Summary of External Peer Review and Public Comments and Disposition

This document summarizes the public and external peer review comments that the EPA's Office of Pollution Prevention and Toxics (OPPT) received for the draft work plan risk assessment for 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-γ-2-benzopyran (HHCB). It also provides EPA/OPPT's response to the comments received from the public and the peer review panel.

EPA/OPPT appreciates the valuable input provided by the public and peer review panel. The input resulted in significant revisions to the risk assessment.

Peer review charge questions[1] are used to categorize the peer review and public comments into specific issues related to four main themes.

- General Issues on the Risk Assessment Document
- Environmental Exposure Assessment
- Hazard and Dose-Response Assessments
- Risk Characterization

A separate section, *Other Comments,* organizes the response to those public comments that are unrelated to the charge question themes listed above.

[1]These are the questions that EPA/OPPT submitted to the panel to guide the peer review process.

General Issues on the Risk Assessment Document

Charge Question 1-1: Please comment on whether the assessment provides a clear and logical summary of EPA's approach and analysis. Please provide specific suggestions for improving the assessment.

Charge Question 1-2: Please comment on whether appropriate background information is provided and accurately characterized. Please provide any other significant literature, reports or data that would be useful to complete this characterization.

#	Summary of Peer Review and Public Comments for Specific Issues Related to Charge Questions 1-1 and 1-2	EPA/OPPT Response
1	***The discussion of Problem Formulation and the purpose of the assessment are not clearly articulated.*** There should be a Problem Formulation section (based on a systematic framework) that includes the Conceptual Model and outcomes. The purpose of the assessment and relation to risk management goals are missing. Explain rationale for treatment of developmental toxicity and human health assessment. Further explanation would be helpful as to why mammals and birds were beyond the scope of this assessment.	EPA/OPPT has made significant revisions to the HHCB risk assessment to improve the clarity of the document. *Chapter 1* of the final risk assessment has been restructured to include additional sections describing Problem Formulation, Scope of the Assessment, Conceptual Model and the Analysis Plan for HHCB. In addition, the purpose and audience have been described in the *Introduction* section of *Chapter 1, Section 1.1* of the final HHCB risk assessment. A discussion of the rationale for excluding an assessment of risk to human health based on measured data has been included in *Chapter 1, Background and Scope*. A more detailed review of the available mammalian toxicity data and recently published biomonitoring data was conducted to determine if there are adequate data to conduct a human health assessment. The review found minimal developmental toxicity at relatively high oral exposures and no developmental toxicity at levels several times greater than detected in human breast milk. This information is summarized in *Appendix A, Human Health Toxicity Studies, Biomonitoring Data, and Risk Assessment.* Additional explanation for excluding mammals and birds from the scope of this assessment is provided in *Chapter 1, Background and Scope.* Briefly, HHCB has a low to moderate potential to bioaccumulate and trophic transfer (biomagnification) does not appear to be a concern based on review of the bioaccumulation data, monitoring data in biota, and aquatic food-chain modeling is included in the final scope of the assessment. In addition, a plant

		study cited in the 2008 EU Risk Assessment Report for HHCB indicates transfer of HHCB from soil to plants in not likely to represent a significant exposure pathway. In light of this available study data, modeling for assessing plant uptake and trophic transfer of HHCB to birds and mammals was deemed unnecessary. Furthermore, despite the comment, EPA did not find such models to be publicly available and validated for use in this assessment.
2	***Pathways, data, and analyses should be added to the scope of the assessment.*** The Conceptual Model should include other points of entry, a discussion of wastewater treatment processes, worst case scenarios, routes of exposure, and trophic transfer.	The Conceptual Model diagram is presented as Figure 1-1 in *Section 1.3* of *Chapter 1, Conceptual Model for HHCB* and has been revised to clarify what was evaluated in this assessment. In addition, a new accompanying text section entitled *Conceptual Model for Environmental Assessment* has been added to more clearly articulate the scenarios that were evaluated. Points of entry, wastewater treatment processes, worst case scenarios, routes of exposure, and trophic transfer are also more fully discussed within the document.

3	***Terminology, methods, and results are not clear.*** This is a screening-level assessment or a screening deterministic hazard assessment. It is a hazard assessment, not a risk assessment. Use the term hazard quotient, not risk quotient. Hazard is the possibility of an occurrence; risk is the probability of occurrence. An HQ≥1 only indicates "potential" concern. Need to be consistent in terms used to characterize risk. Various fate terms are not consistently used or defined.	This assessment includes both exposure assessment and hazard assessment as well as risk estimation conducted by comparing exposures and hazards via a Risk Quotient approach; hence, it is a risk assessment. Comparing point exposure and effects via a ratio or quotient is a simple and commonly used method for estimating risk, EPA (1998). The quotient method has long been used by EPA/OPPT in our new chemicals program. **Reference:** EPA (1998). Guidelines for Ecological Risk Assessment. *Fed. Regist*. **63**(93):26846-26924. http://www.epa.gov/raf/publications/pdfs/ECOTXTBX.PDF. There is not clear consensus on whether a simple ratio or quotient should be referred to as a 'hazard quotient' or a 'risk quotient'; however, in this assessment we are calling the ratio a 'risk quotient' to reflect that the ratio includes exposure and hazard components. This approach is consistent with long-standing practice in other EPA programs – to refer to the quotient as a Risk Quotient or RQ (http://www.epa.gov/oppefed1/ecorisk_ders/toera_risk.htm#Deterministic). EPA/OPPT has made efforts to more consistently use appropriate fate terminology throughout the document and particularly *in Chapter 2, Sources and Environmental Fate*. Where terms were not clear, a brief definition is provided (see *Chapter 2, Table 2-6* for example).

