig 7-11. This looks like the same study as Fig 7.9, with the same high MDL (and all samples below this: 111 ug/kg).

8. Pentachlorothiophenol (PCTP). P. 144.

8.5. Environmental Monitoring. The document states: "No studies were identified that reported extractable PCTP data in environmental media. Therefore, no summary charts or graphs are presented here." Hence it is impossible to evaluate exposure. Clearly there needs to be more monitoring if a satisfactory review of exposure is to be conducted.

8.6.1. Human (other). The PCTP detected here arises as an *in-vivo* metabolite of hexachlorobenzene in human urine or feces, not direct use of PCTP. So I am not sure how this corresponds to "highly-exposed" (to PCTP), as this population does not seem to be exposed externally to PCTP at all. Without any characterization of the media sampled the *high-end* and *general population* data appear illogical (lower and higher concentrations respectively). The article mentions several different biological media (urine, feces).

References:

Cao et al. 2017. Organophosphate Esters in Sediment of the Great Lakes. Environ. Sci. Technol., 51 (3), pp 1441–1449.

Chen et al. 2008. Polybrominated Diphenyl Ethers in Peregrine Falcon (Falco peregrinus) Eggs from the Northeastern US. Environ. Sci. Technol. 42(20):7594-600.

Chen et al. 2013. European Starlings (Sturnus vulgaris) Suggest That Landfills Are An Important Source of Bioaccumulative Flame Retardants to Canadian Terrestrial Ecosystems. Environ. Sci. Technol. 47(21), 12238-12247.

Christensen et al. 2005. Persistent organic pollutants in British Columbia grizzly bears: consequence of divergent diets. Environ Sci Technol 39:6952-6960.

Farrar et al. 2004. Atmospheric Emissions of Polybrominated Diphenyl Ethers and Other Persistent Organic Pollutants during a Major Anthropogenic Combustion Event. Environ. Sci. Technol. 2004, 38, 1681-1685

Gaylor et al**.** 2014. Polybrominated diphenyl ether accumulation in an agricultural soil ecosystem receiving wastewater sludge amendments. *Environ. Sci. Technol.* 48(12):7034–7043.

Hale et al. 2003. Polybrominated diphenyl ether flame retardants in the North American environment. Environ. Intern. 29, 771-779.

Hale et al. 2008. Antarctic research bases: Local sources of polybrominated diphenyl ether (PBDE) flame retardants. Environ. Sci. Technol. 42:1452-1457.

Hale et al. 2012. Polybrominated Diphenyl Ethers in U.S. Sewage Sludges and Biosolids: Temporal and Geographical Trends and Uptake by Corn Following Land Application Environ. Sci. Technol. 46, 2055−2063.

Hoffman, et al. 2015. Monitoring indoor exposure to organophosphate flame retardants: hand wipes and house dust. Environ. Health Persp. 123(2), 160-5.

Huiru L. et al. 2019. Levels and risks associated with brominated and organophosphate flame retardants in sediments upstream and downstream of the Guiyu, China e-waste recycling zone. *Sci. Total Environ.* 646, 58–67.

La Guardia et al. 2006. Detailed polybrominated diphenyl ether (PBDE) congener composition of the widely used Penta-, Octa-, and Deca-PBDEs technical flame-retardant mixtures. Environ. Sci. Technol. 40: 6247-6254.

La Guardia, M. J.; Hale, R. C.; Harvey, E. 2007. Evidence of debromination of decabromodiphenyl ether (BDE-209) in biota from wastewater receiving stream Environ. Sci. Technol. 41 (19) 6663– 6670.

Li, B., Danon-Schaffer, M.N., Li, L.Y. et al. Occurrence of PFCs and PBDEs in Landfill Leachates from Across Canada . 2012. Water Air Soil Pollut 223: 3365.

Potter et al. 2009. Polybrominated diphenyl ether flame retardants in Chesapeake Bay region, U.S.A., peregrine falcon (Falco peregrinus) eggs: urban/rural trends. Environ Toxicol Chem. 28(5):973-81.

Stapleton HM, Kelly SM, Allen JG, McClean MD, Webster TF. 2008. Measurement of polybrominated diphenyl ethers on hand wipes: estimating exposure from hand to mouth contact. Environ Sci Technol. 42(9):3329–3334.

U.S. EPA Targeted National Sewage Sludge Survey. EPA-822-R-08-018 https://www.epa.gov/biosolids/sewage-sludge-surveys.

Reviewer 7 - Exposure and Use Assessment Peer Review

Do you have any general comments or concerns about the review process? (Reviewer question)

As experts in the realm of exposure or toxic effects to humans from chemicals, we are presented with draft documents assessing the exposure and the hazard of 5 PBT compounds. Unfortunately, there is no information given as to how the final risk characterization will be done to form a technical document to support a threshold of EPA regulatory activities on these chemicals.

The assessment of risk should be linked to the probable or likely threshold(s) of the subsequent decisions relative to managing or regulating the risk. For example, will the risk characterization be a Margin of Exposure (MOE) approach in which the ratio of effect level (or Toxicological Point of Departure (POD)) to estimated exposure is deemed small enough to support regulation? If so what MOE or range of MOE is under consideration? How will uncertainty be factored in? How large does an adversely affected sub-population within the general population (from MOE determination) have to be to warrant regulation?

Knowing and understanding the EPA's methodology for using these assessments to inform regulatory decisions is an important piece of our review of them. The quality of the monitoring and modeling data will drive the confidence of regulatory decisions. The requirement of a relatively large MOE typically means having information with much lower uncertainty and thus a higher level of confidence. Indeed, some of the chemicals under consideration are woefully underserved with meaningful data. In these cases the threshold for regulation should be relatively low and the regulatory mandate should be directly aimed at getting the needed information to do a reasonable assessment of risk.

As a general comment, I plan to focus on the human exposure potential to these chemicals from near-field sources within residences and workplaces as opposed to the far-field environmental exposure occurring in soil, air and water. In that regards, EPA studies for years have demonstrated that except for relatively rare "hot spots" like industrial waste sites, the general population receives the vast majority of its exposure from near-field exposures indoor in residential microenvironments. Most of these humans are not occupationally exposed but get their exposures from sources within their residence. Whether the occupational subpopulation is large enough to trigger regulatory actions is a decision for the Agency but this decision needs to be informed as to how large this population might be and its level of exposure.

The above paragraph can be applied to most of the PBT chemicals in this review with the possible exception of TTBP whose dearth of data and widespread used in manufacture of golf balls suggest a potential significant far-field source of environmental and human exposure.

0. Do you have any general comments or concerns about the review process? (Reviewer question)

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Knowing and understanding the EPA's methodology for using these assessments is an important piece of our review of them. The quality of the monitoring and modeling data will drive the confidence of regulatory decisions. The requirement of a relatively large MOE typically means having information with much lower uncertainty and thus a higher level of confidence.

As a general comment, I plan to focus on the human exposure potential to DecaBDE as opposed to the environmental exposure and risk to non-humans. In that regards, except for relatively rare "hot spots" like industrial waste sites, human received the vast majority of their exposure from near-field exposures indoor in residential microenvironments. Most of these humans are not occupationally exposed but get their exposures from sources within their residence.

1. This information, when finalized will inform a technical support document to support EPA's regulatory activities on PBTs. Please comment on the organization and structure of this document to inform this use. Do you have specific recommendations to improve clarity and presentation of this information?

Having done these types of reviews for over a decade, I can tell you that I found this one to be remarkably complete and well organized. The linking of references to the HERO database is a Godsend. The use of plain and well-constructed graphics is outstanding and very helpful to the reviewer.

Some critical references were difficult to locate for this reviewer. I was interested in the details of :

Figure 4-27. Concentration of DecaBDE (ng/wipe) in dermal wipes from a monitoring database (CTD). The range of values reported is presented by the entire length of the bar.

This figure contains data for the following: (MDI, 2002).

This appeared to be important data for the evaluation of potential hand-to-mouth exposure potential; however, I wanted details as to what was meant by "dermal wipes". Does it mean wiping the hands of persons or wiping surfaces which people might subsequently contact? The details of these reported studies were clearly important, thus, I pursued the 2002 reference.

Going to HERO for this reference indicated that it is a "Comparative Toxicogenitics Database". It provided a link to "Get" this database which I tried without success. Going to the HERO-provided URL: http://ctdbase.org , I was able to locate DecaBDE and 32 references within its exposure tab – set url; http://ctdbase.org/detail.go?type=chem&acc=C010902&view=expStudies. Unfortunately, the Author's Summary for these 32 references did not provide any indication that "dermal wipe" samples were taken. My suggestion is that the authors of this report on DecaBDE drill a bit further and provide the specific references or copies of the salient pages from the database for Figure 4-27.

Starting on page 59 with the reference Mathieu and McCall (2016) through to the end of the section on DecaBDE on page 72, one finds that a good many, but not all, of the references do not autolink to HERO. When one goes to the references at the end of the document they do all seem to autolink to HERO; however, fixing the links in the text would be helpful.

2. Please comment on the clarity of the descriptions of how the data were searched for, screened, and evaluated for inclusion in the exposure assessment.

As someone who has done some literature searching, I found the descriptions to be reasonably clear and descriptive.

I am familiar with and appreciative of the EPA's EPI-Suite model for the estimation of physical-chemical properties particularly for SVOCs. Also appreciated is the time-honored approach of using the references in seminal exposure or risk assessment reports as the basis for backwards source exploration.

It is mentioned in the draft that the EPA "… did not conduct its own exposure modeling from identified sources." My sense is that this represents a lost opportunity which will be discussed in more detail later. As I will elaborate on future in this document, I believe that modeling should form the basis for exposure assessment with support and validation from monitoring results.

3. Please identify any additional information and data sources that EPA should also consider.

My prejudice in human health exposure assessment is that too much emphasis and value has been placed on monitoring data versus modeled estimates. Clearly, the two entities are inextricably connected in the rational assessment of exposure with modeling providing the theoretical scientific bases or hypothesis and monitoring delivering either the ground-truthing or the stuff of model evaluation or hypothesis adjustment. My sense is that we have relied too heavily on the "one-off" and shallow nature and input of monitoring data that was not done in conjunction with or comparison to a predictive model.

That is, human health exposure assessment should have a theoretical underpinning in order to inform, evaluate or even put available monitoring studies into context. Weschler and Nazaroff are pioneers in the development of holistic models of the fate of semivolatile organic chemicals in indoor near-field microenvironments. Their seminal paper (Weschler and Nazaroff, 2008) should be studied and, if possible, incorporated into this analysis.

Modeling could help to determine which monitoring results are most representative or realistic for either worst case (occupational) or the general population exposures.

Models could also inform the exposure scenarios and their predictions. For example, it is fairly evident from reading this assessment that the primary source of DecaBDE exposure in the general population is from its use as a flame retardant at relatively high concentrations in the plastic cases of electronics and perhaps also from treated furniture. DecaBDE migrates from the treated polymer(s) and sorbs onto or into house dust. The predominant exposure route from this source appears to be hand-to-mouth activity in children and adults with a lesser amount coming from the inhalation of re-suspended dust. Understanding the nature, mechanism and strength of these emission sources would help with the specifics of scenario development relative to what is a typical or worst case loading of these items in the indoor environment. Combined with lifecycle information on these indoor items, modeling could also predict the time course of future exposure patterns.

The online User's Guide for the EPA Consumer Exposure Model (CEM) mentions emissions models applicable to these scenarios especially the i-SVOC (indoor semi-volatile chemical model) and PARAMS which is a sub-model program to estimate parameters needed for i-SVOC and other modeling programs. The EPA website for downloading i-SVOC and its user manual: https://www.epa.gov/chemical-research/indoor-semi-volatile-organic-compounds-i-svoc-version-10. The web site for PARAMS and it user manual is: https://www.epa.gov/air-research/parameters-params-program-version-11-indoor-emission-source-modeling .

EPA has a rich history and infrastructure of models and modelers that could substantially enhance this exposure assessment. From what I can determine the current datasets do not included DecaBDE; however, I believe that they certainly could.

References:

Weschler CJ, Nazaroff WW. Semivolatile organic compounds in indoor environments. Atmospheric Environment. 2008;42:9018–9040.

4. Due to the large number of references identified during the literature search for Decabromodiphenyl ether, EPA used a prioritization approach to evaluate and extract exposure data for this chemical. Please comment on the prioritization approach that was used for Decabromodiphenyl ether (see section A.2.4 of the Supplemental Information for the Exposure and Use Assessment document). Please comment on whether further characterization lower priority studies are expected to significantly affect the exposure characterization for Decabromodiphenyl ether. Please comment on the strengths/limitations associated with prioritizing use of studies/data sources with larger sample sizes versus smaller sample sizes.

From what I have read in and understand about Varghese *et al* 2017, the approach set out by the authors seems to work. In keeping with my comments relative to question 3, I believe that lower priority studies that happened to emphasize or even include modeling should be reconsidered for higher priority.

Relative to the merits or limitations of giving priority to data sources with larger sample sizes, my sense is that it is a difficult question to answer without a lot of work. Studies with smaller sample sizes may have been superior in other areas; for example, they could have been much better (more discerning) in subject selection criteria and analytical techniques and sensitivity which would result in less censored data. One would not know about this without examining the studies with smaller sample size in greater detail.

There were actually 3 criteria listed for study priority in the document:

– Sample size of >10
– Study published after 2000
– Quantitative data was available in a table, rather than graph or chart.

Sample size is addressed above. It certainly makes sense that studies published after 2000 should have priority for a number of obvious reasons; however, the last criteria could possibly be challenged. In my experience some very important studies have presented their data primarily as a graph or chart. I agree that it is challenging and somewhat disconcerting to extract the information as quantitative numbers from a graph, especially if it is deemed to be a critical element of the assessment. One solution I have found is a commercial software program: UnGraph. A published study (Shadish *et al*, 2009) provides an excellent review of this program:

UnGraph is available: http://www.biosoft.com/w/ungraph.htm

Reference:

Shadish WR, Brasil ICC, Illingworth DA, White KD, Galindo R, Nagler ED, Rindskopf DM. Using UnGraph to extract data from image files: verification of reliability and validity. Behav Res Methods. 2009 Feb;41(1):177-183. doi: 10.3758/BRM.41.1.177.

5. EPA identified specific core exposure data: environmental monitoring, biomonitoring, estimated environmental concentrations, or estimated doses. Please comment on any additional core data that EPA should evaluate for each chemical.

It should be obvious at this point that I believe that core data from and for physical chemical models should be included in the evaluation for each chemical. The reasons for the importance of these data are provided above.

For example, has the migration and transfer to house dust of DecaBDE ever been measured in the laboratory. This would be critical information. If not available, it should at least be looked for and mentioned if not found.

6. Please comment on the approach to consider read-across of data from similar chemical substances for Phenol, isopropylated, phosphate (3:1) (PIP (3:1)) and 2,4,6-Tris(tert-butyl) phenol (2,4,6 TTBP).

These comments are for DecaBDE, thus, I will address this question when I cover the above compounds.

7. Please comment on whether EPA has appropriately captured the exposure scenarios. Please identify any existing exposure scenarios EPA may have missed. Please keep in mind the purpose of this document is to inform regulatory decisions under TSCA only.

The draft assessment does a very credible job of identifying the primary route(s) of exposure and thus the appropriate exposure scenarios for the general public are shown in the following excerpt:

> [Available studies] suggest that indoor dust and dietary exposures are **primary exposure pathways**. Based on its physical-chemical properties, ingestion is likely the primary exposure route. Inhalation would likely be comprised of particles which could be swallowed, and dermal absorption is likely low. [Emphasis added]

My sense is that all of the scenarios presented from DecaBDE are appropriate and astutely determined. I was particularly impressed with the occupational scenario for the processing of DecaBDE into textiles. Their research reportedly results in mist generated from squeezing immersed fabric with rollers and from roll coating applications and results in particulates generated from transfer of solid DecaBDE flame retardant formulations into mixing vessels.

In looking at the dermal exposure potential for DecaBDE indicated for some of the scenarios, its dermal exposure potential (resulting a significant absorbed dose) would appear to be quite limited even for a significant topical application. These reason for this is the relatively large MW and octanol water partitioning coefficient of DecaBDE. These properties would tend to have this molecule hang up in the stratum cornium (SC) or the very top layer of skin and only very slowly migrate to and diffuse into the circulating elements of the aqueous dermis. Meanwhile the SC is constantly upwelling and shedding at a cell layer or two per day, essentially eliminating any DecaBDE within it, ultimately returning it to house dust.

Since we typically are clothed, we contact solid objects primarily with our hands. Indeed, my experience in measuring dermal exposure is that this means exposure predominantly to the hands. Previous work with brushed, rolled and sprayed paint indicated that about 80-90% of dermal exposure to paint was to the hands. Dermal exposure of DecaBDE to the hands means oral exposure in both children and adults from hand-to-mouth activity which is stronger in children but still significant in adults.

All scenarios should be addressed but, knowing what we know about this chemical, it would appear that the majority of non-occupational exposure (number of people and dose) will come under the scenario currently labeled consumer. The occupational exposures will most like provide the highest doses but applied to much fewer people. From a human health perspective these near-field micro-environmental exposures would appear to predominate over the far-field environmental sources of air, water and soil. All this should focus the resources applied to this assessment.

8. Please comment on whether inclusion of additional information on monitoring data would significantly enhance the exposure assessment for the intended purpose of this document. For example, characterization of sampling year vs. study year, characterization of free vs. particle bound chemicals in water and air, lipid normalization for biomonitoring data, and further characterization of studies that had incomplete reporting for their limits of detection. Please identify any specific chemicals for which this additional information would be helpful.

Implicit within this question is the predominance of exposure monitoring data over the development and evaluation of data to feed modeling. Additional information is needed on what appears to be a critical source of exposure to DecaBDE. Specifically, what is needed is monitored indoor dust concentrations occurring as a function of time tied to the characterization of sources. The characterization of these sources; namely, plastic cabinets with DecaBDE (total number and square cm^2) and total square area of treated furniture within the monitored home would be very informative in sharpening the exposure assessment. Of course, specific biomonitoring in homes with high and low exposure potential would also be very valuable. Again, all of this presupposes using an exposure model to evaluate and inform additional monitoring.

Also, tying various workplace exposures (dermal/oral and inhalation) to biomonitoring would enhance our understanding of the exposure potential.

9. Please comment on the reliability and relevance of the identified data sets for each chemical and on the strengths and weaknesses of individual data sets that will help to better inform future regulatory actions.

As shown in Table 4-3, there are literally hundreds of datasets in the peer-reviewed literature for DecaBDE. Not surprisingly, a good portion of the datasets is for indoor dust which appears to be a, if not the, primary source for human exposure to this chemical. It seems to me that the rank ordering of the media in this table is roughly equivalent to the importance of the media to human exposure with dust as the first, indoor air as the second and ambient air as the third media listed.

Clearly one needs to examine each of the 75 datasets for indoor dust individually for their particular strength and weaknesses and with some, but less, effort on the 16 datasets for indoor air. This task is not a reasonable request for a reviewer but rather for the authors; however, some general guidance will be offered below.

Since any regulation is going to occur in the US, data from North American and European sources should be considered significantly more relevant than datasets from Asia. For the same reasons, given sufficient data may be available from North American sources, they could reasonably be used in favor of European sources. For example, the study by Lagalante *et al,* 2008 test 60 US used automobiles and found relatively high numbers for DecaBDE in dust. Ward *et al,* 2014 looked at over 200 dusts samples from California homes. These appear to be very good and relevant studies. Some dust studies from Denmark also seem to be worthy of examination assuming that the Danish folks are more culturally similar and thus more relevant to exposure to North Americans than to individuals from Asia.

My sense is that the weakness of all this monitoring work is that most, if not all, of the studies failed to quantitatively characterize the time course of potential sources for the DecaBDE. Source characterization is vital information to link the source as a predictor of exposure levels.

1. This information, when finalized will inform a technical support document to support EPA's regulatory activities on PBTs. Please comment on the organization and structure of this document to inform this use. Do you have specific recommendations to improve clarity and presentation of this information?

I found the information to be complete and rationally organized relative to its approach. The linking of references to the HERO database was extremely helpful; however, I had trouble accessing some critical information as discussed below. The use of plain and well-constructed graphics is outstanding and very helpful to the reviewer.

We are told that "HCBD is primarily generated as a by-product of the manufacture of chlorinated hydrocarbons, particularly perchloroethylene, trichloroethylene, and carbon tetrachloride,.."; however, in exploring the references I could not determine the percentage of HCBD that might be expected as a by-product in these chlorinated hydrocarbons. This is ostensively important information related to possible regulatory activities.

We are advised that waste containing HCBD is blended with conventional fuels and burned in cement kilns for energy recovery. The report mentions that the removal or destruction of HCBD is "significant by not complete." My sense is that more details are needed here relative to the available data from the kilns on the distribution of parent chlorinated hydrocarbons and this information will definitely help to inform possible regulatory activities. Also, I believe that there should be some regulator criteria for these kilns as to percentage destroyed and these criteria should be mentioned.

The vapor pressure of HCBD is an important property determining its fate in the indoor and outdoor environment. The primary reference appears to be autolinked in HERO but one cannot see any details of this vapor pressure determination. From searching the Internet I was able to find other comparable values with added to my confidence that this was a reasonable number.

On page 87 we are informed:

> …Only studies or databases that reported measurements of the chemical of interest above the limit of detection were extracted and included in the "# of studies" count….

Thus, the number of studies shown for human blood biomonitoring or any other human biomonitoring is zero (0). From my perspective, it would have been more informative to present all data (or at least the number) of the human biomonitoring studies in which HCBD was looked for, or would have been found, which had non-detects along with their limits of detection.

Exposure from consumer products is shown but not quantified at all. Instead we are told that the use of these products "…may lead to consumer exposures (inhalation and dermal exposure)

when products are worn or used." Looking at the references the concentrations of HCBD seem quite low. I would recommend an attempt to do modeling of inhalation and dermal exposure in a reasonably worst case consumer exposure scenario for comparison with point of departure toxicological effects.

2. Please comment on the clarity of the descriptions of how the data were searched for, screened, and evaluated for inclusion in the exposure assessment.

As someone who has done literature searching at a much lower level of sophistication, I found the descriptions to be reasonably clear and descriptive.

I am familiar with and appreciative of the EPA's EPI-Suite model for the estimation of physical-chemical properties particularly for SVOCs. Also appreciated is the time-honored approach of using the references in seminal exposure or risk assessment reports as the basis for backwards source exploration.

It is mentioned in the draft that the EPA "… did not conduct its own exposure modeling from identified sources." My sense is that this represents a lost opportunity which will be discussed in more detail later.

Going back to searching strategy, I believe, that there would be value in reviewing the outputs coming out of the strategy after one does an initial analysis. That is, the initial analysis helps to identify the critical elements of what is actually driving the majority of exposure to HCBD. Given this information at second search would be more focused within these areas. This will be discussed in the context of HCBD later in this review.

3. Please identify any additional information and data sources that EPA should also consider.

My prejudice in human health exposure assessment is that too much emphasis and value has been placed on monitoring data versus modeled estimates. Clearly, the two entities are inextricably connected in the rational assessment of exposure with modeling providing the theoretical scientific bases or hypothesis and monitoring either the ground-truthing or the stuff of model calibration or hypothesis adjustment. My sense is that we have relied too heavily on the "one-off" nature and input of monitoring data that was not done in conjunction with or comparison to a predictive model.

In the case of HCBD the monitoring data can be considered to be relatively sparse and the need for modeling is even more acute.

That is, human health exposure assessment should have a theoretical underpinning in order to inform or even put available monitoring studies into context. Weschler and Nazaroff are pioneers in the development of holistic models of the fate of semivolatile organic chemicals especially in indoor near-field microenvironments. Their seminal paper (Weschler and Nazaroff, 2008) should be studied and, if possible, incorporated into this analysis.

Modeling could help to determine which monitoring results are most representative or realistic for either worst case or the general population exposures.

Models could also inform the exposure scenarios and their predictions. For example, it is fairly evident from reading this assessment that a primary source of HCBD exposure in the general population (or at least a significant subpopulation of non-occupationally exposed people) is from contaminated soil infiltrating into residencial air and well water. An important exposure route from this source appears to be inhalation of contaminated indoor air. Understanding the nature, mechanism and strength of these emission sources would help with the specifics of scenario development relative to what is a typical or worst exposure potential within these scenarios. Combined with depuration information on these concentrations in soil, modeling could also predict the time course of future exposures.

EPA has a rich history and infrastructure of models and modelers that could substantially enhance this exposure assessment. These folks should be capable of enhancing and informing this assessment.

Reference:

Weschler CJ, Nazaroff WW. Semivolatile organic compounds in indoor environments. Atmospheric Environment. 2008;42:9018–9040.

4. Due to the large number of references identified during the literature search for Decabromodiphenyl ether, EPA used a prioritization approach to evaluate and extract exposure data for this chemical. Please comment on the prioritization approach that was used for Decabromodiphenyl ether (see section A.2.4 of the Supplemental Information for the Exposure and Use Assessment document). Please comment on whether further characterization lower priority studies are expected to significantly affect the exposure characterization for Decabromodiphenyl ether. Please comment on the strengths/limitations associated with prioritizing use of studies/data sources with larger sample sizes versus smaller sample sizes.

This response is for HCBD.

5. EPA identified specific core exposure data: environmental monitoring, biomonitoring, estimated environmental concentrations, or estimated doses. Please comment on any additional core data that EPA should evaluate for each chemical.

As mentioned above, the first harvest of exposure data should reveal the primary sources of HCBD exposure. Revisiting and drilling down into those areas of core data would be very helpful.

It should be obvious at this point that core data from physical chemical models should be included in the evaluation for each chemical. The reasons for the importance of these data are provided above.

For example, in this case of HCBD, what is in the polymer(s) used in "children's products", how much residual monomeric HCBD is or could be in these products and what is the theoretical rate of migration of this monomer out of the polymer?

Relative to HCBD in contaminated well and ground water and the subsequent intrusion of HCBD into homes on contaminated soil, data on the concentrations and other environmental factors driving exposure should be sought out and captured.

6. Please comment on the approach to consider read-across of data from similar chemical substances for Phenol, isopropylated, phosphate (3:1) (PIP (3:1)) and 2,4,6-Tris(tert-butyl) phenol (2,4,6 TTBP).

These comments are for HCBD, thus, I will address this question when I cover the above compounds.

7. Please comment on whether EPA has appropriately captured the exposure scenarios. Please identify any existing exposure scenarios EPA may have missed. Please keep in mind the purpose of this document is to inform regulatory decisions under TSCA only.

Information in the draft points to contaminated soil which presumably causes contaminated well water as presenting perhaps one of the highest non-occupational exposure potential to HCDB. Also, Crump *et al* 2004 shows homes on contaminated soil have elevated levels of HCDB in their indoor air. ATSDR 2013 shows relatively high levels of HCDB in drinking and bathing water. As such, the scenario of a home on contaminated soil with contaminated well water should definitely be included.

Exposure from HCDB in potable, drinking and bathing water should be modeled. That is, exposure from the known or measured concentrations of HCDB in contaminated well water source should be modeled for:

- Direct ingestion of drinking water and water used in cooking
- Whole-body dermal exposure from bathing and showering
- Inhalation of steam-distilled HCDB during showering and bathing

Contaminated soil proximate to the house should be modeled for:

- Ingestion of contaminated soil by children
- Inhalation from soil-to-interior infiltration to residential indoor air

References:

Agency for Toxic Substances and Disease Registry (ATSDR) (2005) Silver Creek Subdivision Health Consultation TUCSON, PIMA COUNTY, ARIZONA

D. Crump , V. Brown , J. Rowley & R. Squire (2004) Reducing Ingress of Organic Vapours into Homes Situated on Contaminated Land, Environmental Technology, 25:4, 443-450, DOI: 10.1080/09593332508618453

8. Please comment on whether inclusion of additional information on monitoring data would significantly enhance the exposure assessment for the intended purpose of this document. For example, characterization of sampling year vs. study year, characterization of free vs. particle bound chemicals in water and air, lipid normalization for biomonitoring data, and further characterization of studies that had incomplete reporting for their limits of detection. Please identify any specific chemicals for which this additional information would be helpful.

I had to do some digging to determine that relatively high levels of drinking water ingestion were associated with contaminated well water. Similarly, the occurrence of HCBD in indoor air was associated with contaminated soil under the residence. These may seem obvious but they were not to this reviewer; as such, highlighting, then examining and mining the higher levels of exposure from these media and the reasons for these exposures would be helpful to the reader.

Indeed, relating relatively high values of media concentrations should always be linked to their causes and, if possible, information should be obtained and provided on how widespread and recent these data are within current US sub-populations.

As mentioned above, once a specific area presents itself as perhaps a dominant source, e.g., contaminated soil and well water, further effort should be made to uncover all of the available information in that area.

9. Please comment on the reliability and relevance of the identified data sets for each chemical and on the strengths and weaknesses of individual data sets that will help to better inform future regulatory actions.

My sense is that the weakness of all these monitoring studies is that most, if not all, failed to quantitatively characterize the potential sources for the HCBD. This is vital information to link the strength and time-course of the source(s) as a predictor(s) of the exposure levels. It should be specifically sought after and noted as not available if that is the case.

1. This information, when finalized will inform a technical support document to support EPA's regulatory activities on PBTs. Please comment on the organization and structure of this document to inform this use. Do you have specific recommendations to improve clarity and presentation of this information?

In general, I found this review to be complete, well documented and well organized. The linking of references to the HERO database was very helpful to this reviewer. The use of plain and well-constructed graphics was also very helpful to the reviewer.

From reviewing the references for the biomonitoring data for PCTP, it is obvious to this reviewer that the highest presence of this compound in persons was not from environmental exposure to PCTP but rather as a metabolite of hexachlorobenzene exposure. This should have been made clear in the document.

Except for the above lapse, the lack of available data is well documented in this report. This should help to inform regulatory decisions to get these data and modeling studies to support an exposure/risk assessment of PCTP.

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2. Please comment on the clarity of the descriptions of how the data were searched for, screened, and evaluated for inclusion in the exposure assessment.

As someone who has done literature searching at a much lower level of sophistication, I found the descriptions to be reasonably clear and descriptive.

I am familiar with and appreciative of the EPA's EPI-Suite model for the estimation of physical-chemical properties particularly for SVOCs. Also appreciated is the time-honored approach of using the references in seminal exposure or risk assessment reports as the basis for backwards source exploration.

It is mentioned in the draft that the EPA "… did not conduct its own exposure modeling from identified sources." My sense is that this represents a lost opportunity which will be discussed in more detail later.

3. Please identify any additional information and data sources that EPA should also consider.

It would appear that a significant use of PCTP is in the manufacture of golf balls. The report indicates that PCTP is used and mostly reacts during the manufacture of golf balls. It is unclear but highly likely that some residual, unreacted PCTP may remain in the golf balls. Reportedly, PCTP is used at 10-15% within the rubber phase of the golf balls. In the modern golf ball the majority of its weight is in the rubber phase. If it has not been determined what the level of residual PCTP is or might be within the golf balls, it should be. Reportedly an estimated 300 million golf balls are lost to the environment per year in the US alone. If the amount of PCTP that is reacted is 99% that leaves 1000 ppm by weight of PCTP in the rubber of the golf ball available for leaching.

A significant number of golf balls lost to the maintained rough are sliced open during lawn cutting operations. This further exposes the rubber to leaching.

Quoting from the reference below:

> It was found that during decomposition [in the environment], the golf balls dissolved to release a high quantity of heavy metals. Dangerous levels of zinc were found in the synthetic rubber filling used in solid core golf balls. When submerged in water, the zinc attached itself to the ground sediment and poisoned the surrounding flora and fauna.

Clearly, understanding how much PCTP is leachable from intact and sliced golf balls is a critical first step. Perhaps the PCTP reacts in the environment to form other toxic species. This is another question for evaluation.

My prejudice in human health exposure assessment is that too much emphasis and value has been placed on monitoring data versus modeled estimates. Clearly, the two entities are inextricably connected in the rational assessment of exposure with modeling providing the theoretical scientific bases or hypothesis and monitoring either the ground-truthing or the stuff of model calibration or hypothesis adjustment. My sense is that we have relied too heavily on the "one-off" nature and input of monitoring data that was not done in conjunction with or comparison to a predictive model.

That is, human health exposure assessment should have a theoretical underpinning in order to inform or even put available monitoring studies into context.

Environmental modeling in the case of PCTP could help to determine which monitoring studies would be most fruitful, most representative or realistic for either worst case (*e.g.*, near golf courses) or the general population.

Models could also inform the exposure scenarios and their predictions. For example, it is fairly evident from reading this assessment that a primary source of widespread human exposure could be residual PCTP migrating out of cured rubber. Its existence in and rate of migration out of rubber apparently has not be tested.

EPA has a rich history and infrastructure of models and modelers that could substantially enhance this exposure assessment. Give some reasonable data on source(s), these folks should be capable of enhancing and informing this assessment.

References:

http://www.cnn.com/2009/SPORT/11/04/littering.golf.balls/

4. Due to the large number of references identified during the literature search for Decabromodiphenyl ether, EPA used a prioritization approach to evaluate and extract exposure data for this chemical. Please comment on the prioritization approach that was used for Decabromodiphenyl ether (see section A.2.4 of the Supplemental Information for the Exposure and Use Assessment document). Please comment on whether further characterization lower priority studies are expected to significantly affect the exposure characterization for Decabromodiphenyl ether. Please comment on the strengths/limitations associated with prioritizing use of studies/data sources with larger sample sizes versus smaller sample sizes.

This response is for PCTP.

5. EPA identified specific core exposure data: environmental monitoring, biomonitoring, estimated environmental concentrations, or estimated doses. Please comment on any additional core data that EPA should evaluate for each chemical.

It should be obvious at this point that core data from physical chemical models should be included in the evaluation for TTBP. The reasons for the importance of these data are provided above.

6. Please comment on the approach to consider read-across of data from similar chemical substances for Phenol, isopropylated, phosphate (3:1) (PIP (3:1)) and 2,4,6-Tris(tert-butyl) phenol (2,4,6 TTBP).

The review is for PCTP.

7. Please comment on whether EPA has appropriately captured the exposure scenarios. Please identify any existing exposure scenarios EPA may have missed. Please keep in mind the purpose of this document is to inform regulatory decisions under TSCA only.

From my perspective, the scenarios presented from PCTP are appropriate and reasonably determined. For example, it is perfectly reasonable to consider the potential airborne exposure of PCTP dust as a solid. It maybe that PCTP powder is not dusty but that determination should be made and quantified. These are relatively simple and inexpensive protocols to determine "dustiness".

My sense is that dermal exposure may be the primary route of near-field occupational exposure even though the exposure potential would be quite limited for the reasons indicated below. Significant topical application of PCTP should result in limited internal dosing because of this compound's relatively large MW and octanol water partitioning coefficient. These properties would tend to have this molecule hang up in the stratum cornium (SC) or the very top layer of skin and only very slowly migrate to and diffuse into the circulating elements of the aqueous dermis. Meanwhile the SC is constantly upwelling and shedding at a cell layer or two per day, essentially eliminating the xxx within it, ultimately returning it to house dust.

Since we typically are clothed, we contact solid objects primarily with our hands. Indeed, my experience in measuring dermal exposure is that this means exposure predominantly to the hands. Previous work with brushed, rolled and sprayed paint indicated that about 80-90% of dermal exposure to paint was to the hands. Dermal exposure of PCTP to the hands means oral exposure in occupationally exposed adults from hand-to-mouth activity which is stronger than in children but still significant. Whether oral or dermal exposure would predominate is unclear with further monitoring or modeling studies to sort out the various factors.

All scenarios should be addressed but, knowing what we know about this chemical, it would appear that the majority of non-occupational exposure (highest combination of number of people and dose) could come from far-field source. That is releases to the general environment that could end up in environmental media, the food chain or food and drinking water sources. The occupational exposures could provide the highest doses but would almost certainly affect much fewer people. Without further data and modeling, the risk from a human health perspective these near-field micro-environmental exposure could predominate over the far-field environmental sources of air, water, soil and food chain. However, absence of data is not evidence of a lack of risk from far-field sources. As mentioned above, we simply need to understand what might be happening with this chemical in golf balls.

8. Please comment on whether inclusion of additional information on monitoring data would significantly enhance the exposure assessment for the intended purpose of this document. For example, characterization of sampling year vs. study year, characterization of free vs. particle bound chemicals in water and air, lipid normalization for biomonitoring data, and further characterization of studies that had incomplete reporting for their limits of detection. Please identify any specific chemicals for which this additional information would be helpful.

As indicated above, there is very little data to evaluate and what there is appears to be of very little value. Thus, we do not have very much real information on the exposure to TTPE. New studies specific to TTBP are clearly needed.

In the meantime, given very little in the way of monitored exposure my sense is that modeling could provide some valuable insight and even provide some estimates of exposure potential. On what appears to be a critical source of exposure to TTPE, characterizing the dustiness or source potential of TTPE dust in manufacturing should be a critical early task. These data could be used for the modeling of dust concentrations and exposure potential as a function of time tied to the characterization of sources.

Tying various workplace exposures (dermal/oral and inhalation) to biomonitoring would enhance our understanding of the exposure potential.

Looking at the body burden of TTPE in the contemporary industrial and general population subjects could be useful in estimating whether near-field or far-field sources of TTPE are active.

9. Please comment on the reliability and relevance of the identified data sets for each chemical and on the strengths and weaknesses of individual data sets that will help to better inform future regulatory actions.

The PCTP exposure assessment data set is generally non-existent and as such does not render information with sufficient utility to estimate exposure.

My sense is that the weakness of all monitoring studies is that most, if not all, typically fail to quantitatively characterize the potential sources for the PCTP. As indicated above, this is vital information to link the strength and time-course of the source(s) as a predictor(s) of the exposure levels.

1. This information, when finalized will inform a technical support document to support EPA's regulatory activities on PBTs. Please comment on the organization and structure of this document to inform this use. Do you have specific recommendations to improve clarity and presentation of this information?

I found the information to be complete and rationally organized relative to its approach. The linking of references to the HERO database is a very helpful feature of the document. The use of plain and well-constructed graphics is outstanding and very helpful to the reviewer.

The organization into different categories and life cycle stages really helps to clarify the exposure potential and should be a template for all such reports. One sees the whole picture and the critical elements within the holistic rendering.

Under **Structure** on page 107 we are shown the structure and advised that "Where R^x = H or $CH(CH_3)_2$ and all three rings have at least one - $CH(CH_3)_2$ group. Logically if all three have at least one - $CH(CH_3)_2$ group then R^x cannot ever equal H.

2. Please comment on the clarity of the descriptions of how the data were searched for, screened, and evaluated for inclusion in the exposure assessment.

As someone who has done literature searching at a much lower level of sophistication, I found the descriptions to be reasonably clear and descriptive.

I am familiar with and appreciative of the EPA's EPI-Suite model for the estimation of physical-chemical properties particularly for SVOCs. Also appreciated is the time-honored approach of using the references in seminal exposure or risk assessment reports as the basis for backwards source exploration.

It is mentioned in the draft that the EPA "… did not conduct its own exposure modeling from identified sources." My sense is that this represents a lost opportunity which will be discussed in more detail later.

3. Please identify any additional information and data sources that EPA should also consider.

From a human exposure potential, it would appears the PIP3 has a similar pattern to DecaBDE; that is, the potential for relatively concentrated occupational exposures during manufacturing and industrial handling and less intense but more widespread consumer exposure from the long term use and existence of material containing PIP3 in consumer products. Page 109 of the report tells us:

> "…PIP (3:1) [is used] as a flame retardant or plasticizer, including toys intended for children's use, and furniture and furnishings, including **furniture coverings** such as **computer casing** and foam in **furniture** or **mattresses**." [Emphasis added]

The information needed for these sources are obvious; namely, breathing zone and dermal exposure concentrations for workers and indoor air, dust and surface concentrations within residences. Also, the potential for dermal exposure from contact with or proximity to furniture and mattresses should be considered. The available monitoring studies provide some insight into these sources but they do not address them directly.

This reviewer remembers reviewing some work in the past (more than a few years ago) for the Consumer Product Protection Agency on the exposure potential of flame retardants used in mattresses. It included some actual laboratory experiments and measurements of migration and exposure potential. This work was most likely not published in the scientific literature but should still be available from the CPSC. Dr. Michael Babich is an expert modeler and primary contact at CPSC.

Critical to determination of relative risk to human health in the US is the relative size of the subpopulation of occupationally exposed persons. They will typically receive a high level of exposure per person but the size of this subpopulation is important is determining the relative risk and decisions about its regulation.

My prejudice in human health exposure assessment is that too much emphasis and value has been placed on monitoring data versus modeled estimates. Clearly, the two entities are inextricably connected in the rational assessment of exposure with modeling providing the theoretical scientific bases or hypothesis and monitoring either the ground-truthing or the stuff of model calibration or hypothesis adjustment. My sense is that we have relied too heavily on the "one-off" nature and input of monitoring data that was not done in conjunction with or comparison to a predictive model.

That is, human health exposure assessment should have a theoretical underpinning in order to inform or even put available monitoring studies into context. Weschler and Nazaroff are pioneers in the development of holistic models of the fate of semivolatile organic chemicals in

indoor near-field microenvironments. Their seminal paper (Weschler and Nazaroff, 2008) should be studied and, if possible, incorporated into this analysis.

Modeling could help to determine which monitoring results are most representative or realistic for either worst case or the general population.

Models could also inform the exposure scenarios and their predictions. For example, it is fairly evident from reading this assessment that a primary source of HCBD exposure in the general population is from contaminated soil infiltrating into residences. An important exposure route from this source appears to be inhalation of contaminated indoor air. Understanding the nature, mechanism and strength of these emission sources would help with the specifics of scenario development relative to what is a typical or worst exposure potential within these scenarios. Combined with depuration of the source over time, the information on these concentrations in soil, modeling could also predict the time course of future exposures.

EPA has a rich history and infrastructure of models and modelers that could substantially enhance this exposure assessment. These folks should be capable of enhancing and informing this assessment.

References:

Weschler CJ, Nazaroff WW (2008). Semivolatile organic compounds in indoor environments. Atmospheric Environment. 2008;42:9018–9040.

4. Due to the large number of references identified during the literature search for Decabromodiphenyl ether, EPA used a prioritization approach to evaluate and extract exposure data for this chemical. Please comment on the prioritization approach that was used for Decabromodiphenyl ether (see section A.2.4 of the Supplemental Information for the Exposure and Use Assessment document). Please comment on whether further characterization lower priority studies are expected to significantly affect the exposure characterization for Decabromodiphenyl ether. Please comment on the strengths/limitations associated with prioritizing use of studies/data sources with larger sample sizes versus smaller sample sizes.

This response is for PIP3

5. EPA identified specific core exposure data: environmental monitoring, biomonitoring, estimated environmental concentrations, or estimated doses. Please comment on any additional core data that EPA should evaluate for each chemical.

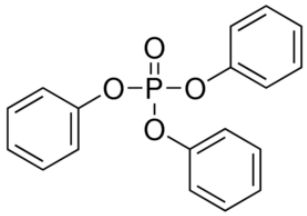
As mentioned above, the first harvest of exposure data should reveal the primary sources of PIP3 exposure. Revisiting and drilling down into those areas of core data would be very helpful.

It should be obvious at this point that core data from physical chemical models should be included in the evaluation for each chemical. The reasons for the importance of these data are provided above.

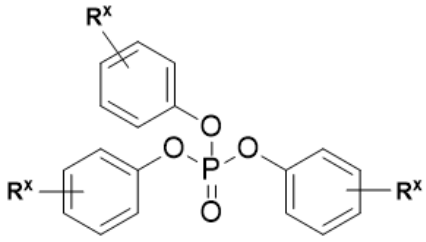
6. Please comment on the approach to consider read-across of data from similar chemical substances for Phenol, isopropylated, phosphate (3:1) (PIP (3:1)) and 2,4,6-Tris(tert-butyl) phenol (2,4,6 TTBP).

Using one chemical as a surrogate for another relative to human health exposure assessment has some specific requirements; perhaps the most important among them is that the surrogate should always be reasonably associated with the chemical in the environments for which it is being used for read across. We are told on page 18 that the choice of a proper surrogate was made "…on closely related chemicals with similar structures and physical-chemical properties".

The structure of triphenyl phosphate (TPP), the read across surrogate for PIP3 is:



The structure of PIP3 is:



Where R^x = H or $CH(CH_3)_2$ and all three rings have at least one -$CH(CH_3)_2$ group.

It would appear that the structures are reasonably similar. The physical properties match up somewhat but one would fully expect TPP to be more mobile out of articles and into dust. Indeed, my sense is that structure and properties are not complete criteria for proper or appropriate exposure surrogacy.

We are told on page 116 that "TPP and PIP (3:1) can be found in the same mixture, formulation, or article." That is clearly not the same as stating that they are typically or even often together in the same article. Even if they were, TPP might be present in much higher concentrations and more detectable.

One of the papers that got my attention was a study of flame retardants in furniture foam and U.S. house dust (Stapleton et al 2009). Graphical values for dust were in Figure 6-3 entitled: **Figure 6-3. Concentration of PIP (3:1) and TPP (ng/g) in indoor dust for commercial locations**

2012 to 2018), residential locations (2009 to 2018), and vehicles (2014 and 2017). Examining this reference carefully they did find and quantify TPP but there was no PIP3. There methodology included GC-mass spectroscopy which should have identified any PIP3 but it was not reported.

The same situation is true of a recent study done in Europe (Bjornsdotter *et al*, 2017) in that they did not find or report any PIP3 only TPP. Both this study and the Stapleton study indicated relatively high levels of exposure as per the graphic which, in my opinion, should not be ascribed to PIP3.

Figure 6-3 should read "…**and/or** TPP…" instead of "…**and** TPP…"

As such, it would appear that TPP is quite common in the indoor environment but we have little idea whether PIP3 is as well. As such, I would say the use of TPP data in a exposure assessment of PIP3 as a surrogate are of very limited value because of the extremely high uncertainty associated with it.

7. Please comment on whether EPA has appropriately captured the exposure scenarios. Please identify any existing exposure scenarios EPA may have missed. Please keep in mind the purpose of this document is to inform regulatory decisions under TSCA only.

I believe that all of the scenarios presented from PIP3 are appropriate and well determined.

Dermal exposure to PIP3 is indicated as significant for some of the scenarios. Its dermal exposure potential would appear to be quite limited even for significant topical application because of its relatively large MW and octanol water partitioning coefficient. These properties would tend to have this molecule partition rapidly into but then hang up in the stratum cornium (SC) or the very top layer of skin and only very slowly migrate to and diffuse into the circulating elements of the aqueous dermis. Meanwhile the SC is constantly upwelling and shedding at the rate of a cell layer or two per day, essentially eliminating any PIP3 contained within the shed cells. This would ultimately return the PIP3 to the house dust or be washed away in bath water.

Since we typically are clothed, we contact solid objects primarily with our hands. Indeed, my experience in measuring dermal exposure is that this means exposure predominantly to the hands. Previous work with brushed, rolled and sprayed paint indicated that about 80-90% of dermal exposure to paint was to the hands. Dermal exposure of PIP3 to the hands means oral exposure in both children and adults from hand-to-mouth activity which is stronger in children but still significant in adults.

All scenarios should be addressed but, knowing what we know about this chemical, it would appear that the majority of non-occupational exposure (highest combination of number of people and dose) will come under the scenario currently labeled consumer. The occupational exposures will most like provide the highest doses but exposure to much fewer people. From a human health perspective these near-field micro environmental exposure would appear predominate over the far-field environmental sources of air, water and soil. All this should focus the resources applied to this assessment.

8. Please comment on whether inclusion of additional information on monitoring data would significantly enhance the exposure assessment for the intended purpose of this document. For example, characterization of sampling year vs. study year, characterization of free vs. particle bound chemicals in water and air, lipid normalization for biomonitoring data, and further characterization of studies that had incomplete reporting for their limits of detection. Please identify any specific chemicals for which this additional information would be helpful.

As indicated above, the available and reported exposure data from PIP3 or TPP as a surrogate is, in my opinion, of little value. Thus, we do not have very much real information on the exposure to PIP3. New studies specific to PIP3 are clearly needed.

In the meantime, given very little in the way of monitored exposure my sense is that modeling could provide some valuable insight and even provide some estimates of exposure potential. On what appears to be a critical source of exposure to PIP3, modeling of migration and subsequent dust concentrations and exposure potential as a function of time tied to the characterization of sources. This is, plastic cabinets around electronics (e.g., TVs) with PIP3 (total number and square cm^2) and total square area of treated furniture within the modeled home could be very informative in forming an exposure assessment.

Given some PIP3 monitoring in homes or workplace, specific biomonitoring in those workplaces and homes with high and low exposure potential would also be very valuable. Again, all of this presupposes using an exposure model to evaluate and inform additional monitoring.

Tying various workplace exposures (dermal/oral and inhalation) to biomonitoring would enhance our understanding of the exposure potential.

9. Please comment on the reliability and relevance of the identified data sets for each chemical and on the strengths and weaknesses of individual data sets that will help to better inform future regulatory actions.

The PIP3 exposure data sets are generally non-existent and, in my opinion, the use of TPP as a surrogate does not render information with sufficient utility to estimate exposure.

My sense is that the weakness of all monitoring studies is that most, if not all, typically fail to quantitatively characterize the potential sources for the PIP3. Subsequent investigation and study should focus on source characterization. This is vital information to link the strength and time-course of the source(s) as a predictor(s) of the exposure levels.

1. This information, when finalized will inform a technical support document to support EPA's regulatory activities on PBTs. Please comment on the organization and structure of this document to inform this use. Do you have specific recommendations to improve clarity and presentation of this information?

In general, I found this review to be remarkably complete, well documented and well organized. The linking of references to the HERO database is very helpful. The use of plain and well-constructed graphics is outstanding and very helpful to the reviewer. In reading through some of these references, one gains an appreciation for the painstaking work involved. The few errors noted are to be expected.

The organization into different categories and life cycle stages really helps to clarify the exposure potential and should be a template for all such reports. One sees the whole picture and the critical elements within the holistic rendering.

As a minor edit, the 1st paragraph on page 129 is a repeat of the first paragraph on page 128 under section **7.2 Uses**.

Figure 7.4 entitled: **Concentration of 2,4,6 TTBP and BHT (ng/m^3) in indoor air for commercial locations in 1989** lead to a bit of head scratching. It references Kosaka *et al* 1989, however, this work only reported on p-tert-butyl phenol (PTBP). There were no tests of or reported data for 2,4,6 TTBP or BHT in this paper. This should be clarified.

2. Please comment on the clarity of the descriptions of how the data were searched for, screened, and evaluated for inclusion in the exposure assessment.

