# 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-γ-2-benzopyran (HHCB) Draft Risk Assessment
# Draft Comments of Seven-Member Peer Review Panel
# January 27, 2014

## Daniel Schlenk (Chair)

**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.***

This is a screening deterministic hazard assessment. A more detailed Problem Formulation step with more details on the Conceptual Model (see question 1-2) is necessary with better description of outcomes/method validation and QA/QC.

Tools that are available through EPA ORD include read across estimates using QSAR or Mechanism based estimates with uncertainty analyses using Interspecies Correlation Estimates (Feng et al. 2013)

Uncertainty evaluations are necessary for the exposure assessment as well as Hazard assessment.

**Reference**

Feng, et al. (2013) Interspecies Correlation Estimation: Applications in Water Quality Criteria and Ecological Risk Assessment, *Environmental Science and Technology* 47: 11382-11383.

**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.***

Overall, the Background and rationale for conducting the risk assessment are logical, although several steps are missing or are unclearly stated. For example, it is unclear how developmental toxicity was used as a rationale for conducting the assessment. It appears that this was purely derived from mammalian studies with a focus on human health. However, it appears that based upon mode of action and other ecotoxicity studies that development may be a target in non-human species. Consequently, it is confusing having statement in the text that developmental toxicity was indicated by HHCB, but also having a footnote saying there is none is somewhat confusing. Text should state that there was previous unsupported evidence in humans for developmental toxicity. As it reads, it would appear the risk assessment was driven by the potential human health effects of HHCB.

There should be a Problem Formulation section that encompasses the Conceptual Model as well as the documented outcomes for the assessment. In addition, there are significant gaps in the Conceptual Model. The Conceptual Model should have a more refined description of treatment (primary vs. secondary/tertiary etc.). Should also incorporate wastewater dominated streams and leachate input from biosolids. In addition, exposure to aquatic biota is assumed to be dermal/branchial via waterborne or pore-water. Oral consumption, particularly for sediment and soil organisms should be included as well. Trophic transfer is also missing from the model. Its persistence in benthic organisms indicates significant exposure via diet. Hence birds or mammals would likely be considered a receptor of interest.

Marine and Freshwater organisms should be separated given differences in susceptibility (Table 3-3 and Table 3-4.) Moreover, the impacts of salinity acclimation in anadromous and catadromous species, as well as some estuarine species have significant impacts on hormonal/endocrine pathways (Bjornsson et al. 2011; McCormick et al. 2005). If there is some concern for Estrogen Receptor activation (albeit weak), interactions with this hormonal system would potentially interact with effects brought on by salinity changes.

**References**


1. Bjornsson BT, Stefansson SO, McCormick SD. 2011. Environmental endocrinology of salmon smoltification. *Gen Comp Endocrinol* 170: 290–298.
2. McCormick, Stephen D.; O'Dea, Michael F.; Moeckel, Amy M.; Lerner, Darren T.; Bjoernsson, Bjoern Thrandur. 2005. Endocrine disruption of parr-smolt transformation and seawater tolerance of Atlantic salmon by 4-nonylphenol and 17β-estradiol. *General and Comparative Endocrinology* 142:280-288.


**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.***

The assessment should include a wastewater dominant stream as worse case surface water exposure scenario.

HHCB chemistry is highly complex. It is chiral with 4 diasteriomers with likely enantioselective uptake, degradation/metabolism and elimination. This combined with its volatility and lipophilicity makes this a very difficult compound to measure particularly in matrices with any organic carbon. There is not an approved EPA method for analysis. There is only limited description of reporting limits from the USGS data and none stating how data was evaluated for QA/QC. For example, extraction methods were not documented nor were MDLs. Just because GCMS was consistently used for detection does not mean that all data points are of equal quality. Given the unique chemical properties of HHCB (chiral, volatile, high LogKow), it is likely much of the analytical evaluations are highly uncertain. This seems consistent with the extreme variability of tissue concentrations in the same species of fish. While the conclusions that HHCB is widespread qualitatively, the quantitative data requires additional inspection, especially if it is to be used in a HQ approach.

Anaerobic sediments are typical of deep oceanic discharges. This is a large data gap and likely requires additional uncertainty evaluations.

DOC concentrations likely influence river water experiments; this should be provided and discussed as a source of uncertainty (page 18). Likewise, the OC content in soil (bottom page 18) should also be provided.

**Bioaccumulation and Bioconcentration**

It is difficult to assess bioaccumulation or environmental monitoring data without discussing the criteria used to validate a data set.

Page 28: Why not provide the data from the Smyth et al. 2008 study? Which season was higher? Which treatment process was different?

Page 29: It would be good to maintain the same units and describe whether the data is dw or stay with ng/g. Was USGS data dw?

Page 31: Table 3-2 Cannot compare wet weight values with lipid normalized.

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?).

**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.***

There seems to be significant uncertainty in the data collection methods and the rationale for the sites used is not present.

Seasonality is the confounding variable here. Attempts should be made to group data according to season and year if possible. If this is not possible, then appropriate uncertainty estimates are needed.

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

Given the uncertainties in the methods for analytical chemistry, it is difficult to determine the quality of the literature data. One would presume that USGS data would have some description of QA/QC and reporting limits and this would be of higher quality. However, this is still unclear in the document.

**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 any recommendations for the hazard characterization.***

It would appear that there are enough values on Table 3-3 for a SSD evaluation for freshwater or at least an ICE study for the other scenarios (Feng et al. 2013). Likewise, Table 3-4 would also appear to have enough datapoints to at least provide an ECx value. It would also be helpful to provide what endpoint is measured in the table (growth, survival or reproduction). Given the Adverse Outcome Pathway for this compound, reproduction or development would be a more sensitive endpoint. There are significant differences between saltwater and freshwater organisms. They should be evaluated separately.

Page 35: I believe that 0.00524 mg/L is 5.24 ppb….The justification for the safety factor assessment is unclear. The document cited does not provide the derivation and it has been my experience that Safety factors can be applied for a number of reasons to approximate uncertainty within a data set (whether it is an EDC or an endangered species, or lack of specific data). Given the occurrence of chronic and acute data, an acute:chronic ratio may be a more appropriate metric. Given the lipophilicity of the compound and the propensity for developmental toxicity, one would expect gonadal concentrations to be targeted for assessment.

Page 36; Table 3-5: Again, significant differences between FW and SW organisms.

Page 38: The information regarding additional studies should be incorporated into an adverse outcome pathway evaluation which could focus the Hazard assessment on specific endpoints or justify specific uncertainty/safety factors. For example, given the evidence of antagonism at the ER and the MXR, one

would focus more on reproduction or development as specific endpoints of concern rather than acute lethality. Thus embryonic tests would have a greater weight of evidence.

**References**

Feng, et al. 2013. Interspecies Correlation Estimation: Applications in Water Quality Criteria and Ecological Risk Assessment, *Environmental Science and Technology* 47: 11382-11383

**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.***

As it currently stands, the document is a Screening Hazard Assessment which is typically used in Problem Formulation steps. A much more defined discussion regarding uncertainty is necessary if this is to be used as a risk assessment. Monte Carlo analyses or similar methods can certainly be used for the exposure assessment and at least fresh water. Probabilistic analyses on the Ecotoxicity effects should be incorporated as much as possible to derive a PNEC or an ECx value. MOA and Adverse Outcome Pathway analyses (Ankley, et al. 2010) should also be used with appropriate justifications for safety factors.

Page 40. It is unclear what concentrations were used to generate the RQs for Table 3-8.

**References**

Ankley, et al. 2010. Adverse outcome pathways: a conceptual framework to support ecotoxicology research and risk assessment. *Environmental Toxicology and Chemistry* 29: 730–741.