4	***Details of the QA/QC for the data sets are required.*** It is difficult to assess bioaccumulation or environmental monitoring data without discussing the criteria used to validate a data set. QA/QC specifics regarding sampling and analysis need further clarification. Multiple studies presented in this section (hazard) do not appear to have followed an internationally validated protocol and likely did not adhere to strict GLP procedures. Acceptability criteria for the toxicity studies have not been provided.	Additional clarification regarding data adequacy criteria for environmental occurrence has been provided in *Chapter 3, Section 3.2.2 Measured Levels of HHCB in the Environment*. Additional descriptions regarding the QA/QC specifics of exposure monitoring data including reporting levels, detection limits, recovery and use of blanks has been added to *Chapter 3, Environmental Exposure Assessment and Appendix G, Environmental Monitoring Data Analysis.* Toxicity tests would, ideally, have been conducted under optimum conditions and follow good laboratory practice (GLP). However, for the purpose of Work Plan Chemical Assessments, EPA/OPPT will consider guideline studies as well as studies using other protocols. For this risk assessment, studies were included if they met data adequacy criteria as described in *Chapter 3, Section 3.3* and EPA/OPPT guidance, EPA (1999c)*:* **Reference:** EPA (1999c). Determining the adequacy of existing data. US Environmental Protection Agency, Office of Pollution Prevention and Toxics. http://www.epa.gov/hpv/pubs/general/datadfin.htm.

Fate Assessment and Sources of HHCB

Charge Question 2-1: Please comment on whether the information (chemistry, environmental fate and transport, production and uses) is used appropriately in the risk characterization. Please provide any specific suggestions for improving the assessment.

#	Summary of Peer Review and Public Comments for Specific Issues Related to Charge Question 2-1	EPA/OPPT Response
5	***Bioaccumulation analysis is incomplete.*** Given the moderate Log Kow value (i.e., 5.3) and fish BCF value, a higher level bioaccumulation assessment would be appropriate.	A revised and more detailed discussion of bioaccumulation has been provided in *Chapter 2, Section 2.3.2 Bioaccumulation and Bioconcentration*. This discussion includes information provided during peer review.

	Suggested using field-derived BAF values and modeling to estimate BCFs. There was no mention of measured or estimated plant bioconcentration factors.	**References:** - Reiner, J. L., and Kannan, K. (2011). Polycyclic musks in water, sediment, and fishes from the upper Hudson River, New York, USA. *Water, Air, & Soil Pollution* **214**(1-4), 235-242. - Nakata, H., Sasak,i H., Takemura, A., Yoshioka, M., Tanabe, S., and Kannan, K. (2007). Bioaccumulation, temporal trend, and geographical distribution of synthetic musks in the marine environment. *Environ. Sci. Technol.* **41**:2216-2222. No additional bioaccumulation information was found in the Nakata reference provided by peer reviewers. The suggested modeling was already performed. Additional discussion regarding plant bioconcentration factors is provided in *Chapter 2, Section 2.3.2.*
6	***No data or estimations of uptake for terrestrial plants.*** There was no information provided for terrestrial plant concentrations and no attempt was made to predict values. It was stated that the long half-life in soil may result in HHCB being available for plant uptake but no estimates were made. There are several plant uptake estimation approaches that could be used.	Additional text describing an unpublished study by Muller et al. (2002) referenced in EC (2008) has been added to the assessment in *Chapter 2, Section 2.3.2*. In brief, in spite of a high concentration of HHCB in biosolids, no relevant accumulation in leaves was observed. The low observed concentrations in the above ground parts of the carrot plant showed that there was no transport within the plant. It was concluded that there is little transfer of HHCB from the soil to plants under environmental conditions. In light of this measured data, applying plant uptake models to predict HHCB uptake was deemed unnecessary for this assessment. Models for assessing plant uptake and trophic transfer of HHCB to birds and mammals were not publicly available and validated for use in this assessment. Insufficient data were available calculate risk to terrestrial plants, and EPA/OPPT acknowledges this as an uncertainty of this assessment, noted in *Chapter 3, Section 3.4.2.7*.