As someone who has done literature searching at a much lower level of sophistication, I found the descriptions to be reasonably clear and descriptive.

I am familiar with and appreciative of the EPA's EPI-Suite model for the estimation of physical-chemical properties particularly for SVOCs. Also appreciated is the time-honored approach of using the references in seminal exposure or risk assessment reports as the basis for backwards source exploration.

It is mentioned in the draft that the EPA "… did not conduct its own exposure modeling from identified sources." My sense is that this represents a lost opportunity which will be discussed in more detail later.

3. Please identify any additional information and data sources that EPA should also consider.

In general, it would appear that the authors have captured most of the information vis-à-vis monitoring available on this compound. Any additional information would come from drilling down further into the areas identified as the primary sources of exposure; namely, industrial sources for occupational exposure and consumer exposure to liquid products containing this chemical. Further details in these areas could help elucidate this evaluation. For example, is 2,4,6 TTBP a dusty powder or is it more waxy in nature or is the powder composed of large relatively non-friable particles that have little potential to become airborne.

As stated elsewhere, my prejudice in human health exposure assessment is that too much emphasis and value has been placed on monitoring data versus modeled estimates. Clearly, the two entities are inextricably connected in the rational assessment of exposure with modeling providing the theoretical scientific bases or hypothesis and monitoring either the ground-truthing or the stuff of model calibration or hypothesis adjustment. My sense is that we have relied too heavily on the "one-off" nature and input of monitoring data that was not done in conjunction with or comparison to a predictive model.

That is, human health exposure assessment should have a theoretical underpinning in order to inform or even put available monitoring studies into context. Weschler and Nazaroff are pioneers in the development of holistic models of the fate of semivolatile organic chemicals in indoor near-field microenvironments. Their seminal paper (Weschler and Nazaroff. 2008) should be studied and, if possible, incorporated into this analysis.

Modeling could help to determine which monitoring results are most representative or realistic for either worst case or the general population.

Models could also inform the exposure scenarios and their predictions. For example, it is fairly evident from reading this assessment that a primary source of …

EPA has a rich history and infrastructure of models and modelers that could substantially enhance this exposure assessment. These folks should be capable of enhancing and informing this assessment.

Reference:

Weschler CJ, Nazaroff WW (2008). Semivolatile organic compounds in indoor environments. Atmospheric Environment. 2008;42:9018–9040.

4. Due to the large number of references identified during the literature search for Decabromodiphenyl ether, EPA used a prioritization approach to evaluate and extract exposure data for this chemical. Please comment on the prioritization approach that was used for Decabromodiphenyl ether (see section A.2.4 of the Supplemental Information for the Exposure and Use Assessment document). Please comment on whether further characterization lower priority studies are expected to significantly affect the exposure characterization for Decabromodiphenyl ether. Please comment on the strengths/limitations associated with prioritizing use of studies/data sources with larger sample sizes versus smaller sample sizes.

This response is for 2,4,6 TTBP

5. EPA identified specific core exposure data: environmental monitoring, biomonitoring, estimated environmental concentrations, or estimated doses. Please comment on any additional core data that EPA should evaluate for each chemical.

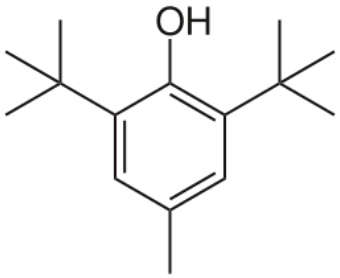
As mentioned above, the first harvest of exposure data should reveal the primary sources of 2,4,6 2,4,6 TTBP exposure. Revisiting and drilling down into those areas of core data could be very helpful to understanding the exposure from this chemical. For example, references within primary documents could have very important information.

It should be obvious at this point that core data from physical chemical models should be included in the evaluation for each chemical. The reasons for the importance of these data are provided above.

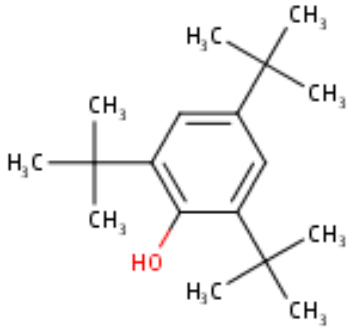
6. Please comment on the approach to consider read-across of data from similar chemical substances for Phenol, isopropylated, phosphate (3:1) (PIP (3:1)) and 2,4,6-Tris(tert-butyl) phenol (2,4,6 TTBP).

Using one chemical as a surrogate for another relative to exposure assessment has some specific requirements; perhaps the most important of which is that the surrogate should be reasonably and positively associated with the chemical in the environments for which it is being used for read across. We are told on page 18 that the choice of a proper surrogate was made on the criteria of "…closely related chemicals with similar structures and physical-chemical properties".

The structure of butylated hydroxyl toluene (BHT)(CAS 128-37-0 , the read across surrogate for 2,4,6 TTBP is:



The structure of 2,4,6 TTBP (CAS 732-26-3)is:



It would appear that the structures are reasonably similar. The physical properties match up somewhat but, as stated in the report, they have <u>different</u> uses. Given different uses, I find it difficult to understand how BHT could it be used as a surrogate for 2,4,6 TTBP exposure.

My sense is that a touchstone of surrogacy for read-across exposure assessment is that they are at least used in the same manner and ideally would appear in the same products or types of product with the same concentration or a known or estimated ratio of concentration.

As a highly used antioxidant it would appear that BHT is quite common in the indoor environment but we have little idea whether 2,4,6 TTBP is as well. As such, I would say the use of BHT exposure

data in an exposure assessment of 2,4,6 TTBP are of essentially no value because of its lack of relevance and the resulting extremely high uncertainty associated with it.

The report states on page 135 that “It may be possible that BHT could degrade to 2,4,6 TTBP in the environment.” My knowledge of environmental chemistry is admittedly limited; however, I am having trouble envisioning a creditable environmental reaction that would strip off a methyl group and add a relatively bulky t-butyl group to BHT to render 2,4,6 TTBP was a degradant. Typically degradants are more water soluble with lower MW than parents. The conversion or degradation of BHT to 2,4,6 TTBP violates both of these rules. If I missed a reasonable degradation route of BHT to 2,4,6 TTBP, it should be included in the report.

7. Please comment on whether EPA has appropriately captured the exposure scenarios. Please identify any existing exposure scenarios EPA may have missed. Please keep in mind the purpose of this document is to inform regulatory decisions under TSCA only.

From my perspective, the scenarios presented from 2,4,6 TTBP are appropriate and reasonably determined; however, I question the statement on page 143 that "Based on its physical-chemical properties, ingestion is likely the primary exposure route." The statement should be further supported. For example, is this primary route of oral exposure from contaminated food or from hand-to-mouth or object-to-mouth activity after exposure to the hands? Surprisingly, none of the scenarios indicate any specific link within the scenario to ingestion.

I agree is that dermal exposure is likely a primary route of exposure even though the exposure potential would be quite limited for the reasons indicated below. Significant topical application of 2,4,6 TTBP should result in limited internal dosing because of this compound's relatively large MW and octanol water partitioning coefficient. These properties would tend to have this molecule diffuse into and hang up in the stratum cornium (SC) or the very top layer of skin and only very slowly migrate to and diffuse into the circulating elements of the aqueous dermis. Meanwhile the SC is constantly upwelling and shedding at about a cell layer or two per day, essentially eliminating the 2,4,6 TTBP within it, ultimately returning it to house dust or down the drain in bath water.

Since we typically are clothed, we contact solid objects primarily with our hands. Indeed, my experience in measuring dermal exposure is that this means exposure predominantly to the hands. Previous work with brushed, rolled and sprayed paint indicated that about 80-90% of dermal exposure to paint was to the hands. Dermal exposure of 2,4,6 TTBP to the hands means oral exposure in both children and adults from hand-to-mouth activity which is stronger in children but still significant in adults. Whether oral or dermal exposure would predominate is unclear with further monitoring or modeling studies to sort out the various factors.

All scenarios should be addressed but, knowing what we know about this chemical, it would appear that the majority of non-occupational exposure (highest combination of number of people and dose) will come under the scenario currently labeled consumer. The occupational exposures will most like provide the highest doses but affecting much fewer people. Without further data and modeling, the risk from a human health perspective these near-field micro-environmental exposure would appear predominate over the far-field environmental sources of air, water and soil. The report seems to point to industrial, commercial and consumer uses of this chemical as an ingredient in fuel additive as a primary source of exposure. As such, the EPA should focus its search and assessment on this use of 2,4,6 TTBP.

8. Please comment on whether inclusion of additional information on monitoring data would significantly enhance the exposure assessment for the intended purpose of this document. For example, characterization of sampling year vs. study year, characterization of free vs. particle bound chemicals in water and air, lipid normalization for biomonitoring data, and further characterization of studies that had incomplete reporting for their limits of detection. Please identify any specific chemicals for which this additional information would be helpful.

There appears to be very little data on the primary exposure scenarios for 2,4,6 TTBP. As indicated above, the data from BHT as a surrogate is, in my opinion, of little value. Thus, we do not have very much real information on the exposure to 2,4,6 TTBP. New studies specific to 2,4,6 TTBP are clearly needed.

In the meantime, given very little in the way of monitored exposure my sense is that developing and feeding exposure models could provide some relatively quick and valuable insight and even provide some reasonable estimates of exposure potential. On what appears to be a critical source of exposure to 2,4,6 TTBP, modeling and monitoring of potential industrial dust concentrations and dermal exposure to consumers would be fruitful enterprises. Given information on the ultimate fate and depuration of sources the exposure potential as a function of time could be estimated. Characterization of industrial and consumer sources in the modeled workplace or home could be very informative to filling out an exposure assessment.

9. Please comment on the reliability and relevance of the identified data sets for each chemical and on the strengths and weaknesses of individual data sets that will help to better inform future regulatory actions.

The 2,4,6 TTBP exposure data set is generally non-existent and, in my opinion, the use of BHT as a surrogate does not render information with sufficient utility to estimate exposure.

My sense is that the weakness of all monitoring studies is that most, if not all, typically fail to quantitatively characterize the potential sources for the 2,4,6 TTBP. Source characterization is vital to link the strength and time-course of the source(s) as a predictor(s) of the exposure levels. It is currently not available.

Reviewer 8 - Exposure and Use Assessment Peer Review

Letter Peer Review for Five PBT Chemicals

(Prefatory note: I am limiting my comments to the Exposure and Use Assessment (EUA) and have focused primarily on human exposure although comments regarding environmental chemistry are also relevant to ecological risk. Concurrence with materials not discussed here should not be assumed.)

Exposure and Use Assessment Peer Review Charge Questions:

1. This information, when finalized will inform a technical support document to support document to support EPA's regulatory activities on PBTs. Please comment on the organization and structure of this document to inform this use. Do you have specific recommendations to improve clarity and presentation of this information?

(Aside: The first line of this charge question includes the word "support" three times and the word "document" twice and has obviously not been proofread. Because this renders Q1 somewhat ambiguous, I am using it address the overall utility of the EUA. Specific comments follow the general comments.)

General Responses to Charge Question #1 (applicable to **all five PBTs**.

Q1-R1) EPA has not provided a clear description of the ultimate use of this document. Is it a first step in a more comprehensive analysis, or does it represent the bulk of the analysis EPA intends to rely upon for regulatory action regarding the five PBTs in question? If the latter, it is substantially inadequate. If the former, the June 22, 2019 due date for EPA's proposed rule does not provide much time to make the improvements/additions needed to rigorously support new rules.

Q1-R2) The EUA is merely a literature review. As such, it is dependent upon prior work that is not evenly distributed among the five compounds and provides a poor precedent for evaluation of sparsely studied (e.g., new) compounds.

Q1-R3) The literature review in the EUA is incomplete in terms of scope. Interpretation of biomonitoring data requires knowledge of pharmacokinetics (PK). Explicit discussion of available PK literature should be added for each compound.

Similarly environmental monitoring data reported do not include consumer products and articles. Concentration data do exist for some consumer products and should be included in the monitoring data review.

Q1-R4) The review of chemical properties is too limited and contains too many cursory dismissals along the lines of chemical X has property Y so won't migrate to medium Z. For instance, on p. 134, the following statement appears: "If released to soil, [2,4,6-TTBP] is unlikely to undergo volatilization based on its organic carbon partitioning and volatility." Generalities of this type are not informative. A small fraction of a very large mass can amount to significant mass transfer. The vapor pressure of 2,4,6-TTBP ($6.6 \cdot 10^{-4}$ mm Hg) is roughly 1000X that of DDT ($1.6 \cdot 10^{-7}$ mm Hg) while the compounds have similar log K_{ow}'s. DDT/DDE is easily detected in the fatty tissues of Inuits who live at latitudes where mosquitos do not live and cotton does not grow (i.e., where DDT has never been sprayed).

The public commentary submitted on behalf of the SI group (Kransler, EPA-HQ-OPPT-2018-0314-0018, posted 7-24-18) regarding 2,4,6-TTBP includes report of results from application of a "Level III Fugacity Model." That citation is not very helpful as it provides no link to the assumptions employed to get that result (and is limited to four environmental compartments), but it does demonstrate that fugacity modeling is not an exotic or inaccessible technique. EPA has personnel that could conduct such an analysis. Fugacity modeling (which is particularly appropriate for designated PBTs) using a standardized unit world would 1) complement and provide a more uniform basis for evaluation of the prior literature, 2) obviate the need for the repetitive generalizations that litter the EUA, and 3) inform estimates of historical production. Whatever fate model EPA adopts can be tested by backcasting against data for historical POPs such as DDT. Then testing of a standardized PBT evaluation protocol using historical POPs (i.e., by assuming they were not already well known and widespread in the environment), would also provide an excellent test of EPA's ultimate PBT screening method.

In addition, a particle/air partition coefficient and a maximum steady state dermal flux (with correction for compound density - see Q1-R9 below) should be added to the default list of physical chemical properties.

[See also response to Charge Question #6]

Q1-R5) The EUA is not adequately systematic. Going forward, EPA will be under pressure to complete assessments at a faster pace. This requires standardization. There is too much reliance in this review on prior publications to identify key exposure pathways (although that is to some extent inevitable for the occupational scenarios). As noted above, EPA's review should include some basic chemical modeling that is uniformly applied to all designated PBTs. PBTs are a special class of chemicals with which we have significant experience. Sometime before WWII (perhaps as early as the late 1920's), Monsanto made the explicit decision to mass produce and market

polychlorinated biphenyls (PCBs). That explicit decision was accompanied by the de facto decision that in the second half of the 20th Century, all American women who chose to breast feed would deliver measurable doses of PCBs to their infants. American women were effectively enrolled (without even a semblance of informed consent) into a mass human experiment. EPA should, via implementation of TSCA, seek to prevent another episode of that type. The physics is simple. If chemicals are released into the environment, they will migrate downhill along thermodynamic gradients. Accordingly, lipophilic compounds that degrade very slowly will partition into mammalian lipids. If those compounds are produced and released in sufficient quantity, lipid levels will eventually exceed detection limits. At a minimum, breast milk exposure to infants and fish consumption by high-consuming populations should be screened for all designated PBTs regardless of whether those pathways have appeared in the prior literature. Nursing infants and high fish consumers are also potentially susceptible groups for PBTs for whom TSCA 6(h) mandates exposure evaluation (EUA, p. 16).

Q1-R6) The EUA is not a critical review. References are generally cited without commentary as to general quality and without examination of plausibility of assumptions or results. Various exposure studies are lumped together without clear explanation that they may have examined different questions. Many of the cited studies examine a single or only a few selected pathways. Estimated doses may be highly dependent upon speculative exposure parameters and subject to high uncertainty. Nevertheless all such predictions, whether or not they are anchored to biomonitoring results, are graphed in the EUA.

First, EPA should provide a matrix that summarizes the literature in a manner that permits readers to better understand the scope of prior studies. That might look something like the following (where X indicates inclusion of the pathway):

Study	Pathway							
	Dust Inh	Dust Ing	Dust Derm	Water Ing	Water Derm	Non-diet Ing	Diet dairy	Etc.
1	X	X						
2							X	
Etc.								

A matrix of this type would reveal that some pathways have been seldom examined and that very few of the available studies are aggregate in a meaningful sense.

Second, EPA should specifically call out (and expand upon) efforts to compare predicted doses with observed biomarkers. Lorber (*JESEE*, 2008) tabulated and totaled estimated intakes of nine specific PBDEs (including DecaBDE) from thirteen exposure sources. Corresponding predicted lipid-normalized body burdens were then compared with observed serum and breast milk measurements, which were under predicted.

Compilation of results from multiple studies that make the same underlying (flawed) assumptions may give an appearance of consensus that is not justified. A literature review that reports estimates without challenging them is inadequate.

Q1-R7) The EUA is deterministic. On p. 15 (Executive Summary), the EUA states that:

"This Exposure and Use Assessment will be used by EPA in determining, under TSCA section 6(h)(1)(B), whether exposure to each identified PBT is likely, under the conditions of use."

"Likely" implies probability, but there is no attempt to survey or describe data suitable for probabilistic exposure assessment here. I participated in a review of EPA assessments for methylene chloride and N-methylpyrrolidione. EPA did attempt probabilistic analyses in those cases. Unless such activity is still planned, this appears to be a step backwards in sophistication.

Q1-R8) The EUA is repeatedly and unnecessarily ambiguous. It reads as if the staffers who wrote it were so busy enumerating data sources and preparing graphs that they did not have time to write accompanying explanatory text.

Concentrations in aquatic invertebrates, fish, aquatic mammals, terrestrial invertebrates, birds and amphibians are routinely just stated as ng/g. Is this wet weight or dry weight? Whole carcass basis? Lipid basis? Is the definition uniform within each plot? Or is the reader expected to check each citation? If so, what is the point of the review?

In numerous Figure captions, "minimum and maximum" of central tendency estimates are graphed. These seem to be medians and means. Those are not confidence limits about the central tendency. This usage is non-standard.

The title (used in multiple places) "Vegetation/diet" is ambiguous and should be explained in accompanying text.

The title (used in multiple places) "Human (other)" is ambiguous and should be explained in accompanying text.

Trends should not be asserted on the basis of bar graphs without error bars.

Q1-R9) The EUA deals with dermal absorption in an oversimplified manner. This is a chronic problem in human exposure assessment. The shortcomings of the fractional absorption approach to dermal absorption are well known (Kissel, *JESEE*, 2011; Frasch et al., *JESEE*, 2014). Nevertheless, most of the papers cited in the EUA that actually include a dermal exposure pathway utilize the fixed fractional approach.

Less recognized is the fact that heavily halogenated compounds are typically not as large as their molecular weight would suggest and hence may be more mobile than a QSAR may predict. QSARs that use molecular weight as a surrogate for molecular volume can give very poor predictions if the data set from which the QSAR is derived doesn't include halogenated compounds. A relevant example is the modified Potts-Guy equation recommended in EPA guidance for prediction of dermal permeability coefficients from water. The modified Potts-Guy equation is based on the Flynn database of permeability experiments, which is comprised of hydrocarbons with specific gravities less than one. Figure 1 displays molecular weights and effective (i.e., density corrected) molecular weights for the five PBTs in question here and some familiar chemical agents. The difference between molecular weight and effective molecular weight is most striking for brominated compounds (due to the high elemental mass of bromine), but also significant for chlorinated compounds. DecaBDE is a smaller molecule than permethrin and the compounds have similar log K_{ow}'s. Rossbach et al., (*Tox Ltrs*, 2010) observed a dramatic increase in urinary metabolites among soldiers who wore permethrin impregnated battle dress. Uptake of flame retardants from treated fabric cannot be assumed a priori to be negligible.

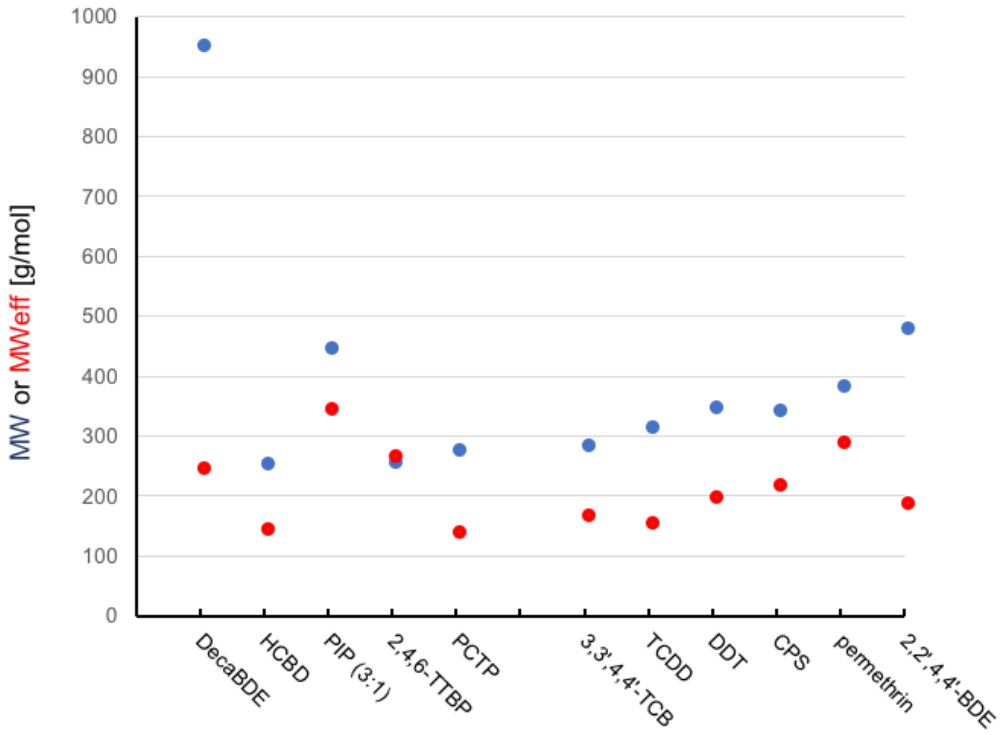


Figure 1. Comparison of molecular weights (MW) and effective molecular weights (MW_{eff}*) for purposes of dermal permeability coefficient prediction for the five PBTs being reviewed and for selected referent compounds. (*See Vecchia & Bunge, Ch. 3 in Transdermal Drug Delivery, Guy & Hadgraft eds., Marcel Dekker, 2003.)

Compound Specific Responses to Charge Question #1

Decabromodiphenyl ether (DecaBDE)

Fig 4-1, p. 26: Current manufacturing is estimated to be < 25,000 lbs/yr due to voluntary withdrawal. If low production leads to estimation of low risk, what happens if the product is brought back to the market? EPA would be better positioned to address this question if more robust modeling were conducted now. See Q1-R4 above.

Sections 4.4.3, p. 27 and 4.4.5, p. 28: Inhalation and dermal exposures in occupational settings are mentioned. Why is adult hand-to-mouth exposure not discussed?

Fig 4-22, p. 48: Concentration is expressed as [ng/g] in serum. This seems unlikely. Is this lipid-normalized?

Fig 4-23, p. 49: Concentration in [ng/g lw] would be preferable to [ng/L] for serum.

Section 4.7.1-4.74, pp. 57-59: Trends are discussed without error bars, or discussion of potential effect of seasonality sampling results.

Fig. 4-39, p. 60: Y-axis says ng/g lw, caption says ng/m^3.

Section 4.8, pp. 62-63: The first paragraph on page 62 pertains to Fig. 4-43, but the figure is not called out in the text. Similarly the text on p. 63 pertains to Fig 4-44 without mention in the text.

Figures 4-43 and 4-44 (pp. 63-64) are distinguished by whether the original data sources presented their estimates as ng/day or ng/kg/day. EPA could have converted one or the other and put all the results on a single graph.

On both Figures 4-43 and 4-44 (pp. 63-64), some x-axis captions do not specify whether the estimate is limited to a single pathway, leaving the impression that they could be aggregate estimates.

Sec. 4.9, p. 67: The text draws upon language from a NAS (2000) report that implies lipophilic compounds must first dissolve in sweat before they can be absorbed into the skin. This is folklore. The NAS committee took two approaches that varied in predicted dose by almost 9 orders of magnitude. Those estimates should be considered guesses.

Sec. 4.10, p. 68: "… dermal absorption is likely low". What does "low" mean? (See Q1-R9.)

Sections 4.11.4 and 4.11.5, pp. 72-73: The opportunity to compare predicted doses to to observed biomarker data is not taken. Agreement is asserted between 10 ng/day

(EPA, 2010) and 10-90 ng/kg/day (Health Canada, 2012) estimates without mention of ages, body weights, or era to which the estimates apply.

Hexachlorobutadiene (HCBD)

Section 5.3, p.75: "If released to air … HBCD is expected to exist solely as vapor." Nothing exists solely as vapor.

Section 5.7.3, p.94: A reference is missing.

Table 5.3, p.88: The table declares that no human biomonitoring data are available. A sentence on p. 104 states that limited data from one study exist. On the top of p. 106, detection in human urine, blood and tissues is asserted.

Section 5.11, p. 106. Doses in ng/kg/day are declared to be intakes. In section 4, doses (ng/kg/day) and intake (ng/day) are distinguished. Usage should be standardized.

Phenol, isopropylated, phosphate (3:1) (PIP 3:1)

Table 6.1 pp. 106-107: A comparable table should be provided for TPP.

Section 6.6.2, Fig. 6-10, p. 122: Concentration [ng/L] in "Human (other)" is uninformative if "other" is not defined in the text.

2,4,6-Tris(tert-butyl) phenol (2,4,6 TTBP)

Table 7.1 p. 127: A comparable table should be provided for BHT.

Section 7.2, pp. 128-129: The first paragraph on each page is the same paragraph.

Pentachlorothiophenol (PCTP)

Sec. 8.6.1, Fig 8-3, p. 151: Concentration [ng/L] in "Human (other)" is uninformative if "other" is not defined in the text.

Sec. 8.6.1, Fig 8-3, p. 151: Per the figure, "General exposures" from a 1992 reference exceed "high-end" exposures from a year 2000 publication with no comment or explanation in the text.

2. *Please comment on the clarity of the descriptions of how the data were searched for, screened, and evaluated for inclusion in the exposure assessment.*

Data search strategies are explained at length in the Supplemental Information document and appear generally satisfactory. However, as noted in Q1-R3 above, the review does not include pharmacokinetic data. The only place I found "ADME" in the Supplemental Information, was in Appendix G under exclusion criteria. This may not have been determinative, but certainly was not helpful.

3. *Please identify any additional information and data sources that EPA should also consider.*

Decabromodiphenyl ether (DecaBDE)

EPA has not cited Lorber (*JESEE*, 2008). Perhaps it is assumed to be superseded by USEPA (2010) as cited in the EUA. Lorber (2008) is shorter and more accessible and should be included.

The EUA does cite a Trudel et al. (*JESEE*, 2011) paper dealing with dietary exposure in Ireland, but skips another Trudel et al. (*ES&T*, 2011) paper dealing with aggregate PBDE exposure. The latter paper does include information specifically about DecaBDE in the Supplemental Information.

The EUA ignores relevant dermal absorption literature for DecaBDE including Hughes et al., (*Food Chem & Tox*, 2001) and Knudsen et al. (Xenobiotica, 2017).

The EUA ignores PK-related studies of DecaBDE including Thuresson et al. (*EHP*, 2006) and multiple rat studies.

4. *Due to the large number of references identified during the literature search for Decabromodiphenyl ether, EPA used a prioritization approach to evaluate and extract exposure data for this chemical. Please comment on the prioritization approach that was used for Decabromodiphenyl ether (see section A.2.4 of the Supplemental Information for the Exposure and Use Assessment document). Please comment on whether further characterization lower priority studies is expected to significantly affect the exposure characterization for Decabromodiphenyl ether. Please comment on the strengths/limitations associated with prioritizing use of studies/data sources with larger sample sizes versus smaller sample sizes.*

This question is specific to DecaBDE.

EPA's evaluation of exposure to DecaBDE would benefit more from more critical examination of the collected data than from examination of more data. See, for example, the answer to Charge Question #9.

5. *EPA identified specific core exposure data: environmental monitoring, biomonitoring, estimated environmental concentrations, or estimated doses. Please comment on any additional core data that EPA should evaluate for each chemical.*

All five PBTs:
Interpretation of biomonitoring data routinely requires knowledge of compound pharmacokinetics. The EUA does not include review of available PBPK data for any of the compounds.

For some of the compounds, concentration data from consumer products and articles are available. Compilations of environmental monitoring data sources presented in the EUA do not specifically include these data.

6. *Please comment on the approach to consider read-across of data from similar chemical substances for Phenol, isopropylated, phosphate (3:1) (PIP (3:1)) and 2,4,6-Tris(tert-butyl) phenol (2,4,6 TTBP).*

This question is specific to **PIP (3:1)** and **2,4,6 TTBP**.

Use of read-across data for screening purposes has some value when primary compound monitoring data are sparse or unavailable. However, this information should be supplemented with modeling for the primary compound of interest. (See Q1-R4.) EPA has proposed that BHT and TPP serve as surrogates for PIP (3:1) and 2,4,6-TTBP respectively. Physical-chemical properties of the surrogates should be provided so that readers can assess comparability.

7. *Please comment on whether EPA has appropriately captured the exposure scenarios. Please identify any existing exposure scenarios EPA may have missed. Please keep in mind the purpose of this document is to inform regulatory decisions under TSCA only.*

General comments applicable to **all five PBTs**:

"Under TCSA only" implies that TSCA determinations can ignore ultimate disposal as that would fall under the purview of the CAA, CWA, or RCRA. The EUA explicitly includes Life Cycle Assessment (LCA) schematics for each of the compounds. LCA, by definition, requires full accounting. Suggestion that assessment of exposures

subsequent to disposal in air, water or landfills should be excluded because those mass flows are regulated under statutes other than TSCA is inconsistent with both the express language of TSCA and with invocation of LCA.

See also Q1-R9.

Hexachlorobutadiene (HCBD)

In Section 5.4.5, p.78, it is asserted that HCBD is "used" as a waste fuel. This is not strictly accurate. HCBD has a negative heat of combustion and no value as a fuel. "Fuel blending" permits mixing of poorly combusted (typically heavily halogenated) compounds such as HCBD with compounds that actually do have heating value. Incineration of such mixtures is allowed in cement kilns. Fuel blending, however, is a means of disposal of HBCD, not a "use" of HBCD.

Generally inadequate treatment of dermal exposure in the EUA was discussed in Q1-R9. In addition, the properties of HCBD are such that it presents potential for whole-body dermal uptake from the vapor phase (See Weschler & Nazaroff, ES&T, 2014) and it should be screened for this pathway.

8. *Please comment on whether inclusion of additional information on monitoring data would significantly enhance the exposure assessment for the intended purpose of this document. For example, characterization of sampling year vs. study year, characterization of free vs. particle bound chemicals in water and air, lipid normalization for biomonitoring data, and further characterization of studies that had incomplete reporting for their limits of detection. Please identify any specific chemicals for which this additional information would be helpful.*

See Q1-R8.

9. *Please comment on the reliability and relevance of the identified data sets for each chemical and on the strengths and weaknesses of individual data sets that will help to better inform future regulatory actions.*

Generally the problem in the EUA is not identification of data sets, but rather interpretation of the prior data. (See also Q1-R6.) The following example concerns DecaBDE, but is indicative.

Decabromodiphenyl ether (DecaBDE)

The following passage is extracted verbatim from Section 4.8 (pp. 62-63) of the EUA:

Eleven studies that modeled DecaBDE dose were identified: (Ali et al., 2016; Civan and Kara, 2016; Gou et al., 2016b; Gou et al., 2016a; Polder et al., 2016; Li et al., 2015a; Chao et al., 2014; Asante et al., 2011; Trudel et al., 2011; Roosens et al., 2010a; Chen et al., 2009). On average, estimated doses were below 5 ng/kg/day. The highest estimated average daily dose resulted from ingestion, followed by inhalation. Dermal exposure had a negligible contribution to estimated doses.

In addition to modeled doses, 14 studies were identified that estimated intake of DecaBDE (Anh et al., 2017; Han et al., 2016; Harrad et al., 2016; Tao et al., 2016; Sahlström et al., 2015; Jiang et al., 2014; Liu et al., 2014b; de Wit et al., 2012; Chen et al., 2011b; D'Hollander et al., 2010; Jin et al., 2010; U.S. EPA, 2010; Covaci et al., 2009; Roosens et al., 2009).

Eleven studies are cited in the first paragraph and fourteen in the second. They are distinguished merely by whether they reported results as ng/day or ng/kg/day. No attempt is made to combine the studies by conversion of results using estimated body weights. Findings are summarized at the bottom of the first paragraph. The entire discussion is three sentences. Results are apparently accepted at face value. No discussion of alternative assumptions regarding exposure pathways or exposure factor values is presented. No summary (no discussion at all) is offered of the collective results of the Table 2 studies. The EUA transitions immediately to the next section (4.9), which describes in more detail one of the Table 2 studies (EPA, 2010).

The studies cited in these two paragraphs are listed in Tables 1 and 2. The claim that dermal exposure contributed negligibly is not surprising given that a dermal pathway was included in only three of the 25 cited sources. This is not a critical review.

Table 1. Studies from which EPA has extracted human dose estimates for DecaBDE (EUA, p. 62)

Study	Comment
Ali et al., 2016	Dermal pathway mentioned, but not considered
Civan and Kara, 2016	Dermal contact with dust considered, estimated to be primary pathway for adults, secondary for children
Gou et al., 2016b	Dermal pathway not even mentioned
Gou et al., 2016a	Dermal pathway not even mentioned
Polder et al., 2016	Dermal pathway not even mentioned
Li et al., 2015	Dermal pathway not even mentioned
Chao et al., 2014	Dermal pathway not even mentioned
Asante et al., 2011	Dermal pathway not even mentioned
Trudel et al., 2011	Dermal pathway mentioned, but not considered
Roosens et al., 2010a	Dermal pathway dismissed without evidence
Chen et al., 2009	Includes dermal contact with toys, apparently to hands only; mouthing of toys estimated to dominate child exposures

Table 2. Studies from which EPA has extracted human intake estimates for DecaBDE (EUA, p. 63)

Study	Comment
Anh et al., 2017	Dermal pathway not even mentioned
Han et al., 2016	Dermal pathway not even mentioned
Harrad et al., 2016	Dermal pathway mentioned only to note that it was not considered
Tao et al., 2016	Dermal pathway not even mentioned
Sahlström et al., 2015	Dermal pathway not even mentioned
Jiang et al., 2014	Dermal pathway not even mentioned
Liu et al., 2014b	Dermal pathway not even mentioned
de Wit et al., 2012	Dermal pathway not even mentioned
Chen et al., 2011b	Dermal pathway mentioned in introduction, but not considered
D'Hollander et al., 2010	Dermal pathway not even mentioned
Jin et al., 2010	Dermal pathway not even mentioned
U.S. EPA, 2010	Includes dermal contact with soil/dust only; estimated to be second most important pathway for adults
Covaci et al., 2009	Dermal pathway not even mentioned
Roosens et al., 2009	Dermal pathway not even mentioned

Reviewer 9 - Exposure and Use Assessment Peer Review

Response to Charge Questions for 5 PBT Chemicals Exposure and Use Assessment

I was assigned the hazard summary charge questions, and so the majority of my charge question responses can be found there. However, in reading the Exposure and Use Assessment for background information on the chemicals, I had some thoughts that may be of use to the writers of this assessment, and I put my thoughts under the most appropriate charge question here.

Charge Question 1: This information, when finalized will inform a technical support document to support EPA's regulatory activities on PBTs. Please comment on the organization and structure of this document to inform this use. Do you have specific recommendations to improve clarity and presentation of this information?

These comments are pertinent to all 5 of the PBT chemicals.

- In general I recommend a careful review of the text for errors, and for appropriate references (e.g. there are several locations in the text with the statement "Error! Reference source not found").
- Ensure that all figures contain the references for the data that they are presenting (e.g. there is no reference in Figure 6-15).
- Only a single chemical acronym should be used consistently throughout all the documents. This will help the reader to better follow the information. For example, PIP (3:1) is used in the main exposure and use assessment, but ITPP, PIP3 and IPTPP are all used in the exposure and use assessment supplement. Similarly, for 2,4,6-TTBP, which is also referred to as TTBP, or 2,4,6 TRIS.
- Acronyms should be defined in figures (e.g. MMDB).
- Uses Sections:
    - The Uses sections are repetitive and need to be better organized. For example, section 4.4.1 is a repeat of section 4.2, so one of them is not necessary; similarly, in section 7.2 the paragraph about the prohibition of use of TTBP in Japan on pg 128 is repeated almost verbatim on pg 129.
    - A single template for the Uses section that could be shared across chemicals would help with the organization and would make it easier on the reader. For example, for 2,4,6-TTBP there is more specific information on the Uses than there is for the other chemicals (e.g. brands of fuel additives that may contain 2,4,6-TTBP) – it is not clear why there are different standards of information for the different chemicals.
    - All use information should be contained in the Uses section and should follow in a logical progression without overlap of information. An example method of organizing this information is as follows: start with physical-chemical properties (including chemical state, chemical class, etc). Then provide information on historically how it is produced, how it is used, and in what final products it can be found. Next the information about current production, use, and products should be discussed. Following this should be a discussion about relevant use categories for

the assessment. Finally, information that was gathered from the requests for information should be discussed.

- Environmental Monitoring Sections:
  - The EPA notes that the patterns of chemical detections in the tables that summarize monitoring data (e.g. Table 4-3, Table 5-2) are consistent with concentration patterns in certain media. However, these tables do not include concentration data, only % of samples with concentrations above the LOD (which may be different for different studies), and so the conclusion that concentrations are higher in different media cannot be made. Either these statements should be removed, or they should reference tables or figures that include concentration data.
  - It should be specified (if this is the case) that the figures that report the frequency of peer-reviewed publications that contain monitoring data (e.g. Figure 4-2, Figure 4-21) include only those studies whose data was extracted for use in this review. Alternatively, if they are inclusive of a wider data set that should be described.
  - It would be helpful to the reader if the notation on the graph axes were more consistent. For example, in Figure 4-4 the axes are labeled with 10^-6, 10^-4, 0.01, 1, 100, 10^4, 10^6. A better choice would be 10^-6, 10^-4, 10^-2, 10^0, 10^2, 10^4, 10^6. The graphs for the different environmental media should also be consistent in formatting with one another, for example Figure 4-8 and Figure 4-9 have different vertical lines within the graph, even though they all seem to be using a similar scale. Similarly, in Figure 5-3 compared to Figure 5-4.
  - "influent/effluent near facilities" should be defined, and probably separated (it seems that influent and effluent near a facility would be separate considerations because one is what is flowing onto the facility, and perhaps is "background", and the other is what is flowing out of the facility and is likely due to the actions of the facility). For example, sections 4.5.9 and 5.5.9. If these are defined in a TSCA guidance document, that should be referenced in this text, together with a short definition.
  - In the vegetation/diet sections, "diet" should be defined. Whose diet? E.g. Sections 4.5.11 and 5.5.11. If this is defined in a TSCA guidance document, that should be referred to in this text, together with a short definition.
- Biomonitoring Sections:
  - In the figure legends and/or text, "high-end" sources should be defined.
  - The units in the figures should be defined – for example Figure 4-22 has concentration of DecaBDE in units of ng/g. Per gram of what? If the studies used different units (per gram of total blood contents, versus per gram of lipids, for example), then they should be on separate graphs. More information about the studies provided in the figure legends, figure descriptions, or at the beginning of each section, would help to clarify the study result summaries.
  - In the section that describes biomonitoring in "human (other)", it would be good to state somewhere what the "other" is. Is this tissue? This information could be

added directly onto the figure, perhaps in parentheses after the study author and year. Similarly, in the sections for aquatic invertebrates, fish, aquatic mammals, etc. the species that was studied could be added in parentheses after the study author and year.
    - It seems like the category "dermal wipes" belongs in environmental monitoring, not in biomonitoring.
- Trends in Monitoring Data Sections:
    - Some of the figure legends use HERO database reference numbers to refer to studies, but this is confusing to the reader, especially because they aren't labeled as HERO database reference numbers. To be clear to the reader, these should be labeled as study author and year, as they are in other areas of the document.
- Summary of Review Articles Sections:
    - These sections should explicitly state the species for which the dose intake is being modeled. Presumably this is for humans, but because so many species are being discussed in this document, the species should be stated.
    - As in the Trends section, studies referenced in figures should be identified by the study author and date, and not by the HERO database reference number.
    - When referencing the dose or intake estimates that are provided by other groups, the population to which they are referring should be referenced. E.g. the last sentence of Section 5.11: "More recently, Environment Canada and Health Canada (Canada, 2000), conducted an HCBD exposure assessment and estimated daily intakes on the order of 10^1 to 10^2 ng/kg/day." Does this refer to children? Adults? General population or high exposures?

Decabromodiphenyl Ether (DecaBDE):

- Section 4.7. Monitoring Trends:
    - Section 4.7.6. states that "Levels [of DecaBDE] appear relatively stable, with a possible peak in the early 2000's." However, Figure 4-39 does not support that conclusion – the levels are slightly higher in 2002, and lower in 2004, compared to the other years, but no "peak" is evident. This statement should be reconsidered and rewritten so that it is more consistent with the presented data.
    - Section 4.7.8. Figure 4-41: The graph seems to be about the USGS dataset only, although another dataset is discussed in the text – is there a reason why only one dataset was graphed? If so, this should be stated (and there should be a reference for the USGS dataset, not just a note that it is from USGS).
    - De Boer et al. (2004) is referenced for fish tissue data, but that study measured BDE concentration in birds. In the bird section (4.7.9) the Ismail et al. (2009) reference is about fish. Presumably these references were reversed and should be corrected.
- Section 4.8. Modeled Intake and Dose Data:
    - The first paragraph of this section states that "The highest estimated average daily dose resulted from ingestion, followed by inhalation." However, Figure 4-43 shows that the highest average daily dose was estimated for inhalation by

reference 3019050. This should be corrected, or it should be specified that *most references* found that the highest average daily dose came from ingestion, except for one study.

- Section 4.9. Overview of Existing Exposure Assessments:
    - In Table 4-5 the EPA's 2010 assessment estimates that house dust dermal contact is the second highest cause of adult intake, but this is inconsistent with the modeling results, and the statements made, in Section 4.8. This should be corrected, or the discrepancy should be explained.
- Section 4.10. Representative Exposure Scenarios:
    - The last paragraph on page 68 notes that "Several biomonitoring studies have reported levels in serum and breast milk (see Sections 4.6.1 and 4.6.2)." However, there is no mention of breast milk in Sections 4.6.1 or 4.6.2. Presumably the "human (other)" category includes breast milk, but it is not specified. A method for fixing this concern would be to use my suggestion described above and identify directly in the figure the substrate that was measured (in this case, in Figure 4-24).
- Section 4.11. Summary of Review Articles:
    - In the first paragraph, EPA summarizes the results from ATSDR's reported concentrations of DecaBDE. However, the form of the concentration is different for many of the different media. For example, a concentration range is presented for ambient air, sediment, sewage sludge, human blood, and breast milk; a mean concentration is presented for food; a geometric mean concentration is presented for soil; and a maximum concentration is presented for indoor dust. It would be easier if a single form for the concentration was used for the different media, and I suggest a mean and range.
    - In section 4.11.5. Dose, the last sentence states that the US EPA's (2010) estimated daily intake from dust ingestion is 10 ng/day. However, in section 4.9 (Table 4-5), the adult intake estimate from house dust ingestion is 1×10^2 ng/day (or 100 ng/day). Is this discrepancy caused because the intake is for a different population? This discrepancy should be fixed or explained.
    - Section 4.9 notes that US EPA (2010) only provided total PBDE intakes for children and infants (ie. intakes weren't separated out for decaBDE). Is the daily intake provided in Section 4.11.5 (10 ng/day) for children? If so, it should be specified as being an estimate of exposure for total PBDE, not decaBDE.
    - In addition, in section 4.11.5 Dose, the authors note in the last sentence that the findings from Malliari and Kalantzi (2017) "generally align with those of U.S. EPA (2010) and Health Canada (2012) who estimate daily intake from dust ingestion at 10 ng/day and 10-90 ng/kg/day." However, there is a several order of magnitude difference between 10 ng/day and 10-90 ng/kg/day (for a 20 kg child, the latter translates to 200-1,800 ng/day). The US EPA estimate (10 ng/day ~ 0.5 ng/kg/day for a 20 kg child) is also quite different from the US estimate provided by Malliari and Kalantzi (2017) of 0.0069 ng/kg/day. Because these numbers are

so different they should not be described as “generally aligning”, and it would be best if the discrepancies in the estimates were discussed.

Hexachlorobutadiene (HCBD):

- Section 5.5. Environmental Monitoring:
    - Section 5.5.1 states that “There are not expected to be indoor sources of HCBD (e.g. consumer products or building materials).”. However, in the Uses section 5.4.1 EPA states that HCBD is “a component of consumer products and drywall.” These two statements appear to be deriving opposite conclusions and should be clarified so that there is no discrepancy.
    - Figures 5-5 and 5-6 have data that is labeled as “IPCHEM”, but it is unclear what reference in the text this data is associated with (i.e. there is no “IPCHEM” reference in the reference list on page 83).
- Section 5.7. Trends in Monitoring Data:
    - In Figures 5-28 through 5-32 the y-axis labels contain the same as the information in the legend – this could be simplified by only using the y-axis labels.
    - Figure 5-32 has 4 y-axis labels, but only two data bars. It should be investigated whether this figure is missing data, or if it has been mis-plotted.
    - Section 5.7.7 provides two datasets for aquatic mammals with concentration data, but Table 5-3 says that only one dataset is available for aquatic mammals and that HCBD presence was not detected. This discrepancy should be resolved.
- Section 5.10. Representative Exposure Scenarios:
    - The second paragraph of this section states “Human exposure to HCBD has limited documentation from one biomonitoring study.” The biomonitoring study should be referenced here and should be included in Section 5.6. Biomonitoring, because that section states that there are no human HCBD biomonitoring data. Similarly, the EPA reference IPCS (1994) when they state in section 5.11. Summary of Review Articles that “HCBD has also been detected in human urine, blood, and tissues.” If those data are available, they should be included in the biomonitoring data section. Even if they are not available they should be discussed in that section, to make the information in this document consistent.

Phenol, Isopropylated, Phosphate (3:1) – PIP (3:1):

- I suggest that the first paragraph of Section 6.5 be rewritten for clarity, because it is confusing as currently written.
- The synonyms list in Chemistry and Physical-Chemical Properties Section should be expanded to include more of the synonyms for this chemical (e.g. isopropylphenyl phosphate, the chemical name associated with the CASRN given in the hazard summary; or tris(4-isopropylphenyl) phosphate, which is the chemical name associated with the CASRN given in the exposure and use document), not just some acronyms. This is especially important because many different names are used in the literature.

- In Section 6.9 and Section 6.11, an existing review is cited as the European Environment Agency. However, that reference appears to just be the Environment Agency (serves England and Wales).
- The first two sentences of Section 6.6 state: "A small number of studies show PIP (3:1) detected in any biological matrix. No monitoring data were identified for PIP (3:1)." These two sentences seem to contradict one another (i.e. either there is a small amount of monitoring data, or no monitoring data) and should be clarified.
- The second sentence of section 6.6. states "PIP (3:1) was detected in matrices where it was expected due to physical-chemical properties; however, for many matrices, PIP (3:1) data has not been collected." Does this sentence refer to PIP (3:1), or does it refer to TPP? This should be clarified, and it is important that throughout the text that PIP (3:1) is not used when what you mean is TPP (the figures label this appropriately).

2,4,6-Tris(tert-butyl) phenol (2,4,6-TTBP):

- The text for sections 7.4.2 and 7.4.3 is almost identical – these should be combined for clarity.
- Care should be taken when using butyl hydroxytoluene (BHT) as a surrogate for TTBP. It is important that the two are chemically similar, but because they have different uses (and BHT has more widespread use), it may not provide information about environmental monitoring or biomonitoring that is relevant to TTBP. On the other hand, if BHT is not found in organisms or the environment, then it is unlikely that TTBP will be found. These issues should be discussed when using BHT as a surrogate for TTBP.
- The environmental measurement and biomonitoring figures and tables combine the information from TTBP and BHT together. The chemical being detected should be specified in the figure legends, or on the y-axis after the name of the study.
- In section 7.8, EPA writes that Liu et al. (2017) modeled the average daily dose for the sum of seven synthetic phenolic antioxidant analogues, and that they (the EPA) used this estimate as a surrogate for TTBP. EPA should state in this section that this is an over-estimate of TTBP exposure.
- In section 7.10 the first two "occupational" paragraphs provide the same information, almost verbatim.

Pentachlorothiophenol (PCTP):

- The Use assessment of PCTP is unclear about whether PCTP is currently in use. This should be clarified.
- Why wasn't the use of PCTP in golf balls mentioned in the Uses section? All the Use information should be combined in one place.

Charge Question 2: Please comment on the clarity of the descriptions of how the data were searched for, screened, and evaluated for inclusion in the exposure assessment.

These comments are pertinent to all 5 of the PBT chemicals.

- As I commented in response to the Hazard Summary charge questions, perhaps in the future the exposure and use literature search could be combined with the hazard literature search, with the different types of data screened into separate bins for their appropriate use. For example, the literature search string presented in Table E-1 for PCTP would also provide studies relevant for the hazard summary.
- It is not clear what the study quality criteria were that were used for the exposure and use literature (Appendix I, Data Extraction Fields: the first field is "study quality criteria met?")
- It seems that in the exposure and use assessment supplement PRISMA diagrams, that the first row should be labeled "total found in search" or something similar, not "total searched". The latter suggests that the referenced number is the total number of documents that have been searched for information about the chemical, which is not the case.

Decabromodiphenyl Ether (DecaBDE):

- The EPA included information from Kohler et al. (2008) in their sediments data analysis, but not all the data from that study was considered – there seems to be data in that study from 1938 to 1974 that could have been included in Section 4.7.4.
- Section 4.7.4 discusses 4 studies that provide time trends of DecaBDE monitoring data, but only data from Kohler et al. (2008) is included in Figure 4-38. The reason for this lack of inclusion in the figure should be explained, or the other results should be included.

Phenol, Isopropylated, Phosphate (3:1) – PIP (3:1):

- In the PRISMA document for PIP (3:1) Figure C-3, the search result numbers for PIP (3:1) should be separated from the related compounds, so that it is clear to the reader the amount of literature actually available for PIP (3:1).