# Peter Chapman

**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.***

1. A Problem Formulation is required.

A clear Problem Formulation would have provided a transparent and more complete basis for the subsequent approach and analyses. See also point 5 under this Charge Question, below.

2. The Conceptual Model is incomplete.

The conceptual model shows wastewater treatment plants as the only point of entry of HHCB into aquatic receiving environments. While this is certainly the major point of entry, it is clearly not the only point of entry as noted in the document (e.g., manufacturing is not considered; (Page 27) "*the amount released from industrial sites was estimated at a maximum of 10 percent of the use volume*").

3. Levels of risk (as noted in other comments, the document is evaluating hazard not risk) used in the document are not explained or justified and may be inappropriate. (Note this comment independently echoes a similar concern raised by the American Chemistry Council on December 4, 2013 "*…further clarity is needed concerning what EPA considered to be "negligible" as opposed to "acceptable" risk."*]

Use of hazard (not risk) quotients (i.e., HQs not RQs) provides two possible outcomes: not of concern or of possible concern. The wording "negligible" could be applied to the outcome not of concern (i.e., HQ < 1). However, the wording "acceptable" is inconsistent with the outcome of possible concern (i.e., HQ ≥ 1), and unexplained.

4. Clarification is required that this is a screening exercise, effectively the Problem Formulation stage of a Risk Assessment.

I agree with the American Chemical Council that "*The assessments use a screening-level methodology and the results should not be used for further regulatory action without further refinement and evaluation.*" In other words, if screening indicates a potential concern, then further investigation is needed. If screening indicates no concern, no further investigation is needed.

5. This assessment should have been based on a systematic framework, developed separately.

I agree with the American Chemical Council that "*Systematic and consistent framework is needed*". I have not reviewed other similar assessment documents so cannot confirm that there are inconsistencies. But I would have expected the initial development of a framework document before these assessments proceeded. The USEPA 2009 document Interpretive Assistance Document for Assessment of Discrete Organic Substances does not provide the necessary framework.

**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.***

1. Details of the QA/QC of the data sets are required.

The reliability of the data used in the assessment is a critical consideration. The reliability of these data needs to be fully demonstrated.

2. The representativeness of US data should have been compared to data from other parts of the world, in particular Europe.

As noted in the document (Page 8) "*volume of use in the US has increased steadily since 2000, suggesting that polycyclic musks are not being replaced with other synthetic musks, as may be occurring in Europe*". Given increasing usage and moderate persistence in sediments and soil, maximum concentrations measured to date may not be reflective of maximum concentrations in future. Ground-truthing current US data against available data from other jurisdictions, particularly those with longer usage, would be a useful exercise.

3. Additional literature on anaerobic degradation provided by the International Fragrance Association North America should be included in the assessment along with other information provided by this organization in their Public Comments.

4. In various parts of the document lowest concentrations are reported as ND (i.e., non-detected), but detection limits are not provided, thus whether the detection limits were appropriate cannot be determined.

5. Tissue data (Page 30) are provided but not always distinguished as wet weight or dry weight. Same comments apply to Table 3-2 for tissue, soil, sediment and biosolids data.

**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.***

1. Metabolites need to be identified and discussed relative to potential hazard relative to the parent compound.

2. More information should be provided regarding the fate of HHCB in biosolids prior to land application.

3. 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.

4. Estimates for uptake by terrestrial plants should have been provided.

Such are provided for earthworms; it is unclear why terrestrial plants were omitted from consideration relative to potential uptake. Given the lack of toxicity data for terrestrial plants, this information is important for reducing uncertainty in the hazard assessment.

5. Comparison of toxicity data to "worst case" data in the form of maximum concentrations is appropriate.

This is a screening exercise, effectively the Problem Formulation stage of a Risk Assessment. It is appropriate to use worst case data to screen out contaminants/cases that are not of concern and retain those that may be of concern for further 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.***

1. 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.

2. However, QA/QC to assure data validity and reliability are required (see point 1 under Charge Question 1-2, above).

3. Comparative data should also have been obtained from other jurisdictions and compared to the upper range of the US data and, if higher, given that usage of HCCB is increasing in the US, the higher upper range values should have been used for this screening exercise.

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

1. A screening exercise such as this one requires use of all available data, provided such data have been screened for appropriate QA/QC (see point 1 under Charge Question 1-2 and point 2 under Charge Question 3-1, above).

2. Justification of why (p 30, last sentence) the "data are assumed to be representative" is required (see point 3 under Charge Question 3-1, above).

**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 any recommendations for the hazard characterization.***

1. USEPA has not justified/explained how data used were evaluated for inclusion; in other words, acceptability criteria for the toxicity studies have not been provided. (Note this comment independently echoes a similar concern raised by the American Chemistry Council on December 04 "*The standards applied for study reliability and data adequacy are unclear in the HHCB assessment*.")

The document (Page 32, Paragraph 2) refers to USEPA's HPV Program acceptability criteria for ecotoxicity studies (1999. Determining the Adequacy of Existing Data) and states "*Examples of the scientific quality criteria for the HPV Program are: a clear description of the endpoints, inclusion of appropriate controls, identification of test substance and test organism, stated exposure duration time and administration route, and transparent reporting of effect concentrations.*" The examples provided do not cover all data acceptability parameters; for instance, there is inadequate mention of quality assurance/quality control (QA/QC) including organism health and exposure conditions, and no mention of the need for a clear concentration-response relationship or measured rather than nominal test concentrations (although later in the document it is clarified that nominal concentrations were not used). Further, if acceptability criteria were met, how could the sediment study with *Potamopyrgus antipodarum* have been included given that it was a non-GLP study that did not conform to either USEPA or OECD test guidelines and which has QA/QC issues? Note that on December 4, 2013 USEPA were asked to clarify acceptability criteria applied to the toxicity studies and declined to answer at that time. Note that 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.

2. USEPA has too small a data set 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.

USEPA references their 2009 document Interpretive Assistance Document for Assessment of Discrete Organic Substances. This document states on page 32:

> *The standard EPA New Chemicals Program aquatic toxicity profile consists of 3 acute values (fish LC50, daphnid LC50, and algae EC50), 3 chronic values (fish ChV, daphnid ChV, and algae ChV). EPA/OPPT generally focuses on aquatic toxicity to fresh water organisms because most releases of industrial chemicals go to fresh water bodies. Terrestrial and marine species are only evaluated on a case by case basis depending on the manufacturing, processing, and use of the chemicals.*

The document is not correct in stating that there are "*robust ecotoxicology data for multiple species*" (Page 9). Acute and chronic freshwater toxicity data for HHCB exist for fish, daphnid, and algae and are used in the document. Thus, pending confirmation of data acceptability (point 1, above), the data are sufficient for screening purposes.

For sediments data exist for 5 invertebrates: an amphipod, a midge, an oligochaete, a polychaete, and a mud snail. As noted above (point 1), 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). The logic of basing protection of US species on the sensitivity of an unwelcome invasive species escapes me. In addition, it is not clear for the Pedersen et al. (2009) study (bottom of Page 35)

exactly what is a "calculated chronic value" for this test. This question was asked of USEPA on December 4, 2013, but was not answered. The polychaete is a marine species which should not be included with freshwater toxicity data without clear and compelling justification. Such justification is lacking. Thus, the sediment toxicity data consist (pending confirmation of data acceptability – point 1, above), of three freshwater invertebrates. This is probably enough for screening purposes.
For soil invertebrates the toxicity data consist (pending confirmation of data acceptability – point 1, above), of three organisms: springtail, earthworm, and nematode. Again this is probably enough for screening purposes.