7	***Metabolism and degradation discussion is not complete.*** Metabolites need to be identified and discussed relative to potential hazard relative to the parent compound. The assessment should speak to degradation products (e.g. lactone) or specify that they are out of scope. There are also several predictive models that could be used to generate potential metabolites. Any information on differences in biological activity or degradability between isomers? Additional literature provided on anaerobic degradation should be included in the assessment.	Additional information on HHCB-lactone, the primary degradation product of HHCB, has been added to the assessment in *Chapter 2, Section 2.3, Environmental Fate,* based on the suggested reference of Horii et al. (2007). Hazard information on metabolites of HHCB were not available, thus using predictive models to generate potential metabolites was not performed and due to lack of this information, discussion of the potential hazard relative to the parent compound was not included in the final assessment. Information (hazard and exposure) of HHCB isomers and metabolites is also discussed in Section 3.4.2, *Key Sources of Uncertainty and Data Limitations.* HHCB-lactone is the only degradate of HHCB that has been reported in environmental monitoring studies of wastewater and additional information has been added in *Chapter 3, Section 3.2.2.1, Wastewater.* Monitoring data identifying specific isomers of HHCB has not been reported. Information on differences in biological activity or degradability between isomers is not available. A review of the additional literature provided on anaerobic degradation was performed and the studies are discussed in *Chapter 2, Section 2.3.1.1.* **Reference:** Horii, Y., Reiner, J. L., Loganathan, B. G., Senthil Kumar, K., Sajwan, K., and Kannan, K. (2007). Occurrence and fate of polycyclic musks in wastewater treatment plants in Kentucky and Georgia, USA. *Chemosphere* **68**(11), 2011-2020.

8	***Some PChem properties are missing or need clarification.*** Henry's Law constant is missing Melting point range, log K_{ow} and solubility data need to be clarified.	*Table 2-1, Physical-Chemical Properties of HHCB* has been updated to include the Henry's Law Constant and a brief explanation has been added to clarify the melting point range as presented. The log K_{OW} has been footnoted to clarify the source and the solubility data has been culled to present the measured solubility at pH7.
9	***Volatilization as a process affecting the fate of HHCB needs more definitive treatment here.*** The document and this chapter in particular provide conflicting information regarding the importance of volatilization to HHCB fate. If possible, it would be helpful to the reader if some sort of consensuses view on the importance of volatilization could be provided.	EPI Suite's WWTP model (STPWIN) predicts negligible removal due to volatilization. This is consistent with the experimental data presented in the assessment's section on fate in wastewater treatment, *Chapter 2, Section 2.3.1.1*. EPA/OPPT has made efforts to clarify the discussion of volatility in the above noted section and throughout the document. EPA agrees that volatilization is an important fate process. As noted in the document, volatilization seems not to be a major process in activated sludge treatment, although available data are limited. Two studies are cited in the section on water, and they may appear at first glance to be in conflict. In one, 40% of initial radioactivity was lost by volatilization in 300 hr (12.5 days); in the other, ≤16% was volatilized after 28 days. While this may appear to be conflicting information, the amount of volatilization in lab studies and in the environment is highly dependent on the test conditions; for lab studies, specifically, on design of test vessels, degree of mechanical aeration if any; and incubation temperature. Summaries of these studies are provided in *Section 2.3.1.2, Fate in Water*.
10	***Increasing use may affect future risk.*** How do you factor in the increasing use patterns and likely increasing environmental concentrations?	According to IFRA, there has been an increase in HHCB use in the US from 2000-2008 (IFRA, 2012c). **Reference:** IFRA (2012c). REACH Exposure scenarios for fragrance substances. International Fragrance Association, Brussels, Belgium. EPA/OPPT's Work Plan Chemical Assessments are conducted using currently available data and information, and forecasting future trends are generally beyond the scope of these assessments. In examining the range of Production/Import Volumes, as reported to the US EPA Inventory Update Reporting Rule (IUR) and Chemical Data Reporting (CDR) databases, EPA has

		found that these volumes have been steady over the past 20 years; therefore, there is little information for on which to make trend predictions. As discussed *in Section 3.4.2*, *Key Sources of Uncertainty and Data Limitations*, EPA acknowledges that variability in available environmental concentrations may obscure trends such as use practices across the population, differences in sewage treatment plant inputs and removal efficiencies may all affect final concentrations present in any single location or point in time. Risk quotients indicated current environmental exposure concentrations are approximately one to two orders of magnitude below hazard concentrations of concern. Unless environmental levels increase by 1-2 orders of magnitude, risks are expected to be low.
11	***Modifying factors for exposure and toxicity are not considered.*** Exposure and toxicity modifying factors were not mentioned or considered. There should be no effect of pH on HHCB solubility since it is non-ionizable.	Modifying factors were not applied due to the level of uncertainty this would introduce into the assessment in order to account for the diversity of “receiving environments” and were considered beyond the scope of this assessment. It should be noted that some of these parameters such as temperature, pH, salinity, dissolved oxygen, and water hardness, are noted during the course of the experiment which follows recommended guidelines.

Environmental Exposure Assessment

Charge Question 3-1: Please comment on the use of data from multiple years and locations to characterize environmental concentrations in surface water and sediment in the US.

Charge Question 3-2: Please comment on the approach of using both the monitoring data from the literature and the USGS NWIS data.

#	Summary of Peer Review and Public Comments for Specific Issues Related to Charge Question 3-1 and 3-2	EPA/OPPT Response
12	***Comparison of levels of HHCB in US to other countries*** The representativeness of US data should have been compared to data from other parts of the world, in particular Europe.	Revisions have been made to *Chapter 3: Section A, Section 3.2* and to *Appendix G, Environmental monitoring Data Analysis.* Additional summary statements for each media have been added to this section with comparative data from other countries. Levels of HHCB in the US were compared to levels in the EU Risk Assessment Report for HHCB, EC (2008), and levels in Asia as summarized by Lee *et al.,* 2014. Levels of HHCB were also compared to those in Canada in this assessment where the data was available. **References:** - Lee I.S., Kim U.J., Oh J.E., Choi M., Hwang D.W. (2014). Comprehensive monitoring of synthetic musk compounds from freshwater to coastal environments in Korea: with consideration of ecological concerns and bioaccumulation. *Sci. Total Environ.* 470-471, 1502-1508. - EC (2008). European Union risk assessment report for 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-a-2-benzopyran (1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylin-deno[5,6-C]pyran-HHCB), CAS No. 1222-05-5, EINECS No. 214-916-9, Risk assessment, final approved version. European Commission. Office for Official Publications of the European Communities, Luxembourg, The Netherlands.