Pentachlorothiophenol (PCTP):

- There are two biomonitoring studies cited for PCTP, To-Figueras et al. 1992 and 2000. However, in Appendix E, the PRISMA diagram (Figure E-2) states that 0 studies were extracted and passed evaluation criteria. Does this mean that the To-Figueras studies did not pass evaluation criteria? (It seems that data was extracted, because data is presented in Figure 8-3). This discrepancy should be repaired, or the status of the To-Figueras studies in Section 8.6.1 should be clarified.
- Other related chemicals were included in the searches for TTBP and PIP (3:1). It should be stated why this wasn't also done for PCTP. Are there no relevant, related chemicals?

Charge Question 3: Please identify any additional information and data sources that EPA should also consider.

Charge Question 4: Due to the large number of references identified during the literature search for Decabromodiphenyl ether, EPA used a prioritization approach to evaluate and extract exposure data for this chemical. Please comment on the prioritization approach that was used for Decabromodiphenyl ether (see section A.2.4 of the Supplemental Information for the Exposure and Use Assessment document). Please comment on whether further characterization lower priority studies is expected to significantly affect the exposure characterization for Decabromodiphenyl ether. Please comment on the strengths/limitations associated with prioritizing use of studies/data sources with larger sample sizes versus smaller sample sizes.

Charge Question 5: EPA identified specific core exposure data: environmental monitoring, biomonitoring, estimated environmental concentrations, or estimated doses. Please comment on any additional core data that EPA should evaluate for each chemical.

Charge Question 6: Please comment on the approach to consider read-across of data from similar chemical substances for Phenol, isopropylated, phosphate (3:1) (PIP (3:1)) and 2,4,6-Tris(tert-butyl) phenol (2,4,6 TTBP).

Charge Question 7: Please comment on whether EPA has appropriately captured the exposure scenarios. Please identify any existing exposure scenarios EPA may have missed. Please keep in mind the purpose of this document is to inform regulatory decisions under TSCA only.

Charge Question 8: Please comment on whether inclusion of additional information on monitoring data would significantly enhance the exposure assessment for the intended purpose of this document. For example, characterization of sampling year vs. study year, characterization of free vs. particle bound chemicals in water and air, lipid normalization for biomonitoring data, and further characterization of studies that had incomplete reporting for their limits of detection. Please identify any specific chemicals for which this additional information would be helpful.

These comments are pertinent to all 5 of the PBT chemicals.

- For environmental monitoring and biomonitoring datasets for all 5 of the PBT chemicals, the EPA only includes studies or databases where the chemical was measured above the limit of detection. This includes both the studies used for data extraction, as well as for the total study count. I strongly recommend that the EPA include all reliable studies where the PBT chemical was measured for, because it is very important in an exposure assessment to understand both where the chemical was found, and where it was not found. In addition, including these studies would allow the reader of this assessment to tell the difference between the chemical not being found in the media, and the chemical not ever having been measured for. This is a crucial distinction that should be included in this assessment. For example, an extra column could be included in the environmental monitoring table (e.g. Table 4-3) that lists the number of studies that monitored for the relevant chemical, but did not detect it, in the appropriate media. This problem is actually noted in Section 8.6 Biomonitoring for PCTP, where EPA states “Very few detections of PCTP in biomonitoring matrices are reported. This is potentially caused by a lack of monitoring data for PCTP, rather than an absence of PCTP in biomonitoring media”. This question can be answered by expanding the search to studies that have tried to monitor for the chemical, not just those that have found it. By including this data, the EPA would significantly enhance the exposure assessment.
- In the environmental monitoring sections, I suggest that the year of sampling be used when noting the frequency of peer-reviewed publications, rather than the publication year. In this same figure it would also be useful to include the number of studies that measured for the chemical but didn’t detect it (perhaps marked in a different color).

Charge Question 9: Please comment on the reliability and relevance of the identified data sets for each chemical and on the strengths and weaknesses of individual data sets that will help to better inform future regulatory actions.

Environmental and Human Health Hazard Summary Peer Review

Reviewer 1 - Environmental and Human Health Hazard Summary Peer Review

Comments Relevant to All Chemicals

1. This information, when finalized will inform a technical support document to support EPA's regulatory activities on PBTs. Please comment on the organization and structure of this document to inform this use. Do you have specific recommendations to improve clarity and presentation of this information?

This is a little difficult to answer, because the regulatory context and next steps are not entirely clear to me. EPA explained that it will be primarily a hazard-based process. Perhaps EPA is not entirely clear on the process itself, given that this is work is being done under a new provision of TSCA, or perhaps there are multiple regulatory options. Nonetheless, I am disappointed in the level of detail and lack of discussion on the information presented. Am I missing something about the process, such as what is needed to support a regulation?

The summaries for each chemical are quite terse. It is more like an annotated literature search. There is no discussion of the data presented. For example, there is no discussion of the weight of the evidence for each endpoint, the possible relevance to humans, or the adequacy of the database. Normally, these are considered in a hazard assessment. Are these documents the only scientific documentation for the rulemaking process, or is there another step? I cannot see how the environmental and human health reviews could be used to support any rulemaking activity.

2. Please comment on the methodology for collecting and summarizing information from secondary sources. Was the approach appropriate? Is the description for how and where the literature was obtained clearly described?

In general, the use of secondary literature, especially from authoritative sources, is appropriate for this purpose. Did your search strategy supplement the reviews by searching forward from the date of the review (allowing for suitable overlap)?

As you are aware from the public meeting, some stakeholders will criticize anything that is not described as a "systematic review." Systematic review has both advantages and disadvantages. It is not always needed. I do not think it is needed here. I note that this review has some elements of systematic review; the literature search strategy is well-described, and the references are catalogued in the Hero database.

The public meeting also included criticism of the lack of attention to children and other vulnerable populations. In the present case, you are summarizing existing information. If there are no data on vulnerable populations, there is nothing else to say.

Regarding Section 3.2. Human Health Hazard Data:

- Did your search strategy include the National Toxicology Program, Report on Carcinogens, or National Academy of Sciences?

- Did your search strategy include PubMed, ToxNet, or Toxline? Do your other sources, such as the Web of Science include PubMed and Toxline?
- Can you provide the dates of the literature searches?

3. Please comment on the representativeness and adequacy of the selected literature used in the evidence tables and described in the text to summarize the hazard concerns. Are there additional primary peer-reviewed and publicly available literature that warrant further consideration? If so, please identify or provide these sources and comment on whether acquisition and summarization of this additional information would change the hazard characterization already provided in the existing summaries? Does the information presented clearly and accurately represent the hazards associated with each chemical? Are there any studies that should be removed from the summary and evidence tables due to study quality or data transparency concerns?

As far as I can determine, the literature cited covers the available information on each chemical. I saw no major gaps. However, I have identified additional citations for some of the chemicals (see below).

4. Has appropriate and sufficient information been obtained from the literature to support the identification of hazards?

As far as I can determine, the available studies are included. However, as discussed above, the discussion and interpretation of the data are absent. In the case of PCTP, I question whether there is sufficient data (or any data) to establish the human toxicity of PCTP.

5. Please comment on the reliability and relevance of the identified data sets for each chemical and on the strengths and weaknesses of individual data sets that will help to better inform future regulatory actions.

I would strengthen the health effects summary to include a discussion of weight of the evidence some conclusions such as is customarily included in the hazard identification step of risk assessment. I find it difficult to see how the reviews, as written, are sufficient to support any regulation. See above under question 1 for additional comments.

I would like to see additional information on the selection process for these chemicals. Why are data on persistence and bioaccumulation not included in the reviews? Why were these given selected over other chemicals?

Decabromodiphenyl Ether (Decabrom)

1. This information, when finalized will inform a technical support document to support EPA's regulatory activities on PBTs. Please comment on the organization and structure of this document to inform this use. Do you have specific recommendations to improve clarity and presentation of this information?

This is a little difficult to answer, because the regulatory context and next steps are not entirely clear. EPA explained that it will be primarily a hazard-based process. Perhaps EPA is not entirely clear on the process itself, given that this is work is being done under a new provision of TSCA, or perhaps there are multiple regulatory options.

2. Please comment on the methodology for collecting and summarizing information from secondary sources. Was the approach appropriate? Is the description for how and where the literature was obtained clearly described?

In general, the use of secondary literature, especially from authoritative sources, is appropriate for this purpose. Did you perform a de novo the literature search from the dates of the secondary sources to the present?

Some stakeholders will criticize anything that is not designated a "systematic review." I note that this review has some elements of systematic review; the literature search strategy is well-described.

Some specific questions include:

- Did your search strategy include the National Toxicology Program, Report on Carcinogens, or National Academy of Sciences?
- Did your search strategy include PubMed, ToxNet, or Toxline? Do your other sources, such as the Web of Science include PubMed and Toxline?
- Can you provide the dates of the literature searches?

In addition, the National Research Council assessed the health risks of flame retardant chemicals including Decabrom (NRC 2000). This assessment includes a review of the health effects of Decabrom.

3. Please comment on the representativeness and adequacy of the selected literature used in the evidence tables and described in the text to summarize the hazard concerns. Are there additional primary peer-reviewed and publicly available literature that warrant further consideration? If so, please identify or provide these sources and comment on whether acquisition and summarization of this additional information would change the hazard characterization already provided in the existing summaries? Does the information presented clearly and accurately represent the hazards associated with each chemical? Are there any studies that should be removed from the summary and evidence tables due to study quality or data transparency concerns?

Section 4.2 Human Health Hazard Summary:

- There was another 2-two study (Kociba et al. 1975), which might be cited for the sake of completeness.
- Thyroid effects are common among halogenated flame retardants. While they are listed in Table 4-2, I suggest that they are sufficiently important to include in the text.

4. Has appropriate and sufficient information been obtained from the literature to support the identification of hazards?

The review, although brief, includes all of the major human health endpoints, especially developmental neurotoxicity. There are no major emissions. However, there is minimal discussion of the significance of the health endpoints, such as might be included in the hazard identification step of a risk assessment. For example, there are no conclusions regarding which animal endpoints are considered likely to occur in humans. Perhaps this is not necessary for the present purpose, but I find this rather unsatisfying.

5. Please comment on the reliability and relevance of the identified data sets for each chemical and on the strengths and weaknesses of individual data sets that will help to better inform future regulatory actions.

As discussed above and in the comments applicable to all chemicals, the purpose of the regulatory context of this review and the next steps are not entirely clear. The health hazard summary has only about two pages of text. There is no discussion about the relative significance of the information discussed.

More specifically, the strengths and weakness of the individual data sets was not addressed. There are no conclusions drawn. See the comments above. I question whether this review is sufficient to support future regulatory actions, without additional discussion and conclusions.

Hexachlorobutadiene (HCBD)

1. This information, when finalized will inform a technical support document to support EPA's regulatory activities on PBTs. Please comment on the organization and structure of this document to inform this use. Do you have specific recommendations to improve clarity and presentation of this information?

> This is a little difficult to answer, because the regulatory context and next steps are not entirely clear. EPA explained that it will be primarily a hazard-based process. Perhaps EPA is not entirely clear on the process itself, given that this is work is being done under a new provision of TSCA, or perhaps there are multiple regulatory options.

2. Please comment on the methodology for collecting and summarizing information from secondary sources. Was the approach appropriate? Is the description for how and where the literature was obtained clearly described?

> In general, the use of secondary literature, especially from authoritative sources, is appropriate for this purpose. Did you perform a de novo the literature search from the dates of the secondary sources to the present?
>
> Some stakeholders will criticize anything that is not designated a "systematic review." I note that this review has some elements of systematic review; the literature search strategy is well-described.
>
> Specific comments include:
> - Did your search strategy include the National Toxicology Program, Report on Carcinogens, or National Academy of Sciences?
> - Did your search strategy include PubMed, ToxNet, or Toxline? Do your other sources, such as the Web of Science include PubMed and Toxline?
> - Can you provide the dates of the literature searches?

3. Please comment on the representativeness and adequacy of the selected literature used in the evidence tables and described in the text to summarize the hazard concerns. Are there additional primary peer-reviewed and publicly available literature that warrant further consideration? If so, please identify or provide these sources and comment on whether acquisition and summarization of this additional information would change the hazard characterization already provided in the existing summaries? Does the information presented clearly and accurately represent the hazards associated with each chemical? Are there any studies that should be removed from the summary and evidence tables due to study quality or data transparency concerns?

> The most recent review on HCBD, cited on page 17 (Health Canada 2012), is a review of Decabrom. Another recent review (Rabovsky 2000) discusses data on the genetic toxicity of HCBD, which is absent from the present review. Rabovsky also discusses

structure activity relationships (SAR) and mode of action all tend to strengthen the conclusion that HCBD may be carcinogenic to humans. I would include this information.

4. Has appropriate and sufficient information been obtained from the literature to support the identification of hazards?

This rather terse review provides limited discussion of the studies listed in the Table 5-2. However, there is minimal discussion of the significance of the health endpoints, such as might be included in the hazard identification step of a risk assessment. There are no conclusions regarding which animal endpoints are considered likely to occur in humans. For example, is there any evidence whether the kidney lesions might involve α2u-globlulin? Are they considered relevant to humans? Perhaps this is not necessary for the present purpose, but I find this rather unsatisfying.

The review reports that EPA considers HCBD a "possible" human carcinogen based on kidney adenomas and carcinomas. What exactly does this mean? Is "possible carcinogen" sufficient to support a regulation? My understanding is that it represents a minimal weight of the evidence classification.

5. Please comment on the reliability and relevance of the identified data sets for each chemical and on the strengths and weaknesses of individual data sets that will help to better inform future regulatory actions.

As discussed above, the purpose of the regulatory context of this review and the next steps are not entirely clear.

The health hazard summary is very brief. It available lacks information on genotoxicity, structure activity relationships, and mode of action. There is no discussion about the relative significance of the information discussed, or the weight of the evidence with respect to hazard identification.

More specifically, the strengths and weakness of the individual data sets was not addressed. There are no conclusions drawn. See the comments above. I question whether this review is sufficient to support future regulatory actions, without additional discussion and conclusions. I would strengthen the health effects summary to include a discussion of weight of the evidence some conclusions such as is customarily included in the hazard identification step of risk assessment.

Phenol Isopropylated Phosphate (PIP)

1. This information, when finalized will inform a technical support document to support EPA's regulatory activities on PBTs. Please comment on the organization and structure of this document to inform this use. Do you have specific recommendations to improve clarity and presentation of this information?

> The first paragraph on page 20 provides useful information on the chemical identify of PIP. Since the information applies to both the environmental and human health sections, this paragraph should appear before section 6.1.

2. Please comment on the methodology for collecting and summarizing information from secondary sources. Was the approach appropriate? Is the description for how and where the literature was obtained clearly described?

> Many of the references, especially the human health summary, refer to dossiers prepared by the manufacturer. These references adequately support the conclusion that PIP is toxic. However, it is preferable to review and cite original references for key studies if they are readily available, such as data reported to EPA (TSCATS).

3. Please comment on the representativeness and adequacy of the selected literature used in the evidence tables and described in the text to summarize the hazard concerns. Are there additional primary peer-reviewed and publicly available literature that warrant further consideration? If so, please identify or provide these sources and comment on whether acquisition and summarization of this additional information would change the hazard characterization already provided in the existing summaries? Does the information presented clearly and accurately represent the hazards associated with each chemical? Are there any studies that should be removed from the summary and evidence tables due to study quality or data transparency concerns?

> A quick TOXNET search identified recent publications of health effects in C. elegans not cited in the report (Behl et al. 2015; Behl et al. 2016), as well as 20 studies submitted to EPA (TSCATS). PIP and other aryl phosphates were nominated to NTP for testing in 2005.[1] Toxicity studies are underway; perhaps some results may be available before EPA completes its rulemaking.[2]
>
> The database on PIP is relatively data poor. I noticed that "read across" was used to assess PIP exposure. A similar approach might be considered for the human health or ecological effects document, as well. At a minimum, the toxicity of the class of aryl phosphates should be acknowledged.

[1] https://ntp.niehs.nih.gov/testing/noms/search/summary/nm-n20608.html
[2] https://ntp.niehs.nih.gov/testing/status/agents/ts-11037.html

4. Has appropriate and sufficient information been obtained from the literature to support the identification of hazards?

Although not all of the available data are cited, the toxicity of PIP, especially neurotoxicity, is well established.

5. Please comment on the reliability and relevance of the identified data sets for each chemical and on the strengths and weaknesses of individual data sets that will help to better inform future regulatory actions.

On page 24, there should be a brief discussion of the significance of organophosphate induced delayed neurotoxicity (OPIDN) in humans (Abou-Donia 1981). The ability of the assay in hens to predict human neurotoxicity should be noted.

As a class, triaryl phosphates are generally neurotoxic, and structure-activity relationships have been identified. This raises the question as to whether other aryl phosphates, including triphenyl phosphate, should be included in this rulemaking process.

On page 24, third paragraph, “pablobular hypertrophy,” do you mean “panlobular”? In Table 6-2, last entry, “91-evday,” do you mean “90-day” or something else?

2,4,6-Tris-*t*-Butylphenol

1. This information, when finalized will inform a technical support document to support EPA's regulatory activities on PBTs. Please comment on the organization and structure of this document to inform this use. Do you have specific recommendations to improve clarity and presentation of this information?

> This is a little difficult to answer, because the regulatory context and next steps are not entirely clear. EPA explained that it will be primarily a hazard-based process. Perhaps EPA is not entirely clear on the process itself, given that this is work is being done under a new provision of TSCA, or perhaps there are multiple regulatory options.

2. Please comment on the methodology for collecting and summarizing information from secondary sources. Was the approach appropriate? Is the description for how and where the literature was obtained clearly described?

> In general, the use of secondary literature, especially from authoritative sources, is appropriate for this purpose. However, I have some questions
>
> - Did you perform a de novo the literature search from the dates of the secondary sources to the present?
> - Did your search strategy include the National Toxicology Program, Report on Carcinogens, or National Academy of Sciences?
> - Did your search strategy include PubMed, ToxNet, or Toxline? Do your other sources, such as the Web of Science include PubMed and Toxline?
> - Can you provide the dates of the literature searches?

3. Please comment on the representativeness and adequacy of the selected literature used in the evidence tables and described in the text to summarize the hazard concerns. Are there additional primary peer-reviewed and publicly available literature that warrant further consideration? If so, please identify or provide these sources and comment on whether acquisition and summarization of this additional information would change the hazard characterization already provided in the existing summaries? Does the information presented clearly and accurately represent the hazards associated with each chemical? Are there any studies that should be removed from the summary and evidence tables due to study quality or data transparency concerns?

> As far as I can determine, the literature cited covers the available information on each chemical. I saw no major gaps.

4. Has appropriate and sufficient information been obtained from the literature to support the identification of hazards?

> As far as I can determine, the available studies are included. However, as discussed above, the discussion and interpretation of the data are absent.

5. Please comment on the reliability and relevance of the identified data sets for each chemical and on the strengths and weaknesses of individual data sets that will help to better inform future regulatory actions.

I would strengthen the health effects summary to include a discussion of weight of the evidence some conclusions such as is customarily included in the hazard identification step of risk assessment. See above under question 1 for additional comments.

Pentachlorothiophenol

1. This information, when finalized will inform a technical support document to support EPA's regulatory activities on PBTs. Please comment on the organization and structure of this document to inform this use. Do you have specific recommendations to improve clarity and presentation of this information?

The title of Table 8-2 is misleading. It should indicate that only PCTP metabolites or breakdown products are included. In the first sentence on page 32, PCTP is misspelled as "PCPT."

2. Please comment on the methodology for collecting and summarizing information from secondary sources. Was the approach appropriate? Is the description for how and where the literature was obtained clearly described?

In general, the use of secondary literature, especially from authoritative sources, is appropriate for this purpose. However, I have some questions

- Did you perform a de novo the literature search from the dates of the secondary sources to the present?
- Did your search strategy include the National Toxicology Program, Report on Carcinogens, or National Academy of Sciences?
- Did your search strategy include PubMed, ToxNet, or Toxline? Do your other sources, such as the Web of Science include PubMed and Toxline?
- Can you provide the dates of the literature searches?

3. Please comment on the representativeness and adequacy of the selected literature used in the evidence tables and described in the text to summarize the hazard concerns. Are there additional primary peer-reviewed and publicly available literature that warrant further consideration? If so, please identify or provide these sources and comment on whether acquisition and summarization of this additional information would change the hazard characterization already provided in the existing summaries? Does the information presented clearly and accurately represent the hazards associated with each chemical? Are there any studies that should be removed from the summary and evidence tables due to study quality or data transparency concerns?

As far as I can determine, the literature cited covers the available information on each chemical. I saw no major gaps.

4. Has appropriate and sufficient information been obtained from the literature to support the identification of hazards?

In the human health hazards summary, it is noted that PCTP is a metabolite and/or breakdown product of other chemicals. Only data on the parent compounds were identified. Is there any evidence that PCTP is more toxic than the parent compounds or

that it is the active metabolite responsible for toxicity? Otherwise, the toxicity of PCTP in humans has not established.

5. Please comment on the reliability and relevance of the identified data sets for each chemical and on the strengths and weaknesses of individual data sets that will help to better inform future regulatory actions.

According to the human health hazard summary, a two-year feeding study in rats identified liver effects as well as increased pup loss (EPA 1988). Can you elaborate on the design of this two-year study? Was this a two-generation study?

References

Abou-Donia MB (1981) Organo phosphorus ester induced delayed neuro toxicity George, R And R Okun (Ed) Annual Review of Pharmacology and Toxicology, Vol 21 Xii+670p Annual Reviews, Inc: Palo Alto, Calif, USA Illus Isbn 0-8243-0421-7; 0 (0) 1981 P511-548.

Behl M, Hsieh JH, Shafer TJ, et al. (2015) Use of alternative assays to identify and prioritize organophosphorus flame retardants for potential developmental and neurotoxicity. Neurotoxicology and teratology 52(Pt B):181-93

Behl M, Rice JR, Smith MV, et al. (2016) Editor's Highlight: Comparative Toxicity of Organophosphate Flame Retardants and Polybrominated Diphenyl Ethers to Caenorhabditis elegans. Toxicological sciences : an official journal of the Society of Toxicology 154(2):241-252

Kociba RJ, Frauson LO, Humiston CG, et al. (1975) Results of a two-year dietary feeding study with decabromodiphenyl oxide (DBDPO) in rats. J Combust Tox 2:267-285

NRC (2000) Toxicological Risks of Selected Flame Retardant Chemicals. National Research Council, National Academy Press, Washington, DC

Reviewer 2 - Environmental and Human Health Hazard Summary Peer Review

Environmental and Human Health Hazard Summary
Peer Review Charge Questions

Please focus comments and recommendations on those that are critical to identifying and describing the hazards for each chemical. Please provide a separate response to questions for each of the five PBT chemicals as appropriate:

First, the rank and file employees of the Agency have done as good a job as can be expected given the limited resources and flexibility that they have been allowed. The Agency teams that assembled the documents for inclusion in this report should be commended. There are however serious problems in making decisions about all of the chemicals under consideration. Many of the compounds have little if any data defining environmental fate, target biological receptor identification (organism, organ or gene), or long term toxicological effects. In the absence of much basic chemical and biological testing (in vitro or in vivo) there are serious questions about the hazards that these compounds may pose.

1. *This information, when finalized will inform a technical support document to support EPA's regulatory activities on PBTs. Please comment on the organization and structure of this document to inform this use. Do you have specific recommendations to improve clarity and presentation of this information?*

   Section 1:
   This section should CLEARLY state the extreme limitations in data availability for PIP(3:1) and the lack of information about PCTP. Sections for each chemical under consideration should also contain clear language that the data for the specific chemical(s) of interest are not available for assessments.
   Section 3.1
   P.7: The foot note for the literature search is a strange construct given the direct web links in the document for other sources. I suggest altering to include the link address directly in the text.
   Section 4.2
   p.12 The agency should be clear in stating that the NTP study provides evidence, as opposed to the current overly qualified construct "indicates suggestive evidence." While the current wording may best represent the case for mice it OMITS the NTP finding for rats in the same report. Even as the EPA 2008 relied on NTP 1986, as presented the text leads with an incomplete picture of the risks. IF the mouse and rat data are to be kept separate. The paragraph should LEAD with the NTP evidence of cancer and the EPA reliance on this finding to develop a slope factor. That should be

FOLLOWED by the suggestion of cancer risk in mice.
Section 5.1
p.15: More information about which fish species are more or less sensitive would be helpful.
Section 6.1
The lack of PIP toxicity to plants in not surprising. The remaining question is "was PIP or PIP transformation products ACCUMULATED in the plants," thereby providing an ingestion source for wildlife or humans??
Section 8.1
p.30 Also include the EC50 in mg/L or ug/L. This is a simple conversion and will make tabular data (8-1) more consistent.

2. *Please comment on the methodology for collecting and summarizing information from secondary sources. Was the approach appropriate? Is the description for how and where the literature was obtained clearly described?*

Literature from primary sources is always essential. The compilation of information from secondary sources leaves much room for error in the interpretation of the primary literature and in the aggregation of data. For example an average or median LC or EC value loses ALL of the structure of the underlying data set(s). Also, the ECHA 2018 references are basically lengthy fact sheets and as such are useless for review purposes. Actual study data are needed for hazard or risk assessments. If these are proprietary studies from manufacturers, they still must be made available to US regulators and appropriate reviewers before serious consideration can be given to them.

Section 4.1
p.8 The study by Hardy et al DID determine reduced SURVIVAL of midges in 2500 mg/kg dw (nominal) treatments. The omission of this data suggests an implied bias against data demonstrating effects. Perhaps a better estimate of effect would be total test species biomass not average individual biomass.
Using commercially available formulations is not optimal, but in this case is the most representative data and is thus acceptable for use. Hazard assessments do need to include concentrations that are diminished by the percentage of impurities present in the formulations (eg nominal exposure of 100 mg/kg bw using a chemical that is 70% pure should translate to a exposure of 70mg/kg bw, not 100).

3. *Please comment on the **representativeness and adequacy** of the selected literature used in the evidence tables and described in the text to summarize the hazard concerns. Are there additional primary peer-reviewed and publicly available literature that warrant further consideration? If so, please identify or provide these sources and comment on whether*

acquisition and summarization of this additional information would change the hazard characterization already provided in the existing summaries? Does the information presented clearly and accurately represent the hazards associated with each chemical? Are there any studies that should be removed from the summary and evidence tables due to study quality or data transparency concerns?

The lack of long term exposure data for PCTP renders baseless any decision to allow use of that chemical. Exposure data must be provided by users/registrants before any further uses are allowed.
Section 5.1
P.15: The data from Knie et al are unavailable except through interlibrary loan. This should be downloadable in HERO. Further the data from Geiger 1985 contains ONLY the summary sheets and not the experimental detail. There is no way to evaluate how toxicant concentrations were determined. Leeuwangh contains insufficient information to determine if test chemical concentrations were measured or nominal.

4. *Has appropriate and sufficient information been obtained from the literature to support the identification of hazards?*

NO. There are insufficient data to make decisions for any chemical in this report. There is a bit more data for DecaBDE, but there are few if any relevant studies for PIP, TTBP, and PCTP. Many of the studies use compounds that have similar structures but do not use the chemical being considered. Some of the studies compiled are from databases where the primary literature or reports are not identified which should disqualify them from consideration. The Agency is making a mistake to consider approval of uses for these chemicals with little or no chemistry and toxicological data. The Federal Government should have learned the lessons of the last century that substantial risks accompany decision making that is not informed by measures of long term fate and toxicological behaviors of industrial chemicals.

Section 8.1
The data in 8.2 are insufficient to provide any reasonable assurance of safety. Empirical data with PCTP is needed before further use can be reasonably assured.

5. *Please comment on the reliability and relevance of the identified data sets for each chemical and on the strengths and weaknesses of individual data sets that will help to better inform future regulatory actions.*

More information about which fish species are more or less sensitive would be helpful.

Data from Schwetz et al did not measure HCBD concentrations in food and thus there is uncertainty in the reported 10mg/kg food-day threshold reported therein.

All of these uncertainties should be accounted in the risk assessment OR empirical data should be obtained with measured concentrations of toxicants that are under TSCA consideration.

Sections 6.2

P. 28 The ECHA 2018a is NOT for PIP, rather they use 2,4,6, tris (t-butyl) phosphate. ECHA 2018b is the correct reference. Furthermore, ECHA 2018 references are basically lengthy fact sheets and as such are useless for review purposes. Actual study data are needed for this assessment. If these are proprietary studies from manufacturers, they still must be made available to US regulators and appropriate reviewers before serious consideration can be given to them.

Section 7.2

P. 28 Again the data provided from Geiger et al, this time 1990, had only general methods an NO data from the actual study being used for this assessment. To repeat, ECHA 2018 references are basically lengthy fact sheets and as such are useless for review purposes.

Reviewer 3 - Environmental and Human Health Hazard Summary Peer Review

Please focus comments and recommendations on those that are critical to identifying and describing the hazards for each chemical. Please provide a separate response to questions for each of the five PBT chemicals as appropriate:

1. This information, when finalized will inform a technical support document to support EPA's regulatory activities on PBTs. Please comment on the organization and structure of this document to inform this use. Do you have specific recommendations to improve clarity and presentation of this information?

General response for all compounds

First of all, I appreciate all the effort that went into gathering the data and producing this document. Even though my areas of research and expertise are focused on environmental chemistry, fate and exposure, I preferred the organization and style of the draft Environmental and Human Health over that of the draft Exposure and Use Summary. I was much easier to read and follow with each chemical starting off with a concise overview summary followed by the data compilation tables and figures, an almost opposite approach to that used in the other document. The addition of a summary table of physical-chemical properties for each chemical would enable the reader to more easily compare of exposure dose to solubility, route of exposure and distribution within the organism to log Kow, etc. Addition of any available persistence information and metabolic pathways would also be important. Finally, several of the public comments discussed the need to specifically evaluate hazards associated with potential susceptible subpopulations including fire fighters, Tribal people, infants etc. Potentially unique exposures to these subpopulations should be identified and associated risks assessed.

Note: As an environmental chemist, I'm not as well-versed in the toxicology literature as I hope other panel members are and I did not feel comfortable responding to charge questions 3-5. Hopefully, you'll have sufficient feedback from toxicologists and others on the panel to adequate address all the charge questions.

Specific comments by chemical.

Decabromodiphenyl ether (DecaBDE) (CASRN 1163-19-5)

Check aqueous solubility values. Acute toxicity reported at levels above the aqueous solubility value listed in Table 4.1. Are the results based on nominal concentrations? Identified in Table 4.1 but not text. Summary text should reflect the key results of Table 4.1

Text associated with Table 4-2 better reflects results of Table 4.2 than Table 4.1. Adequate for assessment.

Hexachlorobutadiene (HCBD) (CASRN 87-68-3)

Toxicity exposures higher than aqueous solubility. No aqueous solubility data given in table as was done for decabromodiphenyl ether. Suggest adding table of basic physical chemical properties as mentioned in general comment.

Pg 17 of 39 Pointer for Health Canada points to Decabromobiphenyl ether instead of hexachlorobutadiene.

Phenol, isopropylated, phosphate (3:1) (PIP (3:1)) (CASRN 68937-41-7
No specific comments.

2,4,6-Tris(tert-butyl) phenol (2,4,6 TTBP) (CASRN 732-26-3)
No specific comments.

Pentachlorothiophenol (PCTP) (CASRN 133-49-3)
No discussion of ionization and form of chemical (neutral or negatively charged) as related to its potential health impacts and routes of exposure. Dosing also impact by chemical form.

2. Please comment on the methodology for collecting and summarizing information from secondary sources. Was the approach appropriate? Is the description for how and where the literature was obtained clearly described?

General comment applying to all chemicals evaluated. The literature search strategy was adequately described. However, there is no need to repeat this information for all five chemicals. Just explain the general procedure for the collection and organization of the literature data for the first chemical and mention only differences or unique cases for all the other compounds.

3. Please comment on the representativeness and adequacy of the selected literature used in the evidence tables and described in the text to summarize the hazard concerns. Are there additional primary peer-reviewed and publicly available literature that warrant further consideration? If so, please identify or provide these sources and comment on whether acquisition and summarization of this additional information would change the hazard characterization already provided in the existing summaries? Does the information presented clearly and accurately represent the hazards associated with each chemical? Are there any studies that should be removed from the summary and evidence tables due to study quality or data transparency concerns?

Sorry, no general or specific response to these questions.

4. Has appropriate and sufficient information been obtained from the literature to support the identification of hazards?

Information on plant uptake and toxicity complete lacking for all but two of the chemicals.

5. Please comment on the reliability and relevance of the identified data sets for each chemical and on the strengths and weaknesses of individual data sets that will help to better inform future regulatory actions.

Sorry, no general or specific response to these questions.

Reviewer 4 - Environmental and Human Health Hazard Summary Peer Review

Environmental and Human Health Hazard Summary Peer Review Charge Questions

Please focus comments and recommendations on those that are critical to identifying and describing the hazards for each chemical. Please provide a separate response to questions for each of the five PBT chemicals as appropriate:

1. This information, when finalized will inform a technical support document to support EPA's regulatory activities on PBTs. Please comment on the organization and structure of this document to inform this use. Do you have specific recommendations to improve clarity and presentation of this information?

The structure (environmental and then human health hazards) is appropriate and the information presentation is generally clear. However, the extent of information is very limited.

2. Please comment on the methodology for collecting and summarizing information from secondary sources. Was the approach appropriate? Is the description for how and where the literature was obtained clearly described?

The approach appears appropriate and the descriptions of how and where the literature was obtained are adequately described.

3. Please comment on the representativeness and adequacy of the selected literature used in the evidence tables and described in the text to summarize the hazard concerns. Are there additional primary peer-reviewed and publicly available literature that warrant further consideration? If so, please identify or provide these sources and comment on whether acquisition and summarization of this additional information would change the hazard characterization already provided in the existing summaries? Does the information presented clearly and accurately represent the hazards associated with each chemical? Are there any studies that should be removed from the summary and evidence tables due to study quality or data transparency concerns?

Please see my chemical by chemical comments below. Note that my expertise is not in human toxicological studies, hence I am not thoroughly familiar with that literature. That being said, the data seems to be largely grey literature from governmental and industrial sources. I am surprised that more references were not cited and discussed. I did do some quick searches and found some additional citations. These may be useful considering the scarcity of cited work in the document.

4. Has appropriate and sufficient information been obtained from the literature to support the identification of hazards?

In most cases the available data are very sparse. Hence the extent of hazards cannot be fully evaluated.

5. Please comment on the reliability and relevance of the identified data sets for each chemical and on the strengths and weaknesses of individual data sets that will help to better inform future regulatory actions.

Please see my chemical by chemical comments below.

4. Decabromodiphenyl Ether

4.1. Environmental Hazard Summary p. 8. The document states "DecaBDE is acutely toxic to aquatic invertebrates (daphnia) at concentrations as low as 0.02 mg/L." This is the water solubility stated in the use/exposure document. In reality, data exist that its (and it is a mixture of congeners, not a single compound) water solubility is likely an order of magnitude than 0.02 mg/L. Hence the later quoted ">500 mg/L (Nakari and Huhtala, 2010; Chemicals Inspection and Testing Institute, 1992)" has little validity for an aquatic assay. Nor would the statement "1 mg/L, DecaBDE did not inhibit the growth of three species of marine algae (Walsh et al., 1987)" be valid as such a concentration cannot exist in solution. Neurodevelopmental endpoints are are particularly of concern, but are not investigated/discussed in detail here. These are, however, discussed later under 4.2.

The document states: "Most of the available hazard information on DecaBDE are for a product containing DecaBDE". DecaBDE is itself confusing as it is often used synonymously with the commercial product(s). BDE-209 is the specific decabrominated (fully brominated) congener. Our experience with U.S. products is that in the fresh commercial mixtures the amount of less brominated species was <5%. However, it is subject to debromination by UV light and biological processes.

Table 4-1. Concentration units should be consistent: ug/L for waterborne exposures. Water accommodated fraction (Hardy)? Was the concentration in solution measured?

No tox data on birds? Some avian species (especially raptors) exhibit greater tissue burdens of BDE-209 than other species; e.g. see Chen et al. 2010. So they likely are more exposed. Some organisms are capable of partially debrominating BDE-209 and this may affect toxicological impacts; e.g. see La Guardia et al, 2007; Noyes et al 2011. Indeed the EPA document "An exposure assessment of polybrominated diphenyl ethers" (EPA/600/R-08/086F) discusses in-vivo metabolic debromination at some length. Wright et al (2008) states" …the increasing concn. of DecaBDE in anaerobic compartments represents a threat to humans and fish via the higher risk DecaBDE breakdown products".

A quick ACS SciFinder search "toxicity of decabromodiphenylether" (as written) came up with 13 citations, only one of which is listed in this section of the document. Using "closely associated" terms revealed 197 references.

References:

Chen et al. 2010. Species-specific accumulation of polybrominated diphenyl ether flame retardants in birds of prey from the Chesapeake Bay region, USA. Environ. Pollut. 158: 1883-1889.

La Guardia et al. 2007. Evidence of debromination of decabromodiphenyl ether (BDE-209) in biota from a wastewater receiving stream. Environ. Sci. Technol. 41:6663-6670.

Nyes et al. 2011. Accumulation and Debromination of Decabromodiphenyl Ether (BDE-209) in Juvenile Fathead Minnows (*Pimephales promelas*) Induces Thyroid Disruption and Liver Alterations. Toxicol. Sci. 12292), 265-274.

Wright et al. 2008. Integrating economic input-output life cycle assessment with risk assessment for a screening-level analysis. Intern. J. Life Cycle Assess. 13(5), 412-420.

4.2. Human Health Hazard Summary p. 12.

As DecaBDE is/was used commercially as a mixture(s), care as to its composition is needed when assessing toxicity. As noted above, BDE-209 may also be metabolized to a variety of intermediates.

The document states: "Limited information is available on the effects from inhalation and dermal routes of exposure so no conclusion was made regarding these exposure routes." It would be appropriate to cite some studies on the subject, rather than dismissing these pathways. DecaBDE is used in polymer products. Dermal contact and inhalation of microparticles (due to wear and weathering of plastics into fragments) are potentially important exposure scenarios. Microplastics will reside in dust which may be inhaled or ingested.

The text does not fully discuss the studies listed in Table 4-2.

5. Hexachlorobutadiene

5.1. Environmental Hazard Summary

Most of the cited studies are quite old: i.e. 1970-1980s. Purity of the starting compound and knowledge how accurate the dose was and whether it changed over time are critical; especially for volatile chemicals. This was less thoroughly investigated in older studies.

Also whether the studies were static, renewal or continuous-addition exposures control the resulting outcomes. Nonetheless, some of the cited studies suggest substantial toxicity to aquatic fish & invertebrates; e.g. 0.09 mg/L fathead minnow LC50.

Table 5-1. Units should be standardized (e.g. ug/L or mg/L) to reduce confusion.

5.2. Human Health Hazard Summary

Again many of these studies are quite old (>20 years). The papers by Staples et al (2003) and Duprat and Gradiski (1978) might be of interest.

Staples et al. 2003. Land contamination and urinary abnormalities: cause for concern? Occupat. Environ. Medicine 60(7), 463-487.

Duprat and Gradiski. 1978. Percutaneous toxicity of hexachlorobutadiene. Acta Pharm. Toxicol. 43(5), 346-53.

6. Phenol, isopropylated, phosphate (3:1)

I found the UK report: Environmental risk evaluation report: Isopropylated triphenyl phosphate (CAS nos. 28108-99-8, 26967-76-0 & 68937-41-7) to be more detailed for both exposure and toxicology than the current document.

6.1. Environmental Hazard Summary

The document states: “The exposure to other chemicals within the product (e.g., triphenyl phosphate) may have influenced the effects observed. It is possible to chromatographically purify such commercial products if the goal is to assess PIP alone. Effects can derive from interactive mechanisms by components of the commercial mixtures in use.

The document states: “Acute toxicity tests with a variety of products or formulations, most also containing 5% triphenyl phosphate, indicate acute toxicity (96-hr LC50s) ranging from 1.6 in rainbow trout to >1000 mg/L in zebrafish (ECHA, 2018b; U.S. EPA, 2010).” Studies should consider the water solubilities of the constituents. PIP has a low (theoretical) water solubility. Thus mg/L exposures are nonsensical. Use of a mixture in water-borne toxicological studies will result in undetermined exposures to constituents unless the water is analyzed to determine composition; in these cases it will likely be predominantly triphenyl phosphate. Hence one will derive an inaccurate measure of PIP toxicity.

“but the exposure concentrations used in the studies suggest that PIP (3:1) is not acutely toxic to algae at concentrations below 1,000 mg/L” Again, the water solubility of PIP is <0.1 mg/L?

The paper by Behl et al (2016) might be informative.

Behl et al. 2016. Comparative toxicity of organophosphate flame retardants and polybrominated diphenyl ethers to Caenorhabditis elegans. Toxicol. Sci. 154(2), 241-252.

6.2. Human Health Hazard Summary

For these studies it appears PIP itself (alone) was used? The document states: “All available repeated-dose studies were unpublished study reports available on the ECHA database for various molecular compositions of isopropylated phenol phosphate”. No academic research

presented here. It is clearly understudied. Nonetheless, PIP does show substantial toxicological potential.

The paper by Meeker and Stapleton (2010), Meeker et al (2013) and Phillips et al (2017) might be insightful.

Meeker and Stapleton. 2010. House Dust Concentrations of Organophosphate Flame Retardants in Relation to Hormone Levels and Semen Quality Parameters. Environ. Health Perspect. 118(3) 318-323.

Meeker et al. 2013. Urinary Metabolites of Organophosphate Flame Retardants: Temporal Variability and Correlations with House Dust Concentrations. . Environ. Health Perspect. 121(5) 580-585.

Phillips et al. 2017. Characterization of Individual Isopropylated and tert-Butylated Triarylphosphate (ITP and TBPP) Isomers in Several Commercial Flame Retardant Mixtures and House Dust Standard Reference Material SRM 2585. Environ. Sci. Technol. 51(22) 13443-13449.

7. 2,4,6-Tris(tert-butyl) phenol

7.1. Environmental Hazard Summary

Substantial toxicity is suggested by the available studies, but data presented are remarkably sparse. The references are limited to two citations and the Geiger et al reference is old: 1990.

The aquatic studies indicate that TTBP is quite toxic. The document states: “No toxicity data for terrestrial species were identified.” The paucity suggests further investigation of exposure and toxicity are warranted. Perhaps some structure activity relationship work or investigation of the effects of other butylated or alkylated phenols is merited.

Possibly of interest: Halim et al. 2017. 2,4-Di-tert-butylphenol-induced leaf physiological and ultrastructural changes in chloroplasts of weedy plants. S. African J Botany 112, 89-94.

7.2. Human Health Hazard Summary

No inhalation data were identified. Data are quite sparse for all exposure scenarios; i.e. only two citations are included, the Matsumoto et al citation is old, from 1991.

8. Pentachlorothiophenol

8.1. Environmental Hazard Summary

Data very limited, but toxicity appears substantial to aquatic organisms and birds. Clearly more study in needed.

8.2. Human Health Hazard Summary

The document states: “A two-year dietary study in dogs found that pentachloronitrobenzene increased liver weight, elevated serum biochemistry levels associated with liver dysfunction and induced cholestatic hepatosis with secondary bile nephrosis (U.S. EPA, 1987).” Concentrations not provided. A study of HCB is not directly pertinent to PCPT in terms of toxicity. Again, grossly inadequate information is available/presented to adequately assess toxicity.

Possibly of interest due to the paucity of data: Jiwu et al. 1994. Toxicity of pentachlorothiophenol. Xi’an Yike Daxue Xuebao 15(2) 159-63 (Chinese).

Reviewer 5 - Environmental and Human Health Hazard Summary Peer Review

Response to Charge Questions for 5 PBT Chemicals Environmental and Human Health Hazard Summary

Charge Question 1: This information, when finalized will inform a technical support document to support EPA's regulatory activities on PBTs. Please comment on the organization and structure of this document to inform this use. Do you have specific recommendations to improve clarity and presentation of this information?

These comments are pertinent to all 5 of the PBT chemicals:

- In general, I recommend a careful review of the document for errors (e.g. the environmental hazard summary table has some cells that use "per cent" instead of %). Fixing errors and ensuring consistency will make the document easier to understand for the reader.
- Throughout this document, I have only included references in my reference list (found at the bottom of each charge question) that are not included in EPA's documents.
- The executive summary of this document is just a summary of the purpose of the document and is not a summary of the contents of the document. I recommend that the executive summary be expanded to include a short summary of the hazard findings for each of the chemicals.
- This document is very short, particularly compared to the Exposure and Use Assessment. It contains a very short summary of the hazards. More information about the hazards should be included, particularly more study-specific information in the study tables. This is how I suggest organizing these hazard summaries, given that they aren't full hazard assessments that include a thorough and up-to-date review of the literature:
    - Identify key chemical assessments that have completed a thorough literature review for hazard identification, with a short discussion about how those assessment's authors completed their literature review (because the purpose of that assessment's literature review may be different from EPA's, and therefore could have collected a different set of studies than EPA would have).
    - Present the hazard conclusions from previous assessment documents, along with the key studies identified for any endpoints where a significant hazard has been identified.
    - Create summary tables for the key studies, accounting for study quality (reviewed in a separate table using TSCA systematic review guidelines Table G-14), dose administration, doses, and health effects measured in those studies. This will allow EPA and the readers to compare results across key studies and will allow for a greater weight-of-evidence evaluation of the hazards.
    - I used this method in my assessment of the hazards from these 5 PBT chemicals, and they are presented in response to various charge questions below.
- For the environmental hazard summary tables, it would be better to change the label of the "hazard value" column to "concentration", because it seems that concentration is what is being represented in the column.

- It may also be useful to structure the environmental hazard assessment similarly to the human health summary, by including explicit NOAELs and LOAELs. Alternatively, you could use a structure similar to the tables that I present in response to charge question 5.
- A summary that compares the margin of exposure in the animal studies or environmental studies to human exposure (from the Exposure and Use Assessment, if an estimated exposure has been identified) would be useful, particularly because that aspect of the risk assessment is not being completed in this expedited process. For example:

Table 1. Human Daily Intake Exposure Estimate

Chemical	Source	Daily Exposure Estimate
DecaBDE	US EPA 2010 – adults	140 ng/day
	Hays and Pyatt – general exposures child	1200 ng/kg bw•day
	Health Canada 2012 – breast fed infants	50 – 190 ng/kg bw•day
	Health Canada 2012 – adults	7.9-13 ng/kg bw•day
	Jin (2009) highest median blood concentration for general pop	~500 ng/g
HBDE	Health Canada (2000) – gen pop 0.5 – 4 yo	40-200 ng/kg bw•day
	Health Canada (2000) – gen pop 20-70 yo	10-50 ng/kg bw•day
	IPCS (1994) – 70 kg adult (maximum)	0.2 ug/kg bw•day
PIP (3:1)	Multiple studies	< 2 ng/kg bw•day
	Bjornsdotter (2017) - at-home toddlers (average)	~38 ng/day
	European Environment Agency (2009) – gen pop exposures (driven by consumption of contaminated fish)	~ 3 x 10^{-4} mg/kg bw•day
2,4,6-TTBP	Liu et al. (2017) – urban children for the sum of 7 phenolic antioxidants	3-10 ng/kg bw•day

Note: References are from the Exposure and Use Assessment

Table 2. Human Health-Relevant NOAEL/LOAEL

Chemical	Study & Species	Endpoint	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)
decaBDE	Johansson et al. 2008; oral gavage PND3 mice	Neurological	1.34	2.22
	Heredia et al. 2012; oral gavage adults for 15 days	Neurological		20
HBDE	Schwetz et al. 1977; dietary exposure of adult rats for ~150 days	Renal pathological changes	0.2	2

	De Ceaurriz et al. 1988; inhalation exposure of adult mice for 4 hours	Renal pathological changes		2.75 ppm
PIP (3:1)	Unnamed subchronic oral toxicity study 2014; adult rats exposed by gavage for 91 days	Adrenal gland pathological changes		25
	Unnamed subchronic inhalation toxicity study 2014; adult rats exposed via inhalation for 24 hrs per day for 90 days	Liver and adrenal pathological changes		10 mg/m^3
2,4,6-TTBP	Unnamed subchronic oral repeated dose/ reproductive/ developmental study; rats exposed by oral gavage for 21-56 days	Adult liver pathology Decreased litter viability	3	10

Phenol, Isopropylated, Phosphate (3:1) – PIP (3:1)

- In the human health hazard summary of PIP (3:1), the first sentence refers to hazard data for "Isopropylated, phosphate (3:1)". If this is a typo, please fix it. If it is intentional, please note whether this is a synonym (although it isn't labeled as such in the exposure and use assessment), or if a different chemical was assessed for hazard data.

2,4,6-Tris(tert-butyl) phenol (2,4,6-TTBP):

- In the human health hazard summary, the second paragraph contains a sentence that states "One unpublished OECD 422 guideline study report observed reduced body weights in the offspring and increased postnatal." Please finish this sentence to describe *what* was increased postnatally.

References

Ceaurriz, J. De, Gagnaire, F., Ban, M., & Bonnet, P. (1988). Assessment of the Relative Hazard Involved with Airborne Irritants with Additional Hepatotoxic or Nephrotoic Properties in Mice. J Appl Toxicol, 8(June).

Heredia, L., Torrente, M., Colomina, M. T., & Domingo, J. L. (2012). Behavioral effects of oral subacute exposure to BDE-209 in young adult mice : A preliminary study. Food and Chemical Toxicology, 50(3–4), 707–712. https://doi.org/10.1016/j.fct.2011.12.002

Charge Question 2: Please comment on the methodology for collecting and summarizing information from secondary sources. Was the approach appropriate? Is the description for how and where the literature was obtained clearly described?

These comments are pertinent to all 5 of the PBT chemicals:

- The logic of the literature search method used is not immediately obvious – usually a literature search begins with the primary reference databases (e.g. PubMed, ToxNet, Web of Science, EcoTOX, etc), and then goes on to the secondary (review) references and grey literature. By doing so, you don't bias your search results to what the secondary reference author deemed important. I suggest that you begin with the primary literature search, then move to secondary references to avoid unintentionally biasing your search results. This will also allow you to obtain the most up-to-date literature, which you will not get from most secondary references.
- Very little information is provided on the literature search for the hazard summary, particularly in comparison to the substantial information provided for the exposure and use assessment. Is there a reason for this discrepancy? Equal amounts of detail should be provided for the two sets of documents.
- Perhaps in the future the Exposure and Use literature search could be combined with the hazard literature search, with the different types of data screened into separate bins for their appropriate use. For example, the literature search string presented in Table E-1 for exposure and use of PCTP would also provide studies relevant for the hazard summary. In my search of the literature, I used the search strings outlined in the Exposure and Use Supplementary document.
- The inclusion and exclusion criteria for studies should be stated explicitly, not in general.
- There are more studies available for some of the chemicals (e.g. decaBDE) than are provided in the summary tables. This is consistent with the stated purpose of providing a summary, not a comprehensive literature review. However, it is not clear how the studies that were put into the summary tables were chosen. Are these the studies with the lowest measured effect levels? Or the highest study quality? The reason for study choice should be explicitly stated. If there is not currently an explicit criteria for choice of studies in the summary tables, I would suggest those studies that were identified as key studies in other reviews (i.e. that had the lowest LOEALs); or studies that have the lowest measured effect level for the effect of interest, have a NOAEL, and are of medium or high quality (as per the TSCA systematic review guidelines). In my review of the literature for these 5 PBT chemicals, this is the method that I used to choose which studies to read and evaluate (described in detail in response to charge questions 3 and 5).