However, for plants two studies were available but only for wheat; data were not available for other plants. Thus, screening is not possible for terrestrial plants. In the document it is stated (Page 42) "*The risk estimate for terrestrial environments was based on very limited monitoring and toxicity data.*" The presentation provided by USEPA on December 04 (Overview of the HHCB Workplan Risk Assessment) stated on slide 22 "*The risk calculated for terrestrial organisms associated with land application of biosolids is tentative*", which is still too optimistic given the few data available. Additional information related to land application of biosolids is required before definitive conclusions can be made, given that (Page 14) "*about half of all sludge as biosolids is applied to agricultural land each year. Once biosolids containing HHCB are applied to land, HHCB has a long half-life in soil and may be available for uptake by plants and soil invertebrates, leading to potential exposure and toxicity.*"

Finally, see point 1 under Charge Question 5-1, below; USEPA is evaluating hazard, not risk. Note in this regard that the word "hazard" not "risk" is used (correctly) for Charge Question 4-1.

3. USEPA 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.

As noted in point 2, above, sufficient freshwater toxicity data exist for screening freshwater ecosystems. There are not sufficient data for marine toxicity data for screening marine or estuarine ecosystems. USEPA argues in the document (Page 42) that freshwater and marine toxicity data are similar within a factor of 10. But this is based on a very limited data set (see point 2, above). During the December 04, 2013 conference call Dr. Dan Schlenk asked USEPA about the rationale for lumping freshwater and marine data. Dr. Laessig stated (quoted from notes taken by David Clarke and distributed to the Panel) "*EPA considered the appropriatness of combining them; there did not appear to be any reason for not combining them.*" Dr. Laessig also committed to further explanation in responding to my written, similar question. I look forward to this further explanation, particularly since a justification provided on Page 14 of the document is nonsensical: "*Because exposure to HHCB is likely to occur in all types of aquatic environments, no distinction in risk was made between freshwater and marine species*."

On Page 39 it is stated "*No distinction is made between marine and freshwater species because HHCB is assumed to be widely distributed in the environment, there is not a large difference in sensitivity between marine and freshwater species, and the most sensitive species is assumed to be representative of other species*." This statement contains an abundance of uncertainties. Per discussion during the January 09, 2014 peer review meeting, there is no surety that HHCB toxicity will be similar between marine and freshwater environments.

In Section D, Key Sources of Uncertainty and Data Limitations (Pages 41-42) it is stated "*Among the species tested, the acute and chronic aquatic toxicity values varied by about a factor of 10, suggesting that selection of marine or freshwater species as the endpoint of concern would not have a significant effect on the risk assessment*." In fact, based on Table 3-3, acute values varied by a higher factor of about 16 (0.12 to 1.9) while, based on Table 3-4, chronic values varied by a much higher factor of about 67

(0.007 to 0.466 mg/L). There is no technically defensible justification provided for lumping marine and freshwater species; such lumping should not have been done.

4. The use of the marine copepod chronic value for chronic toxicity to aquatic species is inappropriate.

See point 3, above. Also, it is not clear that the authors of this document actually reviewed the above study in detail. The citation is (Page 35) "*Bjornestad (2007) as cited in EC, 2008)*", and key information is not provided, such as the QC for an acceptable study (larval mortality close to 30% seems rather high). Further, it is not clear how the lowest chronic value of 0.0534 mg/L was determined when the EC10 was 43.8 µg/L (= 0.0438 mg/L) [EPA should use the same units; using µg/L in some cases and mg/L in others is confusing). An EC10 value should not require use of a safety factor. Further, as noted in Table 3-4 for this test "*Exposures likely from both water and sediment*" – the test is not a water-only exposure test and thus cannot be considered together with tests that are water-only exposures. Finally, as noted during the January 09, 2014 peer review, testing was conducting under a draft, not a final OECD protocol which could be an important limitation given how difficult this test is to conduct.

5. Exposure and toxicity modifying factors were not mentioned or considered.

Exposure and toxicity modifying factors (e.g., pH, temperature, hardness/salinity) can modify toxicity. The document should have provided information on these if available and documented why such were not considered in the assessment. For instance, there should be no effect of pH on HHCB solubility since it is non-ionizable. The question as to whether exposure and toxicity modifying factors were considered was asked of USEPA on December 04, 2013 but not answered. However, given that freshwater and marine toxicity data were inappropriately lumped, I suspect such factors were not considered.

6. There is no clear rationale for the use of uncertainty factors. 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 (as recommended by the American Chemistry Council) were not considered.

Uncertainty factors or either 5 (for daphnids) or 10 are used. There is no rational basis for such factors other than the fact that humans have 5 fingers on each hand (and 5 toes on each foot). As noted by the American Chemical Council (comments submitted December 04, 2013) there is the alternative of using the MOE approach. As discussed during the January 09, 2014 peer review, SSDs for interspecies correlation estimates (ICEs) should have been considered instead of uncertainty factors.

During the December 04, 2013 conference call, Dr. Dan Schlenk asked about EPA's rationale for its uncertainty factor derivation. Dr. Laessig refered to the USEPA (2009) document Interpretive Assistance Document for Assessment of Discrete Organic Substances. She also stated (quoted from notes taken by David Clarke and distributed to the Panel) "*ecotoxicologists have agreed on the Daphnia UF; it accounts for species differences and other factors. It is the value used for aquatic invertebrates; it is not specific to the study EPA selected.*" This latter statement is curious as, to my knowledge, there has been no agreement in the published literature or among ecotoxicologists (of which I am one) regarding using a UF of 5 for Daphnia versus a UF of 10 for other biota. Further, 5 is not the value use for aquatic invertebrates uniformly in the document: on page 35 of the document it is stated: "*To derive a COC, the ChV was divided by an assessment factor (UF) of 10 for invertebrate species, according to OPPT guidance (USEPA, 2009b).*" However, the document also contradicts itself as on Page 33 it states "*an assessment factor (uncertainty factor (UF)) of 5 for invertebrates, according to Office of Pollution Prevention and Toxics (OPPT) guidance (USEPA, 2009b).*"

The words "safety factor" and "uncertainty factor" do not occur in the USEPA (2009) document Interpretive Assistance Document for Assessment of Discrete Organic Substances; however, the words

"assessment factor" do occur three times. On Page 7 of that document there is an example where a Daphnid ChV is divided by a factor of 10 (not 5) to derive a "calculated daphnid chronic COC". I have read and re-read the USEPA (2009) document and cannot find anywhere a stipulation that the Daphnia UF be 5.

7. Measured responses for the chronic toxicity data are not adequately described in Table 3-4.

Chronic toxicity responses could include reproduction or other chronic responses such as growth. Clarity regarding the responses is critical given that, per the Adverse Outcome Pathway (cf discussion during the January 09, 2014 peer review teleconference), reproduction and development should be the most sensitive endpoints and embryonic tests would have the greatest weight of evidence. No data on fish reproduction are provided, a key uncertainty not noted in the document (cf point 2 under Charge Question 5-1, below).

8. NOECs and LOECs are not preferred endpoints; ECx values are preferred endpoints. Consideration should have been provided to calculating ECx values where possible from the studies cited and to preferentially using 10 or 20% effect endpoints (e.g., EC10, EC20).

NOECs and LOECs are not technically defensible as they do not reflect the concentration-response that forms the basis for toxicology, and they are set based on concentrations tested with associated high variability. There have been many publications and presentations on this topic. The following three publications and references contained therein summarize the problems with NOECs and LOECs:

1. Warne MS, Van Dam R. 2008. NOEC and LOEC data should no longer be generated or used. *Australas J Ecotox* 14:1–5.
2. Landis WG, Chapman PM. 2011. Well past time to stop using NOEL/LOELs. *Integr Environ Assess Manage* 7(4): vi-viii.
3. Jaeger T. 2012. Bad habits die hard: The NOEC's persistence reflects poorly on ecotoxicology. *Environ Toxicol Chem* 31: 228–229.