<table>
<tr><td>13</td><td>Data quality measures are not adequately described.

The use of measured data to determine the range of concentrations to which organisms may be exposed is appropriate; use of data from multiple years and locations is also appropriate provided upper range values are used for this screening exercise.

QA/QC specifics regarding sampling and analysis need further clarification.</td><td>EPA/OPPT agrees that upper range values should be used to evaluate risk. The maximum published surface water and sediment concentrations and 95th percentile USGS values were used for this assessment.

Revisions to Chapter 3, Section 3.2 and Appendix G, Environmental Monitoring Data Analysis have been made to more fully describe the QA/QC specifics. Data quality criteria included currency, geographic scope, accuracy/reliability, representativeness, lack of bias, comparability and applicability.

An additional reference has been added to clarify the USGS data collection guidelines. USGS data from the NWIS database was accepted with the assumption that their internal methodologies were consistent and robust. These data were presumed to be collected under the guidance of the USGS National Field Manual for the Collection of Water-Quality Data, a publication which documents the methods, protocols, procedures and recommended practices for the collection of water-quality data. Data reporting procedures were presumed to follow USGS guidance.

References:

- USGS (variously dated). National field manual for the collection of water-quality data: U.S. Geological Survey Techniques of Water-Resources Investigations, book 9, chaps. A1-A9, available online at http://pubs.water.usgs.gov/twri9A.

- Oblinger Childress, C. J., Foreman, W. T., Connor, B. F., and Maloney, T. J. (1999). New reporting procedures based on long-term method detection levels and some considerations for interpretations of water-quality data provided by the US Geological Survey National Water Quality Laboratory. US Geological Survey. Open-File report 99-193, 1-19.</td></tr>
<tr><td>14</td><td>Details on analytical methods are not provided.

HHCB is a ubiquitous chemical and frequently found in laboratory and field blanks. It would be helpful to capture that the general range of occurrence in blanks.</td><td>Additional information regarding the QA/QC specifics (reporting levels, detection limits, recovery and use of blanks), where provided in the studies from the open literature, have been incorporated into the appendix text for</td></tr>
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	Detection limits are not provided. Extraction methods were not documented nor were Minimum Detection Limits. Whether analytical methods employed are measuring all of the isomers of HHCB present or if only one primary isomer is analytically determined.	each media. An additional reference to describe the QA/QC specifics for the USGS NWIS data sets has also been included as mentioned in Item 13 above. The measurement of specific isomers of HHCB were not described in the USGS data set nor the studies reviewed for this assessment. Hazard as it relates to specific isomers of HHCB is also unknown. A brief statement has been added to the discussion in *Chapter 3, Section 3.4.2, Key Sources of Uncertainty and Data Limitations*.
15	***For the USGS data analysis, more information would be useful.*** An added column for percent or number of data points which are <LRL is desired. It is clear from the descriptive statistics that some of the datasets were largely composed of substituted values. It would be useful to know the percent of each group that is <LRL.	As suggested by a peer reviewer, an additional table summarizing the laboratory reporting level (LRL) and substituted values has been included in *Appendix G*. Two additional columns have been added to *Table G-8, Summary of Box Plots for USGS HHCB Data*: the number of sample measurements (n), and the fraction of sample measurements lower than the laboratory reporting level (% <LRL). From these tables, it is more readily apparent that a large fraction (up to 100% in some cases) of the values were substituted low-end values as described in *Appendix G*.
16	***Probabilistic analysis of monitoring data is desirable.*** Monte Carlo analyses or similar methods can certainly be used for the exposure assessment given the apparent large number of data points. Given the probabilistic data set from USGS, this seems like a more appropriate value to use with perhaps an uncertainty assessment (Monte Carlo or something similar Bayesian analyses?).	As described in Item 15 above, a large fraction of the values within the USGS dataset were substituted low-end values for many scenarios; therefore, additional probabilistic analysis, such as Monte Carlo, would not be expected to alter the exposure estimates. For the USGS effluent and outfall data sets the small size of the data set (generally 10-50) precluded a robust Monte Carlo analysis.
17	***Analysis of non-detect data points is not clear.*** The summary occurrence data should include information regarding the method reporting limits (MRLs) and how "non-detect" data were handled in the summary statistics. For the box plot analyses and associated statistics, geometric mean and geometric standard deviation data would also be useful. For the categories with small n, and	Additional information regarding reporting levels and detection limits, where provided in the studies from the open literature, have been incorporated into the appendix text for each media. Annotations have been added to the summary occurrence *Table 3-1, Summary of Measured Concentrations of HHCB in Environmental Media and Biota,* and associated tables in *Appendix G*. In addition, a notation in *Chapter3, Section 3.2.2* referring the reader to the more detailed discussion in *Appendix G* has been added to guide the reader.