Charge Question 3: Please comment on the representativeness and adequacy of the selected literature used in the evidence tables and described in the text to summarize the hazard concerns. Are there additional primary peer-reviewed and publicly available literature that warrant further consideration? If so, please identify or provide these sources and comment on whether acquisition and summarization of this additional information would change the hazard characterization already provided in the existing summaries? Does the information presented clearly and accurately represent the hazards associated with each chemical? Are there any studies that should be removed from the summary and evidence tables due to study quality or data transparency concerns?

These comments are pertinent to all 5 of the PBT chemicals.

- Most of my comments address the human health summary. However, many can be directly applied to the methods for conducting the environmental hazard summary.
- A better description should be provided explaining why only repeat-dose studies are relevant to these chemicals ("given the PBT nature of the chemicals of interest" – page 1 of the charge question document). Not all the studies listed for the human health assessment are repeat-dose studies – e.g. for decaBDE Johansson et al. (2008) or Viberg et al. (2007).
- The nature of this document as a hazard *summary*, instead of a comprehensive hazard *assessment*, makes it very likely that there will be additional studies that were not identified in your summary. The most important consideration, instead of asking if you have all the studies, is to ask if you have enough studies to perform an adequate weight-of-evidence evaluation to determine the hazards. Looking at a single study can lead to erroneous conclusions about hazard. For example, you may use the results from one study (e.g. Van der Ven et al. 2008) to show that intermediate exposures to decaBDE can change brain weights, and then extrapolate this to neurological effects, whereas other studies show no changes in brain weight with decaBDE exposure of varying lengths (NTP 1986, Tseng et al. 2008, Biesemeier et al. 2011). Does this mean that decaBDE has impacts on brain weight, or not? Therefore, it is important to collect all *key* studies for a chemical and evaluate all the findings from those studies to reach a balanced conclusion about hazard. This is the method that I used to evaluate hazard for these 5 PBT chemicals (described below and in response to charge question 5).
- Related to the importance of a weight-of-evidence approach, it is also important to provide information to the reader about your confidence in a hazard conclusion. The current summary does not present the hazards with enough detail to accurately portray the nuances of the data. Different levels of confidence could be expressed in the endpoints, for example strong evidence of hepatoxicity from adult or developmental exposure; moderate evidence for thyroid impacts; limited evidence of immunotoxicity, that would help provide more information to the audience about the confidence of the hazard identification. My hazard summaries (described below) use these types of confidence levels.

Decabromodiphenyl Ether (DecaBDE):

Representativeness and accuracy of presented literature:

- The current human health hazard summary is not representative of the literature for decaBDE hazard identification, because available summary documents were not used, and a primary literature search was not conducted. Since this decaBDE hazard summary does not complete a full review of the primary literature, there are many studies not cited here (e.g. ATSDR (2017) cites 91 studies on decaBDE for human health-related toxicity, whereas this hazard summary cites 14). As noted above, the reason for EPA's choice of these 14 particular studies is unclear and should be explained.

Additional primary peer-reviewed and publicly available literature that warrant further consideration:

- The ATSDR (2017) polybrominated diphenyl ether (PBDE) toxicology assessment should be considered in this summary. It is recent and provides a fairly comprehensive literature review of the human toxicity of decaBDE. As discussed above, the hazard conclusions from ATSDR as well as other assessments (e.g. Health Canada 2012) should be directly used in this assessment, because those assessments conducted a thorough literature review, and this one does not.
- Health Canada 2012: Human Health State of the Science Report on decaBDE: "The health effects of decaBDE have been well studied. In laboratory animals, decaBDE affects early fetal/neonatal development, the liver, the thyroid and potentially the endocrine system. The available studies suggest that decaBDE does not have significant genotoxic potential, and there is limited evidence for carcinogenicity in experimental animals."
- Key studies identified by Health Canada (2012) include:
    - Neurodevelopmental: Johansson et al. (2008); Fujimoto et al. (2011); Rice et al. (2007); Rice et al. (2009); Biesemeier et al. (2011)
    - Neurological: Liang et al. (2010); Van der Ven et al. (2008)
    - General developmental toxicity: Hsu et al. (2006); Tseng et al. (2008); Tseng et al. (2013)
    - Immunodevelopmental: Teshima et al. (2008)
- ATSDR 2017: Toxicological Profile for Polybrominated Diphenyl Ethers (PBDEs): The ATSDR assessed the organ-specific toxicity of oral administration of decaBDE, and concluded that there was a risk of toxicity from human exposure to decaBDE in the following systems: hepatic (developmental and adult exposure); endocrine (specifically thyroid and potentially pancreatic); immunological and lymphoreticular (decaBDE may have immunosuppression potential in women and children, but the overall evidence are limited and inconsistent); neurological (developmental, evidence less clear on adults); development (low birth weights, neurodevelopment, thyroid development, limited data for immunodevelopment and reproductive development); limited evidence of cancer in animals.

- ATSDR (2017) also noted that the evidence is limited or unlikely for human hazards from exposure to decaBDE at environmentally relevant concentrations for the following endpoints: respiratory (unlikely); cardiovascular (unlikely); gastrointestinal (unlikely at environmentally-relevant concentrations); hematological (unlikely); musculoskeletal (unlikely); renal (unlikely at environmentally relevant concentrations); body weight changes (unlikely at environmentally-relevant concentrations); immunological and lymphoreticular (insufficient information); reproductive (insufficient information); embryotoxicity and fetotoxicity (unlikely); immunodevelopment (insufficient information)
- Key studies identified by ATSDR (2017) include:
    - Neurodevelopmental: Buratovic et al. (2014); Johansson et al. (2008); Viberg et al. (2003b)
    - Cancer: NTP (1986); Sakamoto et al (2013)
    - Hepatic: Lee et al. (2010); Liu et al. (2012) (developmental); Fujimoto et al. (2011) (developmental); Tseng et al. (2008) (developmental); Tseng et al. (2013) (developmental)
    - Endocrine: Zhang et al. (2013); Xing et al. (2009) (developmental); Heredia et al. (2012)
    - Immunodevelopmental: Watanbe et al. (2008)
- I completed a literature search of PubMed with exactly the search string identified for the Exposure and Use Assessment (Supplement page 8), restricting to primary literature published since 2017 using other animals. This identified 38 articles, 5 of which had treated mice or rats with decaBDE:
    - Sarkar & Singh (2018; PMID 29578053) – lactating mice were gavaged with 500 or 700 mg/kg BDE-209 from PND 1 to PND 28 and investigated testis effects in the pups. Reproductive effects from developmental or adult exposure have not been clearly demonstrated, so I included this paper in my assessment in response to charge question 5.
    - Sarkar & Singh (2017; PMID 28572024) – lactating mice were gavaged with 500 or 700 mg/kg BDE-209 from PND 1 to PND 28 and investigated germ cell effects in the pups. Reproductive effects from developmental or adult exposure have not been clearly demonstrated, so I included this paper in my assessment in response to charge question 5.
    - Li et al. (2017; PMID 28104350) – gavaged S-D rat pups from PND 5 – PND 10 with 0, 1, 10, or 20 mg/kg BDE 209 and investigated spatial learning and memory. Because these types of studies have already been done at this exposure time, dose, and for this outcome, this was unlikely to add to the hazard identification and so I do not further assess it here.
    - Jung et al. (2017; PMID 27442109) – investigated metabolic profile of rats exposed to PBDE-209. Adversity of results are unclear, so this is not further assessed here.

- Curcic et al. (2017; PMID 27181932) – exposed rats to high doses of BDE-209 with and without co-exposure to Cadmium to investigate effects on hematological parameters. Not further assessed here.

- Altogether I identified 21 key studies from the Health Canada (2012) and ATSDR (2017) chemical assessments that inform the hazard characterization of decaBDE. I also added two from a literature search for studies conducted in 2017 or 2018. I summarize these studies, and discuss their strengths, weaknesses, reliability, and relevance, in response to charge question 5.

<u>Would acquisition and summarization of this additional information change the presented hazard characterization?</u>

- Acquisition of this information and assessment of study quality and weight of evidence does change the hazard characterization. In this hazard summary EPA concludes that "Oral repeated dose animal data for DecaBDE indicate developmental neurological effects, developmental immunological effects, general developmental toxicity, and liver effects." And "Dose-related brain effects were reported in adult rats as well, which was demonstrated by a decrease in brain weight following 28-days of oral gavage (Van der Ven et al., 2008)." My conclusions are outlined below and differ somewhat from those quoted here.
- Based on the literature analysis detailed in response to charge question #5 (Tables 3, 4a and 4b) my assessment of the hazard is:
    - Body weight – gestational, neonatal, or adult exposures to decaBDE are unlikely to affect body weight.
    - Neurological effects – moderate evidence, primarily related to neonatal and gestational exposure, suggests that decaBDE can impact neurological development down to concentrations of 1.34-2.2 mg/kg/day. These effects are likely enhanced by the method of exposure (oral gavage with decaBDE dissolved in oil), which delivers a bolus dose and would maximize bioavailability. None of the studies assessed here investigated the effects of decaBDE in diet on neurodevelopment, so the impact of the gavage dosing with a lipophilic vehicle is unknown. There is limited evidence of neurological effects of animals exposed to decaBDE as adults.
    - Endocrine effects – moderate evidence suggests that exposure during gestation or neonatally may impact thyroid function, with changes in thyroid cell morphology or serum thyroid hormone occurring at as low as 66 mg/kg/day decaBDE. Two studies show effects on thyroid parameters when dams were fed a diet containing decaBDE, suggesting that this parameter is unlikely to be dictated by the effects of gavage dosing with a lipophilic vehicle. Adult exposure to decaBDE may also impact thyroid function, but the evidence is less clear.
    - Hepatic effects – gestational, neonatal, or adult exposures to decaBDE, via diet or oral gavage, causes hepatotoxicity at a lowest dose in the range of 0.7-7 mg/kg (with gestational exposure), 300 mg/kg (with neonatal exposure), or 1120 mg/kg with adult exposure.

- Reproductive effects – most evidence shows that gestational, neonatal, or adult exposures to decaBDE do not affect reproductive parameters. Several studies by Sarkar & Singh (2017, 2018) demonstrate possible testes effects with lactational exposure, although this data is somewhat difficult to interpret because none of the endpoints demonstrate dose-responsiveness, and the maternal exposure is via oral gavage.
- Immunological effects – there is limited evidence that gestational, neonatal, or adult exposures to decaBDE affect the immune system. One rat gestational-neonatal exposure study demonstrated a change in lymphocyte distributions at 5 mg/kg/day decaBDE in diet, but the adversity of these distributional changes are unclear. Similarly, a chronic 103 week feeding study in rats demonstrated some gross changes to the spleen and lymph nodes, but this was not seen in mice treated in the same manner. The strongest data may come from Watanabe et al. (2008) who showed an increase in respiratory syncytial viral titers at higher dietary exposure of decaBDE during lactation.
- Development - gestational, neonatal, or adult exposures to decaBDE are unlikely to affect general developmental parameters.

Are there any studies that should be removed?

- Based on study quality review (discussed in response to charge question 5), Liang et al. (2010) and Viberg et al. (2003) should be removed, because their study quality is unacceptable (as defined by the TSCA systematic review guidelines), and Hsu et al. (2006), because this study does not appear to be available. Similarly, the raw results from van der Ven et al. (2008) were not available, and so this study was not assessed. Several of the key studies identified in the Health Canada (2012) and ATSDR (2017) assessments were also removed because of unacceptable study quality (Zhang et al. (2013), Xing et al. (2009)).

Hexachlorobutadiene (HCBD)

Representativeness and accuracy of presented literature:

- The current human health hazard summary is fairly representative of the literature for HCBD hazard identification. Most of the available summary documents were used. However, a primary literature search was not conducted, and not all the studies cited in the available assessment documents were included in summary table 5-2. As noted above, the reason for EPA's choice of the 9 studies that are cited in Table 5-2 is unclear and should be explained.

Additional primary peer-reviewed and publicly available literature that warrant further consideration:

- There is no Health Canada (2012) assessment of HCBD – the study cited in the hazard summary is the decaBDE assessment. Presumably the Health Canada (2000) study was

intended to be cited – "Priority Substances List Assessment Report: Hexachlorobutadiene".

- EPA identified several risk assessments that have been completed on HCBD. In addition to those cited by EPA, I identified another: US EPA Office of Water 2003 Health Effects Support Document on Hexachlorobutadiene.
- I used the Health Canada (2000), Rabovsky (2000), US EPA (2003), and US EPA (2007) assessments for a preliminary hazard summary and identification of key studies.
- Health Canada 2000: Priority Substances List Assessment Report: Hexachlorobutadiene: Health Canada concludes that oral or inhalation studies with HCBD in rats or mice indicate toxic effects in the pars recta of the proximal tubules of the kidneys, as well as increased incidence of renal tubule tumors in rats. The weight of the evidence also indicates that HCBD may be genotoxic when metabolically activated. There is some information for reproductive, developmental, and neurotoxic effects of HCBD.
- Key studies identified by Health Canada (2000) include:
    - Renal: Jonker et al. (1993), Harleman and Seinen (1979), Schwetz et al. (1977), Kociba et al. (1977a), Yang et al. (1989), NTP (1991)
- Rabovsky 2000: Evidence on the Carcinogenicity of 1,3-Hexachlorobutadiene focused on the carcinogenicity of HCBD and concluded that HCBD induced renal tubular tumors in rats, and there is evidence of genotoxicity for HCBD.
- Key studies identified by Rabovsky (2000):
    - Carcinogenicity: Kociba et al. (1977); Van Duuren et al. (1979), Nakagawa et al. (1998)
- US EPA Office of Water 2003 Health Effects Support Document on Hexachlorobutadiene: concluded that HCBD causes renal toxicity in animals regardless of route of administration. HCBD causes damage to the proximal tubule of the kidneys, and also induces kidney neoplasms. HCBD also causes developmental effects and neurotoxicity, but reproductive effects are only observed at doses that cause maternal toxicity.
- Key studies identified by US EPA (2003) include:
    - Short-term exposure: Kociba et al. (1971), Harleman and Seinen (1979), Stott et al. (1981), Yang et al. (1989), NTP (1991), Jonker et al. (1993), Nakagawa et al. (1998)
    - Subchronic exposure: Harleman and Seinen (1979), NTP (1991), Schwetz et al. (1977), Nakagawa et al. (1998)
    - Chronic exposure: Kociba et al (1977)
    - Developmental and Reproductive: Harleman and Seinen (1979), Schwetz et al. (1977)
- US EPA 2007 Provisional Peer Reviewed Toxicity Values for Hexachlorobutadiene. In this document US EPA notes that there is data demonstrating that HCB causes renal toxicity and is a possible human carcinogen (Group C).
- Key studies identified by US EPA (2007) include:
    - Oral Studies: Yang et al. (1989), NTP (1991), Harleman and Seinen (1979), Kociba et al (1977), Schwetz et al. (1977)

    - Inhalation studies: Saillenfait et al. (1989), Gage (1970), DeCeaurriz et al. (1988)
- I completed a literature search of PubMed with exactly the search string identified for the Exposure and Use Assessment (Supplement page 24), restricting to primary literature published since 2007 using other animals. This identified 27 articles, of which 9 had treated mice or rats with HCBD. I did not add any of them to my review, either because they did not use a relevant exposure pathway (intraperitoneal injection), or they were investigating renal effects of HCBD, which are already well-established.
    - Sadeghenia et al. (2013; PMID 23876083) – female rats were treated with 100 mg/kg HCBD ip, and the effects of the flavonoid rutin were investigated on renal damage.
    - Maguire et al. (2013; PMID 23136149) – male rats were treated with 45 mg/kg HCBD ip.
    - Christofori et al. (2013; PMID 21913211) – rats were treated with 100 mg/kg HCBD ip.
    - Swain et al. (2011a; PMID 21905055) – rats were treated with 5-90 mg/kg HCBD and kidney damage biomarkers were assessed.
    - Swain et al. (2011b; PMID 21259293) – rats were treated with a single dose of HCBD and kidney damage biomarkers were assessed.
    - Bouroshaki et al. (2010; PMID 20486845) – male rats were treated with 50 mg/kg HCBD ip, and the effects of the pomegranate seed oil were investigated on renal damage.
    - Chiusolo et al. (2010; PMID 20305092) – rats were treated with 25-100 mg/kg of HCBD and kidney damage biomarkers were assessed.
    - Zanetti et al. (2010; PMID 19742859) – rats were treated with HCBD and kidney damage biomarkers were assessed.
    - Chiusolo et al. (2008; PMID 18805471) – rats were treated with 25-100 mg/kg of HCBD and kidney damage biomarkers were assessed.
- Altogether I identified 13 key studies from the Health Canada (2000), Rabovsky (2000) and US EPA (2003, 2007) chemical assessments that inform the hazard characterization of HCBD. There was one additional study included in the summary tables of this hazard summary document (Field et al. (1990)), however, I could not locate the full text of this study, and so it was not included in my assessment. I discuss the strengths and weaknesses of these studies in response to charge question 5. I did not add any studies from the PubMed literature search.

<u>Would acquisition and summarization of this additional information change the presented hazard characterization?</u>

- Acquisition of this information and assessment of study quality and weight of evidence does change the hazard characterization. In this hazard summary EPA concludes that:
    - “Inhalation and oral animal data for HCBD indicate renal, reproductive, and developmental effects.”
    - “Renal adenomas and carcinomas were observed after 2 years and HCBD was considered to be a possible human carcinogen.”

- "Reproductive effects were observed in an inhalation developmental study in rats and was characterized by reduced body weight gains in maternal adults (Saillenfait et al., 1989). Developmental effects characterized by reduced fetal body weights in the F1 generation were observed following either oral or inhalation exposures in rats."

- My conclusions are outlined below and differ somewhat from those quoted above.
- Based on the literature analysis detailed in response to charge question #5 and summary Tables 6, 7a, and 7b, my assessment of the hazard is:
  - Body weight – subacute (LOAEL 5.4 mg/kg•day), subchronic (LOAEL 6.3 mg/kg•day), or chronic (LOAEL 20 mg/kg•day) oral administration of HCBD, either in adults or during development (LOAEL 11 mg/kg•day), causes decreases in body weight. The same is true with inhalation exposure (LOAEL 5.3 ppm, 6hrs/day for 14 days).
  - Renal effects – there is strong evidence that HCBD is a renal toxicant, particularly causing damage to the proximal tubules of the kidneys. Increases in kidney weights have been observed with subacute (LOAEL 5.4 mg/kg•day), subchronic (LOAEL 6.3 mg/kg•day), or chronic (LOAEL 20 mg/kg•day) oral administration of HCBD in adult rats or mice. Similarly, kidney damage identified by histopathological changes have been demonstrated with subacute (LOAEL 5.4 mg/kg•day), subchronic (LOAEL 2 mg/kg•day), or chronic (LOAEL 2 mg/kg•day) oral administration of HCBD in adult rats or mice, or with inhalation exposure in adult mice (LOAEL 2.75 ppm for 4 hours).
  - Neurological effects – there is limited evidence from a single study that administration of high concentrations of HCBD can cause neurological effects (ataxia, neurodegeneration) with 18 weeks of dietary exposure to HCBD (LOAEL 110 mg/kg•day). However, other studies have not demonstrated pathological effects on the nervous system with subchronic or chronic HCBD exposure (doses up to 100 mg/kg•day for 30 days, or 18 mg/kg•day for 13 weeks).
  - Other effects – Some of the studies have shown changes in various organ weights (e.g. spleen, liver) with HCBD exposure. However, these occurred at doses that caused decreased body weights and renal toxicity, so most study authors concluded that these organ weight changes were secondary to body weight and renal effects.
  - Reproductive effects – HCBD is unlikely to cause reproductive effects. Several studies have investigated the reproductive effects of HCBD exposure, both by oral and inhalation exposure. One study showed decreased fertility at acutely toxic concentrations (110 mg/kg•day for up to 18 weeks), but other studies have shown no reproductive changes with oral or inhalation exposure to HCBD.
  - Development – gestational or neonatal exposures to HCBD are unlikely to affect general developmental parameters. The only developmental changes that have been noted are decreases in fetal body weight, but these occur at doses that cause maternal toxicity (decreased body weight).

- Cancer – There is some evidence that HCBD is a carcinogenic chemical. The only chronic HCBD study demonstrated an increase in kidney carcinomas with HCBD exposure (LOAEL 20 mg/kg•day). Repeated dermal exposure for > 1 year did not induce skin tumors or tumors at distant sites. Other studies have not shown that HCBD to initiate or promote tumors, and it may or may not have genotoxic effects.

Are there any studies that should be removed?

- Based on study quality review (discussed in response to charge question 5), Gage (1970) (identified in US EPA 2007) should be removed because the study quality is unacceptable (as defined by the TSCA systematic review guidelines), and Field et al. (1990) should be removed, because this study does not appear to be available.

Phenol, Isopropylated, Phosphate (3:1) – PIP (3:1)

- In the environmental hazard summary, the % of PIP (3:1) contained in the test mixture is included in the summary table. This information should also be included for the human health hazard summary. If it is not available, this should be stated in the text or in the table.
- Because TPP is generally included in the mixture with PIP (3:1) and TPP has its own known toxicological effects, data should be presented that describes hazard assessments of TPP so that the hazards from each can be compared to determine what may be a PIP (3:1)-specific effect.
- In the Hazard summary (ecotox section), the cas number is given as: 68937-41-7; in the exposure and use assessment the cas number is 2502-15-0. The CASRN being used for this assessment of PIP (3:1) should be clarified.
- The hazard summary references both ECHA 2018a and 2018b for PIP (3:1). However, only 2018b should be referenced – 2018a is for 2,4,6 TTBP.
- In Table 6-2, there is no information about the dose timing or number of days of dosing for the OECD 422 oral gavage study in Sprague-Dawley rats. This information should be added to the table.

Representativeness and accuracy of presented literature:

- The current human health hazard summary is not very representative of the literature for PIP (3:1) hazard identification. Most of the available summary documents were used. However, a primary literature search was not conducted.
- EPA should have conducted a primary literature search to determine if new studies had been published since the most recent assessment (since 2015, because it is not clear if the ECHA dossier includes a thorough literature search).

Additional primary peer-reviewed and publicly available literature that warrant further consideration:

- I identified one summary document from the exposure and use assessment that wasn't cited in the hazard summary: UK 2009: Environmental risk evaluation report: Isopropylated triphenyl phosphate (CAS nos. 28108-99-8, 26967-76-0 & 68937-41-7). I assessed the hazard conclusions from this report as well as EPA (2015) and ECHA (2018b).
- UK 2009: Environmental risk evaluation report: Isopropylated triphenyl phosphate (CAS nos. 28108-99-8, 26967-76-0 & 68937-41-7). The UK Environmental Agency concludes from animal experiments that there is evidence of PIP (3:1) effects on blood chemistry, changes in the adrenal cortex, changes in body weight, and neurotoxicity. They conclude that there is no evidence to determine carcinogenicity, or reproductive or development toxicity. They note that there are limited available studies for hazard conclusions, and most are provided as summaries only in IUCLID 2000 or IUCLID 2001.
- EPA (2015): Flame Retardants Used in Flexible Polyurethane Foam: concluded that there was low evidence of acute mammalian toxicity and genotoxicity; moderate evidence of carcinogenicity (no adequate carcinogenicity studies were located); there is high evidence for reproductive effects based on available data; and there is high evidence of developmental effects based on analogy to Kronitex TCP (tricresyl phosphate CASRN 1330-78-5); high evidence of neurotoxicity based on analogy to ortho-cresyl phosphate; and high evidence of repeated dose effects based on available data.
- Key studies identified by EPA (2015):
    - IUCLID 2000, ECHA 2013, Patisaul et al. 2013
- ECHA (2018b) Registration Dossier Phenol, Isopropylated, Phosphate (3:1): provided hazard categories for reproductive toxicity based on fertility, effects on the epididymis, and maternal effects that decreased litter sizes; and repeated oral dose specific organ toxicity for adrenal gland effects.
- Key studies identified by ECHA (2018b):
    - Unnamed subchronic oral toxicity study (2014)
    - Unnamed subchronic inhalation toxicity study (1990)
    - Unnamed subchronic oral/reproductive toxicity study (2005)
    - Unnamed subchronic reproductive/ developmental toxicity screening study (2005)
    - Unnamed prenatal developmental oral toxicity study (2014)
    - Unnamed neurotoxicity study (2014)
- I completed a literature search of PubMed with exactly the search string identified for the Exposure and Use Assessment (Supplement page 36), and only identified 4 articles, none of which were relevant to this human health hazard summary. I also searched PubMed for the closely related chemicals listed in EPA (2015) on page 7-270, except for triphenyl phosphate, which may have a distinct toxicity. This did not generate any additional studies.
- Altogether I identified only one published study that described health effects attributed to PIP (3:1) from EPA (2015) (Patisaul et al. (2013)), in addition to 6 studies that are described in ECHA (2018b) as key studies and have reliability scores of 1 or 2, but for which I do not have access to the primary data. I discuss the strengths and weaknesses of

these studies in response to charge question 5 using the information provided by ECHA in the case of the unnamed studies.

Would acquisition and summarization of this additional information change the presented hazard characterization?

- Acquisition of this information and assessment of study quality and weight of evidence does change the hazard characterization. In this hazard summary EPA concludes that:
    - "Surveyed inhalation and oral animal data for Isopropylated, phosphate (3:1) indicate reproductive and developmental effects, increased mortality, neurological effects and effects on systemic organs, specifically adrenals, liver, ovary, heart, and lungs."
    - "…dose-dependently reduced copulation and reduced conception indices… postnatal survival and early postnatal development were reduced in this study"
- My conclusions are outlined below and differ somewhat from those quoted above.
- Based on the literature analysis detailed in response to charge question #5 and summary tables 7, 8a and 8b, my assessment of the hazard is:
    - Body weight – high dose oral administration of mixtures containing PIP (3:1) either subacutely (LOAEL 400 mg/kg•day) or subchronicly (LOAEL 325 mg/kg•day) causes decreases in body weight in adult rats. Whether the same is true for developmental exposure seems to depend on the particular mixture used (LOAEL 400 mg/kg•day). Subchronic inhalation exposure to high concentrations of mixtures containing PIP (3:1) also decreases body weight in rats (LOAEL 100 mg/m^3, 24 hrs/day for 90 days).
    - Organ effects – there is strong evidence that oral exposure to mixtures containing PIP (3:1) impact several organs, particularly causing increased weight and histopathological changes in the adrenal glands and liver (LOAEL 25 mg/kg•day for 91 days). These effects are also caused by inhalation exposure (LOAEL 10 mg/m^3, 24 hrs/day for 90 days), but do not seem to be a consequence of developmental exposure. The available studies have not shown consistent effects in other organ systems.
    - Neurological effects – there is limited evidence in rodents that subchronic ingestion (LOAEL 325 mg/kg•day for 91 days) or inhalation (LOAEL 100 mg/m^3, 24 hrs/day for 90 days) of mixtures containing PIP (3:1) can cause subtle neurological effects. One study in hens demonstrated some ataxia from a single acute exposure (LOAEL 4 g/kg) to a mixture containing PIP (3:1), but the effect was not dose-responsive.
    - Respiratory effects – The single inhalation study (24 hrs/day for 90 days) of a mixture containing PIP (3:1) demonstrated some nasal and lung effects (rat LOAEL 100 mg/m^3, rabbit LOAEL 10 mg/m^3).
    - Reproductive effects – There is good evidence that mixtures containing PIP (3:1) cause reproductive effects in rats. There is evidence that oral exposure or inhalation exposure causes histopathological changes to the ovaries (LOAEL 25 mg/kg•day, or 10 mg/m^3) and testicles (LOAEL 100 mg/m^3), and high oral dose

exposures to some of the PIP (3:1) mixtures causes decreased fertility (LOAEL 400 mg/kg•day).
    - Development – gestational exposures to mixtures containing PIP (3:1) are unlikely to affect general developmental parameters. The only developmental changes that have been noted are decreases in survival and fetal body weight, but these occur at doses that cause maternal toxicity (decreased body weight, adrenal gland and liver pathology). These effects also do not occur with all of the tested PIP (3:1) mixtures.

Are there any studies that should be removed?

- Based on study quality review (discussed in response to charge question 5), Patisaul et al. (2013) (identified in US EPA 2015) should be removed because the compound tested (FireMaster 550) seems to contain mostly non-PIP (3:1) chemicals.

2,4,6-Tris(tert-butyl) phenol – 2,4,6 TTBP

Representativeness and accuracy of presented literature:

- The current human health hazard summary is representative of the literature for 2,4,6-TTBP. The available summary documents were used, but a primary literature search was not conducted.

Additional primary peer-reviewed and publicly available literature that warrant further consideration:

- I did not identify any additional summary documents that provided information about human health hazards of 2,4,6-TTBP.
- ECHA (2018a) Registration Dossier 2,4,6-tri-tert-butylphenol provided hazard categories for acute toxicity, skin sensitization, and repeated dose toxicity.
- Key studies identified by ECHA (2018a):
    - Unnamed skin sensitization study, 2015
    - Unnamed repeated dose reproductive/developmental oral toxicity study, 2015
    - Unnamed genetic toxicity studies – *in vitro* (bacteria, 2015); *in vitro* (mammalian cells, 2015); *in vitro* cytogenicity (mammalian cells, 2015);
    - Repeated dose oral toxicity and carcinogenicity – Matsumoto et al. (1991)
- I completed a literature search of PubMed with exactly the search string identified for the Exposure and Use Assessment (Supplement page 52), and only identified 24 articles, none of which were relevant to this human health hazard summary. I also searched ToxNet Hazardous Substances Data Bank (HSDB), which yielded one additional study that was referenced to EPA's High Production Volume Information System (HPVIS – Tokyo Metropolitan Research Lab, 1987).
- Altogether there seems to be only one published study that described health effects attributed to 2,4,6 TTBP (Matsumoto et al. (1991)), in addition to 1 study from the EPA

HPVIS and 2 studies that are described in ECHA (2018a) as key studies and have reliability scores of 1 or 2, but for which I do not have access to the primary data. ECHA (2018a) also describes data from several unpublished genotoxicity studies that I include in the hazard summary. I discuss the strengths and weaknesses of these studies in response to charge question 5, using the information provided by ECHA in the case of the unnamed studies.

Would acquisition and summarization of this additional information change the presented hazard characterization?

- Acquisition of this information and assessment of study quality and weight of evidence does not change the hazard characterization. In this assessment EPA concludes that:
    - "Surveyed animal data for 2,4,6-Tris(tert-butyl) phenol (2,4,6 TTBP) indicate liver and developmental effects based on oral animal studies. No inhalation data were identified."
    - "Maternal liver weights were dose-dependently increased… A two-year oral carcinogenicity study observed increased liver weights, focal necrosis, and corresponding changes in blood biochemistry… One unpublished OECD 422 guideline study report observed reduced body weights in the offspring and increased postnatal… Another unpublished OECD 422 guideline study observed reduced pup viability index and reduced weight gain"
- My conclusions are outlined below.
- Based on the literature analysis detailed in response to charge question #5 and summary tables 9, 10a and 10b, my assessment of the hazard is:
    - Body weight – body weight is decreased by chronic oral administration of 2,4,6-TTPB at high exposure concentrations (LOAEL 1000 ppm), or during lactation in female rats (LOAEL 10 mg/kg).
    - Hepatic effects - oral exposure to 2,4,6-TTBP increases liver weight and causes liver pathology such as cellular hypertrophy and necrosis (LOAEL 10 mg/kg). It also causes changes in serum chemistry parameters consistent with hepatic injury, such as increased serum cholesterol.
    - Organ effects – chronic oral exposure to 2,4,6-TTBP increased relative kidney weights and adrenal gland weights (LOAEL 100 ppm), but this was not seen with subchronic exposures up to 30 mg/kg.
    - Dermal Sensitization – There is some evidence that exposure to 2,4,6-TTBP can cause dermal sensitization (LOAEL 25% w/w in dimethyl-formamide, 3-day exposure).
    - Reproductive effects – Available evidence suggests that 2,4,6-TTBP does not cause reproductive effects.
    - Development – gestational exposures to 2,4,6-TTBP cause decreased pup viability and decreased pup body weights (LOAEL 10 mg/kg), but these effects occur at concentrations that also cause maternal toxicity (decreased body weight gain, liver pathology and blood chemistry changes).

- Cancer – a 2-year bioassay in rats did not reveal any neoplastic changes in response to 2,4,6-TTBP exposure, and several genotoxicity assays have no found mutagenic effects of 2,4,6-TTBP in bacterial or mammalian test systems.

Are there any studies that should be removed?

- There is not enough data in the study identified in the EPA HPVIS database (repeated oral exposure in beagle dogs) to use the study in this hazard summary.

Pentachlorothiophenol (PCTP):

- Human health hazard data was collected and summarized for the fungicides PCNB and HCB, because data for PCTP was not available and PCTP is a metabolite of both. Evidence should be presented that demonstrates that PCTP is an ultimate toxicant in the metabolic chain for PCNB and HCB. In addition, if available, the amount of PCTP generated from PCNB and HCB metabolism should be provided (e.g. does 10% of PCNB get metabolized into PCTP?). The reference cited for PCTP being a metabolite/biodegradation product of PCNB and HCB (Khan et al. 2011) doesn't seem to identify PCTP as one of the intermediates in soil. The statement that PCTP is a metabolite or biodegradation product of PCNB and HCB should be supported by references that fully demonstrate this fact.
- The exposure and use assessment Section 8.2 stated that PCTP has been banned in most parts of the world because it forms several teratogenic decomposition products. The information about PCTP's decomposition products and their potential teratogenic properties is very important to include in this hazard assessment.

Representativeness and accuracy of presented literature:

- This hazard summary currently presents no literature for the health hazards of PCTP. There may be some data for this chemical (discussed below), which should be added to generate a data-informed health hazard summary about PCTP.

Additional primary peer-reviewed and publicly available literature that warrant further consideration:

- The ToxNet Hazardous Substances Database (referenced in the Exposure and Use Assessment) provides some toxicological information about PCTP. Many of the references are for studies in the ECHA IUCLID database. While I could not figure out how to access those studies, EPA should be able to do so, and this would provide information about the toxicity of PCTP. There were also some peer-reviewed studies described in ToxNet, one of which I could access and I reviewed. The ToxNet summaries of these studies are provided below in order to make some preliminary hazard identifications.
- ToxNet HSDB studies:
  - 5 acute exposure studies (referenced IUCLID 2000)

- 2 subchronic exposure studies (referenced IUCLID and Koss et al. 1979)
- 2 developmental/reproductive studies (referenced IUCLID and Korhonen et al. 1982)

- I completed a literature search of PubMed with exactly the search string identified for the Exposure and Use Assessment (Supplement page 68), and it identified 98 articles, none of which were relevant to this human health hazard summary.
- Altogether there seems to be only two published studies that described health effects attributed to PCTP (Koss et al (1979) and Korhonen et al. (1982)), in addition to several studies described in the IUCLID database, but for which I do not have access to the primary data or the study reports. I discuss the strengths and weaknesses of the one study that I have access to (Korhonen et al (1982)), in response to charge question 5.

<u>Would acquisition and summarization of this additional information change the presented hazard characterization?</u>

- Acquisition of this information and assessment of study quality and weight of evidence could completely change the hazard characterization of PCTP, because the current characterization is not based on PCTP data.
- My conclusions based on the ToxNet data summaries and the few published studies are outlined below.
    - Irritation – exposure to vapor or aerosol PCTP causes mucous membrane irritation in rats, rabbits, and guinea pigs (ToxNet, referencing IUCLID, 2000).
    - PCTP did not produce any body or organ weight effects in dietary studies in rats treated with 113 mg/kg every other day for 7 weeks (ToxNet, referencing IUCLID, 2000).
    - Female Wistar rats exposed orally every other day for several weeks to PCTP did not have changes in body weight gain or liver, spleen, or kidney weight (ToxNet, referencing Koss et al. (1979)).
    - PCTP did not produced any developmental effects in chicken embryo (Korhonen et al. (1982)).
    - Injection of PCTP into chicken embryos led to an increase in hepatic porphyrin levels (ToxNet, referencing IUCLID, 2000).
    - Genotoxicity studies in Salmonella were negative after treatment with PCTP, with and without metabolic activation (ToxNet, referencing IUCLID, 2000)
- Koss et al (1979) and others (e.g. Legault et al. (1997)) have concluded that the formation of PCTP is a detoxication pathway for HCB, resulting from conjugation with glutathione. Therefore, it is not valid to conclude that the hazards from HCB (or PCNB, which is also metabolized to PCTP) are the same as the hazards from PCTP.
- I did not find any literature in my search that supports the statement that PCTP use has been banned because its metabolites are teratogenic (as discussed in the Exposure and Use Assessment). If this is the case, it is very important that this be further explored in this hazard assessment.

<u>Are there any studies that should be removed?</u>

- None of the studies should be removed from the review.

References

ATSDR (Agency for Toxic Substances and Disease Registry). (2017). Toxicological profile for Polybrominated Diphenyl Ether. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service.

Buratovic, S., Viberg, H., Fredriksson, A., & Eriksson, P. (2014). Developmental exposure to the polybrominated diphenyl ether PBDE 209 : Neurobehavioural and neuroprotein analysis in adult male and female mice. Environmental Toxicology and Pharmacology, 38(2), 570–585. https://doi.org/10.1016/j.etap.2014.08.010

Ceaurrizt, J. De, Gagnaire, F., Ban, M., & Bonnet, P. (1988). Assessment of the Relative Hazard Involved with Airborne Irritants with Additional Hepatotoxic or Nephrotoic Properties in Mice. J Appl Toxicol, 8(June).

Gage, J. C., & Park, A. (1970). The subacute inhalation toxicity of 109 industrial chemicals. Br J Ind Med, 13, 1–18.

Heredia, L., Torrente, M., Colomina, M. T., & Domingo, J. L. (2012). Behavioral effects of oral subacute exposure to BDE-209 in young adult mice : A preliminary study. Food and Chemical Toxicology, 50(3–4), 707–712. https://doi.org/10.1016/j.fct.2011.12.002

Kociba, R.J., P.G. Gehring, C. G. H. and, & Sparschu., G. L. (1971). Toxicologic study of female rats administered hexachlorobutadiene or hexachlorobenzene for thirty days. Dow Chemical Company, Midland, Michigan.

Korhonen, A., Hemminki, K., & Vainio, H. (1982). Embryotoxicity of Benzothiazoles, Benzenesulfohydrazide, and Dithiodimorpholine to the Chicken Embryo. Arch Environm Contam Toxicol, 759, 753–759.

Koss G., Seubert S., Seubert A., Koransky, W., Ippen H., and Straub M. (1979) Chemical Porphyria in Man. pp. 175-180. Elsevier/North-Holland, Amsterdam

Lee, E., Kim, T. H., Choi, J. S., Nabanata, P., Kim, N. Y., Ahn, M. Y., … Kim, H. S. (2010). Evaluation of liver and thyroid toxicity in Sprague-Dawley rats after exposure to polybrominated diphenyl ether. J Toxicol Sci, 35(4), 535–545.

Legault, N., Sabik, H., Cooper, S. F., & Charbonneau, M. (1997). Effect of Estradiol on the Induction of Porphyria by Hexachlorobenzene in the Rat. Biochem Pharmacol, 54(June 1996), 19–25.

Liu, X., Zhan, H., Zeng, X., Zhang, C., & Chen, D. (2012). The PBDE-209 Exposure during Pregnancy and Lactation Impairs Immune Function in Rats. Mediators of Inflammation, 2012. https://doi.org/10.1155/2012/692467

Nakagawa Y1, Kitahori Y, Cho M, Konishi N, Tsumatani K, Ozono S, Okajima E, Hirao Y, H. Y. (1998). Effect of Hexachloro-l , 3-butadiene on Renal Carcinogenesis in Male Rats Pretreated with N-Ethyl-N-hydroxyethylnitrosamine *. Toxicol Pathol, 26(3), 361–366.

Patisaul, H. B., Roberts, S. C., Mabrey, N., Mccaffrey, K. A., Gear, R. B., Braun, J., … Stapleton, H. M. (2013). Accumulation and Endocrine Disrupting Effects of the Flame Retardant Mixture Firemaster 550 in Rats : An Exploratory Assessment. J Biochem Molec Toxicol, 27(2), 124–136. https://doi.org/10.1002/jbt

Sakamoto Y1, Inoue K, Takahashi M, Taketa Y, Kodama Y, Nemoto K, Degawa M, Gamou T, Ozawa S, Nishikawa A, Y. M. (2013). Different Pathways of Constitutive Androstane Receptor – mediated Liver Hypertrophy and Hepatocarcinogenesis in Mice Treated with Piperonyl Butoxide or Decabromodiphenyl Ether. Toxicol Pathol, 1078–1092. https://doi.org/10.1177/0192623313482055

Sarkar, D., & Singh, S. K. (2017). Maternal exposure to polybrominated diphenyl ether (BDE-209) during lactation a ff ects germ cell survival with altered testicular glucose homeostasis and oxidative status through down-regulation of Cx43 and p27Kip1 in prepubertal mice o ff spring. Toxicology, 386(March), 103–119. https://doi.org/10.1016/j.tox.2017.05.016

Sarkar, D., & Singh, S. K. (2018). Inhibition of testicular steroidogenesis and impaired di ff erentiation of Sertoli cells in peripubertal mice o ff spring following maternal exposure to BDE-209 during lactation suppress germ cell proliferation. Toxicology Letters, 290(March), 83–96. https://doi.org/10.1016/j.toxlet.2018.03.026

Tokyo Metropolitan Research Lab. 1987. Toxicity of 2,4,6-tri-tert-butylphenol in Beagle Dogs, Tokyo Metrop. Res. Lab. Public Health, Tokyo. 32-2, 67-68.

UK Environment Agency. (2009). Environmental risk evaluation report: Isopropylated triphenyl phosphate (CAS nos. 28108-99-8, 26967-76-0 & 68937-41-7). In Using Science to Create a Better Place. Bristol, United Kingdom: Environment Agency.

US EPA. (2003). Health Effects Support Document on Hexachlorobutadiene. Office of Water.

Van Duuren BL, Goldschmidt BM, Loewengart G, Smith AC, Melchionne S, Seldman I, R. D. (1979). Carcinogenicity of halogenated olefinic and aliphatic hydrocarbons in mice. J Natl Cancer Inst., 1433–9.

Watanabe, W., Shimizu, T., Hino, A., & Kurokawa, M. (2008). Effects of decabrominated diphenyl ether (DBDE) on developmental immunotoxicity in offspring mice. Environmental Toxicology and Pharmacology, 26, 315–319. https://doi.org/10.1016/j.etap.2008.06.004

Xing, T., Chen, L., Tao, Y., Wang, M., Chen, J., & Ruan, D. (2018). Effects of Decabrominated Diphenyl Ether (PBDE 209) Exposure at Different Developmental Periods on Synaptic Plasticity in the Dentate Gyrus of Adult Rats In Vivo. Toxicological Sciences, 110(January), 401–410. https://doi.org/10.1093/toxsci/kfp114

Zhang, Z., Zhen, Z., Xue, S., Shixin, X., Chen, X., Jun, W., … Lin, S. (2013). Mechanism of BDE209 - induced impaired glucose homeostasis based on gene microarray analysis of adult rat liver. Arch Toxicol, 1557–1567. https://doi.org/10.1007/s00204-013-1059-8

Charge Question 4: Has appropriate and sufficient information been obtained from the literature to support the identification of hazards?

These comments are pertinent to all 5 of the PBT chemicals.

- As was noted in my responses to the charge questions above, using the weight of all the evidence is the best way to determine hazards from a chemical. Because this assessment is not a thorough literature review, it is difficult for the weight of the evidence to be ascertained. Therefore, I suggest presenting the hazard identifications from other assessments, and then going into detail about the key studies identified in those assessments.
- For decaBDE, HCBD, and PCTP, appropriate and sufficient information was not obtained from the literature to support a weight-of-evidence evaluation of the hazards. The reasons for this statement are outlined in my responses to charge questions 3 and 5.

Charge Question 5: Please comment on the reliability and relevance of the identified data sets for each chemical and on the strengths and weaknesses of individual data sets that will help to better inform future regulatory actions.

These comments are pertinent to all 5 of the PBT chemicals.

- Most of my comments address the human health summary. However, many can be directly applied to the methods for conducting the environmental hazard summary.
- The references below that cannot be found in the hazard summary document can be found in response to charge question 3.

Decabromodiphenyl Ether (DecaBDE)

Environmental Hazard Summary:

- Hardy et al. (2012) actually tested decabromodiphenyl *ethane*, not *ether*.

Human Health Hazard Summary:

- Many of the decaBDE studies treated animals with oral gavage using a lipophilic medium. This both increased the acute dose (a gavage dose is administered all at once so the body has more difficulty recovering from it), and it increases bioavailability in a manner that may not be relevant to exposure in the general public (with the possible exception of breast feeding babies). This should be addressed in decisions about hazards from decaBDE, as I did in my hazard summary outlined in response to charge question 3.
- I assessed the 21 peer-reviewed studies that I identified from the Health Canada (2012) and ATSDR (2017) assessments, as well as 2 identified from the literature published in 2017 or 2018, as described in response to charge question 3. 10 of these studies were not included in the EPA's summary tables.
- I reviewed these studies using EPA's TSCA systematic review guidelines and assigned study quality scores of high, medium, low, or unacceptable. These details of my ratings for each study are in Appendix A, and the summary of strengths, weaknesses, reliability, and relevance are displayed in Table 3.
- Tables 4a and 4b summarize results from these 23 reviewed studies (excluding those that were unacceptable or unavailable) and formed the basis for my hazard summary conclusions described in reply to charge question 3. Using a similar method would help the EPA to provide a better weighted and more justified hazard summary of PBT chemicals.
- General Strengths: test design, test organism, exposure characterization, outcome assessment, variable control.
- General Weaknesses: Often data for non-significant changes was inadequately presented; often no independent verification of the identity of the chemical being used to expose the animals or how the chemical was stored was provided; sometimes there was no information about randomization of animals to treatment groups, or blinding of data assessors to the dose received by the animal.

- General Relevance: often only moderate, because the exposure pathways were usually oral gavage, which is not relevant to human exposure.
- General Reliability: often medium or high because the overall study qualities were rated as medium or high.