9. In Table 3-3, acute aquatic toxicity, all data should be LC as in lethal concentration–some data are in EC as in effects concentration (the term EC is typically applied to chronic, not acute data).

10. It is not clear why the section on "Additional Studies" (Page 38) is provided. So what? This information is not used in the assessment and thus is not useful in the document.

**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.***

1. USEPA is evaluating hazard, not risk.

Hazard is the possibility of an occurrence; risk is the probability of an occurrence. USEPA is incorrectly referring to Hazard Quotients (HQs) as Risk Quotients (RQs). The exercise by USEPA is an evaluation of hazard, basically the Problem Formulation phase of a Risk Assessment (RA). This is not a Screening Level RA and certainly not a Detailed Level RA. Thus, the title of this and any similar documents and wording in this and those documents needs to be changed. Note also that a HQ $\geq$ 1 only indicates potential. Slide 19 of USEPA's December 04, 2013 presentation incorrectly noted a value equal to or greater than 1 as "*of concern*". Such a value would be of potential concern; risk has not been established and the HQ is based on a relatively high level of conservatism.

2. Uncertainty is not adequately addressed in the document.

Section D, Key Sources of Uncertainty and Data Limitations, is incomplete. I fully agree with the American Chemical Council that, with regard to this section, "*the discussion provided is minimal and incomplete*." There are many cases in the document where the work "*assumed*" is used. However, these cases almost always do not link to uncertainties documented in this section of the report. A major uncertainty not mentioned is the very low n for tests used to develop effects benchmarks (ranging from 6 for acute in water, 7 for chronic in water, 5 for sediments, 3 for soil invertebrates, and 1 for terrestrial plants) – see comments 2 and 3 in response to Charge Question 4-1, above. As another example, note that on Page 21 of the document the following major uncertainty is noted but not included in Section D: "*The lack of measured half-lives for anaerobic conditions (benthic sediments and sludge digesters) was considered a significant data gap."*

# William Doucette

The document provides a thorough review of the literature describing the environmental fate and impact of HHCB. However, there are several general and specific comments/questions listed below that should be addressed before the document is finalized.

**General Comments**

1. Consistency of terminology
   There are several places within the document that inconsistencies in terminology that impact the readability of the document. For example, the terms sorption and adsorption are used interchangeably when in most cases sorption is the most appropriate terms. Another example is the use of the terms biosolids and sludge.

2. Importance of specific fate processes
   a) To illustrate the effectiveness of wastewater treatment plants (WWTP) on the removal of HHCB from influent streams, ranges of influent and effluent concentrations are presented that in many case show similar ranges. Presentation of the wide ranges of influent and effluent concentrations gives the reader the impression that little HHCB is removed within WWTPs. The presentation of pair influent and effluent samples as shown in Table G-3 likely provides a more realistic assessment of the effectiveness of WWTPs in removing HHCB from influent streams.
   b. The literature cited within the document reported that the volatilization losses of HHCB in various fate studies ranged from negligible to as much as a 40%. If possible, it would be helpful to the reader if some sort of consensuses view on the importance of volatilization could be provided. If this can't be done, it should be recommended that additional data on the importance of volatilization should be collected.
   c. There was no information provided for terrestrial plant concentrations and no attempt was made to predict values. There was no mention of measured or estimated plant bioconcentration factors. This should be mentioned as a limitation.
   d. Given the increasing use trends of HHCB in the US provided in the document, it is important that the document discuss how this might impact future environmental concentrations and the associated risk assessments?
   e. During the panel discussions it was mentioned that 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.
   f. Additional information on the fate and biological activity of the HHCB metabolites should be provided.

**Specific Comments by Section and/or Page**

**Glossary of Terms**

Page 6:
$K_d$ typically defined as a linear sorption coefficient derived from the slope of a linear sorption isotherm. Also used to denote a single point sorption coefficient (ratio of HHCB concentration in solid phase to that in aqueous phase at equilibrium). Throughout text the term "adsorption" coefficient was intermixed with "sorption coefficient". If specific mechanism is unknown, as it is for most environmental solids, the term sorption is more appropriate.

Page 7:
Suggest using "organic carbon normalized sorption coefficient" instead of "organic carbon partition coefficient" since it's Kd/fraction of organic carbon

**Executive Summary**

Page 8:
Is HHCB found in humans as a result of its direct application to skin via personal care products or from environmental exposures? This should be briefly discussed in the executive summary and early on in the report.

In subsequent text, it is only suggested that SC Johnson was not a manufacturer since the specific information was not provided. This wording should be consistent throughout report.

There was no information provided for terrestrial plant concentrations and no attempt was made to predict values. There was no mention of measured or estimated plant bioconcentration factors. This should be mentioned as a limitation. Probably should also evaluate the potential impact of reclaimed wastewater containing HHCB.

**Background and Scope**

Page 10:
Should mention the main route of exposure to humans? Is it the environment or direct application of consumer products?

How can it be listed as an inert ingredient if it has a moderate hazard potential for developmental toxicity?

Page 11:
The document states that "Potential risk concerns were identified for certain highly contaminated sediments in Europe (HERA, 2004) and for HHCB in surface runoff from biosolids-amended land in Australia (Langdon et al., 2010). In addition, a screening-level risk assessment for California recently identified a risk concern for HHCB in surface water and recommended monitoring in inland waterways (Anderson et al., 2012). What triggered the surface water risk concern in California and the other potential risks identified in Europe and Australia? Are these unique risk concerns? Please provide some additional explanation.

Page 12:
Is it appropriate to assume that environmental concentrations will continue to increase with the increasing production trends? Should an attempt be made to predict if and when HHCB level may exceed COCs in the future based on projected production levels?

Page 13:
Are (or should) metabolites (be) considered?
Use the term “sorption” instead of “adsorption” throughout document.

Page 14:
It was stated that the long half-life in soil may result in HHCB being available for plant uptake but no estimates were made.

Was any consideration given to the application of reclaimed wastewaters to selected crops?

**Chapter 2: Sources and Environmental Fate**

Page 15:
Any information on differences in biological activity or degradability between isomers? Only mentioned some have little or no odor.

What is the isomeric composition of typical commercial products?

The HHCB commercial product is diluted (65 % wet weight) in diethyl phthalate, benzyl benzoate, or isopropyl myristate prior to compounding and formulation into products. Any information on potential interactions with respect to biological activity? Mixture effects?

Page 16:
No Henry's Law constant (measured or estimated) was provided in Table 2-1? This information should be added since volatilization was discussed as a possible fate mechanism later in the document.

Please provide clarification on melting point range? What is indicated by this range? -10 to 0 °C; -20°C

A log Kow value of 5.3 yields an estimated solubility closer to the measured than 5.9. Suggest using log Kow = 5.3 to be consistent with the experimental solubility data.

Aqueous solubility data presented as pH values of 5,7, and 9 are likely statistically equivalent. Should mention that there is no expected impact of pH on HHCB solubility since it’s non-ionizable.

Page 17:
Provide list or table of specific metabolites that have been identified. Are there data for the fate or biological activity of the metabolites?

No significant volatilization was detected in the study of Langworthy but in later literature citations volatilization losses were considered significant (up to 40% loss). Can a conclusion on the potential importance of volatilization be reached within the document?

Identity of specific metabolites? Are there data for the biological activity of metabolites?

Need to be consistent in sorption terminology throughout text. Koc definition different than in Glossary of Terms.