	also not apparently all or mostly substituted <LRL values, a log-normal or other probability analysis with distribution fitting may be appropriate.	For the summary statistics, “non-detect” data, or data below the LRL, were replaced by substituted values as described in Section G-7 of Appendix G. Briefly, for monitoring data sets where the geometric standard deviation was <3.0, values recorded as “less than LRL” or “estimated” were replaced by the LRL divided by the square root of two, as per the US EPA OPPT guidance document (EPA, 1994). Likewise, where the geometric standard deviation was >3.0, values recorded as “less than LRL” or “estimated” were replaced by the LRL divided by two, EPA (1994). **Reference:** EPA (1994). Guidelines for statistical analysis of occupational exposure data. Final. US Environmental Protection Agency, Office of Pollution Prevention and Toxics http://www.epa.gov/oppt/exposure/pubs/stat_guide_occ.pdf. For the data collected by the USGS, information regarding the LRLs is provided in *Appendix G, USGS National Water Quality Information System Data*. Additional information regarding geometric mean and geometric standard deviation was not added to the assessment. As stated in the assessment and endorsed by peer reviewers (see # 12 above) upper range values were used in the risk assessment and hence, the mean values were not necessary for the assessment. For the data collected from the open literature, concentrations were reported as presented in the original reference (e.g. where the ‘mean’ or ‘average’ value was reported, this was noted). Further inspection of the limited number of categories with a small sample size (n) and not all substituted values, determined that the data did not fit standard distributions; therefore, distribution fitting was not performed.
18	***Variability in monitoring data is not described for different situations.*** Environmental variability is accessed geographically, but only sparsely temporally.	For the data collected from the published literature, the year that the sampling was performed is provided in the summary tables of *Chapter3, Section 3.2.2* and associated tables of *Appendix G*. The season that the sampling occurred was not readily available for many of these studies, thus additional analyses was not possible.

	Attempts should be made to group data according to season and year if possible. More specific investigation into the types of WWTPs that emit the highest and lowest levels of HHCB would be quite valuable in this document and would help better characterize the extent of the issue within the USA.	EPA/OPPT acknowledges that using data from all locations and seasons may obscure temporal or geographical trends, however, consistent and sufficient data with regard to these variables was not available to make this analysis. The sampling year is noted in the tables provided in *Appendix G.* EPA/OPPT's Work Plan Chemical Assessments are conducted using currently available data and information. Therefore an 'investigation' of the types of WWTPs that emit HHCB is outside the scope of this assessment. A brief discussion summarizing two currently available studies of the efficiency of WWTP processes with regard to removal of HHCB, has been added to *Appendix G, Section G-1, Measured Concentrations in Wastewater.* Additional discussion has been added to *Chapter 3, Section 3.4.2, Key Sources of Uncertainty and Data Limitations*. **References:** - Simonich, S. L., Federle, T. W., Eckhoff, W. S., Rottiers, A., Webb, S., Sabaliunas, D., and de Wolf, W. (2002). Removal of fragrance materials during U.S. and European wastewater treatment. *Environ. Sci. Technol.* **36**(13), 2839-2847. - Smyth, S. A., Lishman, L. A., McBean, E. A., Kleywegt, S., Yang, J. J., Svoboda, M. L., Lee, H. B., and Seto, P. (2008). Seasonal occurrence and removal of polycyclic and nitro musks from wastewater treatment plants in Ontario, Canada. *Journal of Environmental Engineering and Science* **7**(4), 299-317.

Hazard/Dose-Response Assessment

Charge Question 4-1: Please comment on the ecotoxicity studies selected to represent the most sensitive species in each of the risk scenarios (acute aquatic, chronic aquatic, chronic sediment, chronic terrestrial invertebrate, and chronic terrestrial plant). Please comment on the use of the marine copepod chronic value for chronic toxicity to aquatic species. Please provide discussion, suggestions, and references to support and recommendations for the hazard characterization.

#	Summary of Peer Review and Public Comments for Specific Issues Related to Charge Question 4-1	EPA/OPPT Response
19	***The explanation for the selection and use of assessment factors is unclear.*** Given the occurrence of chronic and acute data, an acute:chronic ratio may be a more appropriate metric. It is not clear why uncertainty factors were used, where the different uncertainty factors (5 or 10) came from, nor why other alternatives such as the MOE (margin of exposure) approach were not considered.	In certain cases, EPA will use the acute to chronic ratio to calculate a chronic value for an ecological endpoint (i.e., fish, aquatic invertebrates, or green algae) when there are not data for the trophic level endpoint (i.e., the endpoint is a data gap). However, sufficient toxicity test data were available to identify the chronic hazard values for this assessment. Additional discussion regarding the use of uncertainty factors are provided in *Chapter 3, Section 3.3, Environmental Hazard Assessment.* The uncertainty factors that OPPT/EPA applies to ecotoxicity data in this assessment are those used in EPA's New Chemicals Program. This practice/methodology is described in OPPT's *Sustainable Futures Interpretive Assistance Document*, EPA (2013). In summary: • Application of uncertainty factors based on established EPA/OPPT methods were used to calculate lower bound effect levels (referred to as the concentration of concern; COC) that would likely encompass more sensitive species not specifically represented by the available experimental data. • When deriving acute concentrations of concern (COC), EPA/OPPT applies (divides by) a factor of 5 to fish, aquatic invertebrate and algae toxicity values to account for inter-species and lab-to-field uncertainty. • When deriving chronic concentrations of concern (COC), EPA/OPPT applies a factor of 10 to the chronic effect value for fish, aquatic invertebrates, and aquatic plants to account for inter-species and lab-to-