Table 3. DecaBDE Human Health Hazard Summary Table – Strengths, Weaknesses, Relevance, Reliability

Study	Strengths	Weaknesses	Relevance	Reliability
Johansson et al. (2008)	Test organism, Outcome assessment	Test substance, Test design, Confounding/ variable control, Data presentation and analysis	Moderate (single exposure study, oral gavage with vehicle intended to increase bioavailability)	Moderate (study quality medium)
Viberg et al. (2003)	Source, identity, and purity of test substance not provided; study unacceptable			
NTP (1986)	Test substance, Test design, Exposure characterization, Test organism, Outcome assessment, Data presentation and analysis	Confounding/ variable control	High	High (study quality high)
Liang et al. (2010)	Test animal source not reported; treatments unclear; outcome assessment methods not reported; study unacceptable			
Fujimoto et al. (2011)	Test design, Test organism, confounding/ variable control,	Data presentation and analysis	High	Medium (study quality medium)
Sakamoto et al. (2013)	Test organism, Outcome assessment, Confounding/variable control, Data presentation and analysis	Test design	Moderate (pre-initiated mice)	Moderate (study quality medium)
Lee et al. (2012)	Exposure characterization, Test organism, Outcome assessment	Test substance, Test design, Confounding/variable control, Data presentation and analysis	Moderate (oral gavage with vehicle intended to increase bioavailability)	Moderate (study quality medium)
Liu et al. (2010)	Test design	Exposure Characterization, Test organism, Confounding/variable control, Data presentation and analysis	Moderate (oral gavage with vehicle intended to increase bioavailability)	Low (study quality low) – concerns about equal exposure times for treated and control
Tseng et al. (2008)	Test design, Exposure characterization, Test organism, Outcome assessment	Data presentation and analysis	Moderate (oral gavage with vehicle intended to increase bioavailability)	High (high study quality)
Tseng et al. (2013)	Test design, Exposure characterization,	Data presentation and analysis	Moderate (oral gavage with	High (high study quality)

	Test organism, Outcome assessment		vehicle intended to increase bioavailability)	
Buratovic et al. (2014)	Test organism, Confounding/variable control	Test substance, Data presentation and analysis	Moderate (oral gavage with vehicle intended to increase bioavailability)	Moderate (medium study quality)
Zhang et al. (2013)	Exposure frequency not reported; age of treated animals not reported; exposure method not reported; study unacceptable			
Xing et al. (2009)	Control exposure protocol not reported, should have been controls for every exposure protocol; statistical unit should have been litter, not individual animals; study unacceptable			
Heredia et al. (2012)	Test design, Test organism, Outcome assessment, Confounding/variable control	Test substance	Moderate (oral gavage with vehicle intended to increase bioavailability)	Moderate (medium study quality)
Rice et al. (2007)	Test design, Exposure characterization, Test organism, Outcome assessment, Confounding/variable control	Test substance, Data presentation and analysis	Moderate (oral gavage with vehicle intended to increase bioavailability)	High (high study quality)
Rice et al. (2009)	Test design, Exposure characterization, Outcome assessment, Confounding/variable control	Test substance, Data presentation and analysis	Moderate (oral gavage with vehicle intended to increase bioavailability)	Moderate (medium study quality)
Biesemeier et al. (2011)	Test substance Exposure characterization, Test organism, Outcome assessment, Confounding/variable control, Data presentation and analysis		Moderate (oral gavage with vehicle intended to increase bioavailability)	High (high study quality)
Teshima et al. (2008)	Test design, Outcome assessment, Confounding/variable control	Test substance, Test organism Data presentation and analysis	High	Moderate (medium study quality)
Sarkar & Singh (2017)	Outcome assessment	Test organism, Confounding/variable control, Data presentation and analysis	Moderate (oral gavage with vehicle intended to increase bioavailability)	Moderate (medium study quality)
Sarkar & Singh (2018)		Test organism	Moderate (oral gavage with vehicle intended to increase bioavailability)	Moderate (medium study quality)
Watanabe et al. (2008)	Test design, Exposure characterization, Outcome assessment, Confounding/variable control	Test substance, Test organism, Data presentation and analysis	High	Moderate (medium study quality)

Table 4a. DecaBDE Human Health Hazard Summary Table – Body Weight, Organ Weight, Neurological, Endocrine

Study	Study Quality	Doses (mg/kg/day)	Species	Dosing	Medium	Body Weight	Organ Weight	Neuro	Endo
Developmental Exposure - Pups									
Johansson et al. 2008	Medium	0, 1.34, 2.2, 14, 20.1	Mice	PND3	Gavage (peanut oil)			2.2	
Buratovic et al. 2014	Medium	0, 1.34, 5.76, 13.4	Mice	PND3	Gavage (peanut oil)	NC		1.34	
Lee et al. 2010	Medium	0, 100, 300, 600	Rats	PND10-42	Gavage oil (Tween)	NC	↑ liver 300, adrenal & thyroid 600		Thyr: 100
Rice et al. 2007	High	0, 6, 20	Mice	PND2-15	Gavage (peanut oil)	NC		20	
Rice et al. 2007	Medium	0, 6, 20	Mice	PND2-15	Gavage (peanut oil)			20	
Developmental Exposure – Dams (pup effects)									
Fujimoto et al. 2011	Medium		Rats	GD 10 – PND20	Diet	NC	↑ liver 7	NC	Thyr: 66.3
Tseng et al. 2008	High	0, 10, 500, 1500	Mice	GD0-17	Gavage (corn oil)				Thyr:1500
Tseng et al. 2008	High	0, 10, 500, 1500	Mice	GD0-17	Gavage (corn oil)	NC	NC		NC
Biesemeier et al. 2011	High	0, 10, 100, 1000	Rats	GD6-LD21	Gavage (corn oil)	NC	NC	1000	
Teshima et al. 2008	Medium	0, 5, 50, 500	Rats	GD10-PND21	Diet	NC	↑ Liver 5		Thyr: 500
Sarkar & Singh 2017	Medium	0, 500, 700	Mice	PND1-21	Gavage (corn oil)				Estrogen: 500
Sarkar & Singh 2018	Medium	0, 500, 700	Mice	PND1-28	Gavage (corn oil)	NC	↓ Testis, prostate		Estrogen: NC Testosterone, Thyr: 500
Watanabe et al. 2008	Medium	0, 3.3, 33.6, 257.1, 2600	Mice	PND10-21	Diet	↓ 257			
Adult Exposure									
NTP 1986	High	0, 3200-3760, 6650-7780	Mice	103 wks	Diet	NC	NC	Gross NC	Thyr: 3200
NTP 1986	High	0, 1120-1200, 2240-2550	Rats	103 wks	Diet	NC	NC	Gross NC	Gross NC
Sakamoto et al. 2013	Medium	0, 9800	Mice	1 wk	Diet	NC	NC		
		0, 9400		4 wks	Diet		Liver ↑ 9400		
		0, 9100		27 wks	Diet + DEN		Liver ↑ 9100		
Liu et al. 2012	Low	0, 300	Rats	14 wks?	Gavage (arachis oil)	↓ 300	Spleen ↑ 300		Thyr: 300
Heredia et al. 2012	Medium	0, 20	Mice	15 days	Gavage (sunflower oil)	NC		20	

Adult Exposure – Maternal Effects									
Fujimoto et al. 2011	Medium	0, 0.7, 7, 66.3 o	Rats	GD 10 – PND20	Diet	NC			NC
Tseng et al. 2008	High	0, 10, 500, 1500	Mice	GD0-17	Gavage (corn oil)	NC	NC		
Biesemeier et al. 2011	High	0, 10, 100, 1000	Rats	GD6-LD21	Gavage (corn oil)	NC			
Sarkar & Singh 2018	Medium	0, 500, 700	Mice	PND1-28	Gavage (corn oil)	NC			NC
Watanabe et al. 2008	Medium	0, 3.3, 33.6, 257.1, 2600	Mice	PND10-21	Diet	NC			

Note: number in column denotes a LOAEL; NC is no change; blank cells mean the endpoint was not measured

Table 4b. DecaBDE Human Health Hazard Summary Table – Hepatic, Reproductive, Immunological, Developmental

Study	Study Quality	Doses (mg/kg/day)	Species	Dosing	Medium	Hepatic	Repro	Immuno	Develop
Developmental Exposure - Pups									
Johansson et al. 2008	Medium	0, 1.34, 2.2, 14, 20.1	Mice	PND3	Gavage (peanut oil)				
Buratovic et al. 2014	Medium	0, 1.34, 5.76, 13.4	Mice	PND3	Gavage (peanut oil)				
Lee et al. 2010	Medium	0, 100, 300, 600	Rats	PND10-42	Gavage oil (Tween)	300	NC		
Rice et al. 2007	High	0, 6, 20	Mice	PND2-15	Gavage (peanut oil)				NC
Rice et al. 2007	Medium	0, 6, 20	Mice	PND2-15	Gavage (peanut oil)				
Developmental Exposure – Dams (pup effects)									
Fujimoto et al. 2011	Medium		Rats	GD 10 – PND20	Diet	0.7-7	NC		NC
Tseng et al. 2008	High	0, 10, 500, 1500	Mice	GD0-17	Gavage (corn oil)	500			NC
Tseng et al. 2008	High	0, 10, 500, 1500	Mice	GD0-17	Gavage (corn oil)		1500		1500
Biesemeier et al. 2011	High	0, 10, 100, 1000	Rats	GD6-LD21	Gavage (corn oil)				NC
Teshima et al. 2008	Medium	0, 5, 50, 500	Rats	GD10-PND21	Diet			Lympho-cyte types 5	
Sarkar & Singh 2017	Medium	0, 500, 700	Mice	PND1-21	Gavage (corn oil)		Testes - 500		
Sarkar & Singh 2018	Medium	0, 500, 700	Mice	PND1-28	Gavage (corn oil)		Testes - 500		
Watanabe et al. 2008	Medium	0, 3.3, 33.6, 257.1, 2600	Mice	PND10-21	Diet			IFN-γ 34	
Adult Exposure									
NTP 1986	High	0, 3200-3760, 6650-7780	Mice	103 wks	Diet	3200	Gross NC	Gross NC	
NTP 1986	High	0, 1120-1200, 2240-2550	Rats	103 wks	Diet	1120	Gross NC	Lymph, spleen	

								morph 1120	
Sakamoto et al. 2013	Medium	0, 9800	Mice	1 wk	Diet	NC			
		0, 9400		4 wks	Diet	9400			
		0, 9100		27 wks	Diet + DEN	9100			
Liu et al. 2012	Low	0, 300	Rats	14 wks?	Gavage (arachis oil)	300	Ovary: 300	Lympho-cyte types 300	
Heredia et al. 2012	Medium	0, 20	Mice	15 days	Gavage (sunflower oil)				
Adult Exposure – Maternal Effects									
Fujimoto et al. 2011	Medium	0, 0.7, 7, 66.3	Rats	GD 10 – PND20	Diet		NC		
Tseng et al. 2008	High	0, 10, 500, 1500	Mice	GD0-17	Gavage (corn oil)		NC		
Biesemeier et al. 2011	High	0, 10, 100, 1000	Rats	GD6-LD21	Gavage (corn oil)		NC		
Sarkar & Singh 2018	Medium	0, 500, 700	Mice	PND1-28	Gavage (corn oil)				
Watanabe et al. 2008	Medium	0, 3.3, 33.6, 257.1, 2600	Mice	PND10-21	Diet		NC		

Note: number in column denotes a LOAEL; NC is no change; blank cells mean the endpoint was not measured

Hexachlorobutadiene (HCBD)

Human Health Hazard Summary:

- I assessed the 13 HCBD studies that I identified from the Health Canada (2000), Rabovsky (2000), US EPA (2003), and US EPA (2007). The method for the choice of these studies is described in response to charge question 3. 5 of these studies were not included in the EPA's summary tables.
- I reviewed these studies using EPA's TSCA systematic review guidelines and assigned study quality scores of high, medium, low, or unacceptable. These details of my ratings for each study are in Appendix A, and the summary of strengths, weaknesses, reliability, and relevance are displayed in Table 5.
- Tables 6a and 6b summarize results from these studies (excluding those that were unacceptable or unavailable) and form the basis for my hazard summary conclusions described in the reply to charge question 3. Using a similar method would help the EPA to provide a better weighted and more justified hazard summary of PBT chemicals.
- General Strengths: relevant exposure pathways (dietary studies, inhalation, dermal), exposure characterization, outcome assessment, variable control.
- General Weaknesses: Often data for non-significant changes was inadequately presented; often there was no independent verification of the identity of the chemical being used to expose the animals or on how the chemical was stored; sometimes there was no

information about randomization of animals to treatment groups, or blinding of data assessors to the dose received by the animal.

- General Relevance: often high, because the exposure pathways were relevant.
- General Reliability: often medium or high because the overall study qualities were rated as medium or high.

Table 5. HBDE Human Health Hazard Summary Table – Strengths, Weaknesses, Relevance, Reliability

Study	Strengths	Weaknesses	Relevance	Reliability
Gage (1970)	No information about source or purity of test substance. Study unacceptable			
Harleman & Seinen (1979)	Exposure characterization, Test organism, Outcome assessment, Confounding/variable control	Data presentation and analysis	High for range-finding and reproductive study Moderate for subchronic study (oral gavage with vehicle intended to increase bioavailability)	High (study quality high)
De Ceaurriz et al. (1988)	Test substance, Test design, Outcome assessment, Data presentation and analysis	Test organism	High	Moderate (study quality medium)
Jonker et al. (1993)	Test design, Exposure characterization, Test organism, Outcome assessment, Confounding/variable control,	Data presentation and analysis	High	High (study quality high)
Kociba et al. (1971)	Exposure characterization, Outcome assessment, Confounding/variable control, Data presentation and analysis	Test design, Test organism	High	Moderate (study quality moderate)
Kociba et al. (1977)	Exposure characterization, Outcome assessment, Confounding/variable control, Data presentation and analysis		High	High (study quality high)
Nakagawa et al. (1998)	Test organism, Outcome assessment, Confounding/variable control	Data presentation and analysis	High	Moderate (study quality moderate)
NTP (1991)/ Yang et al. (1989)	Test substance, Test design, Exposure characterization, Test organism,	Data presentation and analysis	High	High (study quality high)

	Outcome assessment, Confounding/variable control			
Saillenfait et al. (1989)	Test substance, Test design, Exposure characterization, Outcome assessment, Confounding/variable control, Data presentation and analysis		High	High (study quality high)
Schwetz et al. (1977)	Test substance, Exposure characterization, Confounding/variable control,	Data presentation and analysis	High	High (study quality high)
Stott et al. (1981)	Test substance, Test design, Outcome assessment, Data presentation and analysis	Test organism	High	Moderate (study quality moderate)
Van Duuren et al. (1979)	Outcome assessment, Confounding/variable control	Data presentation and analysis	High	Moderate (study quality moderate)

Table 6a. HBDE Human Health Hazard Summary Table – Body Weight, Organ Weight, Renal, Neurological

Oral Exposure Studies									
Study	**Study Quality**	**Doses (mg/kg/day)**	**Species**	**Dosing**	**Medium**	**Body Weight**	**Organ Weight**	**Renal**	**Neuro**
Sub-Acute Oral Exposure – Adults									
Harleman & Seinen 1979	High	0, 8, 23, 68	Rat	2 weeks	Diet	↓ 8	↑ Kidney 23	Path 8	
Jonker et al. 1993	High	0, 3, 11, 37	Young Rat	4 weeks	Diet	↓ 11	↑ Kidney 11	Path, urine 11	
Jonker et al. 1993	High	0, 1.4, 5.4	Rat	4 weeks	Diet	↓ 5.4	↑ Kidney 5.4	Path, urine 5.4	
Nakagawa et al. 1998	Medium	0, 7.2, 36, 108	Rat	3 weeks	Diet	↓ 36	NC	Path 108	
NTP 1991/Yang et al. 1989	High	0, 2.5, 14, 45	Mice	15 days	Diet	↓ 100		Path 100?	
Stott et al. 1977	Medium	0, 0.2, 20	Rat	3 weeks	Gavage (corn oil)	↓ 20	↑ Kidney 20	Path 20	
Sub-Chronic Oral Exposure – Adults									
Harleman & Seinen 1979	High	0, 0.4, 1, 2.5, 6.3, 15.6	Rat	13 weeks	Gavage (arachid oil)	↓ 6.3	↑ Kidney, liver, spleen 6.3	Path, urine 6.3	NC
Kociba et al. 1971	Medium	0, 1, 3, 10, 30, 65, 100	Young rat	30 days	Diet	↓ 10	↑ Kidney 30	Path 30	NC
NTP 1991/Yang et al. 1989	High	0, 0.2, 0.5, 1.6, 4.7, 18	Mice	13 weeks	Diet	↓ 100	↓ kidney 10, ↑ liver 100	Path 3	NC
Schwetz et al. 1977	High	0, 0.2, 2, 20	Rat	~150 days	Diet	↓ 20	↑ Kidney, liver 20	Path 2	NC
Chronic Oral Exposure – Adults									

Kociba et al. 1977	High	0, 0.2, 2, 20	Rat	2 years	Diet	↓ 20	↑ Kidney 20	Path 2; Tumors 20	NC
Nakagawa et al. 1998	Medium	0, 90	Rat	30 weeks	Diet	↓ 90	↑ Kidney 90	NC; Tumors with EHEN initiation only	
Oral Exposure – Developmental (pup effects)									
Harleman & Seinen 1979	High	0, 11, 110	Rat	GD0-PND21	Diet	↓ 11			
Schwetz et al. 1977	High	0, 0.2, 2, 20	Rat	GD0-PND21	Diet	↓ 20	NC		
Oral Exposure – Developmental (maternal effects)									
Harleman & Seinen 1979	High	0, 11, 110	Rat	Up to 7 weeks pre-GD0, 18 weeks total	Diet	↓ 11	↑ Kidney 11	Path 11	Ataxia, nerve effects 110
Schwetz et al. 1977	High	0, 0.2, 2, 20	Rat	105 days, GD0-PND21	Diet	↓ 20	↑ Kidney 20	Path 2	NC
Inhalation Studies									
Study	**Study Quality**	**Doses (ppm)**	**Species**	**Exposure Time**	**Respirat**	**Body Weight**	**Organ Weight**	**Renal**	**Neuro**
De Ceaurriz et al. 1988	Medium	0, 83, 143, 155, 210, 246	Mice	15 min	↓ Respir Rate 155				
De Ceaurriz et al. 1988	Medium	0, 2.75, 5, 10, 25	Mice	4 hours				Path 2.75	
Saillenfait et al. 1989	High	0, 2.1, 5.3, 10.4, 14.8	Rats	6hrs/day GD6-20		↓ 5.3 Maternal ↓ fetal 15			
Dermal Studies									
Study	**Study Quality**	**Doses (mg)**	**Species**	**Exposure Time**	**Respirat**	**Body Weight**	**Organ Weight**	**Renal**	**Neuro**
Van Duuren	Medium	0, 6	Mice	3X week, 440-594 days					

Note: number in column denotes a LOAEL; NC is no change; blank cells mean the endpoint was not measured

Table 6b. HBDE Human Health Hazard Summary Table – Endocrine, Hepatic, Reproductive, Developmental

Oral Exposure Studies									
Study	**Study Quality**	**Doses (mg/kg/day)**	**Species**	**Dosing**	**Medium**	**Endo**	**Hepatic**	**Repro**	**Develop**
Sub-Acute Oral Exposure – Adults									
Harleman & Seinen 1979	High	0, 8, 23, 68	Rat	2 weeks	Diet		NC		

Jonker et al. 1993	High	0, 3, 11, 37	Young Rat	4 weeks	Diet				
Jonker et al. 1993	High	0, 1.4, 5.4	Rat	4 weeks	Diet				
Nakagawa et al. 1998	Medium	0, 7.2, 36, 108	Rat	3 weeks	Diet				
NTP 1991/Yang et al. 1989	High	0, 2.5, 14, 45	Mice	15 days	Diet				
Stott et al. 1977	Medium	0, 0.2, 20	Rat	3 weeks	Gavage (corn oil)				
Sub-Chronic Oral Exposure – Adults									
Harleman & Seinen 1979	High	0, 0.4, 1, 2.5, 6.3, 15.6	Rat	13 weeks	Gavage (arachid oil)	NC		NC	
Kociba et al. 1971	Medium	0, 1, 3, 10, 30, 65, 100	Young rat	30 days	Diet		Hepato-cellular swelling 100		
NTP 1991/Yang et al. 1989	High	0, 0.2, 0.5, 1.6, 4.7, 18	Mice	13 weeks	Diet	NC	NC	NC	
Schwetz et al. 1977	High	0, 0.2, 2, 20	Rat	~150 days	Diet	NC	NC	NC	NC
Chronic Oral Exposure – Adults									
Kociba et al. 1977	High	0, 0.2, 2, 20	Rat	2 years	Diet	NC	NC	NC	
Nakagawa et al. 1998	Medium	0, 90	Rat	30 weeks	Diet				
Oral Exposure – Developmental (pup effects)									
Harleman & Seinen 1979	High	0, 11, 110	Rat	GD0-PND21	Diet				NC
Schwetz et al. 1977	High	0, 0.2, 2, 20	Rat	GD0-PND21	Diet				NC
Oral Exposure – Developmental (maternal effects)									
Harleman & Seinen 1979	High	0, 11, 110	Rat	Up to 7 weeks pre-GD0, 18 weeks total	Diet	NC	NC	Fertility 110	
Schwetz et al. 1977	High	0, 0.2, 2, 20	Rat	105 days, GD0-PND21	Diet	NC	NC	NC	NC
Inhalation Studies									
Study	**Study Quality**	**Doses (ppm)**	**Species**	**Exposure Time**	**Respirat**	**Endo**	**Hepatic**	**Repro**	**Develop**
De Ceaurriz et al. 1988	Medium	0, 83, 143, 155, 210, 246	Mice	15 min	↓ Respir Rate 155				
De Ceaurriz et al. 1988	Medium	0, 2.75, 5, 10, 25	Mice	4 hours					
Saillenfait et al. 1989	High	0, 2.1, 5.3, 10.4, 14.8	Rats	6hrs/day GD6-20				NC	NC
Dermal Studies									

Study	Study Quality	Doses (mg)	Species	Exposure Time	Dermal	Endo	Hepatic	Repro	Cancer
Van Duuren	Medium	0, 6	Mice	3X week, 440-594 days					No tumors with repeated dose or with PMA promotion

Note: number in column denotes a LOAEL; NC is no change; blank cells mean the endpoint was not measured

Phenol, Isopropylated, Phosphate (3:1) – PIP (3:1)

Human Health Hazard Summary:

- I assessed one PIP (3:1) study from the published literature, and 6 unpublished studies available in ECHA (2018b). The method for the choice of these studies is described in response to charge question 3. Three of these studies were not included in the EPA's summary tables.
- I reviewed these studies using EPA's TSCA systematic review guidelines and assigned study quality scores of high, medium, low, or unacceptable. For the unpublished studies, I used ECHA's reliability ratings, and rated a reliability of 1 as a High study quality, and a reliability of 2 as a Moderate study quality. The details of my ratings for each study are in Appendix A, and the summary of strengths, weaknesses, reliability, and relevance are displayed in Table 7 below.
- Tables 8a and 8b summarize results from these studies (excluding those that were unacceptable or unavailable) and serves as the basis for my hazard summary conclusions described in the reply to charge question 3. Using a similar method would help the EPA to provide a better weighted and more justified hazard summary of PBT chemicals.
- General Strengths: Mostly OECD/GLP studies.
- General Weaknesses: Mixtures of chemicals were tested, not a single chemical, making it unclear to what chemical the effects should be ascribed; the oral studies were via gavage, which is not a particularly relevant method for human exposure.
- General Relevance: often moderate, because the exposure pathways were typically oral gavage.
- General Reliability: often medium or high because the overall study qualities were rated as medium or high.

Table 7. PIP (3:1) Human Health Hazard Summary Table – Strengths, Weaknesses, Relevance, Reliability

Study	Strengths	Weaknesses	Relevance	Reliability
Patisaul et al. (2013)	Used FireMaster 550, which contains ~ 50% 50% 2-ethylhexyl-2,3,4,5-tetrabromobenzoate (TBB) and bis(2-ethylhexyl)2,3,4,5-tetrabromopthalate (TBPH), with no information about the levels of PIP(3:1) of triphenyl phosphate; study deemed unacceptable			

Subchronic Oral Toxicity Study: Unnamed (2014)	OECD 408, GLP study	Mixture of multiple chemicals (Reofos 35)	Moderate (exposure by oral gavage)	High (study quality high)
Subchronic Inhalation Toxicity Study: Unnamed (1990)	3 animal species tested, continuous 90 day exposure, investigated all organ systems	Mixture of multiple chemicals (MIL-J-194S7e and MII-H-194578 aerosol) Lack of information about some considerations such as blinding of assessors and randomization of animals to treatment groups, some animals died from Pasteurella multocida infection	High (inhalation exposure)	Moderate (study quality medium)
Subchronic Oral/Reproductive Toxicity Study: Unnamed (2005)	OECD 422, GLP study	Mixture of multiple chemicals (Reofos 65)	Moderate (exposure by oral gavage)	High (study quality high)
Subchronic Reproductive/ Developmental Toxicity Screening Study: Unnamed (2005)	OECD 421, GLP study Tested 5 isopropylated triphenyl phosphate mixtures, including PIP (3:1) (called mpIPTPP) alone	Mixture of multiple chemicals (Reofos 35, 65, 65 washed, 120, mpIPTPP)	Moderate (exposure by oral gavage)	High (study quality high)
Prenatal Developmental Toxicity Study: Unnamed (2014)	OECD 414, GLP study	Mixture of multiple chemicals (Reofos 35)	Moderate (exposure by oral gavage)	High (study quality high)
Neurotoxicity Study: Unnamed (1980)	GLP study	Mixture of multiple chemicals (Kronitex 50) Effects were not dose-responsive	Moderate (exposure by oral gavage)	High (study quality high)

Table 8a. PIP (3:1) Human Health Hazard Summary Table – Body Weight, Organ Weight, Renal, Neurological

Oral Exposure Studies									
Study	**Study Quality**	**Doses (mg/kg/day)**	**Species**	**Dosing**	**Medium**	**Body Weight**	**Organ Weight**	**Renal**	**Neuro**
Acute Exposure, Adults									
Neurotoxicity Study: Unnamed (1980)	High	0, 2000, 4000, 6000, 8000	Hens	Single exposure	Gavage (corn oil)	NC			Ataxia 4, path 4
Sub-Acute/Sub-chronic Oral Exposure – Adults									
Subchronic Oral Toxicity Study: Unnamed (2014)	High	0, 25, 100, 325 Reofos 35	Rat	91 days	Gavage (corn oil)	↓ 325	↑ Adrenal 25, ↑ liver 100, ↑ ovaries 25	NC	Fine movement, rearing 325
Subchronic Oral/Reproductive Toxicity Study:	High	0, 25, 100, 400 Reofos 65	Rat	29-54 days	Gavage (corn oil)	NC	↑ Adrenal 25, ↑ liver 100,	NC	NC

Unnamed (2005)							↑ ovaries 25 ↓ epididym		
Subchronic Reproductive/ Developmental Toxicity Screening Study: Unnamed (2005)	High	0, 400 Reofos 35, 65, 65 washed, 120, mpIPTPP	Rat	42-54 days	Gavage (corn oil)	↓ R35, R65	↑ Adrenal, ↑ liver, ↑ ovaries w R35, R65, R65w, R120	NC	NC
Prenatal Developmental Toxicity Study: Unnamed (2014)	High	0, 100, 200, 400 Reofos 35	Rat	GD 0-19	Gavage (corn oil)	↓ weight gain 400	Swollen stomach 400	NC	NC
Study	**Study Quality**	**Doses (mg/kg/day)**	**Species**	**Dosing**	**Medium**	**Body Weight**	**Organ Weight**	**Renal**	**Neuro**
Developmental Exposure - Pups									
Subchronic Oral/Reproductive Toxicity Study: Unnamed (2005)	High	0, 25, 100, 400 Reofos 65	Rat	GD0-PND 4	Maternal Gavage (corn oil)	↓ 400			
Subchronic Reproductive/ Developmental Toxicity Screening Study: Unnamed (2005)	High	0, 400 Reofos 35, 65, 65 washed, 120, mpIPTPP	Rat	42-54 days	Gavage (corn oil)	↓ R65, R65w	NC	NC	NC
Prenatal Developmental Toxicity Study: Unnamed (2014)	High	0, 100, 200, 400 Reofos 35	Rat	GD 0-19	Gavage (corn oil)	NC	NC	NC	NC
Study	**Study Quality**	**Doses (mg/m^3)**	**Species**	**Exposure Time**	**Respirat**	**Body Weight**	**Organ Weight**	**Renal**	**Neuro**
Sub-Acute Inhalation Exposure – Adults									
Subchronic Inhalation Toxicity Study: Unnamed (1990)	Medium	0, 10, 100 MIL-J-194S7e and MII-H-194578	Rat	90 days, 24 hrs/day	Nasal effects 100	↓ 100, kyphosis	↑ liver 10	Necrosis 100	↓ tail tip 100
	Medium	0, 10, 100 MIL-J-194S7e and MII-H-194578	Rabbit	90 days, 24 hrs/day	Nasal& lung effects 10	Death 100			

Note: number in column denotes a LOAEL; NC is no change; blank cells mean the endpoint was not measured

Table 8b. PIP (3:1) Human Health Hazard Summary Table – Endocrine, Hepatic, Reproductive, Developmental, Hematological

Oral Exposure Studies									
Study	**Study Quality**	**Doses (mg/kg/day)**	**Species**	**Dosing**	**Medium**	**Endo**	**Hepatic**	**Repro**	**Hematological**
Acute Exposure, Adults									
Neurotoxicity Study: Unnamed (1980)	High	0, 2000, 4000, 6000, 8000	Hens	Single exposure	Gavage (corn oil)				
Sub-Acute/Sub-chronic Oral Exposure – Adults									
Subchronic Oral Toxicity Study: Unnamed (2014)	High	0, 25, 100, 325 Reofos 35	Rat	91 days	Gavage (corn oil)	Path adrenal 25, path thyroid 100	Path 25	Ovary path 25	↑ Fibrinogen, urea nitrogen, cholesterol 100
Subchronic Oral/Reproductive Toxicity Study: Unnamed (2005)	High	0, 25, 100, 400 Reofos 65	Rat	29-54 days	Gavage (corn oil)	Path adrenal 25	Path 100	↓ fertility 400, ovary path 25	↑ cholesterol 400
Subchronic Reproductive/ Developmental Toxicity Screening Study: Unnamed (2005)	High	0, 400 Reofos 35, 65, 65 washed, 120, mpIPTPP	Rat	42-54 days	Gavage (corn oil)	Path adrenal, ovary w R35, R65, R65w, R120	Path w R35, R65, R65w, R120	↓ fertility R65	
Prenatal Developmental Toxicity Study: Unnamed (2014)	High	0, 100, 200, 400 Reofos 35	Rat	GD 0-19	Gavage (corn oil)	NC	NC	NC	
Study	**Study Quality**	**Doses (mg/kg/day)**	**Species**	**Dosing**	**Medium**	**Endo**	**Hepatic**	**Repro**	**Develop**
Developmental Exposure - Pups									
Subchronic Oral/Reproductive Toxicity Study: Unnamed (2005)	High	0, 25, 100, 400 Reofos 65	Rat	GD0-PND 4	Maternal Gavage (corn oil)				↓ survival 400
Subchronic Reproductive/ Developmental Toxicity	High	0, 400 Reofos 35, 65, 65 washed, 120, mpIPTPP	Rat	42-54 days	Gavage (corn oil)	NC	NC		↓ survival w R35, R65, R65w, R120

Screening Study: Unnamed (2005)									
Prenatal Developmental Toxicity Study: Unnamed (2014)	High	0, 100, 200, 400 Reofos 35	Rat	GD 0-19	Gavage (corn oil)	NC	NC		NC
Study	**Study Quality**	**Doses (mg/m^3)**	**Species**	**Exposure Time**	**Respirat**	**Endo**	**Hepatic**	**Repro**	**Develop**
Sub-Acute Inhalation Exposure – Adults									
Subchronic Inhalation Toxicity Study: Unnamed (1990)	Medium	0, 10, 100 MIL-J-194S7e and MII-H-194578	Rat	90 days, 24 hrs/day	Nasal effects 100	↑ Adrenal + path 10, Pituitary cell hypertrophy 100	Cell swelling 10	Testic atrophy 100, ovary cell hypertrophy 10	
	Medium	0, 10, 100 MIL-J-194S7e and MII-H-194578	Rabbit	90 days, 24 hrs/day	Nasal& lung effects 10		Path 100		

Note: number in column denotes a LOAEL; NC is no change; blank cells mean the endpoint was not measured

2,4,6-Tris(tert-butyl) phenol – 2,4,6 TTBP

Human Health Hazard Summary:

- I assessed one 2,4,6-TTBP study from the published literature, and 2 unpublished studies available in ECHA (2018a).
- I reviewed these studies using EPA's TSCA systematic review guidelines and assigned study quality scores of high, medium, low, or unacceptable. For the unpublished studies, I used ECHA's reliability ratings, and rated a reliability of 1 as a High study quality, and a reliability of 2 as a Moderate study quality. The details of my ratings for each study are in Appendix A, and the summary of strengths, weaknesses, reliability, and relevance are displayed below, as well as in Table 9.
- Tables 10a and 10b summarize the results from these studies (excluding those that were unacceptable or unavailable) and form the basis for my hazard summary conclusions described in the reply to charge question 3. Using a similar method would help the EPA to provide a better weighted and more justified hazard summary of PBT chemicals.
- General Strengths: OECD/GLP studies.
- General Weaknesses: Mixtures of chemicals were tested, not a single chemical, making it unclear to what chemical the effects should be ascribed; the repeated toxicity oral study used exposure via gavage, which is not a particularly relevant method for human exposure. Similarly, dermal exposure in a vehicle that ensures dermal penetration (dimethyl formamide) is not particularly relevant for human exposure.

- General Relevance: often moderate as noted above. The relevance of the chronic study was high, because it used dietary exposure.
- General Reliability: medium or high because the overall study qualities were rated as medium or high.

Table 9. 2,4,6-TTBP Human Health Hazard Summary Table – Strengths, Weaknesses, Relevance, Reliability

Study	Strengths	Weaknesses	Relevance	Reliability
Matsumoto et al. 1991	Test organism	Data presentation and analysis	High	Moderate (study quality medium)
Tokyo Research Lab study, 1987	This study was only available as a short summary on the EPA HPVIS database. This summary did not have information about chemical purity or source, primary methodological information, and only 2 dogs per dose were exposed.			
Unnamed skin sensitization study 2015	OECD 429, GLP study	Mixture of chemicals	Moderate (skin application in DMF)	High (study quality high)
Unnamed repeated dose, reproductive & developmental study 2015	OECD 422, GLP	Mixture of chemicals	Moderate (treatment via oral gavage)	High (study quality high)

Table 10a. 2,4,6-TTBP Human Health Hazard Summary Table – Body Weight, Organ Weight, Renal, Neurological

Oral Exposure Studies									
Study	**Study Quality**	**Doses (mg/kg/day)**	**Species**	**Dosing**	**Medium**	**Body Weight**	**Organ Weight**	**Renal**	**Neuro**
Chronic Exposure, Adults									
Matsumoto et al. 1991	Medium	0, 30, 100, 300, 1000 ppm	Rat	24 months	Diet	↓ weight gain 1000	↑ liver, kidney 100, ↑ adrenal 1000	NC	NC
Sub-Acute/Sub-chronic Oral Exposure – Adults									
Repeated dose/ repro/ developmental study 2015	High	0, 3, 10, 30	Rat	21-56 days	Gavage (corn oil)	↓ during lactation 10	↑ liver 10	NC	NC
Study	**Study Quality**	**Doses (mg/kg/day)**	**Species**	**Dosing**	**Medium**	**Body Weight**	**Organ Weight**	**Renal**	**Neuro**
Developmental Exposure - Pups									
Repeated dose/ repro/ developmental study 2015	High	0, 3, 10, 30	Rat	GD0-PND 4	Maternal Gavage (corn oil)	↓ 10			
Dermal Exposure Studies									
Study	**Study Quality**	**Doses (w/w)**	**Species**	**Dosing**	**Medium**	**Body Weight**	**Organ Weight**	**Skin Effects**	
Unnamed skin sensitization study 2015	High	0, 10, 25, 50%	Mouse	3 days	Dermal (in DMF)	NC		No visible irritation; ↑ lymph node size 25	

Note: number in column denotes a LOAEL; NC is no change; blank cells mean the endpoint was not measured

Table 10b. 2,4,6-TTBP Human Health Hazard Summary Table – Immunological, Endocrine, Hepatic, Reproductive, Developmental, Hematological

Oral Exposure Studies									
Study	**Study Quality**	**Doses (mg/kg/day)**	**Species**	**Dosing**	**Medium**	**Immuno**	**Hepatic**	**Repro**	**Hematological**
Chronic Exposure, Adults									
Matsumoto et al. 1991	Medium	0, 30, 100, 300, 1000 ppm	Rat	24 months	Diet	NC	Path 300	NC	↓ Hb, MCV, GOT, ↑ T-Chol, Plt, PL, γ-GTP 30
Sub-Acute/Sub-chronic Oral Exposure – Adults									
Repeated dose/ repro/ developmental study 2015	High	0, 3, 10, 30	Rat	21-56 days	Gavage (corn oil)	WBC & RBC changes 30	Path 10	NC	Total protein, albumin, cholesterol, 10
Study	**Study Quality**	**Doses (mg/kg/day)**	**Species**	**Dosing**	**Medium**	**Endo**	**Hepatic**	**Repro**	**Develop**
Developmental Exposure - Pups									
Repeated dose/ repro/ developmental study 2015	High	0, 3, 10, 30	Rat	GD0-PND 4	Maternal Gavage (corn oil)				↓ viability 10
Dermal Exposure Studies									
Study	**Study Quality**	**Doses (w/w)**	**Species**	**Dosing**	**Medium**	**Endo**	**Hepatic**	**Repro**	**Hematological**
Unnamed skin sensitization study 2015	High	0, 10, 25, 50%	Mouse	3 days	Dermal (in DMF)				

Note: number in column denotes a LOAEL; NC is no change; blank cells mean the endpoint was not measured

Pentachlorothiophenol (PCTP):

Human Health Hazard Summary:

- I could only access a single PCTP study from the published literature (Korhonen et al. (1982)). I reviewed this study using EPA's TSCA systematic review guidelines and assigned study quality scores of high, medium, low, or unacceptable. The details of my ratings for this study are in Appendix A, and the summary of strengths, weaknesses, reliability, and relevance are outlined below.
- General Strengths: Available published study.
- General Weaknesses: Test substance, test organism, confounding/variable control, and data presentation and analysis.
- General Relevance: Moderate, because the exposure pathway was injection of the test chemical into a chicken embryo's heart.

- General Reliability: Moderate, because the overall rating for the study was medium.
- Korhonen et al. (1982) injected chicken embryos with 5 µmoles PCTP and did not observe any changes in chick mortality or any embryo malformations.

DecaBDE

Metric	Descriptive Score	Numeric Score
Johansson et al. (2008)		
1 – Test Substance Identity (x2) – PBDE-209 no verification of identity	Medium	2 (4)
2 – Test Substance Source - Donated by Ake Bergman, not a known source	Medium	2
3 – Test Substance Purity – stated as >98%	High	1
Test Substance	**Low**	**2.33**
4 – Negative and Vehicle Controls (x2) – vehicle controls included	High	1 (2)
5 – Positive Controls –	N/A	
6 – Randomized Allocation of Animals – method for allocation of animals not reported	Low	3
Test Design	**Low**	**2.5**
7 – Preparation and Storage of Test Substance – information provided about preparation, but not storage	Medium	2
8 – Consistency of Exposure Administration – information provided about exposure administration, don't give information to ensure that all exposures were equal (e.g. same time of day).	Medium	2
9 – Reporting of Doses/Concentrations (x2) – doses were reported, but not without ambiguity (i.e. point estimate but no range)	Medium	2 (4)
10 – Exposure Frequency and Duration – single gavage exposure on PND 3	High	1
11 – Number of Exposure Groups and Dose/Concentration Spacing – number of exposure groups and dose spacing was adequate	High	1
12 – Exposure Route and Method – gavage with decaBDE in a vehicle that enhances bioavailability above what is typical in the diet, neonatal mice are too small to safely gavage	Low	3
Exposure Characterization	**Medium**	**2.17**
13 – Test Animal Characteristics (x2) – No information about mice breeding	Medium	2 (4)
14 – Adequacy and Consistency of Animal Husbandry Conditions – Good description, appropriate conditions	High	1
15 – Number of Animals per Group – adequate number of animals per group	High	1
Test Organism	**Medium**	**2**
16 – Outcome Assessment Methodology (x2)	High	1 (2)
17 – Consistency of Outcome Assessment	High	1
18 – Sampling Adequacy – outcome assessment occurred on individual animals, not on litters	High	1
19 – Blinding of Assessors – no information to suggest that assessors were blinded but data was collected in an automated manner	High	1
20 – Negative Control Response	High	1
Outcome Assessment	**High**	**1.2**
21 – Confounding Variables in Test Design and Procedures (x2) – no reported differences	High	1 (2)
22 – Health Outcomes Unrelated to Exposure – data on attrition not reported	Low	3
Confounding/Variable Control	**Low**	**2.5**
23 – Statistical Methods – unclear if litter is statistical unit	Medium	2
24 – Reporting of Data (x2) – Data wasn't reported for some outcomes (e.g. for maze test only stated that there were no significant differences, not what the numbers were)	Medium	2 (4)
Data Presentation and Analysis	**Low**	**3**
Total Score = 48/23	**Medium**	**2.1**

Notes: Neurodevelopmental study. Treated NMRI mice at PND 3 with one oral gavage dose of decaBDE in lipophilic vehicle (enhances bioavailability) and measured behavior (neuronal effects) at 2 and 4 months of age. Doses were 0, 1.34, 2.2, 14, and 20.1 mg/kg. no overt signs of clinical toxicity or changes in body weight with PBDE treatment. Spontaneous movement: Mice treated at 2.2 mg/kg and above were significantly less active at early time points, and at 14 mg/kg and above were significantly more active at later time points. Slight decrease in habituation behavior at 2.2 mg/kg and higher. Significant change in nicotine-induced locomotion with increasing dose, starting at 14 mg/kg. No significant effects on performance in elevated plus-maze.

Metric	Descriptive Score	Numeric Score
National Toxicology Program (1986)		
1 – Test Substance Identity (x2) –	High	1 (2)
2 – Test Substance Source –	High	1
3 – Test Substance Purity – 95%, contained some less brominated diphenyl ethers	Medium	2
4 – Negative and Vehicle Controls (x2) –	High	1 (2)
5 – Positive Controls – no positive control required	N/A	
6 – Randomized Allocation of Animals –	High	1
7 – Preparation and Storage of Test Substance –	High	1
8 – Consistency of Exposure Administration –	High	1
9 – Reporting of Doses/Concentrations (x2) –	High	1 (2)
10 – Exposure Frequency and Duration –	High	1
11 – Number of Exposure Groups and Dose/Concentration Spacing – several effects occurred at the lowest tested dose – would prefer a study with a NOAEL	Medium	2
12 – Exposure Route and Method –	High	1
13 – Test Animal Characteristics (x2) –	High	1 (2)
14 – Adequacy and Consistency of Animal Husbandry Conditions –	High	1
15 – Number of Animals per Group –	High	1
16 – Outcome Assessment Methodology (x2) –	High	1 (2)
17 – Consistency of Outcome Assessment –	High	1
18 – Sampling Adequacy –	High	1
19 – Blinding of Assessors – blinding not required for initial evaluation; in-depth evaluation was blinded	High	1
20 – Negative Control Response –	High	1
21 – Confounding Variables in Test Design and Procedures (x2) –	High	1 (2)
22 – Health Outcomes Unrelated to Exposure – substantial attrition amongst control groups	Low	3
23 – Statistical Methods –	High	1
24 – Reporting of Data (x2) –	High	1 (2)
Total Score = 34/23	**High**	**1.48**

Notes: From ATSDR 2017 “However, although it was concluded that there was some evidence of carcinogenicity in male and female rats based on “neoplastic nodules,” this is a poorly defined and understood term that is no longer used by NTP to characterize hepatoproliferative lesions in rats.”

No effects of 14 day and 13 week exposure studies. Daily consumption of DecaBDE estimated at 1120 mg/kg and 2240 mg/kg for low and high dose male rats, and 1200 mg/kg and 2550 mg/kg for low and high dose female rats. Daily consumption of DecaBDE estimated at 3200 mg/kg and 6650 mg/kg for low and high dose male mice, and 3760 mg/kg and 7780 mg/kg for low and high dose female mice. Hepatocellular effects in male mice were not dose-dependent (nor were they present in female mice). DecaBDE was not mutagenic in in vitro tests. Conclude that there is some evidence of carcinogenicity in rats; equivocal evidence in male mice; and no evidence in female mice.

Metric	Descriptive Score	Numeric Score
Liang et al. (2010)		
1 – Test Substance Identity (x2) –	High	1 (2)
2 – Test Substance Source –	High	1
3 – Test Substance Purity – > 98%	High	1
4 – Negative and Vehicle Controls (x2) –	High	1 (2)
5 – Positive Controls –	N/A	
6 – Randomized Allocation of Animals –	High	1
7 – Preparation and Storage of Test Substance –	High	1
8 – Consistency of Exposure Administration – Information not provided	Low	3
9 – Reporting of Doses/Concentrations (x2) – used the word "infected", but it is not clear if any animals were infected with anything. Does this mean treated?	Unacceptable	
10 – Exposure Frequency and Duration – Exposure frequency reported only in the Abstract	Low	3
11 – Number of Exposure Groups and Dose/Concentration Spacing – Jumps from 0.1 to 40 mg/kg	Medium	2
12 – Exposure Route and Method – Gavage, but no information provided about method	Low	3
13 – Test Animal Characteristics (x2) – Test animal source was not reported	Low	3 (6)
14 – Adequacy and Consistency of Animal Husbandry Conditions –	High	1
15 – Number of Animals per Group – 3 per sex per dose/time	Medium	2
16 – Outcome Assessment Methodology (x2) – Some of the outcome assessment methods were not reported	Unacceptable	
17 – Consistency of Outcome Assessment –	High	1
18 – Sampling Adequacy –	High	1
19 – Blinding of Assessors – all automated	High	1
20 – Negative Control Response – no specific discussions about the responses of control animals	Medium	2
21 – Confounding Variables in Test Design and Procedures (x2) – No reported differences	High	1
22 – Health Outcomes Unrelated to Exposure – Did not discuss health outcomes unrelated to exposure	Medium	2
23 – Statistical Methods –	High	1
24 – Reporting of Data (x2) – Did not discuss inconsistent results from dosing for different periods of time	Low	3 (6)
Total Score	**Unacceptable**	

Notes: Adult CD-1 Swiss mice were treated starting at 10 weeks of age with BDE-209 dissolved in peanut oil by gavage to attain doses of 0, 0.1, 40, 80, and 160 mg/kg. Refer to infected groups of mice – infected with what? The English is poor in this paper. Treated for 15, 30, or 60 days – daily? Animals treated for 60 days were allowed to recover for 20, 40, or 60 days, to determine the reversibility of the responses (called self-repair). No sig change in brain weight (brain index? What is this?) but a decrease in female body weight at the highest dose. Measured enzyme activity in brain, but no information about how (according to manufacturer's instructions – what manufacturer?). TchE effects after 15 days of exposure, but not 30 or 60 days?

Metric	Descriptive Score	Numeric Score
Fujimoto et al. (2011)		
1 – Test Substance Identity (x2) – DBDE, no independent verification	Medium	2 (4)
2 – Test Substance Source – Wako Pure Chemical Industries	High	1
3 – Test Substance Purity – > 98%	High	1
Test Substance	**Medium**	**2**
4 – Negative and Vehicle Controls (x2) –	High	1 (2)
5 – Positive Controls –	N/A	
6 – Randomized Allocation of Animals –	High	1
Test Design	**High**	**1.5**
7 – Preparation and Storage of Test Substance – Information about preparation and storage not provided	Low	3
8 – Consistency of Exposure Administration –	High	1
9 – Reporting of Doses/Concentrations (x2) –	High	1 (2)
10 – Exposure Frequency and Duration – Did not report total days of exposure – just GD 10 to PND 20 (gestation is not equal in all animals)	Medium	2
11 – Number of Exposure Groups and Dose/Concentration Spacing –	High	1
12 – Exposure Route and Method –	High	1
Exposure Characterization	**Medium**	**1.7**
13 – Test Animal Characteristics (x2) –	High	1 (2)
14 – Adequacy and Consistency of Animal Husbandry Conditions –	High	1
15 – Number of Animals per Group –	High	1
Test Organism	**High**	**1.33**
16 – Outcome Assessment Methodology (x2) –	High	1 (2)
17 – Consistency of Outcome Assessment –	High	1
18 – Sampling Adequacy –	High	1
19 – Blinding of Assessors – not reported	Low	3
20 – Negative Control Response – non-dose responsive endpoints weren't discussed very well	Medium	2
Outcome Assessment	**Medium**	**1.8**
21 – Confounding Variables in Test Design and Procedures (x2) –	High	1 (2)
22 – Health Outcomes Unrelated to Exposure –	High	1
Confounding/Variable Control	**High**	**1.5**
23 – Statistical Methods – Used litter as statistical unit as appropriate	High	1
24 – Reporting of Data (x2) – Negative data only reported in text, not in figures or tables	Medium	2 (4)
Data Presentation and Analysis	**Low**	**2.5**
Total Score = 40/23	**Medium**	**1.1**

Notes: Treated pregnant CD (SD) IGS rats (soy-free diet) with decaBDE at 0, 10, 100, or 1000 ppm from GD 10 to PND 20. Equivalent to 0, 0.7, 7, 66.3 mg/kg/day. Some pups were necropsied at this point, and the rest were left untreated until 11 weeks of age. No evidence of maternal toxicity, except for increased thyroid weight with 10 or 1000 ppm decaBDE. No reproductive effects in dams or offspring. At PND 20 sig increased liver weight in males at 10 and 1000 ppm, and in females at 1000 ppm. Relative brain weight was decrease in 10 and 100 ppm males and 100 ppm females. In male offspring serum T3 and T4 was measured and was decreased in the 1000 ppm group at PND 20 and PNW 11, respectively. Diffuse hypertrophy of thyroid follicular cells at PND20 – stat sig incidence and severity in males only at 1000 ppm (no stat sig difference at PNW 11). Increased cytoplasmic eosinophilia in kidneys of males at 100 ppm and up, and in females at 10 ppm and higher. No effects of decaBDE on hippocampal CA1 neurons, non-dose related effects on oligodendoglial development parameters.

Significant effects: increased maternal thyroid weight (non dose-responsive); pups at PND20: increased liver weight (LOAEL 66.3 mg/kg; NOAEL 7 mg/kg), liver cell hypertrophy (LOAEL 0.7 mg/kg), increased renal cytoplasmic eosinophilia (LOAEL 0.7 mg/kg), decreased T3 hormone (LOAEL 66.3 mg/kg; NOAEL 7 mg/kg), increased follicular cell hypertrophy (non dose-responsive); PNW 11 pups had decreased area of corpus callosum and a decreased number of SNPase-positive oligodendrocytes (non dose-responsive).

Non-significant effects: No change in maternal and offspring reproductive parameters; no change in maternal body weight, or maternal thyroid follicular cell morphology; PND1 pups: no evidence of fetotoxicity or embryotoxicity; PND20 pups: no change in T4 or TSH hormones; PNW 11 pups: no change in hippocampal CA1 neurons, no change in T3 or TSH hormones, no significant dose-responsive change in organ weights, no significant difference in thyroid follicular cell morphology, no significant changes in other histopathological analyses (other than those above).

Metric	Descriptive Score	Numeric Score
Viberg et al. (2003)		
1 – Test Substance Identity (x2) – decaBDE 209 – no test substance information provided	Unacceptable	
2 – Test Substance Source – No source information	Low	3
3 – Test Substance Purity – No purity information	Low	3
Test Substance		
4 – Negative and Vehicle Controls (x2) –		
5 – Positive Controls –		
6 – Randomized Allocation of Animals –		
Test Design		
7 – Preparation and Storage of Test Substance –		
8 – Consistency of Exposure Administration –		
9 – Reporting of Doses/Concentrations (x2) –		
10 – Exposure Frequency and Duration –		
11 – Number of Exposure Groups and Dose/Concentration Spacing –		
12 – Exposure Route and Method –		
Exposure Characterization		
13 – Test Animal Characteristics (x2) –		
14 – Adequacy and Consistency of Animal Husbandry Conditions –		
15 – Number of Animals per Group –		
Test Organism		
16 – Outcome Assessment Methodology (x2) –		
17 – Consistency of Outcome Assessment –		
18 – Sampling Adequacy –		
19 – Blinding of Assessors –		
20 – Negative Control Response –		
Outcome Assessment		
21 – Confounding Variables in Test Design and Procedures (x2) –		
22 – Health Outcomes Unrelated to Exposure –		
Confounding/Variable Control		
23 – Statistical Methods –		
24 – Reporting of Data (x2) –		
Data Presentation and Analysis		
Total Score =	**Unacceptable**	

Study Details: PBDE-209 dissolved in egg lecithin and peanut oil (enhances distribution); single gavage dose at PND 3 (0, 2.22, 20.1 mg/kg), or at PND 10 (0, 1.34, 13.4, or 20.1 mg/kg), or at PND 19 (0, 2.22, 20.1 mg/kg). Tested behavior at 2, 4, or 6 months of age.

Significant Effects:

Non-Significant Effects:

Notes: No test source information provided; reference considered unacceptable and review stopped.