Page 18:
Removal from influent is not equivalent to removal from environment. Specific ratios of influent to effluent are more appropriate for presentation than ranges of influent and effluent concentrations. The ranges are similar. Paired values of influent and effluent values as provided in Table G-3 are more informative.

It was stated that degradation is expected to be slower in streams that do not receive WWTP effluents. Why? Concentration dependence or lack of adapted microorganisms?

Page 19:
Is there any information of the fate of HHCB specifically in biosolids before they are land applied? Is the sludge referred to in Table 2-2 the same as biosolids? If so, be consistent with terminology throughout document.

At the bottom of Table 2-2 it was stated half-disappearance time differs from degradation half-life in that it includes all mechanisms contributing to disappearance (*e.g.*, volatilization in addition to degradation). What do the values in the table refer to? Please be consistent with terminology throughout document.

**Fate in Water**

Was the degradation half-life in EC, 2008 transformation or disappearance of parent compound?
It was stated that 40% was lost by volatilization when it was stated earlier in the document that volatilization was not significant. Please try to help the reader understand which reference is likely to be most environmentally realistic. EPISutie WWTP prediction suggests volatilization is not important relative to other removal mechanisms.

Page 20:
Is there any information on the fate of HHCB metabolites? Is this information required for an assessment of this type?

**Fate in Air**

HHCB is likely to be sorbed to particulate matter in air. Is the calculated half-life provided here for gas phase HHCB or HHCB sorbed to particulates? Has HHCB been identified in polar locations?

**Bioaccumulation and Concentration**

No data or estimations of uptake for terrestrial plants. Based on the hydrophobicity of the compounds there is a high potential for root concentration. Root to shoot transfer is likely limited. This should be addressed. Calculations were made for earthworms, why not for plants?

**Conclusions of Environmental Fate**

Page 21:
Mention that wide range of reported effluent concentrations is similar to the range of influent concentrations.

Page 22:
Show only relatively recent data on production trends unless you can relate measured environmental concentrations to changes in production values. How will the increasing production trends impact estimated influent concentrations and how might this impact the RQs?

**Chapter 3: Environmental Assessment**

Page 27:
Is there any evidence to suggest concentrations near “compounding and formulation” sites are higher than near the outlets of WWTPs?

Page 28:

**WasteWater**
Effluent ranges of HHCB are the same as the influent ranges. Suggests no removal. Refer reader to paired samples in Table G-3.

What wastewater treatments types were least effective and are these treatments used in large population areas? Why do the concentrations vary seasonally?

**Surface Water**

Based on the existing data, can you suggest what types of treatment technologies are more or less effective in HHCB removal?

Page 29:

**Biosolids and Soil**
Biosolids application to crops or animals living on biosolids amended soils are likely the worst cases for potential exposure.

Page 30:
Are humans considered biota? Is it appropriate to add information on humans?

Page 31:
Table 3-2
Are the sediment, soil and biosolids concentrations presented on a dry weight basis? Please clarify.

Page 32:
Should this section be titled Hazard or Risk?

Page 33:
0.0564 mg/L was stated to be equal to 56.4 ppm. Should be ppb. mg/L is ppm.

Page 34:
Sorption instead of adsorption.
Volatilization was said to not be significant in other sections.

Page 35:
0.00524 mg/L should be 5.24 ppb

Page 36:
Assessment or uncertainty factor?
Wasn't 5 used previously? Better justify the use of the factors.

Page 39:
How do you factor in the increasing use patterns and likely increasing environmental concentrations?

Pg 61:
Add references showing relationship between cosmetic use and blood levels. See Hutter et al.

1. Hutter, H. P., P. Wallner, W. Hartl, M. Uhl, G. Lorbeer, R. Gminski, V. Mersch-Sundermann and M. Kundi. 2010. "Higher blood concentrations of synthetic musks in women above fifty years than in younger women." *International Journal of Hygiene and Environmental Health* 213(2): 124-130.
2. Hutter, H. P., P. Wallner, H. Moshammer, W. Hartl, R. Sattelberger, G. Lorbeer and M. Kundi. 2009. "Synthetic musks in blood of healthy young adults: Relationship to cosmetics use." *Science of the Total Environment* 407(17): 4821-4825.
3. Hutter, H. P., P. Wallner, H. Moshammer, W. Hartl, R. Sattelberger, G. Lorbeer and M. Kundi. 2005. "Blood concentrations of polycyclic musks in healthy young adults." *Chemosphere* 59(4): 487-492.

Page 65:
All references in Table A-1 are 1999 or older.

Page 67:
Update references. See Hutter et al. 2009 for blood levels.

Hutter, H. P., P. Wallner, H. Moshammer, W. Hartl, R. Sattelberger, G. Lorbeer and M. Kundi. 2009. "Synthetic musks in blood of healthy young adults: Relationship to cosmetics use." *Science of the Total Environment* 407(17): 4821-4825.

Page 72:
Where are root crop data (estimated or measured) presented?

Page 75:
This does not seem to be a correct statement given the cosmetic information presented in Hutter et al. 2009 and 2010

Page 82:
Table D-4. Why no information from SC Johnson?

Page 94:
No estimation of plant uptake and subsequent transfer to plant eating organisms.

Page 95:
When presented as ranges, reported influent and effluent concentrations are essentially the same. The presentation in Table G-1 is more appropriate.

# Bob Gensemer

1. Page 12, Scope of Assessment, last paragraph. Further explanation would be helpful as to why mammals and birds were beyond the scope of this assessment. Is this based on limited potential for bioaccumulation and/or biomagnification as discussed later in the document? If so, a brief explanation would helpful here.

2. Page 30 and Table 3-2. Are fish "tissue concentrations" reported on the basis of ng/g as dry weight? I would assume so given that wet or lipid weight concentrations are reported separately, but its always helpful to clearly provide dry or wet weight unit designations to any tissue concentration wherever reported.

3. Page 30, last sentence. Additional explanation of why EPA concludes that the "data are assumed to be representative" should be provided. Is it just the large number of studies (at least for water and wastewater), types and geographic ranges of environments encountered?

4. Table 3-3. It would be helpful to provide the test exposure durations for all tests. Some are only labeled as "LC50" and if the reader is not immediately familiar with the particular OECD method, the duration can not be determined from the table for all tests.

5. Page 33+, chronic toxicity data. I concur with Peter Chapman's statement (and from further discussion during the January 9 peer review panel meeting) in his preliminary comments that ECx values are strongly preferred over NOEC/LOEC data, or over EPA's use of geometric mean as the basis of the ChVs. Is there something in EPA guidance for OPPT or TSCA risk assessments that precludes use of the ECx values?

6. Page 38, Additional Studies. 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. I am assuming, as would be appropriate for most ecological risk assessments, that these sublethal indicators are not being directly used because they do not provide information with respect to survival, growth, or reproduction. I agree with that (i.e., only using survival, growth, or reproduction data in this kind of an assessment), but a statement to that effect would be helpful to the reader or concerned stakeholders. This context is particularly needed given that at least one estrogen binding study for juvenile zebrafish indicated some level of effect at concentrations below NOECs from ELS studies.

   Perhaps, as discussed during the January 9 peer review panel meeting, an Adverse Outcome Pathway analysis may assist in determining the extent to which the sublethal endpoints discussed on this page would or would not provide value or alter the outcome of the EPA risk assessment for HHCB. However, as also discussed during the peer review panel meeting, what ultimately drives what kind of assessment to do (and what endpoints to select) would be some kind of guidance or description from EPA as to what kind of assessment is needed to meet TSCA program objectives. Is a screening level analysis adequate? Are the species selected and test endpoints adequate? Without knowing what TSCA program needs require, it is difficult to specifically advise EPA as to whether the current analysis is appropriate or not. I agree with other peer review panelists that generating a Problem Formulation section of the assessment is needed, and that this section should be provide the basis of explaining what kind of assessment is needed, and thus can help us determine if the current assessment meets these needs or not.