		field uncertainty. This factor of 10 is consistent with factors reported in the literature or those used by other countries. • The difference in approaches for setting concern levels for acute risk versus chronic risk is based on comparison of data sets and species sensitivity distributions among acute and chronic studies. It has been shown that the median variability among species in chronic toxicity is about four times greater than the median variability among species for acute toxicity (Forbes and Calow, 2002). • For aquatic plants, EPA/OPPT typically sets the acute COC at the reported ChV value or NOEC effect level, if a ChV cannot be determined. The difference in assessment factors for aquatic plants is related to study design. For unicellular algae, which usually constitute the most common test organisms, the tests cover several generations and in most cases acute (EC50) and chronic (ChV) are obtained from the same study. Additionally, the effects levels are set not based on observations of lethality, but rather on more sensitive endpoints of growth rate and/or biomass production. **References:** - EPA (2013) Interpretive Assistance Document for the Assessment of Discrete Organic Chemicals. U.S. Environmental Protection Agency, Office of Chemical Safety and Pollution Prevention. http://www.epa.gov/oppt/sf/pubs/iad_discretes_june2013.pdf - EPA (2012f) Sustainable Futures P2 Framework Manual. U.S. Environmental Protection Agency, Office of Chemical Safety and Pollution Prevention. EPA-748-B12-001, http://www.epa.gov/oppt/sf/pubs/sf-p2-manual.html - Forbes, V., and Calow, P. (2002) Extrapolation in Ecological Risk Assessment: Balancing Pragmatism and Precaution in Chemical Control Legislation. BioScience, Vol 52-3, pp 249 – 257.

		EPA/OPPT is currently evaluating the feasibility of applying alternative approaches for assessing potential risks using the margin of exposure or MOE approach; however, these approaches are still under development.
20	***It is not clear why the section on "Additional Studies" is provided.*** While it is helpful to summarize these additional sublethal studies, there is no discussion putting these data into the context of the rest of the risk assessment. The information regarding additional studies should be incorporated into an AOP which could focus the Hazard assessment on specific endpoints or justify specific uncertainty/safety factors.	EPA/OPPT agrees that the additional studies have not been used in the risk assessment, but did identify them in developing the risk assessment. This has been acknowledged in the Problem Formulation section and the descriptions of these studies have been moved to *Appendix F, Additional Studies*. Development of an Adverse Outcome Pathway (AOP) is beyond the scope of this risk assessment.
21	***The dataset is too small for definitive conclusions.*** Worst case screening decisions relative to hazard not risk can be made for fresh waters, fresh water sediments, and for soil invertebrates but not for terrestrial plants, marine waters, or sediments. The document is not correct in stating that there are "robust ecotoxicology data for multiple species".	The available ecotoxicity information for HHCB is summarized in *Chapter 3, Section 3.3*. Acute and chronic toxicity data for HHCB exist for freshwater fish, daphnia, and algae, and for marine copepods. For sediment toxicity, data exist for five invertebrates: an amphipod, a midge, an oligochaete, a polychaete, and a mud snail. For soil invertebrates the toxicity data include springtail, earthworm, and nematode. Two toxicity studies were conducted in the wheat plant. Relative to typical datasets available for many industrial chemicals, this is a rather large dataset; however, EPA/OPPT acknowledges that several of the studies have methodological limitations, therefore the characterization of "robust" has been removed. EPA/OPPT agrees that the dataset for plants and the marine environment is insufficient for assessment. The document has been revised to more clearly reflect which data are adequate and which are not.
22	***Criteria for study evaluation and selection are not described adequately. Endpoint selection and justification for considering freshwater and marine species together are not clear.***	EPA/OPPT followed the guidance for adequacy of toxicity studies described in EPA (1999c). **Reference:** EPA (1999c). Determining the adequacy of existing data. US Environmental Protection Agency, Office of Pollution Prevention