Metric	Descriptive Score	Numeric Score
Sakamoto et al. (2013)		
1 – Test Substance Identity (x2) – DecaBDE; no independent verification	Medium	2 (4)
2 – Test Substance Source – Wako Pure Chemical Industries	High	1
3 – Test Substance Purity – > 98%	High	1
Test Substance	**Medium**	**2**
4 – Negative and Vehicle Controls (x2) – no vehicle-only control for DEN administration for 27 week exposure study	Medium	2 (4)
5 – Positive Controls – piperonyl butoxide positive control	High	1
6 – Randomized Allocation of Animals – No information about randomization provided	Low	3
Test Design	**Low**	**2.67**
7 – Preparation and Storage of Test Substance – minimal information about storage and preparation of test diet	Medium	2
8 – Consistency of Exposure Administration –	High	1
9 – Reporting of Doses/Concentrations (x2) – Have to estimate mg/kg dose	Medium	2 (4)
10 – Exposure Frequency and Duration –	High	1
11 – Number of Exposure Groups and Dose/Concentration Spacing – Only one dose of decaBDE used	Medium	2
12 – Exposure Route and Method –	High	1
Exposure Characterization	**Medium**	**1.83**
13 – Test Animal Characteristics (x2) –	High	1 (2)
14 – Adequacy and Consistency of Animal Husbandry Conditions – some animal husbandry information not provided	Medium	2
15 – Number of Animals per Group –	High	1
Test Organism	**High**	**1.67**
16 – Outcome Assessment Methodology (x2) –	High	1 (2)
17 – Consistency of Outcome Assessment –	High	1
18 – Sampling Adequacy –	High	1
19 – Blinding of Assessors – no information about blinding	Medium	2
20 – Negative Control Response –	High	1
Outcome Assessment	**High**	**1.4**
21 – Confounding Variables in Test Design and Procedures (x2) –	High	1 (2)
22 – Health Outcomes Unrelated to Exposure –	High	1
Confounding/Variable Control	**High**	**1.5**
23 – Statistical Methods –	High	1
24 – Reporting of Data (x2) –	High	1 (2)
Data Presentation and Analysis	**High**	**1.5**
Total Score = 43/24	**Medium**	**1.8**

Study Details: 6 week-old C4H/HeNCrlCrlj male mice fed a diet containing 50,000 ppm decaBDE for 1 week or 4 weeks; 3rd group of mice were initiated with an injection of diethylnitrosamine at 5 weeks, then were fed a diet containing 50,000 ppm decaBDE for 27 weeks, starting at 6 weeks old. Use ATSDR's estimate of 9100, 9400, and 9800 mg/kg for the 1, 4, and 27 week exposures.

Significant Effects: increased liver weights at 4 and 27 weeks of exposure, not 1 week; moderate hepatocellular hypertrophy and Cyp2B expression at 4 weeks & 27 weeks exposure; with 27 weeks decaBDE exposure after DEN injection, there was a statistically significant increase in "other type" hepatic foci, and a higher multiplicity of basophilic and "other type" proliferative lesions.

Non-Significant Effects: body weights; no change in hepatic neutrophil infiltration, focal necrosis, or vacuolization; no clinical signs in treatment group; no change in labeling indices in hepatocytes at 1 week exposure; with 27 weeks

decaBDE exposure after DEN injection, there was no change in the number of animals with eosinophilic or basophilic hepatic foci, or in hepatocellular adenomas.

Notes:

Metric	Descriptive Score	Numeric Score
Lee et al. (2010)		
1 – Test Substance Identity (x2) – BDE-209, not independently verified	Medium	2 (4)
2 – Test Substance Source – No source provided	Low	3
3 – Test Substance Purity – 98% pure	High	1
Test Substance	**Low**	**2.7**
4 – Negative and Vehicle Controls (x2) – Tables 2 and 3 stated that controls received DMSO in corn oil, but this wasn't in the methods section	Medium	2 (4)
5 – Positive Controls –	N/A	
6 – Randomized Allocation of Animals – No information on random allocation of pups fathered by same sire	Medium	2
Test Design	**Low**	**3**
7 – Preparation and Storage of Test Substance – No information on storage	Medium	2
8 – Consistency of Exposure Administration –	High	1
9 – Reporting of Doses/Concentrations (x2) –	High	1 (2)
10 – Exposure Frequency and Duration –	High	1
11 – Number of Exposure Groups and Dose/Concentration Spacing –	High	1
12 – Exposure Route and Method – oral gavage is not as relevant to dietary ingestion; and lipophilic carrier increases bioavailability	Medium	2
Exposure Characterization	**High**	**1.5**
13 – Test Animal Characteristics (x2) –	High	1 (2)
14 – Adequacy and Consistency of Animal Husbandry Conditions –	High	1
15 – Number of Animals per Group – Number of litters is not clear, can affect analysis	Medium	2
Test Organism	**High**	**1.67**
16 – Outcome Assessment Methodology (x2) –	High	1 (2)
17 – Consistency of Outcome Assessment –	High	1
18 – Sampling Adequacy –	High	1
19 – Blinding of Assessors – not reported	Medium	2
20 – Negative Control Response –no discussion about vehicle effects on rats	Medium	2
Outcome Assessment	**High**	**1.6**
21 – Confounding Variables in Test Design and Procedures (x2) – used Tween-80 for drug delivery, which has been shown to cause liver effects, although the control was also administered Tween-80	Medium	2 (4)
22 – Health Outcomes Unrelated to Exposure –	High	1
Confounding/Variable Control	**Low**	**2.5**
23 – Statistical Methods – not clear if the litter was used as the statistical unit	Medium	2
24 – Reporting of Data (x2) – histological information only presented in the text, with sample histology in the figures	Medium	2 (4)
Data Presentation and Analysis	**Low**	**3**
Total Score = 46/23	**Medium**	**2**

Study Details: Neonatal S-D rats treated with daily oral gavage of PBDE-209 (mixed in Tween-20 and corn oil, increases bioavailability) from PND 10 through PND 42 at doses of 0, 100, 300, or 600 mg/kg.

Significant Effects: Dose-dependent increase in liver, thyroid, and adrenal gland weights (liver: NOAEL 100 mg/kg, LOAEL 300 mg/kg; thyroid and adrenal NOAEL 300 mg/kg, LOAEL 600 mg/kg); increased expression of CYP enzymes in liver with decaBDE treatment; decreased serum T3 hormone levels (LOAEL 100 mg/kg) and increased serum TSH levels (NOAEL 100 mg/kg, LOAEL 300 mg/kg); changes in thyroid and liver histology with decaBDE treatment (NOAEL 100 mg/kg, LOAEL 300 mg/kg).

Non-Significant Effects: No clinical signs of toxicity, no changes in body weight; no changes in weight of kidneys, testes, prostate and epididymis glands; no change in gene expression of steroidogenesis-related genes; no effect of decaBDE on serum T4 levels; normal spermatogenesis and testicular morphology in decaBDE-treated rats;

Notes: Suchecka 2011 et al introduced some information about potential reliability issues with this study (reflected in my rankings)

Metric	Descriptive Score	Numeric Score
Liu et al. (2012)		
1 – Test Substance Identity (x2) – PBDE-209 not independently verified	Medium	2 (4)
2 – Test Substance Source – Sigma-Aldritch	High	1
3 – Test Substance Purity – 98%	High	1
Test Substance	**Medium**	**2**
4 – Negative and Vehicle Controls (x2) –	High	1 (2)
5 – Positive Controls –		
6 – Randomized Allocation of Animals –	High	1
Test Design	**High**	**1.5**
7 – Preparation and Storage of Test Substance – Little information about test substance preparation and no storage information	Medium	2
8 – Consistency of Exposure Administration – rats were dosed from age 21 days until pups were weaned – were controls and exposed dosed for the same period of time?	Low	3
9 – Reporting of Doses/Concentrations (x2) –	High	1 (2)
10 – Exposure Frequency and Duration – Duration is not clear (about 14 weeks)	Medium	2
11 – Number of Exposure Groups and Dose/Concentration Spacing – only one dose group	Medium	2
12 – Exposure Route and Method – oral gavage is not as relevant to dietary ingestion; and lipophilic carrier increases bioavailability; intragastric administration is assumed to be oral gavage – no details about how this was done	Low	3
Exposure Characterization	**Low**	**2.33**
13 – Test Animal Characteristics (x2) – Little information about how rat litters were controlled	Medium	2 (4)
14 – Adequacy and Consistency of Animal Husbandry Conditions – Some information not provided	Medium	2
15 – Number of Animals per Group –	High	1
Test Organism	**Low**	**2.33**
16 – Outcome Assessment Methodology (x2) – not clear what "spleen index number" or "thymus index number" is, or how it is calculated, very unclear description of lymphocyte viability assay	Low	3 (6)
17 – Consistency of Outcome Assessment –	High	1
18 – Sampling Adequacy –	High	1
19 – Blinding of Assessors –	High	1
20 – Negative Control Response – No discussion of the potential effects of the vehicle (arachis oil) on the measured effects	Medium	2
Outcome Assessment	**Medium**	**2.2**
21 – Confounding Variables in Test Design and Procedures (x2) – may be differences in time to pregnancy – not addressed	Medium	2 (4)
22 – Health Outcomes Unrelated to Exposure – Not discussed	Medium	2
Confounding/Variable Control	**Low**	**6**
23 – Statistical Methods –	High	1
24 – Reporting of Data (x2) – data reporting was unclear (e.g. all histological analysis was combined into one metric)	Medium	2 (4)
Data Presentation and Analysis	**Low**	**2.5**
Total Score = 52/23	**Low**	**2.3**

Study Details: female S-D rats administered 300 mg/kg/day intragastrically (oral gavage?) from PND 21 – weaning at 3 weeks (> 14 week exposure). PDBE-209 was dissolved in arachis oil (presumably increases bioavailability); rats euthanized and assays completed when pups were weaned.

Significant Effects: Decreased body weight, increased spleen weight and spleen index number (?); decrease in number of CD3+, CD4+ lymphocytes, increase in CD4-CD8- lymphocytes; significant change in lymphocyte viability (I think); evidence of histological changes in thymus, spleen, liver and ovaries.

Non-Significant Effects: No change in thymus weigh or thymus index number (?); No change in CD4+CD8+, CD4-CD8+ or CD4+CD8- lymphocytes.

Notes:

Metric	Descriptive Score	Numeric Score
Tseng et al. (2008)		
1 – Test Substance Identity (x2) – PBDE-209 not independently verified	Medium	2 (4)
2 – Test Substance Source – Sigma	High	1
3 – Test Substance Purity – 98%	High	1
Test Substance	**Medium**	**2**
4 – Negative and Vehicle Controls (x2) –	High	1
5 – Positive Controls –	N/A	
6 – Randomized Allocation of Animals –	High	1
Test Design	**High**	**1**
7 – Preparation and Storage of Test Substance – PBDE-209 mixed in corn oil, no storage information	Medium	2
8 – Consistency of Exposure Administration –	High	1
9 – Reporting of Doses/Concentrations (x2) –	High	1 (2)
10 – Exposure Frequency and Duration –	High	1
11 – Number of Exposure Groups and Dose/Concentration Spacing – big spacing between doses	Medium	2
12 – Exposure Route and Method – oral gavage is not as relevant to dietary ingestion; and lipophilic carrier increases bioavailability;	Medium	2
Exposure Characterization	**High**	**1.67**
13 – Test Animal Characteristics (x2) –	High	1 (2)
14 – Adequacy and Consistency of Animal Husbandry Conditions –	High	1
15 – Number of Animals per Group –	High	1
Test Organism	**High**	**1.33**
16 – Outcome Assessment Methodology (x2) –	High	1 (2)
17 – Consistency of Outcome Assessment –	High	1
18 – Sampling Adequacy –	High	1
19 – Blinding of Assessors – No mention of blinding of assessors	Medium	2
20 – Negative Control Response –	High	1
Outcome Assessment	**High**	**1.4**
21 – Confounding Variables in Test Design and Procedures (x2) –	High	1 (2)
22 – Health Outcomes Unrelated to Exposure – not discussed	Medium	2
Confounding/Variable Control	**Medium**	**2**
23 – Statistical Methods – Litter was statistical unit, as appropriate	High	1
24 – Reporting of Data (x2) – some non-significant data were not shown	Medium	2 (4)
Data Presentation and Analysis	**Low**	**2.5**
Total Score = 38/23	**High**	**1.65**

Study Details: Pregnant female CD-1 mice were gavaged with PBDE-209 in corn oil daily from GD 0-17 with 0, 10, 500, or 1500 mg/kg. Dams were euthanized at weaning. 3 male offspring per litter were euthanized at PND 71 (no investigation of female pups).

Significant Effects: slight increase in liver EROD enzyme in male pups (LOAEL 1500 mg/kg, NOAEL 500 mg/kg); significant decrease in male pups T3 hormone at 10 and 1500 mg/kg (non dose-responsive). Liver cell hypertrophy and degeneration in male pups at all doses (not quantified, assume NOAEL is 10 mg/kg), and minor histological changes in the thyroid gland (NOAEL 500 mg/kg, LOAEL 1500 mg/kg).

Non-Significant Effects: no difference in dam's body weight, gestational length, litter size, or average pup weight. No significant developmental delays in pups; no significant effects on dam's organ weights (brain, thymus, liver, kidney, adrenal glands, spleen, or ovaries). No significant effects on male pup's body or organ weights (brain, thymus, liver, kidney, adrenal glands or spleen). No effects on male pups live UDPGT enzyme. No change in male pups serum T4 hormone.

Metric	Descriptive Score	Numeric Score
Tseng et al. (2013)		
1 – Test Substance Identity (x2) – PBDE-209 not independently verified	Medium	2 (4)
2 – Test Substance Source – Sigma	High	1
3 – Test Substance Purity – 98%	High	1
Test Substance	**Medium**	**2**
4 – Negative and Vehicle Controls (x2) –	High	1
5 – Positive Controls –	N/A	
6 – Randomized Allocation of Animals –	High	1
Test Design	**High**	**1**
7 – Preparation and Storage of Test Substance – PBDE-209 mixed in corn oil, solution remade every week, no storage information	Medium	2
8 – Consistency of Exposure Administration –	High	1
9 – Reporting of Doses/Concentrations (x2) –	High	1 (2)
10 – Exposure Frequency and Duration –	High	1
11 – Number of Exposure Groups and Dose/Concentration Spacing – big spacing between doses	Medium	2
12 – Exposure Route and Method – oral gavage is not as relevant to dietary ingestion; and lipophilic carrier increases bioavailability;	Medium	2
Exposure Characterization	**High**	**1.67**
13 – Test Animal Characteristics (x2) –	High	1 (2)
14 – Adequacy and Consistency of Animal Husbandry Conditions –	High	1
15 – Number of Animals per Group –	High	1
Test Organism	**High**	**1.33**
16 – Outcome Assessment Methodology (x2) –	High	1 (2)
17 – Consistency of Outcome Assessment –	High	1
18 – Sampling Adequacy –	High	1
19 – Blinding of Assessors – No mention of blinding of assessors	Medium	2
20 – Negative Control Response –	High	1
Outcome Assessment	**High**	**1.4**
21 – Confounding Variables in Test Design and Procedures (x2) –	High	1 (2)
22 – Health Outcomes Unrelated to Exposure – not discussed	Medium	2
Confounding/Variable Control	**Medium**	**2**
23 – Statistical Methods – Litter was statistical unit, as appropriate	High	1
24 – Reporting of Data (x2) – some non-significant data were not shown	Medium	2 (4)
Data Presentation and Analysis	**Low**	**2.5**
Total Score = 38/23	**High**	**1.65**

Study Details: Pregnant female CD-1 mice were gavaged with PBDE-209 in corn oil daily from GD 0-17 with 0, 10, 500, or 1500 mg/kg. 3 male offspring per litter were euthanized at PND 71 (no investigation of female pups).

Significant Effects: Increase in sperm morphological abnormalities (NOAEL 500 mg/kg, LOAEL 1500 mg/kg); increase in sperm DNA damage parameters (non dose-responsive); increase in sperm hydrogen peroxide (non-dose responsive); significant reduction in anogenital distance (NOAEL 500 mg/kg, LOAEL 1500 mg/kg); increased vacuolization of testis cells (no statistics, but likely significantly higher at 1500 mg/kg).

Non-Significant Effects: No effect on body weight, or weights of testis, epididymis, cauda epididymis, or seminal vesicles; no effect on sperm count, motility, or motion parameters; no change in sperm superoxide generation; no significant change in testis index or serum testosterone levels;

Metric	Descriptive Score	Numeric Score
Buratovic et al. (2014)		
1 – Test Substance Identity (x2) – decaBDE – no independent verification	Medium	2 (4)
2 – Test Substance Source – Donated by Ake Bergman, not a known source	Medium	2
3 – Test Substance Purity – 98%	High	1
Test Substance	**Low**	**2.33**
4 – Negative and Vehicle Controls (x2) –	High	1
5 – Positive Controls –	N/A	
6 – Randomized Allocation of Animals – Litters weren't randomized into treatment groups	Low	3
Test Design	**Medium**	**2**
7 – Preparation and Storage of Test Substance – Dissolved in egg lecithin and peanut oil, no storage information	Medium	2
8 – Consistency of Exposure Administration –	High	1
9 – Reporting of Doses/Concentrations (x2) –	High	1 (2)
10 – Exposure Frequency and Duration –	High	1
11 – Number of Exposure Groups and Dose/Concentration Spacing –	High	1
12 – Exposure Route and Method – oral gavage is not as relevant to dietary ingestion; and lipophilic carrier increases bioavailability; neonatal mice are too small to safely gavage	Low	3
Exposure Characterization	**Medium**	**1.7**
13 – Test Animal Characteristics (x2) –	High	1 (2)
14 – Adequacy and Consistency of Animal Husbandry Conditions –	High	1
15 – Number of Animals per Group –	High	1
Test Organism	**High**	**1.3**
16 – Outcome Assessment Methodology (x2) – all assessments not completed on all dose groups (dropped the lowest dose groups)	Medium	2 (4)
17 – Consistency of Outcome Assessment –	High	1
18 – Sampling Adequacy –	High	1
19 – Blinding of Assessors – no mention of blinding	Medium	2
20 – Negative Control Response –	High	1
Outcome Assessment	**Medium**	**1.8**
21 – Confounding Variables in Test Design and Procedures (x2) –	High	1 (2)
22 – Health Outcomes Unrelated to Exposure –	High	1
Confounding/Variable Control	**High**	**1.5**
23 – Statistical Methods – statistical unit does not seem to be the litter	Medium	2
24 – Reporting of Data (x2) – primary slot blot data not shown	Medium	2 (4)
Data Presentation and Analysis	**Low**	**3**
Total Score = 43/23	**Medium**	**1.9**

Study Details: PND3 NMRI mice were given a single oral gavage dose of decaBDE in egg lecithin + peanut oil at concentrations of 0, 1.4, 6, or 14 umol/kg (equivalent to 1.34, 5.76, 13.43 mg/kg). Mice assayed at 2 months old for susceptibility to cholinergic agents, at 2 and 4 months for spontaneous behavior, and male mice were assayed in a swim maze at 5 and 7 months old. Mice were euthanized at 7 months old.

Significant Effects: Decreased locomotion, rearing, and total activity in the first 20 minutes of the spontaneous behavior test at 2 months old in male and female mice (LOAEL 1.34 mg/kg), increased locomotion, rearing, and activity in the last 40-60 minutes (LOAEL 5.76, NOAEL 1.34); similar pattern at 4 months, but with lesser effects. Sig effects on locomotion, rearing, and total activity in males exposed to paraoxon and treated with decaBDE versus controls (NOAEL 1.34 mg/kg, LOAEL 5.76 mg/kg); similar effects of nicotine in females. Deca-BDE treated mice had a significantly increased latency in the swim maze on the last trials (LOAEL 5.76 mg/kg, 1.34 mg/kg not tested); at 7 months, swim maze latency was

significantly greater in decaBDE-treated mice for every swim trial (LOAEL 5.76 mg/kg, 1.34 mg/kg not tested); increase in tau, CAMKII, Gap-43 and synaptophysin in the cortex and hippocampus of male rats at 7 months, and of tau in female rats at 7 months (LOAEL 13.43 mg/kg, no lower doses tested).

Non-Significant Effects: No change in body weight or visible clinical toxicity; No difference between decaBDE and control mice on the first 27 swim trials at 5 months.

Notes:

Metric	Descriptive Score	Numeric Score
Zhang et al. (2013)		
1 – Test Substance Identity (x2) – BDE-209– no independent verification	Medium	2 (4)
2 – Test Substance Source –Tokyo Chemical Industry company	High	1
3 – Test Substance Purity – not stated	Low	3
Test Substance	**Low**	**2.33**
4 – Negative and Vehicle Controls (x2) –		
5 – Positive Controls –		
6 – Randomized Allocation of Animals – No information about this		
Test Design		
7 – Preparation and Storage of Test Substance – dissolved in corn oil		
8 – Consistency of Exposure Administration –		
9 – Reporting of Doses/Concentrations (x2) –		
10 – Exposure Frequency and Duration – exposure frequency not reported	Unacceptable	
11 – Number of Exposure Groups and Dose/Concentration Spacing –		
12 – Exposure Route and Method – exposure method not reported	Unacceptable	
Exposure Characterization		
13 – Test Animal Characteristics (x2) – No start age provided		
14 – Adequacy and Consistency of Animal Husbandry Conditions –	High	1
15 – Number of Animals per Group –		
Test Organism		
16 – Outcome Assessment Methodology (x2) –		
17 – Consistency of Outcome Assessment –		
18 – Sampling Adequacy –		
19 – Blinding of Assessors –		
20 – Negative Control Response –		
Outcome Assessment		
21 – Confounding Variables in Test Design and Procedures (x2) –		
22 – Health Outcomes Unrelated to Exposure –		
Confounding/Variable Control		
23 – Statistical Methods –		
24 – Reporting of Data (x2) –		
Data Presentation and Analysis		
Total Score =	**Unacceptable**	

Study Details: Adult male S-D rats were treated orally with BDE-209 in corn oil daily (?) for 8 weeks at doses of 0.05, 1, and 20 mg/kg (no start age was given, no exposure frequency was provided, no method for dosing was given). Rats were euthanized 24 hours after final treatment.

Significant Effects:

Non-Significant Effects:

Notes:

Metric	Descriptive Score	Numeric Score
Xing et al. (2009)		
1 – Test Substance Identity (x2) – PBDE209 – no independent verification	Medium	2 (4)
2 – Test Substance Source – Alfa Aesar	High	1
3 – Test Substance Purity – 99%	High	1
Test Substance		
4 – Negative and Vehicle Controls (x2) – exposure protocol of control not specified; because the intervention is substantive (daily oral gavage), each exposure protocol should have its own control	Unacceptable	
5 – Positive Controls –		
6 – Randomized Allocation of Animals – no discussion of randomization	Low	3
Test Design		
7 – Preparation and Storage of Test Substance – prepared in egg lecithin and peanut oil, no mention of storage	Medium	2
8 – Consistency of Exposure Administration –		
9 – Reporting of Doses/Concentrations (x2) –		
10 – Exposure Frequency and Duration –		
11 – Number of Exposure Groups and Dose/Concentration Spacing –		
12 – Exposure Route and Method –		
Exposure Characterization		
13 – Test Animal Characteristics (x2) –		
14 – Adequacy and Consistency of Animal Husbandry Conditions –		
15 – Number of Animals per Group –		
Test Organism		
16 – Outcome Assessment Methodology (x2) –		
17 – Consistency of Outcome Assessment –		
18 – Sampling Adequacy –		
19 – Blinding of Assessors –		
20 – Negative Control Response –		
Outcome Assessment		
21 – Confounding Variables in Test Design and Procedures (x2) –		
22 – Health Outcomes Unrelated to Exposure –		
Confounding/Variable Control		
23 – Statistical Methods – Didn't control for litter effects	Low	3
24 – Reporting of Data (x2) –		
Data Presentation and Analysis		
Total Score =	**Unacceptable**	

Study Details: Wistar rats were orally gavaged daily with 20 umol PBDE/kg (19.1 mg/kg) during gestation (PG), or the dams were dosed during lactation (LAM), or the pups were dosed during lactation (LAI), or the pups were dosed for 20 days after weaning, or the dams were dosed through pregnancy and lactation, then the pups were dosed 20 days after weaning (all stages were 19-21 days long), extracellular recordings were taken at PND 60 (20 days after last dose). The exposure protocol of control not specified; because the intervention is substantive (daily oral gavage), each exposure protocol should have its own control – this makes the study unacceptable.

Significant Effects:

Non-Significant Effects:

Notes:

Metric	Descriptive Score	Numeric Score
Heredia et al. (2012)		
1 – Test Substance Identity (x2) – Saytex 102, not independently verified	Medium	2 (4)
2 – Test Substance Source – LGC Promochem	High	1
3 – Test Substance Purity – Not specified	Low	3
Test Substance	**Low**	**2.7**
4 – Negative and Vehicle Controls (x2) –	High	1 (2)
5 – Positive Controls –	N/A	
6 – Randomized Allocation of Animals –	High	1
Test Design	**High**	**1.3**
7 – Preparation and Storage of Test Substance – Sunflower oil, no information about storage	Medium	2
8 – Consistency of Exposure Administration –	High	1
9 – Reporting of Doses/Concentrations (x2) –	High	1 (2)
10 – Exposure Frequency and Duration –	High	1
11 – Number of Exposure Groups and Dose/Concentration Spacing – Only one dose group	Medium	2
12 – Exposure Route and Method – oral gavage is not as relevant to dietary ingestion; and lipophilic carrier increases bioavailability; exposure method not provided (not details about gavage)	Low	3
Exposure Characterization	**Medium**	**2**
13 – Test Animal Characteristics (x2) –	High	1 (2)
14 – Adequacy and Consistency of Animal Husbandry Conditions –	High	1
15 – Number of Animals per Group –	High	1
Test Organism	**High**	**1.33**
16 – Outcome Assessment Methodology (x2) –	High	1 (2)
17 – Consistency of Outcome Assessment –	High	1
18 – Sampling Adequacy –	High	1
19 – Blinding of Assessors – no blinding described, some of the tests were highly subjective (e.g. FOB)	Low	3
20 – Negative Control Response –	High	1
Outcome Assessment	**High**	**1.6**
21 – Confounding Variables in Test Design and Procedures (x2) –	High	1 (2)
22 – Health Outcomes Unrelated to Exposure –	High	1
Confounding/Variable Control	**High**	**1.5**
23 – Statistical Methods – no multiple-testing statistics used	Medium	2
24 – Reporting of Data (x2) –	High	1 (2)
Data Presentation and Analysis	**Medium**	**2**
Total Score = 41/23	**Medium**	**1.8**

Study Details: 3 month old Tg2576 male mice were treated by oral gavage daily for 15 days with 0 or 20 mg/kg BDE-209 in sunflower oil, and were euthanized at the end of the exposure period.

Significant Effects: FOB parameter arousal (wakefulness) was decreased in BDE-209 treated mice; significant increase in some zero maze test parameters (suggests decreased anxiety in BDE-209 exposed mice);

Non-Significant Effects: no change in body weight or food/water consumption with BDE-209 treatment; 17/18 FOB parameters not different between control and exposed; no change in light/dark test; some zero maze test parameters the same between groups; no difference in water maze test parameters between groups

Notes:

Metric	Descriptive Score	Numeric Score
Rice et al. (2007)		
1 – Test Substance Identity (x2) – decaBDE, no independent verification	Medium	2 (4)
2 – Test Substance Source – Ake Bergman, Stockholm	Medium	2
3 – Test Substance Purity – 99.5%	High	1
Test Substance	**Low**	**2.33**
4 – Negative and Vehicle Controls (x2) –	High	1 (2)
5 – Positive Controls –	N/A	
6 – Randomized Allocation of Animals –	High	1
Test Design	**High**	**1.5**
7 – Preparation and Storage of Test Substance – discussed test substance preparation but not storage	Medium	2
8 – Consistency of Exposure Administration –	High	1
9 – Reporting of Doses/Concentrations (x2) –	High	1 (2)
10 – Exposure Frequency and Duration –	High	1
11 – Number of Exposure Groups and Dose/Concentration Spacing –	High	1
12 – Exposure Route and Method – oral gavage is not as relevant to dietary ingestion; and lipophilic carrier increases bioavailability;	Medium	2
Exposure Characterization	**High**	**1.3**
13 – Test Animal Characteristics (x2) –	High	1 (2)
14 – Adequacy and Consistency of Animal Husbandry Conditions –	High	1
15 – Number of Animals per Group –	High	1
Test Organism	**High**	**1.33**
16 – Outcome Assessment Methodology (x2) –	High	1 (2)
17 – Consistency of Outcome Assessment –	High	1
18 – Sampling Adequacy –	High	1
19 – Blinding of Assessors – FOB observers were blinded	High	1
20 – Negative Control Response –	High	1
Outcome Assessment	**High**	**1.2**
21 – Confounding Variables in Test Design and Procedures (x2) –	High	1 (2)
22 – Health Outcomes Unrelated to Exposure –	High	1
Confounding/Variable Control	**High**	**1.5**
23 – Statistical Methods – litter was statistical unit, as appropriate	High	1
24 – Reporting of Data (x2) – non-significant FOB data not reported; some statistical analyses on individual doses not reported	Medium	2 (4)
Data Presentation and Analysis	**Low**	**2.5**
Total Score = 37/23	**High**	**1.6**

Study Details: C57Bl6/J mouse pups were administered 0, 6, or 20 mg/kg decaBDE in egg lecithin/peanut oil by oral gavage (micropipette method) daily from PND2 through PND 15. FOB tests were conducted every other day from PND 2-20; locomotor activity was measured at PND 70 and 1 year; Thyroid hormone levels were tested at PND21. Litter was used as the statistical unit.

Significant Effects: forelimb grip and palprebral reflex were reduced in DecaBDE-treated animals (LOAEL 20 mg/kg, NOAEL 6 mg/kg); struggling during handling was also decreased (non dose responsive); decaBDE significantly increased locomotor activity in males only at PND 70 (LOAEL 20 mg/kg, NOAEL 6 mg/kg); maybe decreased T4 in males at PND 21 (significant trend, individual doses not significant).

Non-Significant Effects: decaBDE exposure did not affect age of achievement of developmental milestones or body weight; 12/14 FOB parameters not difference with decaBDE exposure. No change in locomotor activity with exposure in females, or in males at 1 year.

Notes: Authors state that neonatal mouse pups are too small to safely dose by intragastric gavage

Metric	Descriptive Score	Numeric Score
Rice et al. (2009)		
1 – Test Substance Identity (x2) – decaBDE, no independent verification	Medium	2 (4)
2 – Test Substance Source – Ake Bergman, Stockholm	Medium	2
3 – Test Substance Purity – 99.5%	High	1
Test Substance	**Low**	**2.33**
4 – Negative and Vehicle Controls (x2) –	High	1 (2)
5 – Positive Controls –	N/A	
6 – Randomized Allocation of Animals –	High	1
Test Design	**High**	**1.5**
7 – Preparation and Storage of Test Substance – discussed test substance preparation and storage (protected from light)	High	1
8 – Consistency of Exposure Administration –	High	1
9 – Reporting of Doses/Concentrations (x2) –	High	1 (2)
10 – Exposure Frequency and Duration –	High	1
11 – Number of Exposure Groups and Dose/Concentration Spacing –	High	1
12 – Exposure Route and Method – oral gavage is not as relevant to dietary ingestion; and lipophilic carrier increases bioavailability;	Medium	2
Exposure Characterization	**High**	**1.33**
13 – Test Animal Characteristics (x2) – did not report the age of the "young adult" mice	Medium	2 (4)
14 – Adequacy and Consistency of Animal Husbandry Conditions –	High	1
15 – Number of Animals per Group –	High	1
Test Organism	**Medium**	**2**
16 – Outcome Assessment Methodology (x2) –	High	1 (2)
17 – Consistency of Outcome Assessment –	High	1
18 – Sampling Adequacy –	High	1
19 – Blinding of Assessors – no discussion of blinding of assessors	Medium	2
20 – Negative Control Response –	High	1
Outcome Assessment	**High**	**1.4**
21 – Confounding Variables in Test Design and Procedures (x2) –	High	1 (2)
22 – Health Outcomes Unrelated to Exposure –	High	1
Confounding/Variable Control	**High**	**1.33**
23 – Statistical Methods – no multiple testing modifications, litter was statistical unit as appropriate	Medium	2
24 – Reporting of Data (x2) – changes in body weight or overt clinical effects not reported	Medium	2 (4)
Data Presentation and Analysis	**Low**	**3**
Total Score = 40/23	**Medium**	**1.7**

Study Details: C57Bl6/J mouse pups were administered 0, 6, or 20 mg/kg decaBDE in egg lecithin/peanut oil by oral gavage (micropipette method) daily from PND2 through PND 15. Started operant training of one male-female pair from each litter after reaching adulthood (what age?) or at 16 months old

Significant Effects: higher rewards were earned for the decaBDE treated group than controls in the aging cohort (NOAEL 6 mg/kg, LOAEL 20 mg/kg); total non-reinforced behaviours were higher in the decaBDE treated animals in the young cohort, and there were more errors in the aging cohort decaBDE animals (NOAEL 6 mg/kg, LOAEL 20 mg/kg); aging males made far fewer first choice errors (NOAEL 6 mg/kg, LOAEL 20 mg/kg)

Non-Significant Effects: No effect of decaBDE on operant training in young group; visual discrimination was unaffected by decaBDE exposure;

Metric	Descriptive Score	Numeric Score
Biesemeier et al. (2011)		
1 – Test Substance Identity (x2) – Test substance characterized	High	1 (2)
2 – Test Substance Source – Composite of 3 decaBDE products	High	1
3 – Test Substance Purity – 97.5%	High	1
Test Substance	**High**	**1.33**
4 – Negative and Vehicle Controls (x2) –	High	1 (2)
5 – Positive Controls –	N/A	
6 – Randomized Allocation of Animals – based on body weight allocation	Medium	2
Test Design	**Medium**	**2**
7 – Preparation and Storage of Test Substance – preparation and storage described	High	1
8 – Consistency of Exposure Administration –	High	1
9 – Reporting of Doses/Concentrations (x2) –	High	1 (2)
10 – Exposure Frequency and Duration –	High	1
11 – Number of Exposure Groups and Dose/Concentration Spacing –	High	1
12 – Exposure Route and Method – oral gavage is not as relevant to dietary ingestion; and lipophilic carrier increases bioavailability;	Medium	2
Exposure Characterization	**High**	**1.33**
13 – Test Animal Characteristics (x2) –	High	1 (2)
14 – Adequacy and Consistency of Animal Husbandry Conditions –	High	1
15 – Number of Animals per Group –	High	1
Test Organism	**High**	**1.33**
16 – Outcome Assessment Methodology (x2) –	High	1 (2)
17 – Consistency of Outcome Assessment –	High	1
18 – Sampling Adequacy –	High	1
19 – Blinding of Assessors – blinding of assessors for appropriate endpoints	High	1
20 – Negative Control Response –	High	1
Outcome Assessment	**High**	**1.2**
21 – Confounding Variables in Test Design and Procedures (x2) –	High	1 (2)
22 – Health Outcomes Unrelated to Exposure –	High	1
Confounding/Variable Control	**High**	**1.5**
23 – Statistical Methods – litter used as experimental unit, when applicable	High	1
24 – Reporting of Data (x2) –	High	1 (2)
Data Presentation and Analysis	**High**	**1.5**
Total Score = 35/23	**High**	**1.5**

Study Details: Study completed by OECD 426 standards; pregnant female S-D rats ~ 85 days old were treated by oral gavage daily with 0, 10, 100, or 1000 mg/kg decaBDE in corn oil from GD 6 through lactation day 21. Pups were tested for development and neurological parameters up to 180 days of age. Pregnant or post-mating females were euthanized at LD21 or post-mating day 25.

Significant Effects: marginal decrease in total activity counts with decaBDE treatment at PND 180 (NOAEL 100 mg/kg, LOAEL 1000 mg/kg); increased at PND 180 in ambulatory movement in the first 10 minutes in response to nicotine (NOAEL 100 mg/kg, LOAEL 1000 mg/kg); thinner mean thickness of the pons in decaBDE male mice at PND 21 (NOAEL 100 mg/kg, LOAEL 1000 mg/kg)

Non-Significant Effects: no gross or detailed clinical findings associated with decaBDE; no changes in grip strength in the pups; no apparent reproductive effects or necropsy findings on pregnant dams; no difference in body weights or food consumption; no changes in developmental landmarks; no effects on motor activity or habituation at any age; other than noted, no effects of decaBDE administration on movement after nicotine administration; no change in auditory startle response at PND 20 or PND 60; no effect of decaBDE on swimming ability, or learning and memory in the maze

test at PND 22 or PND 62; no histopathological or neuropathological findings in necropsied pups or changes in brain weight, length, or width; besides that noted, there were no changes in brain morphometry with decaBDE treatment.

Notes:

Metric	Descriptive Score	Numeric Score
Teshima et al. (2008)		
1 – Test Substance Identity (x2) – DBDE, no independent verification	Medium	2 (4)
2 – Test Substance Source – Wako Pure Chemical Industries	High	1
3 – Test Substance Purity – No purity information	Low	3
Test Substance	**Low**	**2.7**
4 – Negative and Vehicle Controls (x2) –	High	1 (2)
5 – Positive Controls –	N/A	
6 – Randomized Allocation of Animals –	High	1
Test Design	**High**	**1.5**
7 – Preparation and Storage of Test Substance – no information about storage	Medium	2
8 – Consistency of Exposure Administration –	High	1
9 – Reporting of Doses/Concentrations (x2) – provided as ppm, not mg/kg, with no information for conversion	Medium	2 (4)
10 – Exposure Frequency and Duration –	High	1
11 – Number of Exposure Groups and Dose/Concentration Spacing –	High	1
12 – Exposure Route and Method –	High	1
Exposure Characterization	**Medium**	**1.7**
13 – Test Animal Characteristics (x2) – No information on age or breeding of rats	Low	3 (6)
14 – Adequacy and Consistency of Animal Husbandry Conditions –	High	1
15 – Number of Animals per Group –	High	1
Test Organism	**Low**	**2.7**
16 – Outcome Assessment Methodology (x2) –	High	1 (2)
17 – Consistency of Outcome Assessment –	High	1
18 – Sampling Adequacy –	High	1
19 – Blinding of Assessors – no information about blinding of assessors	Medium	2
20 – Negative Control Response –	High	1
Outcome Assessment	**High**	**1.4**
21 – Confounding Variables in Test Design and Procedures (x2) –	High	1 (2)
22 – Health Outcomes Unrelated to Exposure –	High	1
Confounding/Variable Control	**High**	**1.5**
23 – Statistical Methods – no multiple comparisons tests, litter not used as statistical unit	Low	3
24 – Reporting of Data (x2) – some non-significant data not shown	Medium	2 (4)
Data Presentation and Analysis	**Low**	**3.5**
Total Score = 46/23	**Medium**	**2**

Study Details: Pregnant S-D rats were fed 0, 10, 100, or 1000 ppm decaBDE in a soyfree diet from GD10 to PND 21, with necropsy or other examinations completed on pups PND21 or PND77. Low dose was estimated in Health Canada 2012 as 5 mg/kg/day.

Significant Effects: increased in liver weight at PND 21 (LOAEL 10 ppm); increased body weights in males at 10 or 100 ppm (non dose-responsive); increase in T3 hormone at PND 21 (NOAEL 100 ppm, LOAEL 1000 ppm); decrease in T3 hormone at PND 77 (NOAEL 100 ppm, LOAEL 1000 ppm); decreases in some lymphocyte or NK cell types in the spleen or peripheral blood at PND 21 or 77 (different patterns at different time points; LOAEL 10 ppm).

Non-Significant Effects: No differences in body weight, thymus weight, or spleen weight at PND 21; no difference in thymus or spleen leukocyte numbers, or in blood cell counts; no change in T3 or TSH hormones at PND 21, or in T4 or TSH hormones at PND 77; no changes in IgG or IgM antibody titers; no change in histopathology of spleen or thymus.

Notes:

Metric	Descriptive Score	Numeric Score
Sarkar & Singh (2017)		
1 – Test Substance Identity (x2) – BDE-209, not independently verified	Medium	2 (4)
2 – Test Substance Source – Sigma-Aldrich	High	1
3 – Test Substance Purity – >98%	High	1
Test Substance	**Medium**	**2**
4 – Negative and Vehicle Controls (x2) –	High	1 (2)
5 – Positive Controls –	N/A	
6 – Randomized Allocation of Animals – No information on random allocation of pups fathered by same sire	Medium	2
Test Design	**Medium**	**2**
7 – Preparation and Storage of Test Substance – Preparation of test substance was provided, but no storage information	Medium	2
8 – Consistency of Exposure Administration –	High	1
9 – Reporting of Doses/Concentrations (x2) –	High	1 (2)
10 – Exposure Frequency and Duration –	High	1
11 – Number of Exposure Groups and Dose/Concentration Spacing – doses were spaced close together – hard to discern a dose-response	Medium	2
12 – Exposure Route and Method – Information not provided about how gavage was conducted	Medium	2
Exposure Characterization	**Medium**	**1.7**
13 – Test Animal Characteristics (x2) – No information about origin of test mice	Low	3 (6)
14 – Adequacy and Consistency of Animal Husbandry Conditions –	High	1
15 – Number of Animals per Group –	High	1
Test Organism	**Low**	**2.7**
16 – Outcome Assessment Methodology (x2) –	High	1 (2)
17 – Consistency of Outcome Assessment –	High	1
18 – Sampling Adequacy –	High	1
19 – Blinding of Assessors – No mention of blinding of assessors	Medium	2
20 – Negative Control Response –	High	1
Outcome Assessment	**High**	**1.4**
21 – Confounding Variables in Test Design and Procedures (x2) – No information provided about clinical differences between treated and control that could have impacted the outcomes	Low	3 (6)
22 – Health Outcomes Unrelated to Exposure – No information provided	Low	3
Confounding/Variable Control	**Low**	**4.5**
23 – Statistical Methods – Doesn't seem that the litter was used as the statistical unit as it should have been	Medium	2
24 – Reporting of Data (x2) – Information about general health and body weight was supposedly collected, but wasn't reported	Medium	2 (4)
Data Presentation and Analysis	**Low**	**3**
Total Score = 51/23	**Medium**	**2.2**

Study Details: Nursing female Parker mice were treated by oral gavage with 0, 500, or 700 mg/kg decaBDE in corn oil from PND1 (day of birth) to PND21. Male pups were euthanized on PND21 or PND28.

Significant Effects: Increase in serum and intra-testicular estradiol (LOAEL 500 mg/kg), increase in testes lipid peroxidation and decrease in testes activity of SOD, catalase, and LDH (LOAEL 500 mg/kg), and decreased intra-testicular glucose and lactate content (LOAEL 500 mg/kg), increased TUNEL-positive cells (apoptotic) in the testis of decaBDE-treated mice (LOAEL 500 mg/kg) – all were seen at PND 21 and PND 28 and none of these were dose-dependent.

Non-Significant Effects:

Notes: Citing OECD 2001 (OECD, 2001. Guideline for the Testing of Chemicals. Prenatal Developmental Toxicity Study. Organization for Economic Co-operation and Development. OECD/OCDE 414), the authors state that “doses above 1000 mg/kg/day are not relevant for human health risk assessment.”

Metric	Descriptive Score	Numeric Score
Sarkar & Singh (2018)		
1 – Test Substance Identity (x2) – BDE-209, not independently verified	Medium	2 (4)
2 – Test Substance Source – Sigma-Aldrich	High	1
3 – Test Substance Purity – >98%	High	1
Test Substance	**Medium**	**2**
4 – Negative and Vehicle Controls (x2) –	High	1 (2)
5 – Positive Controls – 6-propyl-2-thiouracil (known thyroid toxicant)	High	1
6 – Randomized Allocation of Animals – No information on random allocation of pups fathered by same sire	Medium	2
Test Design	**Medium**	**1.7**
7 – Preparation and Storage of Test Substance – Preparation of test substance was provided, but no storage information	Medium	2
8 – Consistency of Exposure Administration –	High	1
9 – Reporting of Doses/Concentrations (x2) –	High	1 (2)
10 – Exposure Frequency and Duration –	High	1
11 – Number of Exposure Groups and Dose/Concentration Spacing – doses were spaced close together – hard to discern a dose-response	Medium	2
12 – Exposure Route and Method – Information not provided about how gavage was conducted	Medium	2
Exposure Characterization	**Medium**	**1.7**
13 – Test Animal Characteristics (x2) – No information about origin of test mice	Low	3 (6)
14 – Adequacy and Consistency of Animal Husbandry Conditions –	High	1
15 – Number of Animals per Group –	High	1
Test Organism	**Low**	**2.7**
16 – Outcome Assessment Methodology (x2) – Present results about the activity of 3-beta and 17-beta-HSD, but no information about how these were measured	Low	3 (6)
17 – Consistency of Outcome Assessment –	High	1
18 – Sampling Adequacy –	High	1
19 – Blinding of Assessors – No mention of blinding of assessors	Medium	2
20 – Negative Control Response –	High	1
Outcome Assessment	**Medium**	**2.2**
21 – Confounding Variables in Test Design and Procedures (x2) –	High	1 (2)
22 – Health Outcomes Unrelated to Exposure – No information provided	Medium	2
Confounding/Variable Control	**Medium**	**2**
23 – Statistical Methods – Doesn't seem that the litter was used as the statistical unit as it should have been	Medium	2
24 – Reporting of Data (x2) –	High	1 (2)
Data Presentation and Analysis	**Medium**	**2**
Total Score = 48/24	**Medium**	**2**

Study Details: Nursing female Parker mice were treated by oral gavage with 0, 500, or 700 mg/kg decaBDE in corn oil from PND1 (day of birth) to PND28. Male pups were weaned on PND28 and euthanized on PND42.

Significant Effects: Decrease in testis, seminal vesicle, and prostate weight with decaBDE (LOAEL 500 mg/kg; not dose-responsive); decreased activities of steroidogenic enzymes 3-beta- and 17-beta-HSD (measured how?); (LOAEL 500 mg/kg; not dose-responsive); delayed lumen development in seminiferous tubules with decaBDE; (LOAEL 500 mg/kg; not dose-responsive); decreased number of Leydig cells in 500 mg/kg only; decreased number of proliferating germ cells with decaBDE treatment ; decreased serum T3 and T4, and serum or intra-testicular testosterone with decaBDE (LOAEL 500 mg/kg; not dose-responsive); decrease in expression of steroidogenic proteins in testes with decaBDE

Non-Significant Effects: No change in maternal or pup body weights with exposure to decaBDE; no change in 3-beta-HSD positive cells; no change in serum or intra-testicular (in pups) estrogen in decaBDE-treated dams or pups (different than finding in last paper?);

Notes:

Metric	Descriptive Score	Numeric Score
Watanabe et al. (2008)		
1 – Test Substance Identity (x2) – DBDE, no independent verification	Medium	2 (4)
2 – Test Substance Source – Wako Pure Chemicals	High	1
3 – Test Substance Purity – No purity information	Low	3
Test Substance	**Low**	**2.7**
4 – Negative and Vehicle Controls (x2) –	High	1 (2)
5 – Positive Controls – cyclophosphamide as an immunosuppressant	High	1
6 – Randomized Allocation of Animals –	High	1
Test Design	**High**	**1.3**
7 – Preparation and Storage of Test Substance – no information about preparation and storage	Low	3
8 – Consistency of Exposure Administration –	High	1
9 – Reporting of Doses/Concentrations (x2) –	High	1 (2)
10 – Exposure Frequency and Duration –	High	1
11 – Number of Exposure Groups and Dose/Concentration Spacing –	High	1
12 – Exposure Route and Method –	High	1
Exposure Characterization	**High**	**1.5**
13 – Test Animal Characteristics (x2) – no information about the viral status of the mice before treatment	Medium	2 (4)
14 – Adequacy and Consistency of Animal Husbandry Conditions – incomplete information	Medium	2
15 – Number of Animals per Group –	High	1
Test Organism	**Low**	**2.3**
16 – Outcome Assessment Methodology (x2) –	High	1 (2)
17 – Consistency of Outcome Assessment –	High	1
18 – Sampling Adequacy –	High	1
19 – Blinding of Assessors – no information about blinding	Medium	2
20 – Negative Control Response –	High	1
Outcome Assessment	**High**	**1.4**
21 – Confounding Variables in Test Design and Procedures (x2) –	High	1 (2)
22 – Health Outcomes Unrelated to Exposure –	High	1
Confounding/Variable Control	**High**	**1.5**
23 – Statistical Methods – not clear if the litter was used as the statistical unit	Medium	2
24 – Reporting of Data (x2) – some non-significant data not shown	Medium	2 (4)
Data Presentation and Analysis	**Low**	**3**
Total Score = 44/24	**Medium**	**1.8**

Study Details: Balb/c mice were fed a soy-free diet, and dams with litters were fed diets containing 0, 10, 100, or 1,000 ppm decaBDE from PND10 to PND21 (~3.3, 33.6, 257.1 mg/kg/day). A separate group was fed diets containing 0, or 10,000 ppm decaBDE. Pups were weaned on PND21 and infected with respiratory syncytial virus (RSV) on day 28. Mouse pups were euthanized at 5 days post-infection.