7. Page 40, and Table 3-8. Why are RQs not calculated from maximum exposure concentrations from the USGS data? Maximums are used for the published data, so this would seem to be a logical calculation, and make more transparent the likelihood for observing RQ values greater than 1. This would also be more consistent with the narrative on page 41 stating that 9 samples (1.5% of the dataset) had RQ values > 1. This result would not be apparent from just looking at the RQ for the 95$^{th}$ percentile of the USGS data in Table 3-8.

8. Page 40, and Table 3-8. Why are effluent data excluded from this analysis? While it is briefly stated that the calculated RQs are considered conservative estimates for surface water, I'm not sure this is a valid conclusion for sites that might be strongly effluent-dominated. In such cases, effluent data might a reasonable, albeit conservative, estimator of what one might expect for at least acute exposures. Many other commenters agreed with this statement during the January peer review panel meeting. This would likely increase the number of results with RQs > 1, but for sake of transparency, it would be good to provide a fuller picture of potential risk exceedances.

9. I agree with other commenters during the January peer review panel meeting that additional work is needed on the uncertainty analysis. My specific suggestion is that for each uncertainty discussed, EPA should also provide an opinion as to whether any given uncertainty makes the assessment outcome more or less conservative (or even if the uncertainty is neutral or unknown in this respect). This is a common expectation for uncertainty analyses, and should be added to the HHCB assessment. Without this discussion, it is more difficult for the reader (particularly a non-expert reader) to determine the ultimate practical implication of any given uncertainties.

# Duane Huggett

**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.***

The "Scope of Assessment for HHCB" and Conceptual Model for the Environmental Assessment" sections provide a very clear picture in terms of the key questions and assessment scenarios. In particular, Figure 1.1 clearly summarizes EPA's thought process and focus of the assessment. This assessment focuses on effluent discharges to aquatic systems and terrestrial inputs via WWTP sludge. Exposure to aquatic, sediment and soil organisms is expected. Measured environmental concentrations are compared to effective concentrations from toxicity studies for the derivation of a risk quotient (RQ). In addition, other data are presented (e.g. contradictory estrogenic activity, multidrug resistant transporter inhibition), but the data were not addressed in the final conclusions. It is great to present this mechanism based information, but a statement as to its use is needed.

This assessment should be considered as a screening level assessment and needs to be clearly stated in the document. In addition, HHCB has a reported fish BCF value of 1,584 yet an assessment of trophic transfer and effects to "birds and mammals was beyond the scope of this assessment". Given the high Log Kow value (i.e. 5.3) and fish BCF value, a trophic transfer and toxicity analysis would be beneficial.

Lastly, HHCB-lactone, which is a oxidation product of HHCB, is often measured in wastewater samples. Should this assessment address this transformation product in any way? At the very least, it should be stated that the assessment of transformation products is out of scope.

**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.***

Several additional publications should be included in the assessment. In particular, field derived bioaccumulation factors have been published for waters in the United States. In addition, the biotransformation of HHCB to a hydroxylated metabolite in fish should be included in the bioaccumulation section.


1. Fernandes et al. 2013. Metabolism of the polycyclic musk galaxolide and its interference with endogenous and xenobiotic metabolizing enzymes in the European sea bass (*Dicentrarchus labrax*). *Environmental Pollution*. 214-221.
2. Reiner, J.L., Kannan, K. 2011. Polycyclic Musks in Water, Sediment, and Fishes from the Upper Hudson River, New York, USA. *Water, Air and Soil Pollution*. 214:235-242.

**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.***

If possible, the fish BCF data should be lipid normalized, as well as in its current form.
Several additional publications should be included in the assessment. In particular, field derived bioaccumulation factors have been published for waters in the United States. In addition, the biotransformation of HHCB to a hydroxylated metabolite in fish should be included in the bioaccumulation section.

1. Fernandes et al. 2013. Metabolism of the polycyclic musk galaxolide and its interference with endogenous and xenobiotic metabolizing enzymes in the European sea bass (*Dicentrarchus labrax*). *Environmental Pollution*. 214-221.
2. Reiner, J.L., Kannan, K. 2011. Polycyclic Musks in Water, Sediment, and Fishes from the Upper Hudson River, New York, USA. *Water, Air and Soil Pollution*. 214:235-242.

In this section, the assessment should speak to degradation products (e.g. lactone) or specify that they are out of scope.

**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.***

In this type of assessment, all data should be evaluated. However, QA/QC specifics regarding sampling and analysis need further clarification.

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

In this type of assessment, all data should be evaluated. However, QA/QC specifics regarding sampling and analysis need further clarification. Are all of the data of the same or sufficient quality. What metrics were used to ensure quality of the data?

**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 any recommendations for the hazard characterization.***

I am in agreement that all available ecotoxicity data be presented to provide a clear picture of what is known. However, there are often clear differences in the quality of data in studies that follow internationally validated and accepted protocols (e.g. OECD). In addition, studies that follow these protocols often have datasets that have been generated following GLP procedures. 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. By not following a standard protocol and GLP procedures, the data and meaning are somewhat quaestionable. In particular, the mud snail data set presented in the sediment toxicity section falls into this category. The mud snail data should not be used in the final sediment assessment. It may be more appropriate for reasons discussed above to use the *H.azteca* value of 10.8 mg/kg for the sediment assessment.

Where did the sediment assessment factor of 10 come from?

The marine copepod study followed an OECD Draft Guideline, meaning the final protocol parameters had not been set. The fact that these parameters are not set, again calls into question the use of the data. Were these data generated use GLP guidelines? It may be more appropriate to use the Fathead Minnow Early Life Stage Test (OECD 210) presented in Table 3-4 for the chronic aquatic assessment.
Page 33: 0.0564 mg/L is 56.4 ppb, not ppm.

One data gap is vertebrate reproduction. Survival and growth in fish are provided, but no data on reproduction. This gap needs to be addressed in the document. Some work has been done with respect to "read-across" of mammalian data to aquatic vertebrates. This type of analysis could be conducted.

**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.***

This is a screening level assessment for HHCB. Additional data and methodologies would be needed to fully evaluate risk (e.g. probabilistic risk assessment). When considering the exposure and effects data, little information is provided in terms of the quality of those data. Given the data provided and questions of quality, more analyses are needed in terms of uncertainty. Further, the use of assessment in some instances needs clarification.

# Shane Synder

**Charge Question 1-1:** ***Please comment on whether the characterization provides a clear and logical summary of EPA's analysis. Where necessary, please provide specific suggestions for improving the document.***

The draft risk assessment is provided in a clear and logical manner. The information provided is transparent and sufficient evidence is supplied to justify the hazard quotients calculated. The use of maximum and 95% concentration data provides a high degree of conservatism in calculating the risk to the aquatic ecosystem. However, the document fails to provide information regarding the methods applied for monitoring and QA/QC review of those data.

Since the majority of analytical data came from the USGS monitoring programs, there is higher certainty that analytical methods applied were robust and reliable. Regardless, it is advised that some based information regarding blanks and other QA/QC be added to the appendix if possible. From my experience, 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. The EPA should address the QA/QC issue for the largest data sets which weight the conclusions reached.

**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, and if so, what are they?***

As previously requested, the QA/QC information for the most commonly employed analytical methods should be included.