	The examples provided do not cover all data acceptability parameters. Multiple studies presented in this section do not appear to have followed an internationally validated protocol and likely did not adhere to strict GLP procedures. It would also be helpful to provide what endpoint is measured in the table (growth, survival or reproduction). It appears that US EPA did not consider potential differences in the effects of HHCB between fresh and marine organisms. There are significant differences between saltwater and freshwater organisms. They should be evaluated separately. US EPA has sufficient data for screening and determining hazard (not risk) for freshwater ecosystems, not marine or estuarine ecosystems; marine and freshwater toxicity data should not be used interchangeably.	and Toxics. http://www.epa.gov/hpv/pubs/general/datadfin.htm. Accessed September 27, 2012. Toxicity tests would, ideally, have been conducted under optimum conditions and follow good laboratory practice (GLP). However, for the purpose of Work Plan Chemical Assessments, it is important to consider existing information that might not have been generated under ideal conditions. In other words, EPA/OPPT will consider guideline studies as well as studies using other protocols. For this risk assessment, studies were included if they met data quality criteria as described in *Chapter 3, Section 3.3* and EPA/OPPT guidance, EPA (1999c). In the final assessment, Section 3, the toxicity testing summary tables now include designation of the endpoint that was measured in the toxicity test. In the final assessment toxicity testing summary tables now include designation of freshwater and marine organisms and they are divided into separate section within the tables. EPA/OPPT notes that although differences in sensitivity between freshwater and marine organisms appears, based on available data, to be less than an order of magnitude, several peer reviewers expressed that the two types of species should not be combined in the assessment of HHCB. In separating out marine species, EPA/OPPT concurs with the commenters expressing the view that data are insufficient to assess marine or estuarine ecosystems. Therefore, the final risk assessment is focused on freshwater species only and the lack of assessment of marine species is noted as an uncertainty.
23	***Selection of key chronic aquatic toxicity study is not supported.*** Chronic toxicity responses could include reproduction or other chronic responses such as growth. The use of the marine copepod chronic value for chronic toxicity to aquatic species is inappropriate. The marine copepod study followed an OECD Draft Guideline.	EPA/OPPT has considered the multiple comments advising against considering both freshwater and marine species together (i.e., lumping) when selecting a study from which to derive an RQ and regarding the inappropriateness of using the marine copepod to derive a chronic RQ for aquatic organisms. Although EPA notes that the differences in sensitivity between freshwater and marine organisms appears, based on available data, to be less than an order of magnitude, EPA/OPPT agrees that the fathead minnow is a more

	The impacts of salinity acclimation in anadromous and catadromous species, as well as some estuarine species have significant impacts on hormonal/endocrine pathways. Worst case screening decisions relative to hazard, not risk, can be made for fresh waters, fresh water sediments, and for soil invertebrates but not for terrestrial plants, marine waters, or sediments.	representative species for this assessment because the available monitoring data used for estimating exposures is largely freshwater. Furthermore, the study is reliable and demonstrates the chronic effects (i.e., survival and growth) using appropriate, reproducible protocols. EPA also agrees that available toxicity data are insufficient to robustly assess risks to marine or estuarine environments.
24	***Selection of key sediment toxicity study is not appropriate.*** For sediments data exist for 5 invertebrates: an amphipod, a midge, an oligochaete, a polychaete, and a mud snail. Inclusion of the mud snail data are suspect. Further, the New Zealand mud snail, on which the sediment chronic COC is based, is an invasive species that is not welcome in the US (authorities are working to limit its distribution and, where it is now found, to eradicate it). During the January 09, 2014 peer review, it was suggested that the *Hyalella azteca* data may be more appropriate for the sediment assessment than *P. antipodarum*. USEPA should consider this suggestion.	EPA/OPPT has considered the comments regarding freshwater *vs.* marine species and the multiple peer review suggestion to use *Hyalella azteca* data in the sediment assessment. Although EPA notes that the differences in sensitivity between freshwater and marine organisms appears, based on available data, to be less than an order of magnitude, EPA/OPPT agrees that *Hyallela azteca* is a more representative species for this assessment because the available monitoring data used for estimating exposures is largely freshwater. Furthermore, the study is reliable and demonstrates the chronic effects (i.e., survival and growth) using appropriate, reproducible protocols. EPA also agrees that data are insufficient to robustly assess risks to marine or estuarine environments and hence, use of *P. antipodarum* as the sediment-dwelling organism for assessment is not the best choice. *Chapter 3, Section 3.3.3* has been revised to derive the sediment COC based on the *Hyalella azteca* study.
25	***NOECs and LOECs are not preferred endpoints.*** ECx values are preferred endpoints.	EC_X (generally EC_{50}s) were used to evaluate the acute toxicity of the chemical on aquatic and sediment organisms. However, NOEC and LOEC, and the MATC, are endpoints for chronic studies recommended in internationally agreed to test guidelines for evaluating the chronic effects (e.g., growth, survival, and reproduction) of a chemical in the aquatic and sediment environments (OPPT TGs 850.1400, 850.1500, 850.1300, 850.1350, 850.1740, 850.1735, and OCSPP 850.4500; OECD 201, 204, 210, 215, 211, 218, and 219).

26	***Species Sensitivity Distribution could be done to improve hazard data.*** It would appear there are enough values on Table 3-3 for an ICE study for the other scenarios.	EPA/OPPT has considered this comment; however, given that ICE estimates acute toxicity (only for aquatic species and terrestrial birds and mammals) and EPA/OPPT has identified adequate measured acute toxicity tests for aquatic organisms, it is unclear what "other scenarios" the commenter envisioned ICE would be used for.

Risk Characterization and Uncertainty/Variability Discussion

Charge Question 5-1: Please comment on the calculation of risk derived from different datasets and how they account for environmental variability. Please provide specific recommendations as needed for improving the risk characterization and references to support any recommendations.