Significant Effects: decaBDE affected body weights of pups at PND 21 (LOAEL 1000 ppm, NOAEL 100 ppm); increase in pulmonary viral titer and interferon-gamma in BALF with DBDE treatment (LOAEL 1000 ppm, NOAEL 100 ppm) – interferon gamma result is opposite of cyclosporin response; increase in RANTES mRNA in lungs with decaBDE (marker of inflammation; LOAEL 100 ppm, NOAEL 10 ppm); exacerbation of pneumonia histopathologically with decaBDE (LOAEL 10,000 ppm; NOAEL 1000 ppm);

Non-Significant Effects: no effect on body weight or food consumption in dams; no change in litter number, pup survival rates, or food consumption of pups after weaning; no effect of DBDE on RSV growth in a cell culture assay;

Hexachlorobutadiene

Metric	Descriptive Score	Numeric Score
Gage 1970		
1 – Test Substance Identity (x2) – Not fully characterized	Unacceptable	
2 – Test Substance Source – Unknown		
3 – Test Substance Purity – Unknown		
Test Substance		
4 – Negative and Vehicle Controls (x2) –		
5 – Positive Controls –		
6 – Randomized Allocation of Animals –		
Test Design		
7 – Preparation and Storage of Test Substance –		
8 – Consistency of Exposure Administration –		
9 – Reporting of Doses/Concentrations (x2) –		
10 – Exposure Frequency and Duration –		
11 – Number of Exposure Groups and Dose/Concentration Spacing –		
12 – Exposure Route and Method –		
Exposure Characterization		
13 – Test Animal Characteristics (x2) –		
14 – Adequacy and Consistency of Animal Husbandry Conditions –		
15 – Number of Animals per Group –		
Test Organism		
16 – Outcome Assessment Methodology (x2) –		
17 – Consistency of Outcome Assessment –		
18 – Sampling Adequacy –		
19 – Blinding of Assessors –		
20 – Negative Control Response –		
Outcome Assessment		
21 – Confounding Variables in Test Design and Procedures (x2) –		
22 – Health Outcomes Unrelated to Exposure –		
Confounding/Variable Control		
23 – Statistical Methods –		
24 – Reporting of Data (x2) –		
Data Presentation and Analysis		
Total Score =	**Unacceptable**	

Study Details:

Significant Effects:

Non-Significant Effects:

Notes:

Metric	Descriptive Score	Numeric Score
Harleman and Seinen (1979)		
1 – Test Substance Identity (x2) – HCBD, no independent verification	Medium	2 (4)
2 – Test Substance Source – Fluka	High	1
3 – Test Substance Purity – > 95%	High	1
Test Substance	**Medium**	**2**
4 – Negative and Vehicle Controls (x2) –	High	1 (2)
5 – Positive Controls –	N/A	
6 – Randomized Allocation of Animals – – No information on random allocation of pups fathered by same sire	Medium	2
Test Design	**Medium**	**2**
7 – Preparation and Storage of Test Substance –	High	1
8 – Consistency of Exposure Administration –	High	1
9 – Reporting of Doses/Concentrations (x2) –	High	1 (2)
10 – Exposure Frequency and Duration – text wasn't entirely clear on how long animals were dosed (e.g. 18 weeks from the beginning of dosing, or 18 weeks of age for pups?)	Medium	2
11 – Number of Exposure Groups and Dose/Concentration Spacing –	High	1
12 – Exposure Route and Method –	High	1
Exposure Characterization	**High**	**1.3**
13 – Test Animal Characteristics (x2) –	High	1 (2)
14 – Adequacy and Consistency of Animal Husbandry Conditions –	High	1
15 – Number of Animals per Group –	High	1
Test Organism	**High**	**1.3**
16 – Outcome Assessment Methodology (x2) –	High	1 (2)
17 – Consistency of Outcome Assessment –	High	1
18 – Sampling Adequacy –	High	1
19 – Blinding of Assessors – no information about blinding of assessors	Medium	2
20 – Negative Control Response –	High	1
Outcome Assessment	**High**	**1.4**
21 – Confounding Variables in Test Design and Procedures (x2) –	High	1 (2)
22 – Health Outcomes Unrelated to Exposure –	High	1
Confounding/Variable Control	**High**	**1.5**
23 – Statistical Methods – Not clear that the litter was used as the statistical unit in the reproduction studies.	Medium	2
24 – Reporting of Data (x2) – Some non-significant data not shown	Medium	2 (4)
Data Presentation and Analysis	**Low**	**3**
Total Score = 36/23	**High**	**1.6**

Study Details: Range-finding study: Wistar weanling rats were fed diets containing 0, 50, 150, and 450 ppm HCBD for 2 weeks (0, 8, 23, 68 mg/kg/day), euthanized at the end of the study. Reproduction study: Female rats were fed a diet with 0, 150, or 1500 ppm HCBD for 3 weeks (0, 11, 110 mg/kg/day), then were bred, and continued to be fed through gestation and lactation, and rats were euthanized at week 18 (week 18 of treatment); necropsy of 1500 ppm animals at week 10 because of moribund condition. Subchronic study: Weanling rats were given 0, 0.4, 1, 2.5, 6.3, and 15.6 mg/kg/day HCBD in arachid oil by oral gavage for 18 weeks (I think that they mean 13 weeks); animals euthanized at 13 weeks?

Significant Effects: Range-finding: decreased food consumption (LOAEL 450 ppm) and body weight (LOAEL 50 ppm), increased kidney weights (LOAEL 150 ppm), kidney histopathologic changes (LOAEL 50 ppm). Reproduction study: no young born at 1500 ppm (diminished fertility), decreased pup weight at birth and retardation of growth (LOAEL 150 ppm); females lost weight (LOAEL 150 ppm), and displayed hindleg weakness, unsteady gait, ataxia, degeneration of

femoral nerve (LOAEL 1500 ppm); increased kidney weights and kidney histopathological changes in dams (LOAEL 150 ppm). Subacute study: decreased body weights and food consumption (LOAEL 6.3 mg/kg); increased urine production in females (LOAEL 6.3 mg/kg) and increased urine osmolarity in both sexes (LOAEL 15.6 mg/kg); increase in kidney weights (LOAEL 6.3 mg/kg); increase in liver and spleen weights (LOAEL 6.3 mg/kg); pathological changes in the kidneys (LOAEL 2.5 mg/kg; moreso in females) and liver in male rats (LOAEL 6.3 mg/kg).

Non-Significant Effects: Range-finding: no liver changes; Reproduction study: no change in resorption quotient; no grossly observable malformations, non-kidney organs had no change in weight or histopathology (heart, liver, spleen, brain, adrenals, thymus, thyroid, lung, pancreas, digestive tract, bladder, lymph nodes, trachea, spinal cord, femoral nerve). Subacute study: general health was unaffected except for body weight change; no change in blood clinical chemistry; other organ weight data was normal (heart, brain, adrenals, thymus, thyroids, gonads).

Notes:

Metric	Descriptive Score	Numeric Score
De Ceaurriz et al. (1988)		
1 – Test Substance Identity (x2) – HCBD vapor, verified in test atmosphere	High	1 (2)
2 – Test Substance Source – Fluka AG	High	1
3 – Test Substance Purity – > 99%	High	1
Test Substance	**High**	**1.3**
4 – Negative and Vehicle Controls (x2) – 15 min exposure used before exposure measurement as control	Medium	2
5 – Positive Controls –	N/A	
6 – Randomized Allocation of Animals – method for allocation of animals not reported	Low	3
Test Design	**High**	**2.5**
7 – Preparation and Storage of Test Substance –	High	1
8 – Consistency of Exposure Administration –	High	1
9 – Reporting of Doses/Concentrations (x2) – control information available only by inference	Medium	2 (4)
10 – Exposure Frequency and Duration –	High	1
11 – Number of Exposure Groups and Dose/Concentration Spacing –	High	1
12 – Exposure Route and Method – unclear if 4 hour exposure was head-only or whole-body	Medium	2
Exposure Characterization	**Medium**	**1.7**
13 – Test Animal Characteristics (x2) – no age provided	Medium	2 (4)
14 – Adequacy and Consistency of Animal Husbandry Conditions – inadequate description	Medium	2
15 – Number of Animals per Group –	High	1
Test Organism	**Low**	**2.3**
16 – Outcome Assessment Methodology (x2) –	High	1 (2)
17 – Consistency of Outcome Assessment –	High	1
18 – Sampling Adequacy –	High	1
19 – Blinding of Assessors – no information about blinding	Medium	2
20 – Negative Control Response –	High	1
Outcome Assessment	**High**	**1.4**
21 – Confounding Variables in Test Design and Procedures (x2) –	High	1 (2)
22 – Health Outcomes Unrelated to Exposure – no discussion	Medium	2
Confounding/Variable Control	**Medium**	**2**
23 – Statistical Methods –	High	1
24 – Reporting of Data (x2) –	High	1 (2)
Data Presentation and Analysis	**High**	**1.5**
Total Score = 40/23	**Medium**	**1.7**

Study Details: Male Swiss mice (no age) were exposed to HCBD vapor for 4 hours or 15 minutes (respiratory parameters); 15 min exposure concentrations of 83, 143, 155, 210, or 246 ppm (control was pre-exposure effects); 4 hour exposure concentrations of 0, 2.75, 5, 10, or 25 ppm

Significant Effects: decreased respiratory rate with 15 min exposure (LOAEL 155 ppm); 4 hour exposure increased damaged kidney tubules (LOAEL 2.75 ppm)

Non-Significant Effects:

Notes:

Metric	Descriptive Score	Numeric Score
Jonker et al. (1993)		
1 – Test Substance Identity (x2) – HCBD, not independently verified	Medium	2 (4)
2 – Test Substance Source – Merck	High	1
3 – Test Substance Purity – >98%	High	1
Test Substance	**Medium**	**2**
4 – Negative and Vehicle Controls (x2) –	High	1 (2)
5 – Positive Controls –	High	1
6 – Randomized Allocation of Animals –	High	1
Test Design	**High**	**1.33**
7 – Preparation and Storage of Test Substance –	High	1
8 – Consistency of Exposure Administration –	High	1
9 – Reporting of Doses/Concentrations (x2) –	High	1 (2)
10 – Exposure Frequency and Duration –	High	1
11 – Number of Exposure Groups and Dose/Concentration Spacing –	High	1
12 – Exposure Route and Method –	High	1
Exposure Characterization	**High**	**1.2**
13 – Test Animal Characteristics (x2) –	High	1 (2)
14 – Adequacy and Consistency of Animal Husbandry Conditions –	High	1
15 – Number of Animals per Group –	High	1
Test Organism	**High**	**1.3**
16 – Outcome Assessment Methodology (x2) –	High	1 (2)
17 – Consistency of Outcome Assessment –	High	1
18 – Sampling Adequacy –	High	1
19 – Blinding of Assessors – no mention of blinding of assessors	Medium	2
20 – Negative Control Response –	High	1
Outcome Assessment	**High**	**1.4**
21 – Confounding Variables in Test Design and Procedures (x2) – considered the effects of growth retardation	High	1 (2)
22 – Health Outcomes Unrelated to Exposure –	High	1
Confounding/Variable Control	**High**	**1.5**
23 – Statistical Methods –	High	1
24 – Reporting of Data (x2) – some non-significant affects not reported.	Medium	2 (4)
Data Presentation and Analysis	**Low**	**2.5**
Total Score = 36/24	**High**	**1.5**

Study Details: Range-finding: 4 week-old Wistar rats were fed diets containing 0, 25, 100, or 400 ppm HBDE for 4 weeks (estimated based on values provided at 0, 2.9-3.1, 10.2-11.5, 37 mg/kg/day). Main study: 10 week-old Wistar rats were fed diets containing 0, 20, or 100 ppm HBDE for 4 weeks (estimated based on values provided at 0, 1.1-1.6, 5.4 mg/kg/day). Animals were euthanized at the end of the study.

Significant Effects: Range finding: growth retardation, decreased food and water intake (not sig), urine abnormalities, increased relative kidney weight, abnormal kidney histopathology (LOAEL 100 ppm), changes in adrenal and liver weights (not dose-responsive). Main study: HCBD induced kidney histopathology (LOAEL 100 ppm); decreased body weight, increased kidney weight (LOAEL 100 ppm); female rats showed impacts on urinalysis, clinical chemistry, and adrenal and liver weights (LOAEL 100 ppm)

Non-Significant Effects: Main study: no change in food and water intake

Notes: Some of the effects on clinical chemistry and organ weights are likely attributable to the reduced growth and food intake.

Metric	Descriptive Score	Numeric Score
Kociba et al. (1971)		
1 – Test Substance Identity (x2) – HCBD, no independent verification	Medium	2 (4)
2 – Test Substance Source – Dow Chemical Company	High	1
3 – Test Substance Purity – > 99%	High	1
Test Substance	**Medium**	**2**
4 – Negative and Vehicle Controls (x2) –	High	1 (2)
5 – Positive Controls –	N/A	
6 – Randomized Allocation of Animals – no information about randomization	Low	3
Test Design	**Low**	**2.5**
7 – Preparation and Storage of Test Substance – No information provided	Low	3
8 – Consistency of Exposure Administration –	High	1
9 – Reporting of Doses/Concentrations (x2) –	High	1 (2)
10 – Exposure Frequency and Duration –	High	1
11 – Number of Exposure Groups and Dose/Concentration Spacing –	High	1
12 – Exposure Route and Method –	High	1
Exposure Characterization	**High**	**1.5**
13 – Test Animal Characteristics (x2) – No information on rat source or weight	Medium	2 (4)
14 – Adequacy and Consistency of Animal Husbandry Conditions – lack of data	Medium	2
15 – Number of Animals per Group – 4 rats per group	Low	3
Test Organism	**Low**	**3**
16 – Outcome Assessment Methodology (x2) –	High	1 (2)
17 – Consistency of Outcome Assessment –	High	1
18 – Sampling Adequacy –	High	1
19 – Blinding of Assessors – No information about blinding	Medium	2
20 – Negative Control Response –	High	1
Outcome Assessment	**High**	**1.4**
21 – Confounding Variables in Test Design and Procedures (x2) –	High	1 (2)
22 – Health Outcomes Unrelated to Exposure –	High	1
Confounding/Variable Control	**High**	**1.5**
23 – Statistical Methods –	High	1
24 – Reporting of Data (x2) –	High	1 (2)
Data Presentation and Analysis	**High**	**1.5**
Total Score = 42/23	**Medium**	**1.8**

Study Details: Dow Chemical Company report. Weanling Sprague-Dawley rats were treated with diets containing 0, 1, 3, 10, 30, 65, or 100 mg/kg/day HCBD for 30 days

Significant Effects: decreased food consumption (LOAEL 30 mg/kg), decreased body weights (LOAEL 10 mg/kg), decreased abdominal fat (LOAEL 65 mg/kg), hepatocellular swelling (LOAEL 100 mg/kg), renal tubular epithelial degeneration, necrosis, and regeneration (LOAEL 30 mg/kg), increased blood hemoglobin (LOAEL 10 mg/kg), increased relative kidney weight and relative brain weight (LOAEL 30 mg/kg)

Non-Significant Effects: no change in physical appearance or behavior, normal hematologic levels (except hemoglobin), no pathological changes in the brain.

Notes: changes in brain weight are likely due to depression of body weight gain because there were no histopathological alterations in the brain.

Metric	Descriptive Score	Numeric Score
Kociba et al. (1977)		
1 – Test Substance Identity (x2) – HCBD, no independent verification	Medium	2 (4)
2 – Test Substance Source – Dow Chemical Company	High	1
3 – Test Substance Purity – > 99%	High	1
Test Substance	**Medium**	**2**
4 – Negative and Vehicle Controls (x2) –	High	1 (2)
5 – Positive Controls –	N/A	
6 – Randomized Allocation of Animals – no information provided	Medium	2
Test Design	**Medium**	**2**
7 – Preparation and Storage of Test Substance – no information about storage	Medium	2
8 – Consistency of Exposure Administration –	High	1
9 – Reporting of Doses/Concentrations (x2) –	High	1 (2)
10 – Exposure Frequency and Duration –	High	1
11 – Number of Exposure Groups and Dose/Concentration Spacing –	High	1
12 – Exposure Route and Method –	High	1
Exposure Characterization	**High**	**1.3**
13 – Test Animal Characteristics (x2) –	High	1 (2)
14 – Adequacy and Consistency of Animal Husbandry Conditions – Incomplete information	Medium	2
15 – Number of Animals per Group –	High	1
Test Organism	**Medium**	**1.7**
16 – Outcome Assessment Methodology (x2) –	High	1 (2)
17 – Consistency of Outcome Assessment –	High	1
18 – Sampling Adequacy –	High	1
19 – Blinding of Assessors – no information about blinding of assessors	Medium	2
20 – Negative Control Response –	High	1
Outcome Assessment	**High**	**1.4**
21 – Confounding Variables in Test Design and Procedures (x2) –	High	1 (2)
22 – Health Outcomes Unrelated to Exposure –	High	1
Confounding/Variable Control	**High**	**1.5**
23 – Statistical Methods –	High	1
24 – Reporting of Data (x2) –	High	1 (2)
Data Presentation and Analysis	**High**	**1.5**
Total Score = 36/23	**High**	**1.6**

Study Details: 8-week old Sprague-Dawley rats were fed diets containing 0, 0.2, 2, or 20 mg/kg/day for 2 years.

Significant Effects: decreased body weight (LOAEL 20 mg/kg); slight depression of RBC count in males at 24 months (LOAEL 20 mg/kg); increase in coproporphyrin excretion in urine (LOAEL 2 mg/kg); increased kidney weights (LOAEL 20 mg/kg); increase in mortality in males (LOAEL 20 mg/kg); increased incidence of tumorous nodules in kidneys – adenomas and adenocarcinomas and lung metastases (LOAEL 20 mg/kg) as well as other kidney histopathology (LOAEL 2 mg/kg)

Non-Significant Effects: no sig change in food consumption; no changes in hematological parameters besides those noted; no change in histopathology of CV system, liver, respiratory tract, reproductive system, endocrine organs, GI tract, pancreas, salivary glands, musculoskeletal system, lymphoreticular system, eyes, CNS, subcutaneous tissues, integument, or mammary glands; besides the kidney neoplasms, there were no other neoplasms found that were considered to be related to HCBD administration.

Notes: Suppression of RBCs at 20 mg/kg may be due to renal toxicity;

Metric	Descriptive Score	Numeric Score
Nakagawa et al. (1998)		
1 – Test Substance Identity (x2) – HCBD, no independent verification	Medium	2 (4)
2 – Test Substance Source – Nakarai Chemical Ltd	High	1
3 – Test Substance Purity – > 99%	High	1
Test Substance	**Medium**	**2**
4 – Negative and Vehicle Controls (x2) –	High	1 (2)
5 – Positive Controls –	N/A	
6 – Randomized Allocation of Animals – no information about randomization provided	Medium	2
Test Design	**Medium**	**2**
7 – Preparation and Storage of Test Substance – no storage information	Medium	2
8 – Consistency of Exposure Administration –	High	1
9 – Reporting of Doses/Concentrations (x2) – mg/kg could not be calculated from study data because food ingestion was not reported	Low	3 (6)
10 – Exposure Frequency and Duration –	High	1
11 – Number of Exposure Groups and Dose/Concentration Spacing – only one HCBD exposure group for 30 week study	Medium	2
12 – Exposure Route and Method –	High	1
Exposure Characterization	**Medium**	**2.2**
13 – Test Animal Characteristics (x2) –	High	1 (2)
14 – Adequacy and Consistency of Animal Husbandry Conditions –	High	1
15 – Number of Animals per Group –	High	1
Test Organism	**High**	**1.3**
16 – Outcome Assessment Methodology (x2) –	High	1 (2)
17 – Consistency of Outcome Assessment –	High	1
18 – Sampling Adequacy –	High	1
19 – Blinding of Assessors –	High	1
20 – Negative Control Response –	High	1
Outcome Assessment	**High**	**1.2**
21 – Confounding Variables in Test Design and Procedures (x2) –	High	1 (2)
22 – Health Outcomes Unrelated to Exposure –	High	1
Confounding/Variable Control	**High**	**1.5**
23 – Statistical Methods –	High	1
24 – Reporting of Data (x2) – some non-significant changes not discussed in text	Medium	2 (4)
Data Presentation and Analysis	**Low**	**2.5**
Total Score = 41/23	**Medium**	**1.8**

Study Details: Experiment 1 – 3 male Wistar rats each received 0, 0.008%, 0.04% or 0.2% HCBD (mixed in corn oil) in their diet for 3 weeks, and rats were euthanized at 3 weeks (assuming a food consumption factor of 0.09 kg/kg/day: 0, 7.2, 36, 108 mg/kg/day). Experiment 2 – 21 rats received EHEN in water for 2 weeks and 0.1% HCBD in diet for 30 weeks (or the appropriate controls – no EHEN, no HCBD, no treatment); (assuming a food consumption factor of 0.09 kg/kg/day: 0, 90 mg/kg/day). Rats were euthanized after the 30 week exposure.

Significant Effects: Experiment 1: decreased body weight (LOAEL 0.04%); increased PNCA labeling in kidney (LOAEL 0.2%); regeneration of kidney in HCBD treated animals (LOAEL 0.2%). Experiment 2: decreased body weight and increased kidney weight with HCBD (with or without EHEN); increase in BrdU labeling in kidney with HCBD treatment (with or without EHEN); increase in incidence and multiplicity of EHEN-initiated simple or adenomatous hyperplasia and renal cell tumors with HCBD treatment compared to control.

Non-Significant Effects: Experiment 1: no change in kidney weight. Experiment 2: no change in biochemical parameters measured in urine or serum; no change in simple or adenomatous hyperplasia or renal cell tumors with HCBD treatment alone;

Notes:

Metric	Descriptive Score	Numeric Score
NTP (1991)/ Yang et al. (1989)		
1 – Test Substance Identity (x2) – HCBD, identity confirmed	High	1 (2)
2 – Test Substance Source – Aldrich Chemical Company	High	1
3 – Test Substance Purity – 98%	High	1
Test Substance	**High**	**1.3**
4 – Negative and Vehicle Controls (x2) –	High	1
5 – Positive Controls –	N/A	
6 – Randomized Allocation of Animals – distributed via weight classes, then assigned randomly	Medium	2
Test Design	**High**	**1.5**
7 – Preparation and Storage of Test Substance –	High	1
8 – Consistency of Exposure Administration –	High	1
9 – Reporting of Doses/Concentrations (x2) –	High	1 (2)
10 – Exposure Frequency and Duration –	High	1
11 – Number of Exposure Groups and Dose/Concentration Spacing –	High	1
12 – Exposure Route and Method –	High	1
Exposure Characterization	**High**	**1.2**
13 – Test Animal Characteristics (x2) –	High	1 (2)
14 – Adequacy and Consistency of Animal Husbandry Conditions –	High	1
15 – Number of Animals per Group –	High	1
Test Organism	**High**	**1.3**
16 – Outcome Assessment Methodology (x2) –	High	1 (2)
17 – Consistency of Outcome Assessment –	High	1
18 – Sampling Adequacy –	High	1
19 – Blinding of Assessors – no information about blinding	Medium	2
20 – Negative Control Response –	High	1
Outcome Assessment	**High**	**1.4**
21 – Confounding Variables in Test Design and Procedures (x2) –	High	1 (2)
22 – Health Outcomes Unrelated to Exposure –	High	1
Confounding/Variable Control	**High**	**1.5**
23 – Statistical Methods –	High	1
24 – Reporting of Data (x2) – not all data was presented in a quantitative manner that allowed identification of LOAELs or NOAELs	Medium	2 (4)
Data Presentation and Analysis	**Low**	**2.5**
Total Score = 33/23	**High**	**1.4**

Study Details: 6 week old B6C3F1 mice were fed diets containing 0, 30, 100, 300, 1,000, or 3,000 ppm HCBD for 15 days and then euthanized (estimated 0, 3-2, 12-16, 40-49 mg/kg/day); or 7 week old B6C3F1 mice were fed 0, 1, 3, 10, 30, or 100 ppm HCBD for 13 weeks and then euthanized (estimated 0, 0.1-0.2, 0.4-0.5, 1.5-1.8, 4.5-4.9, 16.8-19.2 mg/kg/day).

Significant Effects: 2-week study: All mice fed 1,000 or 3,000 ppm died before the end of the study; body weight decreases (LOAEL 100 ppm); clinical signs of distress (LOAEL 300 ppm); necrosis and regeneration of pars recta of kidneys (LOAEL?); 13-week study: decreased body weight (LOAEL 100 ppm); decreased kidney weights (LOAEL 10 ppm); increased liver weight (LOAEL 100 ppm) and spleen weights (LOAEL 10 ppm) in males only, not dose-responsive; increased renal-tubular epithelial regeneration (LOAEL 3 ppm)

Non-Significant Effects: 13-week study: no compound-related clinical signs; no reproductive changes; no changes in all other examined organs (adrenal glands, brain, cecum, colon, duodenum, epididymis/seminal vesicles/prostate/testes or ovaries/uterus, esophagus, femur or sternebrae or vertebrae including marrow, gallbladder, gross lesions, heart, ileum, jejunum, kidneys, liver, lungs and bronchi, mammary gland, mandibular and mesenteric lymph nodes, nasal cavity and

turbmales, pancreas, parathyroid glands, pituitary gland, rectum, salivary glands, skin, spleen, stomach, thymus, thyroid gland, trachea, and urinary bladder).

Notes:

Metric	Descriptive Score	Numeric Score
Saillenfait et al. (1989)		
1 – Test Substance Identity (x2) – HCBD, measured in chambers	High	1 (2)
2 – Test Substance Source – FLUKA	High	1
3 – Test Substance Purity – 99%	High	1
Test Substance	**High**	**1.3**
4 – Negative and Vehicle Controls (x2) –	High	1 (2)
5 – Positive Controls –	N/A	
6 – Randomized Allocation of Animals –	High	1
Test Design	**High**	**1.5**
7 – Preparation and Storage of Test Substance –	High	1
8 – Consistency of Exposure Administration –	High	1
9 – Reporting of Doses/Concentrations (x2) –	High	1 (2)
10 – Exposure Frequency and Duration –	High	1
11 – Number of Exposure Groups and Dose/Concentration Spacing –	High	1
12 – Exposure Route and Method –	High	1
Exposure Characterization	**High**	**1.2**
13 – Test Animal Characteristics (x2) –	High	1 (2)
14 – Adequacy and Consistency of Animal Husbandry Conditions – incomplete information	Medium	2
15 – Number of Animals per Group –	High	1
Test Organism	**Medium**	**1.7**
16 – Outcome Assessment Methodology (x2) –	High	1 (2)
17 – Consistency of Outcome Assessment –	High	1
18 – Sampling Adequacy –	High	1
19 – Blinding of Assessors – no mention of blinding of assessors	Medium	2
20 – Negative Control Response –	High	1
Outcome Assessment	**High**	**1.4**
21 – Confounding Variables in Test Design and Procedures (x2) –	High	1 (2)
22 – Health Outcomes Unrelated to Exposure –	High	1
Confounding/Variable Control	**High**	**1.5**
23 – Statistical Methods – litter used as statistical unit	High	1
24 – Reporting of Data (x2) –	High	1 (2)
Data Presentation and Analysis	**High**	**1.5**
Total Score = 32/23	**High**	**1.4**

Study Details: Exposure of pregnant S-D rats from GD6-20 to 2.1, 5.3, 10.4, or 14.8 ppm HCBD vapor for 6 hrs/day; controls were exposed in a similar manner to filtered air. Dams were euthanized on GD21 and dams and pups were assessed.

Significant Effects: decrease in maternal weight gain (LOAEL 5.3 ppm); reduction in fetal weight (LOAEL 15 ppm)

Non-Significant Effects: no deaths or change in general appearance in dams; no change in means of implantations, total fetal loss, resorptions, live fetuses, incidence of pregnancy, or sex ratio; no abnormalities in pups by external examination; no major skeletal or soft tissue anomalies in pups;

Notes:

Metric	Descriptive Score	Numeric Score
Schwetz et al. (1977)		
1 – Test Substance Identity (x2) – HCBD in diet confirmed analytically	High	1 (2)
2 – Test Substance Source – Dow Chemical Co	High	1
3 – Test Substance Purity – 99%	High	1
Test Substance	**High**	**1.3**
4 – Negative and Vehicle Controls (x2) –	High	1 (2)
5 – Positive Controls – triethylenemelamine used as positive control for cytogenetic alterations	High	1
6 – Randomized Allocation of Animals – no information about how pups with the same sire were randomized	Medium	2
Test Design	**Medium**	**1.7**
7 – Preparation and Storage of Test Substance – no information provided about storage	Medium	2
8 – Consistency of Exposure Administration –	High	1
9 – Reporting of Doses/Concentrations (x2) –	High	1 (2)
10 – Exposure Frequency and Duration – not clear how long the males were dosed for	Medium	2
11 – Number of Exposure Groups and Dose/Concentration Spacing –	High	1
12 – Exposure Route and Method –	High	1
Exposure Characterization	**High**	**1.5**
13 – Test Animal Characteristics (x2) –	High	1 (2)
14 – Adequacy and Consistency of Animal Husbandry Conditions – Incomplete information	Medium	2
15 – Number of Animals per Group –	High	1
Test Organism	**Medium**	**1.7**
16 – Outcome Assessment Methodology (x2) –	High	1 (2)
17 – Consistency of Outcome Assessment –	High	1
18 – Sampling Adequacy –	High	1
19 – Blinding of Assessors – no mention of blinding	Medium	2
20 – Negative Control Response –	High	1
Outcome Assessment	**Medium**	**1.4**
21 – Confounding Variables in Test Design and Procedures (x2) –	High	1 (2)
22 – Health Outcomes Unrelated to Exposure –	High	1
Confounding/Variable Control	**High**	**1.5**
23 – Statistical Methods – not clear if the litter was used as the statistical unit for the pups	Medium	2
24 – Reporting of Data (x2) – some non-significant data not presented	Medium	2 (4)
Data Presentation and Analysis	**Low**	**3**
Total Score = 39/24	**High**	**1.6**

Study Details: 8-week old male and female S-D rats were fed diets containing 0, 0.2, 2, or 20 mg/kg/day HCBD for 90 days; one male was placed with 2 females for 15 days; females were fed the test diet through gestation and weaning, while males were continually fed the diet for the rest of the period (?).

Significant Effects: Decreased body weight of dams (LOAEL 20 mg/kg); decreased food consumption (LOAEL 20 mg/kg); decrease in pup body weights at PND21 (but not PND 14; (LOAEL 20 mg/kg)); increase in kidney and liver weights in males (LOAEL 20 mg/kg) and kidney weights in females (LOAEL 20 mg/kg); pathological changes in kidneys in males and females (LOAEL 2 mg/kg).

Non-Significant Effects: no treatment-related effects on adult rats or pups demeanor or physical appearance; no changes in reproductive parameters or sex ratios; no change in blood chemistry; no developmental abnormalities in pups; no

significant histopathologic findings in the kidneys of pups; no cytogenetic changes with HCBD treatment; no changes in adults for the eye, pituitary gland, thyroid gland, parathyroid gland, trachea, esophagus, lungs, aorta, stomach, pancreas, small intestine, colon, lymph nodes, muscle, sciatic nerve, spinal cord, sternum, bone marrow, or adrenal gland.

Notes:

Metric	Descriptive Score	Numeric Score
Stott et al. (1981)		
1 – Test Substance Identity (x2) – HCBD, confirmed	High	1 (2)
2 – Test Substance Source – Midwest Research Institute; Dow Chemical Company	High	1
3 – Test Substance Purity – > 98%, >99%	High	1
Test Substance	**High**	**1.3**
4 – Negative and Vehicle Controls (x2) –	High	1 (2)
5 – Positive Controls – genotoxicant dimethylnitrosamine	High	1
6 – Randomized Allocation of Animals –	High	1
Test Design	**High**	**1.3**
7 – Preparation and Storage of Test Substance – no information provided	Low	3
8 – Consistency of Exposure Administration –	High	1
9 – Reporting of Doses/Concentrations (x2) –	High	1 (2)
10 – Exposure Frequency and Duration –	High	1
11 – Number of Exposure Groups and Dose/Concentration Spacing –	High	1
12 – Exposure Route and Method – little information about gavage method	Medium	2
Exposure Characterization	**Medium**	**1.7**
13 – Test Animal Characteristics (x2) – no age of rats provided	Medium	2 (4)
14 – Adequacy and Consistency of Animal Husbandry Conditions – incomplete	Medium	2
15 – Number of Animals per Group –	High	1
Test Organism	**Low**	**2.3**
16 – Outcome Assessment Methodology (x2) –	High	1 (2)
17 – Consistency of Outcome Assessment –	High	1
18 – Sampling Adequacy –	High	1
19 – Blinding of Assessors – no information about assessment blinding given	Medium	2
20 – Negative Control Response – inadequate use of the negative control	Medium	2
Outcome Assessment	**High**	**1.6**
21 – Confounding Variables in Test Design and Procedures (x2) –	High	1 (2)
22 – Health Outcomes Unrelated to Exposure – inadequate discussion of controls	Medium	2
Confounding/Variable Control	**Medium**	**2**
23 – Statistical Methods –	High	1
24 – Reporting of Data (x2) –	High	1 (2)
Data Presentation and Analysis	**High**	**1.5**
Total Score = 40/24	**Medium**	**1.7**

Study Details: Acute study: Male S-D rats (180-260 g) (age?) were exposed once via oral gavage to 0, 0.2, or 20 mg/kg to HCBD in corn oil, and euthanized 7 days later; Subacute study: Male S-D rats were gavaged with 0, 0.2, or 20 mg/kg/day HCBD in corn oil for 3 weeks, then euthanized.

Significant Effects: Acute: one of two trials showed an increase in 3H incorporation into DNA with HCBD treatment (LOAEL 20 mg/kg); Subacute: decrease in body weight, increase in relative kidney weight, presence of kidney histopathology; increase in 3H exposure into DNA (LOAEL 20 mg/kg); some alkylated DNA products were detected in HCBD treated animals (LOAEL 20 mg/kg), but no negative control was presented;

Non-Significant Effects: Acute: no change in body or kidney weights, or kidney histopathology; no mutagenic activity of HCBD in the Ames assay, with or without activation with S9, nor was there an increase in unscheduled DNA synthesis in rat hepatocytes.

Notes:

Metric	Descriptive Score	Numeric Score
Van Duuren et al. (1979)		
1 – Test Substance Identity (x2) – HCBD confirmed by IR film	High	1 (2)
2 – Test Substance Source – Aldrich Chemical Company	High	1
3 – Test Substance Purity – No purity information provided	Low	3
Test Substance	**Medium**	**2**
4 – Negative and Vehicle Controls (x2) –	High	1 (2)
5 – Positive Controls –	High	1
6 – Randomized Allocation of Animals – no information about randomization	Medium	2
Test Design	**Medium**	**1.7**
7 – Preparation and Storage of Test Substance – No information provided	Low	3
8 – Consistency of Exposure Administration –	High	1
9 – Reporting of Doses/Concentrations (x2) –	High	1 (2)
10 – Exposure Frequency and Duration – Not clear how long the duration was for the chronic dermal exposure to HCBD	Medium	2
11 – Number of Exposure Groups and Dose/Concentration Spacing – only one exposure dose tested	Medium	2
12 – Exposure Route and Method –	High	1
Exposure Characterization	**Medium**	**1.8**
13 – Test Animal Characteristics (x2) – no weights given	Medium	2 (4)
14 – Adequacy and Consistency of Animal Husbandry Conditions –	High	1
15 – Number of Animals per Group –	High	1
Test Organism	**Medium**	**2**
16 – Outcome Assessment Methodology (x2) –	High	1 (2)
17 – Consistency of Outcome Assessment –	High	1
18 – Sampling Adequacy –	High	1
19 – Blinding of Assessors – no information provided about blinding	Medium	2
20 – Negative Control Response –	High	1
Outcome Assessment	**High**	**1.4**
21 – Confounding Variables in Test Design and Procedures (x2) –	High	1 (2)
22 – Health Outcomes Unrelated to Exposure –	High	1
Confounding/Variable Control	**High**	**1.5**
23 – Statistical Methods –	High	1
24 – Reporting of Data (x2) – Only some of the data was reported	Medium	2 (4)
Data Presentation and Analysis	**Low**	**2.5**
Total Score = 43/24	**Medium**	**1.8**

Study Details: 6-8 week old HA-ICR Swiss mice; 30 female mice were dosed once with 15 mg HCBD in acetone dermally, then 14 days later were promoted with PMA; or they were dosed 3-times weekly for 440-594 (?) days dermally with 6 mg HCBD in acetone

Significant Effects:

Non-Significant Effects: HCBD was not significantly carcinogenic by the dermal initiation-promotion, or repeated skin application routes, and no distant tumors were found due to skin application.

Notes:

Phenol, Isopropylated, Phosphate (3:1) – PIP (3:1)

Metric	Descriptive Score	Numeric Score
Patisaul et al (2013)		
1 – Test Substance Identity (x2) – Firemaster 550		
2 – Test Substance Source –		
3 – Test Substance Purity – 50% 2-ethylhexyl-2,3,4,5-tetrabromobenzoate (TBB) and bis(2-ethylhexyl)2,3,4,5-tetrabromopthalate (TBPH), with no information about the levels of PIP(3:1) of triphenyl phosphate	Unacceptable	
Test Substance		
4 – Negative and Vehicle Controls (x2) –		
5 – Positive Controls –		
6 – Randomized Allocation of Animals –		
Test Design		
7 – Preparation and Storage of Test Substance –		
8 – Consistency of Exposure Administration –		
9 – Reporting of Doses/Concentrations (x2) –		
10 – Exposure Frequency and Duration –		
11 – Number of Exposure Groups and Dose/Concentration Spacing –		
12 – Exposure Route and Method –		
Exposure Characterization		
13 – Test Animal Characteristics (x2) –		
14 – Adequacy and Consistency of Animal Husbandry Conditions –		
15 – Number of Animals per Group –		
Test Organism		
16 – Outcome Assessment Methodology (x2) –		
17 – Consistency of Outcome Assessment –		
18 – Sampling Adequacy –		
19 – Blinding of Assessors –		
20 – Negative Control Response –		
Outcome Assessment		
21 – Confounding Variables in Test Design and Procedures (x2) –		
22 – Health Outcomes Unrelated to Exposure –		
Confounding/Variable Control		
23 – Statistical Methods –		
24 – Reporting of Data (x2) –		
Data Presentation and Analysis		
Total Score =	**Unacceptable**	

Study Details:

Significant Effects:

Non-Significant Effects:

Notes:

Metric	Descriptive Score	Numeric Score
Unnamed Subchronic Oral Toxicity Study 2015		
1 – Test Substance Identity (x2) – Reofos 35		
2 – Test Substance Source – Sponsor		
3 – Test Substance Purity –		
Test Substance		
4 – Negative and Vehicle Controls (x2) –		
5 – Positive Controls –		
6 – Randomized Allocation of Animals –		
Test Design		
7 – Preparation and Storage of Test Substance –		
8 – Consistency of Exposure Administration –		
9 – Reporting of Doses/Concentrations (x2) –		
10 – Exposure Frequency and Duration –		
11 – Number of Exposure Groups and Dose/Concentration Spacing –		
12 – Exposure Route and Method –		
Exposure Characterization		
13 – Test Animal Characteristics (x2) –		
14 – Adequacy and Consistency of Animal Husbandry Conditions –		
15 – Number of Animals per Group –		
Test Organism		
16 – Outcome Assessment Methodology (x2) –		
17 – Consistency of Outcome Assessment –		
18 – Sampling Adequacy –		
19 – Blinding of Assessors –		
20 – Negative Control Response –		
Outcome Assessment		
21 – Confounding Variables in Test Design and Procedures (x2) –		
22 – Health Outcomes Unrelated to Exposure –		
Confounding/Variable Control		
23 – Statistical Methods –		
24 – Reporting of Data (x2) –		
Data Presentation and Analysis		
Total Score = ECHA Reliability Score 1 (Reliable without restriction)	**High**	

Study Details: Adult male and female CD mice were dosed via oral gavage every day for 91 days with 0, 25, 100, or 325 mg/kg/dy Reofos 35 in corn oil. Study completed according to OECD Guideline 408 and EPA test guidelines in accordance with GLP; no significant deviations, so study quality is considered high.

Significant Effects: lower mean body weight in males (LOAEL 325 mg/kg); increases in cholesterol, urea nitrogen, and globulin (LOAEL 100 mg/kg), and in fibrinogen and prothrombin time (LOAEL 325 mg/kg); decreases in fine movement in week 13 (LOAEL 325 mg/kg); decreases in rearing in males (LOAEL 325 mg/kg); organ weight increases in the adrenal glands (LOAEL 25 mg/kg), liver (LOAEL 100 mg/kg), and ovaries (LOAEL 25 mg/kg); macroscopic findings in the adrenal glands (LOAEL 25 mg/kg); increased salivation (LOAEL 100 mg/kg); microscopic changes in the adrenal glands, ovaries and liver (LOAEL 25 mg/kg), and in the thyroid/parathyroid (LOAEL 100 mg/kg)

Non-Significant Effects: no clinical signs or mortality observed; no opthalmological findings or hematological findings or urinalysis findings; no test-article related neurobehavioural findings; no adverse-test article related findings in the FOB; no change in food consumption;

Notes:

Metric	Descriptive Score	Numeric Score
Unnamed Subchronic Inhalation Toxicity Study 1990		
1 – Test Substance Identity (x2) – MIL-J-194S7e and MII-H-194578 aerosol (hydraulic fluids)		
2 – Test Substance Source –		
3 – Test Substance Purity –		
Test Substance		
4 – Negative and Vehicle Controls (x2) –		
5 – Positive Controls –		
6 – Randomized Allocation of Animals –		
Test Design		
7 – Preparation and Storage of Test Substance –		
8 – Consistency of Exposure Administration –		
9 – Reporting of Doses/Concentrations (x2) –		
10 – Exposure Frequency and Duration –		
11 – Number of Exposure Groups and Dose/Concentration Spacing –		
12 – Exposure Route and Method –		
Exposure Characterization		
13 – Test Animal Characteristics (x2) –		
14 – Adequacy and Consistency of Animal Husbandry Conditions –		
15 – Number of Animals per Group –		
Test Organism		
16 – Outcome Assessment Methodology (x2) –		
17 – Consistency of Outcome Assessment –		
18 – Sampling Adequacy –		
19 – Blinding of Assessors –		
20 – Negative Control Response –		
Outcome Assessment		
21 – Confounding Variables in Test Design and Procedures (x2) –		
22 – Health Outcomes Unrelated to Exposure –		
Confounding/Variable Control		
23 – Statistical Methods –		
24 – Reporting of Data (x2) –		
Data Presentation and Analysis		
Total Score = ECHA Reliability Score 2 (Reliable with restrictions)	**Medium**	

Study Details: 90-day study with 8-10 week old F344 rats (20 M& 20F), 8-10 week old Golden Hamsters (20 M), New Zealand white rabbits (4 M & 4 F). Continuous exposure to 0, 10 mg/m3, and 100 mg/m3.

Significant Effects: Anorexia, lethargy, cachexia, and death in rabbits (LOAEL 100 mg/m3); kyphosis in rats (LOAEL 100 mg/m3); slower growth in female rats (LOAEL 100 mg/m3), but not hamsters or low-dose rabbits; decrease in performance in rats of tail tip curl test (LOAEL 100 mg/m3); increase in liver weight in rats (LOAEL 10 mg/m3); testicular atrophy in male rats (LOAEL 100 mg/m3); adrenal enlargement in rats (LOAEL 10 mg/m3); mild nasal goblet cell hyperplasia in rats (LOAEL 100 mg/m3); mild hepatocellular swelling in female rats (LOAEL 100 mg/m3); renal papillary necrosis and tubular cell fatty change in female rats (LOAEL 100 mg/m3); adrenocortical fatty change in rats (LOAEL 10 mg/m3); ovarian interstitial hypertrophy in female rats (LOAEL 10 mg/m3); degeneration of testicular seminiferous tubules in male rats (LOAEL 100 mg/m3); enlarged pituitary cells in male rats (LOAEL 100 mg/m3); nasal and lung inflammation in male rabbits (LOAEL 10 mg/m3); hepatocellular fatty change in female rabbits (LOAEL 100 mg/m3);

Non-Significant Effects: no change in rats in hindfoot drop test or lateral hop test; no gross pathological lesions in rabbits and hamsters at the conclusion of exposure; no clear histopathological lung changes in rats; no sig change in hematology or clinical chemistry with exposure;

Metric	Descriptive Score	Numeric Score
Unnamed Subchronic Oral Toxicity/Reproductive Study 2005		
1 – Test Substance Identity (x2) – Reofos 65		
2 – Test Substance Source –		
3 – Test Substance Purity –		
Test Substance		
4 – Negative and Vehicle Controls (x2) –		
5 – Positive Controls –		
6 – Randomized Allocation of Animals –		
Test Design		
7 – Preparation and Storage of Test Substance –		
8 – Consistency of Exposure Administration –		
9 – Reporting of Doses/Concentrations (x2) –		
10 – Exposure Frequency and Duration –		
11 – Number of Exposure Groups and Dose/Concentration Spacing –		
12 – Exposure Route and Method –		
Exposure Characterization		
13 – Test Animal Characteristics (x2) –		
14 – Adequacy and Consistency of Animal Husbandry Conditions –		
15 – Number of Animals per Group –		
Test Organism		
16 – Outcome Assessment Methodology (x2) –		
17 – Consistency of Outcome Assessment –		
18 – Sampling Adequacy –		
19 – Blinding of Assessors –		
20 – Negative Control Response –		
Outcome Assessment		
21 – Confounding Variables in Test Design and Procedures (x2) –		
22 – Health Outcomes Unrelated to Exposure –		
Confounding/Variable Control		
23 – Statistical Methods –		
24 – Reporting of Data (x2) –		
Data Presentation and Analysis		
Total Score = ECHA Reliability Score 1 (Reliable without restriction)	**High**	

Study Details: GLP, OECD 422 study. ~12 week old male and female Crl:CD(SD)IGS BR rats (12 rats/sex/treatment group). 0, 25 mg/kg, 100 mg/kg, or 400 mg/kg Reofos 65 in corn oil by oral gavage daily for 15 days before males and females were paired and through 14 days of mating, and females received doses through PND 4; males received 29 doses, females that failed to deliver pups received 41-54 doses, and females surviving to PND 4 received 42-54 doses. The F0 generation was mated once to produce one litter per day (F1).

Significant Effects: Adults: excessive salivation (LOAEL 100 mg/kg); excessive pawing of the cage (LOAEL 400 mg/kg); decreased male fertility and copulation indices (LOAEL 400 mg/kg) and decreases in female fertility indices (LOAEL 400 mg/kg); increased food consumption (and so decreased food efficiency) in maternal food consumption (LOAEL 100 mg/kg); increase in cholesterol in males (LOAEL 400 mg/kg); increased adrenal gland weight (LOAEL 25 mg/kg), and liver weight (LOAEL 100 mg/kg) in males; increased ovary/oviduct weight in females (LOAEL 25 mg/kg); vacuolization of adrenal gland cells (LOAEL 25 mg/kg) and hypertrophy of liver cells (LOAEL 100 mg/kg) caused the weight increases; reduced epididymal weight (LOAEL 400 mg/kg); ovarian cell hypertrophy/hyperplasia (LOAEL 25 mg/kg); F1 Generation: decreased postnatal survival of pups (LOAEL 400 mg/kg);

Non-Significant Effects: Adults: no change in male or female mating indices; no change in male or female body weights or male food consumption; no change in handling, open field, sensory, neuromuscular, physiological observations, mean

ambulatory activity or total motor activity in treated males or females; no change in hematological parameters in adult males or females; no other changes in blood clinical chemistry in males; no test-article related changes in macroscopic findings in males; all other organ weights unchanged; no other microscopic organ changes; no change in gestation length or parturition; no significant changes in number of implantation sites or pups born, or percentage of males per litter; no internal findings in pups exposed gestationally were found;

Notes:

Metric	Descriptive Score	Numeric Score
Unnamed Reproductive/Developmental Toxicity Study 2005		
1 – Test Substance Identity (x2) – Reofos 35, Reofos 65, Reofos 65 washed, Reofos 120, mpIPTPP		
2 – Test Substance Source –		
3 – Test Substance Purity –		
Test Substance		
4 – Negative and Vehicle Controls (x2) –		
5 – Positive Controls –		
6 – Randomized Allocation of Animals –		
Test Design		
7 – Preparation and Storage of Test Substance –		
8 – Consistency of Exposure Administration –		
9 – Reporting of Doses/Concentrations (x2) –		
10 – Exposure Frequency and Duration –		
11 – Number of Exposure Groups and Dose/Concentration Spacing –		
12 – Exposure Route and Method –		
Exposure Characterization		
13 – Test Animal Characteristics (x2) –		
14 – Adequacy and Consistency of Animal Husbandry Conditions –		
15 – Number of Animals per Group –		
Test Organism		
16 – Outcome Assessment Methodology (x2) –		
17 – Consistency of Outcome Assessment –		
18 – Sampling Adequacy –		
19 – Blinding of Assessors –		
20 – Negative Control Response –		
Outcome Assessment		
21 – Confounding Variables in Test Design and Procedures (x2) –		
22 – Health Outcomes Unrelated to Exposure –		
Confounding/Variable Control		
23 – Statistical Methods –		
24 – Reporting of Data (x2) –		
Data Presentation and Analysis		
Total Score = ECHA Reliability Score 1 (Reliable without restriction)	**High**	

Study Details: OECD 421, GLP study, screening for reproductive/developmental toxicity. 12 male and female per dose per chemical Sprague-Dawley rats were treated by oral gavage with 0 or 400 mg/kg of various agents (Reofos 35, Reofos 65, Reofos 65 washed, Reofos 120, mpIPTPP) in corn oil, then mated. Main study males were treated for at least 42 consecutive days, while the main study females were treated for up to 54 days, depending on reproductive performance. Adults were treated for 14 days, then cohabited (1:1 male:female) for up to 14 days. Pups were euthanized on PND4.

Significant Effects: Adults - Increased salivation with treatment in M&F with all chemicals; decrease in M but not F body weights with Reofos 35 and 65; adrenal and liver weights increased in M&F with Reofos 35, 65, 65 washed, 120, and mpIPTPP; vacuolization in adrenal glands in M&F and in ovaries in F with all compounds except mpIPTPP; hepatocellular hypertrophy of livers in F treated with all compounds except mpIPTPP; Reofos 65 sig decreased fertility and fecundity; Pups – increased pup mortality in all groups except mpIPTPP; decreased pup weight at PND 4 with R65 and R65 washed

Non-Significant Effects: no mortality observed; no change in body weights in females, or with R65 washed, R120, or mpIPTPP; no changes in food consumption; no changes in other organ weights; no effects of Reofos 35 (although suggestive changes), 65 washed, 120, or mpIPTPP on fertility and fecundity; no effect of R35, R120, or mpIPTPP on pup

weight at PND 0 or 4; no hematological or clinical biochemistry finding in treated pups; no gross pathological or histopathological findings in pups in any treatment group.

Notes:

Metric	Descriptive Score	Numeric Score
Unnamed Prenatal Developmental Toxicity Study, 2014		
1 – Test Substance Identity (x2) – Reofos 35		
2 – Test Substance Source – Chemtura Manufacturing Ltd		
3 – Test Substance Purity –		
Test Substance		
4 – Negative and Vehicle Controls (x2) –		
5 – Positive Controls –		
6 – Randomized Allocation of Animals –		
Test Design		
7 – Preparation and Storage of Test Substance –		
8 – Consistency of Exposure Administration –		
9 – Reporting of Doses/Concentrations (x2) –		
10 – Exposure Frequency and Duration –		
11 – Number of Exposure Groups and Dose/Concentration Spacing –		
12 – Exposure Route and Method –		
Exposure Characterization		
13 – Test Animal Characteristics (x2) –		
14 – Adequacy and Consistency of Animal Husbandry Conditions –		
15 – Number of Animals per Group –		
Test Organism		
16 – Outcome Assessment Methodology (x2) –		
17 – Consistency of Outcome Assessment –		
18 – Sampling Adequacy –		
19 – Blinding of Assessors –		
20 – Negative Control Response –		
Outcome Assessment		
21 – Confounding Variables in Test Design and Procedures (x2) –		
22 – Health Outcomes Unrelated to Exposure –		
Confounding/Variable Control		
23 – Statistical Methods –		
24 – Reporting of Data (x2) –		
Data Presentation and Analysis		
Total Score = ECHA Reliability Score 1 (Reliable without restriction)	**High**	

Study Details: OECD Guideline 414, GLP. 25 pregnant female Crj:CD(SD) rats (~8-10 weeks old) per dose were dosed by oral gavage with 0, 100, 200 Or 400 mg/kg Reofos 35 from GD0-19.