It would be advantageous to include more specific information about the types of wastewater treatment employed at locations with particularly high HHCB levels. Are the greatest concentrations recorded originating from locations where nitrification is not entirely occurring? Would a WWTP with full

nitrification and denitrification (anaerobic zones) discharge far less HHCB? Lastly, it seems some HHCB transformation products also are released from WWTPs. A bit more discussion on the potential for stable transformation products would be beneficial. One reference that should be considered for treatment and occurrence data is: Snyder, S. A.; Wert, E.; Lei, H.; Westerhoff, P.; Yoon, Y. Removal of EDCs and pharmaceuticals in drinking and reuse treatment processes; American Water Works Association Research Foundation: Denver, 2007[1]. This AwwaRF report refers to HHCB by the trade name Galaxolide. I would be curious if other reports and publications were not included in the literature review because of trade, or other synonymous, chemical naming.

I also would feel more confident if the EPA would provide additional information on the human health risk assessment. While relying on other assessments seems justified, the EPA may wish to include more information regarding the weight of evidence from the assessments utilized and specifically why the EPA agrees with the conclusions reached. This is especially true for claims of endocrine disruptive types of effects.

**Charge Question 2-1:** ***Please comment on whether the information is used appropriately in the risk characterization. Please provide any specific suggestions for improving the assessment.***

The information provided seems to be appropriate for a screening level review. The use of maximum concentrations is therefore appropriate; however, should be recognized clearly as a highly conservative view.

**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.***

The data compiled seem to largely provide a good indication of the occurrence in US water and sediment. This is clearly, and appropriately, biased by the USGS data. As previously stated, QA/QC information should be provided for the USGS methods and data. The data provided for sediment should include organic carbon composition and for biota lipid determination. This is especially true for the sediment data. It also appears that there is very little difference between filtered and unfiltered water sample concentrations. This is quite surprising and deserves some discussion. Again, basic information regarding filtration at WWTPs sampled would be valuable. Regardless, I would have expected more particle bound HHCB then seems to be inferred within the data provided in the appendix of this report. As stated previously, 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.

The summary occurrence data should include information regarding the method reporting limits (MRLs) and how "non-detect" data were handled in the summary statistics. This would help explain if there is bias in the data set from non-detect samples. However, considering the high propensity for occurrence in WWTP outfalls, the lack of efficient removal during some WWTP processes, and the relatively large concentrations (i.e., ug/L) in the maximum concentrations, I doubt the non-detect data will have any influence on the overall conclusions. However, basic information regarding the MRL and treatment of non-detect data would be appropriate to include.

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

It is appropriate to use data only if adequate QA/QC has been provided. At a minimum, only data sets that contained information on blanks, recovery, and replication should be used. However, the document does well to describe the magnitude of the USGS dataset as compared to all other data. Since the USGS data is

by far the most influential, except in soil data as described, the QA/QC should be provided here with a minimum of ranges found in blanks considering the ubiquity of HHCB containing products.

One puzzling question relates to the discussion of the isomeric distribution of HHCB during production. Perhaps a small discussion as to whether analytical methods employed are measuring all of the isomers of HHCB present or if only one primary isomer is analytically determined. If multiple isomers exist in the environment, is the toxicity and bioaccumulation similar?

**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 any recommendations for the hazard characterization.***

It is unclear to me if the most sensitive species were used in each of the risk scenarios. However, I defer a deeper discussion to other panel members with greater expertise than me on this topic. That said, during my term on the FACA for the EPA's EDSP, there was great debate regarding the selection of freshwater and marine fish species.

Other comments related to this charge question have been addressed previously in my responses to other charge questions.

**Charge Question 5-1:** ***Please comment on the calculation of risk derived from the 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.***

The screening assessment conducted seems appropriate for the datasets utilized. Environmental variability is accessed geographically, but only sparsely temporally. WWTPs often have large diurnal flux, with some organic constituents varying by one to two orders of magnitude within one day[2]. Moreover, daily variations and seasonal variations also can be significant[3]. Again, considering that this is a screening exercise and maximum concentrations do not seem to trigger HQ>1, these variables are not likely to greatly influence the conclusions.


1. Snyder, S. A.; Wert, E.; Lei, H.; Westerhoff, P.; Yoon, Y. 2007. *Removal of EDCs and pharmaceuticals in drinking and reuse treatment processes*; American Water Works Association Research Foundation: Denver.
2. Nelson, E. D.; Do, H.; Lewis, R. S.; Carr, S. A. 2011. Diurnal Variability of Pharmaceutical, Personal Care Product, Estrogen and Alkylphenol Concentrations in Effluent from a Tertiary Wastewater Treatment Facility. *Environ. Sci. Technol.***,** *45* (4), 1228-1234.
3. Gerrity, D.; Trenholm, R. A.; Snyder, S. A. 2011. Temporal variability of pharmaceuticals and illicit drugs in wastewater and the effects of a major sporting event. *Water Res. 45* (17), 5399-5411.


# Lawrence Whitehead

Context: My area of work is occupational exposures. Therefore the ecotoxicology reports, analyses and methods are new formats for me. In a sense I am a reasonably informed community reviewer on those points. I have given more attention to the larger dataset analyses, as that area overlaps into issues with which I have worked.

**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.***

I am not aware of added reports or data for ecotoxicology, but this is not my primary area. I did locate several studies of air concentrations, in indoor air, and one in a cosmetic manufacturing plant in China (Chen et al., 2006). In these papers levels were typically low in indoor air, but in the cosmetics plant "workshop" area the average of seven consecutive daily high-volume samples was 4504.97 ± 941.10 $ng/m^3$ in the vapor phase (the particulate phase was much lower, about 2% of total HHCB). The plant was a large cosmetics and household products formulator only, and did not include primary manufacturing of HHCB. No added detail is given about the 'workshop" situation.

Samples of air in other parts of the plant and upwind and downwind were reported, along with data for influent and effluent for plant wastewater treatment, and primary and secondary sludge. The analytical method appears very sensitive, and for air, large volumes were sampled leading to the capability to measure low concentrations while care was taken to not reach breakthrough. The analytical method is described in greater detail in the paper by Zeng et al.


1. 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. Epub 2006 Jun 30.
2. Zeng, X.Y., Sheng, G.Y., Xiong, Y., Fu, J.M., 2005. Determination of polycyclic musks in sewage sludge from Guangdong, China using GC–EI-MS. *Chemosphere* 60, 817–823.


**Other Papers**


1. Den Hond E, Paulussen M, Geens T, Bruckers L, Baeyens W, David F, Dumont E, Loots I, Morrens B, de Bellevaux BN, Nelen V, Schoeters G, Van Larebeke N, Covaci A. Biomarkers of human exposure to personal care products: results from the Flemish Environment and Health Study. FLEHS 2007-2011. *Sci Total Environ.* 2013 Oct 1;463-464:102-10. doi: 10.1016/j.scitotenv.2013.05.087. Epub 2013 Jun 20.

   This paper reports blood HHCB in 204 Belgian adolescents. 100% of samples had detectable levels of HHCB. The geometric mean (95% CI) was 0.717 (0.682–0.753) µg/L

2. Fromme H, Lahrz T, Piloty M, Gebhart H, Oddoy A, Rüden H. Occurrence of phthalates and musk fragrances in indoor air and dust from apartments and kindergartens in Berlin (Germany). *Indoor Air*. 2004 Jun;14(3):188-95.
3. Kallenborn R, Gatermann R, Rimkus GG. Synthetic musks in environmental samples: indicator compounds with relevant properties for environmental monitoring. *J Environ Monit*. 1999 Aug;1(4):70N-74N.
4. Lignell , S., Darnerud , P.O., Aune , M., Cnattingius , S., Hajslova , J., Setkova , L., and Glynn, A. Temporal Trends of Synthetic Musk Compounds in Mother′s Milk and Associations with Personal Use of Perfumed Products. *Environ. Sci. Technol*. 2008, 42, 6743–6748.