#	Summary of Peer Review and Public Comments for Specific Issues Related to Charge Question 5-1	EPA/OPPT Response
27	***Worst case risk scenarios were not included.*** Comparison of toxicity data to "worst case" data in the form of maximum concentrations is appropriate. Several additional worse case scenarios should be considered including: WWTP effluent dominated steams that are relatively common in the arid US west, reclaimed wastewater and biosolids land application.	Calculation of the acute aquatic RQ was based on the maximum reported value for surface water from the literature, the 95th percentile USGS NWIS value for surface water at <u>effluent</u> sites, and the highest mean value overall, in an effort to capture the full range of concentrations observed in this data set. These values encompass the upper range of measured environmental concentrations and are considered to be sufficiently conservative. Additionally, a comparison of the maximum published effluent value and the 95th percentile value for effluent (stream or outfall site) from the USGS NWIS dataset to the acute benchmark for aquatic species also indicates a ratio of less than 1. A biosolids or reclaimed wastewater to land application scenario was not included in this assessment due to the lack of an available, validated model to estimate environmental concentrations resulting from such uses. Sufficient and robust datasets to specifically assess WWTP effluent dominated streams of the US West and reclaimed wastewater scenarios were not available.

28	***Data gaps preclude risk conclusions for all scenarios.*** Worst case screening decisions relative to hazard, not risk, can be made for fresh waters, fresh water sediments, and for soil invertebrates but not for terrestrial plants, marine waters, or sediments.	Upon consideration of peer review comments, EPA/OPPT agrees that risk quotients cannot be calculated for terrestrial plants. Data gaps for the terrestrial plant, terrestrial soil invertebrate, marine water and sediment scenarios are discussed in the uncertainty discussion in *Chapter 3, Section 3.4.2, Key Sources of Uncertainty and Data Limitations*.
29	***Probabilistic analysis of data was not done.*** RQs are presented for a range of exposure values. This brackets the range of RQs given the data so far and the analyses of that data. This may be an opportunity to use Monte Carlo-type analysis. But if that analysis is not feasible for statistical reasons, then the report already describes a range of RQs given different exposures. If only one variable, exposure, is treated as a random variable, a Monte Carlo analysis may not add much useful information.	The majority of the data points (>40%) in the USGS datasets were comprised of values below the laboratory reporting level (LRL), and were thus replaced with substituted values, as discussed more fully in *Appendix G, Section G-7*. Additional probabilistic analysis, such as Monte Carlo, would not be expected to alter the risk conclusions. Also, the exposure assessment component of this risk assessment was based on the use of all available measured data. The use of all data obscures the ability to discern the contribution of any one variable to the measured environmental concentrations, and this is acknowledged in *Section 3.4.2 Key Sources of Uncertainty and Data Limitations*. For these reasons, EPA agrees that Monte Carlos analysis would not add much useful information and therefore was not performed.
30	***Risk characterization terms are not consistent.*** Levels of risk (negligible, acceptable, etc) used in the document are not explained or justified and may be inappropriate.	Terminology with respect to levels of risk have been revised throughout the document. Risk quotient values have been calculated and are provided. The use of qualifiers has been removed.

Other Comments

#	Summary of Other Comments	EPA/OPPT Response
31	Literature on endocrine disruptors should be included in “other studies”	Studies on potential endocrine effects are provided in *Appendix A, Additional Information* and summarized in Table A-1 of this same section.
32	Additional analysis provided using iSTREEM model for DtD uses was provided by the American Cleaning Institute.	EPA/OPPT appreciates the submission of additional analysis provided using the iSTREEM model. EPA/OPPT’s exposure assessment was based on measured data collected by the USGS NWIS and published studies. These values represent a variety of discrete locations, times, WWTP processes and therefore it is not known how they may compare to the modeled values provided.
33	One peer reviewer submitted several studies of air concentrations, including one in a cosmetics manufacturing plant in China and several from indoor air and dust from apartments, kindergartens and women’s sports centers in Berlin, Germany.	The exposure monitoring data provided is not a cause for altering EPA/OPPT’s conclusions about worker risks, which are based largely on the EU RAR for HHCB (EC, 2008). The data reported in Chen et *al.*, 2007 is comparable to the assessment results reported in the EU RAR. The maximum HHCB inhalation exposure concentration that was reported for the manufacturing plant in China (Chen *et al.,* 2007) is equal to 4,504.97 ± 941.10 ng/m^3 and the associated exposure time is 8 hours per day. In comparison, the assessed inhalation exposure concentrations reported in the EU RAR for workers at compounding plants are equal to 0.013 to 0.065 mg/m^3 and the maximum assessed worker exposure time reported in the EU RAR is 8 hours per day. Therefore the submitted data does not alter EPA/OPPT's conclusion about risk to the human health of workers. **References:** - Chen, D., Zeng, X., Sheng, Y., Bi, X., Gui, H., Sheng, G., Fu, J. (2007). The concentrations and distribution of polycyclic musks in a typical cosmetic plant, *Chemosphere* 66, 252-258. - EC (2008). European Union risk assessment report for 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-a-2-benzopyran (1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylin-deno[5,6-C]pyran-

		HHCB), CAS No. 1222-05-5, EINECS No. 214-916-9, Risk assessment, final approved version. European Commission. Office for Official Publications of the European Communities, Luxembourg, The Netherlands. For the reasons described in *Section 1.2, Problem Formulation*, EPA determined that human health exposures need not be addressed in this assessment and defined the scope of this assessment to focus on the assessment of environmental risk to the aquatic environments from the use of HHCB as a fragrance ingredient in commercial and consumer products, as described in *Section 1.2, Problem Formulation*. Therefore, the evaluation of indoor air and dust is outside the scope of this assessment.