Significant Effects: Adults: increased salivation (LOAEL 100 mg/kg; not considered adverse); decreased body weight gain and decreased food consumption from GD 0-3 (LOAEL 400 mg/kg); swollen mucosa of the stomach in several animals (LOAEL 400 mg/kg).

Non-Significant Effects: Adults: no mortality; no gross pathological findings; no change in uterine implantation, corpora lutea, implantation sites, viable fetuses, post-implantation loss, litter size, and resorption sites; no change in mean gravid uterine weight. Pups: no external, skeletal, or visceral malformations observed; no effect on fetal sex ratios, body weights.

Notes:

Metric	Descriptive Score	Numeric Score
Unnamed neurotoxicity study report (1980)		
1 – Test Substance Identity (x2) – Isopropylphenyl Phosphate Ester – Kronitex 50		
2 – Test Substance Source –		
3 – Test Substance Purity –		
Test Substance		
4 – Negative and Vehicle Controls (x2) –		
5 – Positive Controls –		
6 – Randomized Allocation of Animals –		
Test Design		
7 – Preparation and Storage of Test Substance –		
8 – Consistency of Exposure Administration –		
9 – Reporting of Doses/Concentrations (x2) –		
10 – Exposure Frequency and Duration –		
11 – Number of Exposure Groups and Dose/Concentration Spacing –		
12 – Exposure Route and Method –		
Exposure Characterization		
13 – Test Animal Characteristics (x2) –		
14 – Adequacy and Consistency of Animal Husbandry Conditions –		
15 – Number of Animals per Group –		
Test Organism		
16 – Outcome Assessment Methodology (x2) –		
17 – Consistency of Outcome Assessment –		
18 – Sampling Adequacy –		
19 – Blinding of Assessors –		
20 – Negative Control Response –		
Outcome Assessment		
21 – Confounding Variables in Test Design and Procedures (x2) –		
22 – Health Outcomes Unrelated to Exposure –		
Confounding/Variable Control		
23 – Statistical Methods –		
24 – Reporting of Data (x2) –		
Data Presentation and Analysis		
Total Score = ECHA Reliability Score 1 (Reliable without restriction)	**High**	

Study Details: GLP, EPA OPP 81-7; 9-month old 10 adult domestic hens per dose were treated once by oral gavage with 2, 4, 6, or 8 g/kg ilsopropylphenyl phosphate ester, TOCP (positive control), or corn oil, then observed for 21 days.

Significant Effects: non dose-responsive changes in body weight and mortality; signs of ataxia (LOAEL 4 g/kg), but not dose-responsive; neuropathological changes (LOAEL 4 g/kg), not dose-responsive;

Non-Significant Effects:

Notes:

2,4,6-Tris(tert-butyl) phenol – 2,4,6 TTBP

Metric	Descriptive Score	Numeric Score
Matsumoto et al. (1991)		
1 – Test Substance Identity (x2) – 2,4,6-tri-tert-butylphenol, no independent validation	Medium	2 (4)
2 – Test Substance Source – Aldrich Chemical Co	High	1
3 – Test Substance Purity – 97%	High	1
Test Substance	**Medium**	
4 – Negative and Vehicle Controls (x2) –	High	1 (2)
5 – Positive Controls –	N/A	
6 – Randomized Allocation of Animals – no information about randomization	Medium	2
Test Design	**Medium**	**2**
7 – Preparation and Storage of Test Substance – little information about preparation, no storage information	Medium	2
8 – Consistency of Exposure Administration –	High	1
9 – Reporting of Doses/Concentrations (x2) – no information for conversion to mg/kg	Medium	2 (4)
10 – Exposure Frequency and Duration –	High	1
11 – Number of Exposure Groups and Dose/Concentration Spacing –	High	1
12 – Exposure Route and Method –	High	1
Exposure Characterization	**Medium**	**1.7**
13 – Test Animal Characteristics (x2) –	High	1 (2)
14 – Adequacy and Consistency of Animal Husbandry Conditions –	High	1
15 – Number of Animals per Group –	High	1
Test Organism	**High**	**1.3**
16 – Outcome Assessment Methodology (x2) – little methodological information	Medium	2 (4)
17 – Consistency of Outcome Assessment –	High	1
18 – Sampling Adequacy –	High	1
19 – Blinding of Assessors – no information about blinding the assessors	Medium	2
20 – Negative Control Response – little information about negative control response	Medium	2
Outcome Assessment	**Medium**	**2**
21 – Confounding Variables in Test Design and Procedures (x2) –	High	1 (2)
22 – Health Outcomes Unrelated to Exposure – little information	Medium	2
Confounding/Variable Control	**Medium**	**2**
23 – Statistical Methods –	High	1
24 – Reporting of Data (x2) – some non-stat sig data not shown	Medium	2 (4)
Data Presentation and Analysis	**Low**	**2.5**
Total Score = 43/23	**Medium**	**1.9**

Study Details: 40 M and 40 F 5 week-old Wistar rats per dose were fed diets containing 0, 30, 100, 300, or 1000 ppm TTBP for up to 24 months.

Significant Effects: reduction of body weight gain in females (LOAEL 1000 ppm); changes in hematological parameters starting at 6 months (decreased Hb, MCV, GOT, increased Plt, PL, T-Chol, γ-GTP; LOAEL 30 ppm); increased relative liver and kidney weight (LOAEL 100 ppm), and adrenal weights (LOAEL 1000 ppm); swelling, focal necrosis, and vacuolization of liver cells starting at 6 months (LOAEL 300 ppm);

Non-Significant Effects: no change in mortality; no change in food consumption; no histopathological or neoplastic lesions in non-liver organs;

Notes:

Metric	Descriptive Score	Numeric Score
Unnamed Skin Sensitization Study, 2015		
1 – Test Substance Identity (x2) – 2,4,6 – tri-tert butyl phenol		
2 – Test Substance Source –		
3 – Test Substance Purity –		
Test Substance		
4 – Negative and Vehicle Controls (x2) –		
5 – Positive Controls –		
6 – Randomized Allocation of Animals –		
Test Design		
7 – Preparation and Storage of Test Substance –		
8 – Consistency of Exposure Administration –		
9 – Reporting of Doses/Concentrations (x2) –		
10 – Exposure Frequency and Duration –		
11 – Number of Exposure Groups and Dose/Concentration Spacing –		
12 – Exposure Route and Method –		
Exposure Characterization		
13 – Test Animal Characteristics (x2) –		
14 – Adequacy and Consistency of Animal Husbandry Conditions –		
15 – Number of Animals per Group –		
Test Organism		
16 – Outcome Assessment Methodology (x2) –		
17 – Consistency of Outcome Assessment –		
18 – Sampling Adequacy –		
19 – Blinding of Assessors –		
20 – Negative Control Response –		
Outcome Assessment		
21 – Confounding Variables in Test Design and Procedures (x2) –		
22 – Health Outcomes Unrelated to Exposure –		
Confounding/Variable Control		
23 – Statistical Methods –		
24 – Reporting of Data (x2) –		
Data Presentation and Analysis		
Total Score = ECHA Reliability Score 1 (Reliable without restriction)	**High**	

Study Details: GLP, OECD 429 local lymph node assay skin sensitization study; five CBA/J female mice (~11 weeks old) per dose were treated once per day with 0, 10, 25, or 50% w/w TTBP in dimethylformamide on their ears for 3 days, and the local lymph nodes were excised on the 6th day.

Significant Effects: increased size of auricular lymph nodes (LOAEL 25%);

Non-Significant Effects: no irritation of the ears was observed with any test dose; no mortality or signs of clinical toxicity; no change in body weight or body weight gain

Notes:

Metric	Descriptive Score	Numeric Score
Unnamed repeated dose oral reproductive/developmental toxicity study, 2015		
1 – Test Substance Identity (x2) – 2,4,6 – tri-tert butyl phenol		
2 – Test Substance Source –		
3 – Test Substance Purity –		
Test Substance		
4 – Negative and Vehicle Controls (x2) –		
5 – Positive Controls –		
6 – Randomized Allocation of Animals –		
Test Design		
7 – Preparation and Storage of Test Substance –		
8 – Consistency of Exposure Administration –		
9 – Reporting of Doses/Concentrations (x2) –		
10 – Exposure Frequency and Duration –		
11 – Number of Exposure Groups and Dose/Concentration Spacing –		
12 – Exposure Route and Method –		
Exposure Characterization		
13 – Test Animal Characteristics (x2) –		
14 – Adequacy and Consistency of Animal Husbandry Conditions –		
15 – Number of Animals per Group –		
Test Organism		
16 – Outcome Assessment Methodology (x2) –		
17 – Consistency of Outcome Assessment –		
18 – Sampling Adequacy –		
19 – Blinding of Assessors –		
20 – Negative Control Response –		
Outcome Assessment		
21 – Confounding Variables in Test Design and Procedures (x2) –		
22 – Health Outcomes Unrelated to Exposure –		
Confounding/Variable Control		
23 – Statistical Methods –		
24 – Reporting of Data (x2) –		
Data Presentation and Analysis		
Total Score = ECHA Reliability Score 1 (Reliable without restriction)	**High**	

Study Details: OECD Guideline 422, GLP; 10 Wistar rats per sex per dose (11-12 weeks old) were exposed by oral gavage to 0, 3, 10, and 30 mg/kg TTBP in corn oil. Males were exposed for 29 days (2 weeks prior to mating and during mating); females were exposed for 41-56 days (2 weeks prior to mating, during mating, up to PND 4).

Significant Effects: salivation in treated animals (LOAEL 3 mg/kg); weight loss in females during lactation (LOAEL 10 mg/kg); changes in WBC and red blood cell counts in females (LOAEL 30 mg/kg); changes in total protein, albumin, bilirubin, urea, glucose, cholesterol, potassium, and calcium in males and females (LOAEL 10 mg/kg); enlarged liver (LOAEL 30 mg/kg); increased liver weights in males and females (LOAEL 10 mg/kg); hepatocellular hypertrophy (LOAEL 10 mg/kg) and hepatocellular necrosis (LOAEL 30 mg/kg); decreased number of living pups (LOAEL 30 mg/kg); increased postnatal mortality and lower viability index (LOAEL 10 mg/kg); decreased pup body weight (LOAEL 10 mg/kg).

Non-Significant Effects: no mortality; no clinical signs; no change in hematology parameters in males; no change in FOB parameters; no change in macroscopic organ findings except in liver; no non-liver changes in organ weight; no histopathological changes related to the test article in organs other than the liver, including the reproductive organs; no toxicologically-relevant changes in reproductive parameters; no change in other developmental parameters in pups.

Notes:

Pentachlorothiophenol (PCTP)

Metric	Descriptive Score	Numeric Score
Korhonen et al. (1982)		
1 – Test Substance Identity (x2) – Penthachlorothiophenol, not independently verified	Medium	2 (4)
2 – Test Substance Source – Bayer	High	1
3 – Test Substance Purity – 47% with 48% caolin and 5% paraffin oil	Medium	2
Test Substance	**Low**	**2.3**
4 – Negative and Vehicle Controls (x2) –	High	1 (2)
5 – Positive Controls –	N/A	
6 – Randomized Allocation of Animals – no information about randomization	Medium	2
Test Design	**Medium**	**2**
7 – Preparation and Storage of Test Substance – no information about storage	Medium	2
8 – Consistency of Exposure Administration –	High	1
9 – Reporting of Doses/Concentrations (x2) –	High	1 (2)
10 – Exposure Frequency and Duration – only one dose reported	Medium	2
11 – Number of Exposure Groups and Dose/Concentration Spacing – single dose	Medium	2
12 – Exposure Route and Method – not very relevant to humans	Medium	2
Exposure Characterization	**Medium**	**1.8**
13 – Test Animal Characteristics (x2) – no information provided	Low	3 (6)
14 – Adequacy and Consistency of Animal Husbandry Conditions –	High	1
15 – Number of Animals per Group –	High	1
Test Organism	**Low**	**2.7**
16 – Outcome Assessment Methodology (x2) – little information provided	Medium	2 (4)
17 – Consistency of Outcome Assessment –	High	1
18 – Sampling Adequacy –	High	1
19 – Blinding of Assessors – no information about blinding	Medium	2
20 – Negative Control Response –	High	1
Outcome Assessment	**Medium**	**1.8**
21 – Confounding Variables in Test Design and Procedures (x2) – lack of information makes this difficult to judge	Medium	2 (2)
22 – Health Outcomes Unrelated to Exposure –	High	1
Confounding/Variable Control	**Low**	**2.5**
23 – Statistical Methods – little information provided	Medium	2
24 – Reporting of Data (x2) – data only reported in text, not figures, for non-significant effects	Low	3 (6)
Data Presentation and Analysis	**Low**	**4**
Total Score = 50/23	**Medium**	**2.2**

Study Details: 3-day old chicken embryos (in the shell) were injected in the heart with a mixture of 0.5 umoles PCTP and acetone. Eggs were allowed to incubate for a further 11 days.

Significant Effects:

Non-Significant Effects: No effects on early embryonic deaths, late embryonic deaths of normal or malformed embryos, or malformation of live chicks.

Notes:

Reviewer 6 - Environmental and Human Health Hazard Summary Peer Review

Decabromodiphenyl ether (DecaBDE) (CASRN 1163-19-5)
Environmental and Human Health Hazard Summary Peer Review Charge Questions

1. This information, when finalized will inform a technical support document to support EPA's regulatory activities on PBTs. Please comment on the organization and structure of this document to inform this use. Do you have specific recommendations to improve clarity and presentation of this information?

In general, the document is clearly written and well organized. The agency was clear to note for the reviewers that the information in this document is not meant to represent an exhaustive literature review nor an analysis of relative importance or comparative dose-response among hazards, but rather is intended to be an environmental and human health summary of the known hazards of each chemical under review. As such, only a limited amount of information has been identified and summarized by the agency. Even so, some additional clarification and information as follows would be valuable for those reviewing the summarized information provided by the agency.

In order to assess the adequacy of the search of the published and unpublished hazard data, the search strategy should include:

- a list of all chemical identifiers and chemical names and synonyms used as search terms, and
- the rationale for selection of databases searched

Evidence tables should include a columns for

- test material characterization: purity, stability, dose confirmation
- study design: guideline, non-guideline
- study quality, for example, GLP study or non-GLP study and quality scoring framework with citation, e.g., Klimisch score.

2. Please comment on the methodology for collecting and summarizing information from secondary sources. Was the approach appropriate? Is the description for how and where the literature was obtained clearly described?

The Agency peer review draft document clearly describes the secondary source search strategy. The summaries of the individual studies are minimal and limited to species, study design, dose response and adverse effect observed. There is no assessment provided of the study quality and methods that might impact interpretation, such as test material purity, solubility and stability, and study design, e.g., guideline study, GLP, and other methodological considerations affecting study quality.

3. Please comment on the representativeness and adequacy of the selected literature used in the evidence tables and described in the text to summarize the hazard concerns. Are there additional primary peer-reviewed and publicly available literature that warrant further consideration? If so, please identify or provide these sources and comment on whether acquisition and summarization of this additional information would change the hazard characterization already provided in the existing summaries? Does the information presented clearly and accurately represent the hazards associated with each chemical? Are there any studies that should be removed from the summary and evidence tables due to study quality or data transparency concerns?

While some additional studies reporting mammalian- and ecological-toxicity following exposure to DecaBDE were identified in a literature search, the effects reported in these studies do not add any significantly new hazard or dose-response information to that already identified in the studies reviewed by the agency.

4. Has appropriate and sufficient information been obtained from the literature to support the identification of hazards?

The studies summarized by the agency end at 2014. While there have been additional studies on DecaBDE since 2014, in general, most of the studies and endpoints summarized by the agency are relevant to the hazards under consideration and there are a sufficient number to draw conclusions regarding DecaBDE-induced hazards subject to the PBT assessment.

5. Please comment on the reliability and relevance of the identified data sets for each chemical and on the strengths and weaknesses of individual data sets that will help to better inform future regulatory actions.

The dataset for DecaBDE is sufficiently comprehensive for the desired review. The agency should consider that most of the identified studies are not guideline studies conducted under good laboratory practices and so it is often not possible to confirm in these non-GLP studies key critical considerations for establishing an accurate dose or exposure response relationship for observed effects, for example, important information regarding test material purity, dose concentrations, and stability are not always provided in non-GLP studies. Therefore, in its weight of evidence assessment, the agency should place more consideration on those studies conducted following established guidelines and conducted under good laboratory practices.

For the environmental hazards the guideline GLP studies summarized, which are considered the most reliable and of high quality, include the those of Hardy et al., (2011, 2012), Nakari and Huhtala (2010), ECHA (2018), and Wildlife Intl LTD (2001). The study by Feng et al., (2013) should not be considered because the route of exposure was intraperitoneal thus lacking relevance to real world exposures and measured outcomes were oxidative stress biomarkers that are indicative of potential mechanism(s) of action rather than adverse outcomes. The study by Kuo et al. (2010) reported BDE-209-induced changes in the otolith width, for which the hazard relevance for risk assessment has not been established. In addition, the agency should consider that for some studies used DecaBDE concentrations that exceeded the reported solubility limit of DecaBDE in pure water of 0.001 mg/l (1 μg/l), which is an important confounder for interpreting the dose-response relationship and any induced adverse effects.

For the Human Health Hazards, the agency summarized six studies on developmental neurotoxicity, that included five academic studies from Johansson et al. (2008), Rice et al. (2007), Rice et al. (2009), Biesemeier et al. (2011), Viberg et al. (2007), Viberg et al. (2003) and one guideline study conducted under GLP (Biesemeier et al. (2011). These studies were conducted in rats or mice using varying protocol designs that included DecaBDE exposures during pregnancy to single or repeated exposures during PNDs 2–41. Most of the academic studies reported subtle developmental effects largely related to measures of locomotor activity or cognitive behavior. The reported effects from these studies did not agree and were in opposite directions. Rice et al. (2007) reported an initial higher activity and an increased habituation in exposed mice with no effects in Functional Observational Battery in the study, whereas the Viberg et al., (2003b, 2007) studies in mice and rats and Johansson et al. (2008) study in mice observed lower initial activity and decreased habituation. The only guideline GLP study for developmental neurotoxicity did not observe such effects in rat pups at doses higher than those used in these other studies. Since some of the differences in the study outcomes could be related to test material preparation, purity, dosimetry and statistical testing, the agency should give more weight to the studies where the relevant data is provided and can be assessed such as the guideline studies following GLP.

Hexachlorobutadiene (HCBD) (CASRN 87-68-3)
Environmental and Human Health Hazard Summary Peer Review Charge Questions

Response to questions for HCBD:

1. This information, when finalized will inform a technical support document to support EPA's regulatory activities on PBTs. Please comment on the organization and structure of this document to inform this use. Do you have specific recommendations to improve clarity and presentation of this information?

In general, the document is clearly written and well organized. The agency was clear to note for the reviewers that the information in this document is not meant to represent an exhaustive literature review nor an analysis of relative importance or comparative dose-response among hazards, but rather is intended to be an environmental and human health summary of the known hazards of each chemical under review. As such, only a limited amount of information has been identified and summarized by the agency. Even so, some additional clarification and information as follows would be valuable for those reviewing the summarized information provided by the agency.

In order to assess the adequacy of the search of the published and unpublished hazard data, the search strategy should include:

- a list of all chemical identifiers and chemical names and synonyms used as search terms, and
- the rationale for selection of databases searched

Evidence tables should include a columns for

- test material characterization: purity, stability, dose confirmation
- study design: guideline, non-guideline
- study quality, for example, GLP study or non-GLP study and quality scoring framework with citation, e.g., Klimisch score.

2. Please comment on the methodology for collecting and summarizing information from secondary sources. Was the approach appropriate? Is the description for how and where the literature was obtained clearly described?

The Agency peer review draft document clearly describes the secondary source search strategy. The summaries of the individual studies are minimal and limited to species, study design, dose response and adverse effect observed. There is no assessment provided of the study quality and methods that might impact interpretation, such as test material purity, solubility and stability, and study design, e.g., guideline study, GLP, and other methodological considerations affecting study quality.

3. Please comment on the representativeness and adequacy of the selected literature used in the evidence tables and described in the text to summarize the hazard concerns. Are there additional primary peer-reviewed and publicly available literature that warrant further consideration? If so, please identify or provide these sources and comment on whether acquisition and summarization of this additional information would change the hazard characterization already provided in the existing summaries? Does the information presented clearly and accurately represent the hazards associated with each chemical? Are there any studies that should be removed from the summary and evidence tables due to study quality or data transparency concerns?

While some additional studies reporting mammalian- and ecological-toxicity following exposure to HCBD were identified in a literature search, the effects reported in these studies do not add any significantly new hazard or dose-response information to that already identified in the studies reviewed by the agency.

4. Has appropriate and sufficient information been obtained from the literature to support the identification of hazards?

The studies and endpoints summarized by the agency are relevant to the hazards under consideration and there are a sufficient number to draw conclusions regarding HCBD-induced hazards subject to the PBT assessment.

5. Please comment on the reliability and relevance of the identified data sets for each chemical and on the strengths and weaknesses of individual data sets that will help to better inform future regulatory actions.

The dataset for HCBD is sufficiently comprehensive for the desired review. The agency should consider that most of the identified studies are not guideline studies conducted under good laboratory practices and so it is often not possible to confirm in these non-GLP studies key critical considerations for establishing an accurate dose or exposure response relationship for observed effects, for example, important information regarding test material purity, dose concentrations, and stability are not always provided in non-GLP studies. Therefore, in its weight of evidence assessment, the agency should place more consideration on those studies and technical reports conducted following established guidelines and conducted under good laboratory practices (GLP) or principles of GLP for older studies and reports conducted prior to implementation of GLP.

The dataset for HCBD environmental hazards for acute aquatic toxicity covers three trophic levels, i.e. vertebrates (fish), invertebrates (crustaceans - Daphnia) and plants (algae) and one chronic terrestrial toxicity study in birds. The majority of the studies summarized are from book chapter and journal articles in which the accuracy of the data cannot be easily confirmed. The exceptions are two technical reports U.S EPA (1980) and Laseter et al., (1976) on acute aquatic and chronic aquatic toxicity, respectively, that provide sufficient details to determine their reliability and should have more weight in the evaluation.

For the Human Health Hazards, the agency summarized several published oral studies ranging from 2 weeks to 2 years in rats and mice demonstrated renal effects including tissue histopathology, adenomas and carcinomas. The majority of these studies were published prior to the advent of GLP. The guideline GLP studies that are considered the most reliable and of high quality and include the those of NTP (1991) also Yang et al. (1989), and Field et al. (1990) .

Pentachlorothiophenol (PCTP) (CASRN 133-49-3)
Environmental and Human Health Hazard Summary Peer Review Charge Questions

1. This information, when finalized will inform a technical support document to support EPA's regulatory activities on PBTs. Please comment on the organization and structure of this document to inform this use. Do you have specific recommendations to improve clarity and presentation of this information?

In general, the document is clearly written and well organized. The agency was clear to note for the reviewers that the information in this document is not meant to represent an exhaustive literature review nor an analysis of relative importance or comparative dose-response among hazards, but rather is intended to be an environmental and human health summary of the known hazards of each chemical under review. As such, only a limited amount of information has been identified and summarized by the agency. Even so, some additional clarification and information as follows would be valuable for those reviewing the summarized information provided by the agency.

In order to assess the adequacy of the search of the published and unpublished hazard data, the search strategy should include:

- a list of all chemical identifiers and chemical names and synonyms used as search terms, and
- the rationale for selection of databases searched

Evidence tables should include a columns for

- test material characterization: purity, stability, dose confirmation
- study design: guideline, non-guideline
- study quality, for example, GLP study or non-GLP study and quality scoring framework with citation, e.g., Klimisch score.

2. Please comment on the methodology for collecting and summarizing information from secondary sources. Was the approach appropriate? Is the description for how and where the literature was obtained clearly described?

The Agency peer review draft document clearly describes the secondary source search strategy. The summaries of the individual studies are minimal and limited to species, study design, dose response and adverse effect observed. There is no assessment provided of the study quality and methods that might impact interpretation, such as test material purity, solubility and stability, and study design, e.g., guideline study, GLP, and other methodological considerations affecting study quality.

3. Please comment on the representativeness and adequacy of the selected literature used in the evidence tables and described in the text to summarize the hazard concerns. Are there additional primary peer-reviewed and publicly available literature that warrant further consideration? If so, please identify or provide these sources and comment on whether acquisition and summarization of this additional information would change the hazard characterization already provided in the existing summaries? Does the information presented clearly and accurately represent the hazards associated with each chemical? Are there any studies that should be removed from the summary and evidence tables due to study quality or data transparency concerns?

The database of studies on PCTP summarized by the agency is minimal. For the environmental hazards, summaries were provided from two summaries from HSDB summaries of IUCLID reports, two six decades old reports and two data summaries from the EPA ECOTOX database. A search of the literature did not identify any additional relevant information. The agency should obtain the IUCLID data directly for review for the environmental hazards.

The agency has summarized two studies for human health effects on related PCTP analogous pentachloronitrobenzene and hexachlorobenzene. A search of the literature did not identify repeated dose studies in mammals with PCTP. The agency is relying on a read-across from the closely related analogues pentachloronitrobenzene and hexachlorobenzene, which is justified given PCPT is both a metabolite and biodegradation product of pentachloronitrobenzene and a metabolite of hexachlorobenzene.

4. Has appropriate and sufficient information been obtained from the literature to support the identification of hazards?

The studies and endpoints summarized by the agency are relevant to the hazards under consideration and however, given the limitations noted above in the database of studies, it will be especially important for the agency to provide a thorough uncertainty analysis in its risk characterization for PCTP.

5. Please comment on the reliability and relevance of the identified data sets for each chemical and on the strengths and weaknesses of individual data sets that will help to better inform future regulatory actions.

The dataset for environmental and human health hazards for PCTP is minimal and appears limited. The agency should obtain original study reports to assess the quality and validity of the information in order to determine the most reliable for hazard and risk assessment. In its weight of evidence assessment, the agency should place more consideration on those studies and reports conducted following most closely established guidelines and principles of GLP.

Phenol, isopropylated, phosphate (3:1) (PIP 3:1) (CASRN 68937-41-7)
Environmental and Human Health Hazard Summary Peer Review Charge Questions

1. This information, when finalized will inform a technical support document to support EPA's regulatory activities on PBTs. Please comment on the organization and structure of this document to inform this use. Do you have specific recommendations to improve clarity and presentation of this information?

In general, the document is clearly written and well organized. The agency was clear to note for the reviewers that the information in this document is not meant to represent an exhaustive literature review nor an analysis of relative importance or comparative dose-response among hazards, but rather is intended to be an environmental and human health summary of the known hazards of each chemical under review. As such, only a limited amount of information has been identified and summarized by the agency. Even so, some additional clarification and information as follows would be valuable for those reviewing the summarized information provided by the agency.

In order to assess the adequacy of the search of the published and unpublished hazard data, the search strategy should include:

- a list of all chemical identifiers and chemical names and synonyms used as search terms, and
- the rationale for selection of databases searched

Evidence tables should include a columns for

- test material characterization: purity, stability, dose confirmation
- study design: guideline, non-guideline
- study quality, for example, GLP study or non-GLP study and quality scoring framework with citation, e.g., Klimisch score.

2. Please comment on the methodology for collecting and summarizing information from secondary sources. Was the approach appropriate? Is the description for how and where the literature was obtained clearly described?

The Agency peer review draft document clearly describes the secondary source search strategy. The summaries of the individual studies are minimal and limited to species, study design, dose response and adverse effect observed. There is no assessment provided of the study quality and methods that might impact interpretation, such as test material purity, solubility and stability, and study design, e.g., guideline study, GLP, and other methodological considerations affecting study quality.

3. Please comment on the representativeness and adequacy of the selected literature used in the evidence tables and described in the text to summarize the hazard concerns. Are there additional primary peer-reviewed and publicly available literature that warrant further consideration? If so, please identify or provide these sources and comment on whether acquisition and summarization of this additional information would change the hazard characterization already provided in the existing summaries? Does the information presented clearly and accurately represent the hazards associated with each chemical? Are there any studies that should be removed from the summary and evidence tables due to study quality or data transparency concerns?

A literature search of PIP did not identify any new hazard or dose-response information that added to the information already identified in the studies reviewed by the agency.

4. Has appropriate and sufficient information been obtained from the literature to support the identification of hazards?

The studies and endpoints summarized by the agency are relevant to the hazards under consideration and there are a sufficient number to draw conclusions regarding PIP-induced hazards subject to the PBT assessment.

5. Please comment on the reliability and relevance of the identified data sets for each chemical and on the strengths and weaknesses of individual data sets that will help to better inform future regulatory actions.

The dataset for environmental and human health hazards for PIP includes a large number of guideline studies conducted under GLP and is sufficiently comprehensive for the desired review. However, the agency should obtain copies of the original study reports to review the accuracy of the data and information reported in the ECHA database.

2,4,6-Tris(tert-butyl) phenol (2,4,6 TTBP) (CASRN 732-26-3)
Environmental and Human Health Hazard Summary Peer Review Charge Questions

1. This information, when finalized will inform a technical support document to support EPA's regulatory activities on PBTs. Please comment on the organization and structure of this document to inform this use. Do you have specific recommendations to improve clarity and presentation of this information?

In general, the document is clearly written and well organized. The agency was clear to note for the reviewers that the information in this document is not meant to represent an exhaustive literature review nor an analysis of relative importance or comparative dose-response among hazards, but rather is intended to be an environmental and human health summary of the known hazards of each chemical under review. As such, only a limited amount of information has been identified and summarized by the agency. Even so, some additional clarification and information as follows would be valuable for those reviewing the summarized information provided by the agency.

In order to assess the adequacy of the search of the published and unpublished hazard data, the search strategy should include:

- a list of all chemical identifiers and chemical names and synonyms used as search terms, and
- the rationale for selection of databases searched

Evidence tables should include a columns for

- test material characterization: purity, stability, dose confirmation
- study design: guideline, non-guideline
- study quality, for example, GLP study or non-GLP study and quality scoring framework with citation, e.g., Klimisch score.

2. Please comment on the methodology for collecting and summarizing information from secondary sources. Was the approach appropriate? Is the description for how and where the literature was obtained clearly described?

The Agency peer review draft document clearly describes the secondary source search strategy. The summaries of the individual studies are minimal and limited to species, study design, dose response and adverse effect observed. There is no assessment provided of the study quality and methods that might impact interpretation, such as test material purity, solubility and stability, and study design, , e.g., guideline study, GLP, and other methodological considerations affecting study quality.

3. Please comment on the representativeness and adequacy of the selected literature used in the evidence tables and described in the text to summarize the hazard concerns. Are there additional primary peer-reviewed and publicly available literature that warrant further consideration? If so, please identify or provide these sources and comment on whether acquisition and summarization of this additional information would change the hazard characterization already provided in the existing summaries? Does the information presented clearly and accurately represent the hazards associated with each chemical? Are there any studies that should be removed from the summary and evidence tables due to study quality or data transparency concerns?

A literature search of 2,4,6 TTBP did not identify any new hazard or dose-response information that added to the information already identified in the studies reviewed by the agency.

4. Has appropriate and sufficient information been obtained from the literature to support the identification of hazards?

The studies and endpoints summarized by the agency are relevant to the hazards under consideration and there are a sufficient number to draw conclusions regarding 2,4,6 TTBP-induced hazards subject to the PBT assessment.

5. Please comment on the reliability and relevance of the identified data sets for each chemical and on the strengths and weaknesses of individual data sets that will help to better inform future regulatory actions.

The dataset for environmental and human health hazards for 2,4,6 TTBP includes both guideline GLP studies and non-guideline studies. In its weight of evidence assessment, the agency should place more consideration on those studies and reports conducted following established guidelines and conducted under GLP or following GLP principles with adequate information and data provided to confirm such. In addition, the agency should obtain copies of the original study reports to review the accuracy of the data and information reported in the ECHA database.

Reviewer 7 - Environmental and Human Health Hazard Summary Peer Review

Decabromodiphenyl ether (DecaBDE) (CASRN 1163-19-5)

1. This information, when finalized will inform a technical support document to support EPA's regulatory activities on PBTs. Please comment on the organization and structure of this document to inform this use. Do you have specific recommendations to improve clarity and presentation of this information?

The structure of the document was clear and direct. The rationale for the compilation was clearly stated as were the databases, which were used for search. The rationale for database selection was not apparent, nor was the weighting of data obtained from the databases. For example, was data from ECOTOX considered as higher value than other sources. Overall, data for toxicity provided as LC/LD or EC/ED 50s with associated No and lowest adverse effect levels were presented in tabular formats with appropriate citations and links for subsequent analyses in most cases. With data focused on Survival, Growth, Reproduction and Development, endpoints were clear and toxicity values were transparent. There should be text discussing accumulation in the hazard assessment, since it is ranked high.

2. Please comment on the methodology for collecting and summarizing information from secondary sources. Was the approach appropriate? Is the description for how and where the literature was obtained clearly described?

A description was provided in the document regarding EPAs methodology for assessment. However, the description of the methodology was somewhat vague. For example, it was stated that "EPA *leveraged* previous data compilations and existing information, wherever possible, as the initial data gathering approach". It was unclear what data was considered "primary" and "secondary". Was "leveraged" data considered "primary" data? The term "leveraged" is unclear and an example or definition of the process would be very helpful. Would searches outside of EPA's databases be considered "secondary"? Criteria for inclusion of a reference would also be helpful. Listing of citations considered unacceptable would also be useful to assess transparency of the review process.

3. Please comment on the representativeness and adequacy of the selected literature used in the evidence tables and described in the text to summarize the hazard concerns. Are there additional primary peer-reviewed and publicly available literature that warrant further consideration? If so, please identify or provide these sources and comment on whether acquisition and summarization of this additional information would change the hazard characterization already provided in the existing summaries? Does the information presented clearly and accurately represent the hazards associated with each chemical? Are there any studies that should be removed from the summary and evidence tables due to study quality or data transparency concerns?

It was stated in the review document that Web of Science was utilized as a secondary literature review source. An additional resource should be *Scifinder Scholar* produced by *Chemical Abstract Services (CAS)*. Conducting a search using the terms BPE toxicity and refining that to "review", a number of documents were identified that were not included in this search.

An example of a report not included in the original document is the review by Hardy et al. 2009. While reference dose (RfD) determinations were not an aim of the Agency, Hardy et al. 2009 provided an excellent review of the animal toxicology literature to derive an RfD which was screened using the Klimisch criteria with subsequent evaluation using the Agency's general assessment factors for data quality and relevance (i.e., soundness, applicability and utility, clarity and completeness, uncertainty and variability, and evaluation and review). The authors used a chronic 2-year dietary feeding study conducted by the United States National Toxicology Program (NTP, 1986) for a RfD derivation. It should be noted that the NTP study was listed in Table 4-2 with a NOAEL for hepatocellular degeneration in male rats was chosen as the critical endpoint in the RfD development, but additional sources were also provided that were not in the document provided by EPA. It was unclear why or how the un-cited literature was excluded. For example, although ASTDR was used for HCBD, it was not listed for any other compounds, specifically PDEs. However, the first line of section 4.2 states that ASTDR was used.

An example of a more recent study would be Xu et al. 2018. It was a study that provided additional developmental neurotoxicity data but with only low and high doses orally administered at 20, 100 mg/kg bodyweight/day from GD 6 to postnatal day (PND) 16.

An additional recent study would be Lu et al. 2018 which developed water quality criteria for several PBDEs in China. Data used to construct a species sensitivity distributions to derive the criteria for decaPBDE as well as other PBDE and BFRs were reported.

Studies that evaluate mixtures of compounds should be given lower priority than those evaluating decaPBE. Similarly studies that use nominal concentrations without measurement confirmation should also be given lower priority for hazard determination. Similarly, concentrations that exceed water solubility should also be given lower priority or excluded from threshold development.

Although studies are listed in Table 4-1 for bioavailabllity and some bioaccumulation, text responding to bioaccumulation in laboratory studies was not provided. Bioaccumulation and bioconcentraion factors were not provided.

4. Has appropriate and sufficient information been obtained from the literature to support the identification of hazards?

With the exceptions of the above listed references, sufficient information was obtained from the literature to support the identification of hazard. Concentrations for adverse effects were primarily in the sub mg/L ranges for most studies listed in water and sediments for environmental media. For animal studies, similar concentrations in the mg/kg range were also observed. However, additional literature should be used for further and future risk analyses.

5. Please comment on the reliability and relevance of the identified data sets for each chemical and on the strengths and weaknesses of individual data sets that will help to better inform future regulatory actions.

Both peer-reviewed, government and manufacturer-based data were provided and used to provide necessary NOEC, NOAEL and other thresholds that could be used to derive hazard. As mentioned above, strengths of the data sets were the numerous sources of data that have presumably been vetted by the Agency. However, a noticeable weakness would be the lack of description of inclusion/exclusion criteria for non-governmental documents or the peer-reviewed literature. Bioaccumulation information was not present.

Hexachlorobutadiene (HCBD) (CASRN 87-68-3)

1. This information, when finalized will inform a technical support document to support EPA's regulatory activities on PBTs. Please comment on the organization and structure of this document to inform this use. Do you have specific recommendations to improve clarity and presentation of this information?

The structure of the document was clear and direct. The rationale for the compilation was clearly stated as were the databases which were used for search. The rationale for database selection was not apparent, nor was the weighting of data obtained from the databases. For example, was data from ECOTOX considered as higher value than other sources. Overall, data for toxicity provided as LC/LD or EC/ED 50s with associated No and lowest adverse effect levels were presented in tabular formats with appropriate citations and links for subsequent analyses in most cases. With data focused on Survival, Growth, Reproduction and Development, endpoints were clear and toxicity values were transparent.

2. Please comment on the methodology for collecting and summarizing information from secondary sources. Was the approach appropriate? Is the description for how and where the literature was obtained clearly described?

A description was provided in the document regarding EPAs methodology for assessment. However, the description of the methodology was somewhat vague. For example, the document stated that "EPA *leveraged* previous data compilations and existing information, wherever possible, as the initial data gathering approach". It was unclear what data was considered "primary" and "secondary". Was "leveraged" data considered "primary" data? The term "leveraged" is unclear and an example or definition of the process would be very helpful. Would searches outside of EPA's databases be considered "secondary"? Criteria for inclusion of a reference would also be helpful. Listing of citations considered unacceptable would also be useful to assess transparency of the review process. Additional software *Scifinder Scholar* should be an additional source for publically available literature.

3. Please comment on the representativeness and adequacy of the selected literature used in the evidence tables and described in the text to summarize the hazard concerns. Are there additional primary peer-reviewed and publicly available literature that warrant further consideration? If so, please identify or provide these sources and comment on whether acquisition and summarization of this additional information would change the hazard characterization already provided in the existing summaries? Does the information presented clearly and accurately represent the hazards associated with each chemical? Are there any studies that should be removed from the summary and evidence tables due to study quality or data transparency concerns?

It was stated in the review document that Web of Science was utilized as a secondary literature review source. An additional resource should be *Scifinder Scholar* produced by *Chemical Abstract Services (CAS)*. Conducting a search using the terms 87-68-3 toxicity and refining that to "review", a number of documents were identified that were not included in this search.

After a brief search using *Scifinder Scholar*, the reference of Taylor et al. 2003 was found. This was an ecological risk assessment of HCBD in Canada. Taylor et al. 2003 included a study by Laska et al. 1978 that was not provided in Table 5-1, nor was the ambient water criteria document for HCBD from the EPA from 1980. Laska et al. 1978 evaluated the effects of HCBD on crayfish. If this study was excluded due to some criteria, the rationale was not apparent.

4. Has appropriate and sufficient information been obtained from the literature to support the identification of hazards?

With the exceptions of the above listed references, sufficient information was obtained from the literature to support the identification of hazard. Concentrations for adverse effects were primarily in the sub mg/L ranges for most studies listed in water and sediments for environmental media. For animal studies, similar concentrations in the mg/kg range were also observed. Bioaccumulation information was not provided in the document. HCBD tends to bioaccumulate, but not biomagnify in food webs (Taylor et al. 2003).

5. Please comment on the reliability and relevance of the identified data sets for each chemical and on the strengths and weaknesses of individual data sets that will help to better inform future regulatory actions.

Both peer-reviewed, government and manufacturer-based data were provided and used to provide necessary NOEC, NOAEL and other thresholds that could be used to derive hazard. As mentioned above, strengths of the data sets were the numerous sources of data that have presumably been vetted by the Agency. However, a noticeable weakness would be the lack of description of inclusion/exclusion criteria for non-governmental documents or the peer-reviewed literature. Bioaccumulation description was not present.

Phenol, isopropylated, phosphate (3:1) (PIP 3:1) (CASRN 68937-41-7)

1. This information, when finalized will inform a technical support document to support EPA's regulatory activities on PBTs. Please comment on the organization and structure of this document to inform this use. Do you have specific recommendations to improve clarity and presentation of this information?

As this section of the document tried to evaluate a multi-chemical product rather the constituents of the product, the purported hazard was unclear. Indeed the CASRN is actually isopropyl phenyl phosphate. This is a single compound and not a mixture as reported in the assessment. Hazard assessments for the specific constituents would provide a better mechanism for regulators to assess the risks of the mixture. Perhaps a strategy for pesticide registration, which selects an "active ingredient" within the product may improve clarity.

2. Please comment on the methodology for collecting and summarizing information from secondary sources. Was the approach appropriate? Is the description for how and where the literature was obtained clearly described?

A description was provided in the document regarding EPAs methodology for assessment. However, the description of the methodology was somewhat vague. For example, it was stated that "EPA *leveraged* previous data compilations and existing information, wherever possible, as the initial data gathering approach". It was unclear what data was considered "primary" and "secondary". Was "leveraged" data considered "primary" data? The term "leveraged" is unclear and an example or definition of the process would be very helpful. Would searches outside of EPA's databases be considered "secondary"? Criteria for inclusion of a reference would also be helpful. Listing of citations considered unacceptable would also be useful to assess transparency of the review process. Additional software *Scifinder Scholar* should be an additional source for publically available literature.

For this particular agent(s), it was very unclear which compound was being evaluated. Although an alkylated phosphate, triphenyl phosphate is structurally different than 68937-41-7 and has a host of adverse developmental effects already reported (van der Veen and de Boer 2012). It also would likely undergo significantly different biotransformation and disposition.

3. Please comment on the representativeness and adequacy of the selected literature used in the evidence tables and described in the text to summarize the hazard concerns. Are there additional primary peer-reviewed and publicly available literature that warrant further consideration? If so, please identify or provide these sources and comment on whether acquisition and summarization of this additional information would change the hazard characterization already provided in the existing summaries? Does the information presented clearly and accurately represent the hazards associated with each chemical? Are there any studies that should be removed from the summary and evidence tables due to study quality or data transparency concerns?

It was stated in the review document that Web of Science was utilized as a secondary literature review source. An additional resource should be *Scifinder Scholar* produced by *Chemical Abstract Services (CAS)*. Conducting a search using the terms 68937-41-7 and toxicity and refining that to "review", few documents were identified.

One reference on phosphorous flame retardants (van de Veen and de Boer 2012) may be use if an "active ingredient" within the mixture can be identified.

Outside of this reference, none of the studies provided by EPA are peer reviewed, so comparisons are difficult as is causality to a specific compound.

4. Has appropriate and sufficient information been obtained from the literature to support the identification of hazards?

Limited literature is available and given the difficulty in determining the “active ingredient”, it is difficult to justify this mixture as a hazardous material.

5. Please comment on the reliability and relevance of the identified data sets for each chemical and on the strengths and weaknesses of individual data sets that will help to better inform future regulatory actions.

Limited strengths are present for this assessment. There is only one peer-reviewed study provided on a product that was 28% triphenylphosphate. Thus, the literature is extremely limited as is the chemical identity and dose for effect is unclear.

2,4,6-Tris(tert-butyl) phenol (2,4,6 TTBP) (CASRN 732-26-3)

1. This information, when finalized will inform a technical support document to support EPA's regulatory activities on PBTs. Please comment on the organization and structure of this document to inform this use. Do you have specific recommendations to improve clarity and presentation of this information?

As above, the structure and organization of this section is relatively clear regarding hazard to non-human organisms and mammals/humans. However, studies regarding toxicity are limited.

2. Please comment on the methodology for collecting and summarizing information from secondary sources. Was the approach appropriate? Is the description for how and where the literature was obtained clearly described?

A description was provided in the document regarding EPAs methodology for assessment. However, the description of the methodology was somewhat vague. For example, it was stated that "EPA *leveraged* previous data compilations and existing information, wherever possible, as the initial data gathering approach". It was unclear what data was considered "primary" and "secondary". Was "leveraged" data considered "primary" data? The term "leveraged" is unclear and an example or definition of the process would be very helpful. Would searches outside of EPA's databases be considered "secondary"? Criteria for inclusion of a reference would also be helpful. Listing of citations considered unacceptable would also be useful to assess transparency of the review process. Additional software *Scifinder Scholar* should be an additional source for publically available literature.

3. Please comment on the representativeness and adequacy of the selected literature used in the evidence tables and described in the text to summarize the hazard concerns. Are there additional primary peer-reviewed and publicly available literature that warrant further consideration? If so, please identify or provide these sources and comment on whether acquisition and summarization of this additional information would change the hazard characterization already provided in the existing summaries? Does the information presented clearly and accurately represent the hazards associated with each chemical? Are there any studies that should be removed from the summary and evidence tables due to study quality or data transparency concerns?

It was stated in the review document that Web of Science was utilized as a secondary literature review source. An additional resource should be *Scifinder Scholar* produced by *Chemical Abstract Services (CAS)*. Conducting a search using the terms 732-26-3 and toxicity only yielded 6 records.

4. Has appropriate and sufficient information been obtained from the literature to support the identification of hazards?

GLP studies support the identification of hazardous chemical to ecological receptors. Bioaccumulation data was not present. For human health assessment, one peer-reviewed study and few ECHA documents suggested hazard, but confirmation with peer-reviewed literature is uncertain.

5. Please comment on the reliability and relevance of the identified data sets for each chemical and on the strengths and weaknesses of individual data sets that will help to better inform future regulatory actions.

GLP studies indicate hazard, but few peer reviewed studies performed with this specific compound suggest significant uncertainty with regard to hazard.

Pentachlorothiophenol (PCTP) (CASRN 133-49-3)

1. This information, when finalized will inform a technical support document to support EPA's regulatory activities on PBTs. Please comment on the organization and structure of this document to inform this use. Do you have specific recommendations to improve clarity and presentation of this information?

As above, the structure and organization of this section is relatively clear regarding attempts to evaluate hazard to non-human organisms and mammals/humans. However, studies regarding toxicity are limited.

2. Please comment on the methodology for collecting and summarizing information from secondary sources. Was the approach appropriate? Is the description for how and where the literature was obtained clearly described?

Using studies of pentachloronitrobenzene as a surrogate for 133-49-3 is unacceptable. Renner and Nguyen 1982 clearly show that 133-49-3 is 16 times higher than Pentachloronitrobenze. Additional software *Scifinder Scholar* should be an additional source for publically available literature.

3. Please comment on the representativeness and adequacy of the selected literature used in the evidence tables and described in the text to summarize the hazard concerns. Are there additional primary peer-reviewed and publicly available literature that warrant further consideration? If so, please identify or provide these sources and comment on whether acquisition and summarization of this additional information would change the hazard characterization already provided in the existing summaries? Does the information presented clearly and accurately represent the hazards associated with each chemical? Are there any studies that should be removed from the summary and evidence tables due to study quality or data transparency concerns?

It was stated in the review document that Web of Science was utilized as a secondary literature review source. An additional resource should be *Scifinder Scholar* produced by *Chemical Abstract Services (CAS)*. Conducting a search using the terms 133-49-3 and toxicity Renner and Nguyen 1982 was identified. This study conducted LD 50 evaluations of 133-49-3 and compared it to the parent compound of nitrobenzene Bioaccumulation information was not reported.

One ecotox study is reported for chicken and protozoa. Other studies in aquatic systems are few and uncertain. For human health assessements, the use of proproosed “parent compounds pentachloronitrobenzene and hexachlorobenzene is extremely uncertain.

4. Has appropriate and sufficient information been obtained from the literature to support the identification of hazards?

The use of surrogate compounds for is highly uncertain for human health assessment and few ecological endpoints for 133-49-3 suggest uncertain information for hazard assessments.

5. Please comment on the reliability and relevance of the identified data sets for each chemical and on the strengths and weaknesses of individual data sets that will help to better inform future regulatory actions.

Few studies performed with this specific compound suggest significant uncertainty with regard to hazard.

References

Marcia L. Hardy1, Marek Banasik2, and Todd Stedeford Toxicology and human health assessment of decabromodiphenyl ether. *Critical Reviews in Toxicology*, 2009; 39(S3): 1–44

Laska, AL, Bartell CK, Condie DB. Brown, JW, Evans, RL, Laseter, JL. 1978 Acute and chronic effects of hexachlorobenzene and hexachlorobutadiende in red swamp crayfish (Procambarus clarki) and selected species. Toxicol Appl Pharmacol 43:1-12.

Chunxia Lu a,b,1, Suwen Yang c,1, Zhenguang Yan a,⁎, Junhong Ling a, Lixin Jiao c, Huanqi He a, Xin Zheng a,
Weidong Jin c, Juntao Fan (2018) Deriving aquatic life criteria for PBDEs in China and comparison of species
sensitivity distribution with TBBPA and HBCD. Science of the Total Environment 640–641 (2018) 1279–1285

Taylor KW, Caux, P-Y, Moore, DRJ. (2003) An Ecological risk assessment of HCBD in Canada. Human and Ecological Risk Assessment 9:511-525.

Mingrui Xu1,3 · Yingxue Huang2 · Kaikai Li2 · Xinran Cheng2 · Guohong Li2 ·
Mengmeng Liu2 · Yufei Nie4 · Shu Geng1,3,5 · Shanting Zhao Developmental exposure of decabromodiphenyl ether impairs
subventricular zone neurogenesis and morphology of granule cells
in mouse olfactory bulb. Arch Toxicol (2018) 92:529–539

Ike van der Veen ⇑, Jacob de Boer (2012) Phosphorus flame retardants: Properties, production, environmental
occurrence, toxicity and analysis. Chemosphere 88 : 1119–1153