   The Lignell et al. paper reported detectable HHCB concentrations in all breast milk samples from 101 Swedish women (one sample per person) between 1996 and 2003. The slope of ln(concentration) vs time was -0.055 +/-0.036 (p=0.127), not significant.

5. Liu N, Shi Y, Xu L, Li W, Cai Y. Occupational exposure to synthetic musks in barbershops, compared with the common exposure in the dormitories and households. *Chemosphere*. 2013 Nov;93(9):1804-10. doi: 10.1016/j.chemosphere.2013.06.027. Epub 2013 Jul 9.

This paper reports HHCB levels in dust in barbershops and in residential space, and in blood samples of 50 hairdressers and 10 others (94% of samples were >LOQ). In hairdressers the median blood level was 504 ng/L, and 446 ng/L in non-hairdressers. These values are generally comparable to the value of 717 ng/L reported by Den Hond, above.


6. Lu Y, Yuan T, Yun SH, Wang W, Kannan K. Occurrence of synthetic musks in indoor dust from China and implications for human exposure. *Arch Environ Contam Toxicol*. 2011 Jan;60(1):182-9. doi: 10.1007/s00244-010-9595-1. Epub 2010 Aug 31.
7. Sofuoglu A, Kiymet N, Kavcar P, Sofuoglu SC. Polycyclic and nitro musks in indoor air: a primary school classroom and a women's sport center. *Indoor Air*. 2010 Dec;20(6):515-22. doi: 10.1111/j.1600-0668.2010.00674.x.


In the course of discussions during this review, it was suggested that the Henry's Law constant be provided. For the purposes of this discussion, the following values are taken from Episuite, or derived by changing units. Various values are obtained from different models. The values just below are those labeled in Episuite as "for Henry LC comparison purposes":
Henry's Law constant: 8.96E-4 atm-m3/mol (9.078E+1 Pa-m3/mole)
Solubility in water: 0.1943 mg/L(=g/m3) (7.52E-4 mol/m3)
Sat. vapor pressure: 5.12e-4 mmHg (6.74e-7 atm)
As is necessary, these form a consistent set: (8.96E-4 atm-m3/mol) x (7.52E-4 mol/m3) ≡ 6.74e-7 atm

For comparison, odor thresholds of 0.63 ng/L (4S,7R)-(-)-galaxolide) and 1 ng/L ((4S,7S)-(-)-galaxolide) were reported for the two most potent isomers. These are in the 60-100 ppt v/v range. The other two forms had much higher (less potent) odor thresholds. (G. Frater, U. Mueller & P. Kraft, Preparation and Olfactory Characterization of the Enantiomerically Pure Isomers of the Perfumery Synthetic Galaxolide. *Helv. Chim. Acta*, 82(10), 1656-1665.1999.)

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

This is appropriate as long as suitable information is available regarding interpretation of the data.
To be more specific, and especially for the USGS data analysis, more information would be very useful. I have inserted Table G-7 below, with a column for n. I understand that the total n values are reported in other tables or plots, but it seems useful to include them here. I note where it seems that the calculated values inserted for <LRL levels actually make up the largest proportion of the data. Therefore an added column for percent or number of data points which are <LRL (and therefore calculated) would also be very useful. The report does appropriately note that in some of the categories, with many '<LRL' values, the result is not truly a measured exposure, but it still represents useful information.
For incorporated data sets, if the GSD<3, "<LRL" was replaced by LRL/(2^0.5) ; if the GSD >3, "<LRL" was replaced by LRL/2. The water sampling LRLs are: 0.5 ug/L during and 7/2001-9/2009; 0.05 ug/L during 10/2009-2012. That results in the following substitution values:

| | 2001-9/2009 | 10/2009-2012 |
|---|---|---|
| GSD <3 | 0.35 | 0.035 |
| GSD >3 | 0.25 | 0.025 |

It is clear from the descriptive statistics that some datasets were largely composed of such calculated values. For example, 'Surface water/stream' shows every statistic except the 5%-ile as 0.35. It would be useful to know the percent of each group that is <LRL.

The box plot analyses and associated statistics are, I assume, descriptive analyses on raw data. Geometric mean and geometric standard deviation data would also be useful. For the categories with small n, and also not apparently all or mostly substituted <LRL values, a log-normal or other probability analysis with distribution fitting may be appropriate. Perhaps this has been done, if so please label as such. For example, how is the 95 percentile point otherwise estimated with ten data points (filtered water, steam effluent): perhaps as just the mid-point between the two highest data points? If a log-normal (or other) fit looked adequate, then a probability-based upper percentage could be estimated. Or if this has been examined and ruled out, a note to that effect and stating why it was not suitable (e.g., a very bad fit to distributions), would be helpful.

In the very large datasets, USGS, multiple types of situations are surely sampled but all reported in one average. Some situations may be quite different from others. Breaking out the analysis for different populations is of course in theory useful, but I acknowledge that with an apparent low risk for this material, the effort may not add much to the results. Also, some such categories may be largely <LRL values therefore substituted.

And though it would be more complicated to present, similarly consistent notes regarding data from the reviewed studies, where available, would be helpful. For example, the range of detection limits for included data could be added to Table 3-2, where the n values are already presented. Also possibly present how the ND values were treated by the authors, and their prevalence.

**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.***

Looking at Table 3-8 (RQ values), RQs are presented for a range of exposure values. This does at least bracket the range of RQs given the data so far and the analyses of that data. This would seem to be an opportunity to use Monte Carlo-type simulation. A reasonable distribution for the exposure values for each category could possibly be estimated, and use that as a distribution from which to randomly draw in a Monte Carlo analysis of the range of possible RQs and arriving at a most likely range of RQs. But if that analysis is not feasible for statistical reasons, then at least the report already describes a range of RQs given different exposures.

**Table G-7. Summary of Box Plots for USGS HHCB Data.**

| USGS Parameter Code<br>Medium/Site HHCB Concentration<br>5%-tile | | Q1 | Median | Mean | Q3 | 95%-tile |
|---|---|---|---|---|---|---|
| **62075** | | | | | | |
| **Water, filtered, recoverable; HHCB (µg/L)** | | | | | | |
| Effluent/stream | 0.35 | 0.35 | 1.40 | 1.18 | 1.82 | 2.16 |
| Effluent/outfall | 0.09 | 0.35 | 0.76 | 0.98 | 1.2 | 3.40 |
| Surface water/outfall | 0.35 | 0.35 | 0.65 | 1.08 | 1.70 | 2.30 |
| Surface water/stream | 0.10 | 0.35 | 0.35 | 0.35 | 0.35 | 0.35 |
| Surface water/lake, reservoir, impoundment | 0.04 | 0.35 | 0.35 | 0.33 | 0.35 | 0.35 |
| Groundwater/well | 0.04 | 0.35 | 0.35 | 0.32 | 0.35 | 0.35 |
| **62823** | | | | | | |
| **Water, unfiltered, recoverable; HHCB (µg/L)** | | | | | | |
| Effluent/outfall | 0.14 | 0.14 | 1.02 | 1.01 | 1.85 | 2.26 |
| Surface water/stream | 0.02 | 0.05 | 0.14 | 0.12 | 0.14 | 0.15 |
| Surface water/lake, reservoir, impoundment | 0.03 | 0.14 | 0.14 | 0.12 | 0.14 | 0.14 |
| **63209** | | | | | | |
| **Solids, recoverable, dry weight; HHCB (µg/kg)** | | | | | | |
| Bottom material/lake, reservoir, impoundment | 27.93 | 41.02 | 65.42 | 87.46 | 106.08 | 212.87 |
| Bottom material/stream | 17.68 | 24.75 | 40.00 | 67.99 | 67.19 | 200.00 |