

EPA's Response to Selected Major Interagency Comments on the Interagency Science Discussion Draft IRIS Toxicological Review of Hexachloroethane

September 23, 2011

Purpose:

The Integrated Risk Information System (IRIS) assessment development process of May 2009 includes two steps (Step 3 and 6) where White House offices and other federal agencies can comment on draft assessments. The following are EPA's responses to selected major interagency review comments received during the final Agency Review/Interagency Science Discussion step (Step 6) for the draft IRIS Toxicological Review of Hexachloroethane (dated April 2011). All interagency comments provided were taken into consideration in revising the draft assessment prior to posting to the IRIS database. The complete set of all interagency comments is attached as an appendix to this document.

For a complete description of the IRIS process, including Interagency Science Consultation, visit the IRIS website at www.epa.gov/iris.

Topic #1: Mode of action conclusions related to the renal effects observed following oral exposure to hexachloroethane – *ATSDR agreed with EPA that the available data were insufficient to attribute the renal effects of hexachloroethane (HCE) exposure to the accumulation of α_{2u} -globulin in the male rat kidney as the mode of action for the observed noncancer renal effects and renal tumors. DoD disagreed and stated that the available evidence was sufficient to attribute the renal effects of HCE to an α_{2u} -globulin-associated mode of action. OMB and ATSDR requested clarification on EPA's response to peer reviewers in Appendix A that there are insufficient data to support a mode of action whereby chronic progressive nephropathy is exacerbated by α_{2u} -globulin accumulation. OMB also requested clarification as to why EPA did not seek to fill in the data gaps to inform the mode of action evaluation as recommended by two reviewers.*

EPA Response: EPA concluded in both the external peer review draft and completed Toxicological Review that the available data are insufficient to inform the mode of action for renal tubule tumors observed following oral exposure to HCE. Based on the analysis of the data, EPA determined that HCE-induced renal tumors could not be attributed to the accumulation of α_{2u} -globulin, a conclusion

with which four of the reviewers agreed. Two reviewers indicated that the renal tumors were likely to be attributable to α_{2u} -globulin accumulation.

Observations of dose-dependent renal nephropathy in female rats and renal effects in male and female mice, which do not normally accumulate α_{2u} -globulin, provide support for a non- α_{2u} -globulin-related mode of action for HCE. In addition, the presence of α_{2u} -globulin in the hyaline droplets has not been demonstrated. EPA agrees that α_{2u} -globulin immunohistochemical data would inform the mode of action for the renal effects of HCE. Text has been modified in Section 4.7.1 to further clarify the data gaps.

In addition, EPA has concluded that the data are not supportive of the proposal that chronic progressive nephropathy is exacerbated by α_{2u} -globulin accumulation. Severity of the nephropathy increased following HCE exposure, and incidences of mineralization of the renal papillae and hyperplasia of pelvic transitional epithelium were observed in male rats exposed to HCE but not in controls or the HCE-exposed female rats, indicating that these effects resulted from chemical exposure rather than chronic progressive nephropathy. Additional data gaps (e.g., categorization of end stage renal failure in either the control or HCE-exposed animals, presence of foci of atypical hyperplasia, or determination of whether renal adenomas were within the areas of chronic progressive nephropathy) prevent attributing the renal effects of HCE to the exacerbation of chronic progressive nephropathy by α_{2u} -globulin accumulation.

However, in response to the external peer review and interagency review comments, text in Section 4.6.3, Section 4.7.3.1, and Appendix A was modified to provide a clearer evaluation of the available information and rationale for the resulting conclusions.

EPA acknowledges that the additional mechanistic data, including an immunohistochemical assessment of kidneys from the previously conducted studies as suggested by two reviewers, could potentially inform the question of whether the observed renal tumors in rats are relevant to humans. The Agency made inquiries as to current research capabilities and activities related specifically to immunohistochemical and other techniques to identify and quantify α_{2u} -globulin as recommended. No ongoing or planned research efforts were

identified. Any new data will be evaluated in future reassessments of the health effects associated with HCE exposure.

Topic #2: Application of the subchronic-to-chronic uncertainty factor in the derivation of the Reference Dose (RfD) – *DoD, OMB, and ATSDR requested additional clarification on the reduction of the subchronic-to-chronic uncertainty factor from a 10 to a 3 in response to external peer reviewer comments. DoD and OMB recommended an additional reduction to an UF of 1, whereas ATSDR disagreed with the reduction and requested the application of a subchronic-to-chronic uncertainty factor of 10.*

EPA Response: In EPA’s external peer review draft Toxicological Review, EPA applied a subchronic to chronic UF of 10 to account for extrapolation from a subchronic exposure duration study to a chronic exposure duration. Five of the six peer review panelists recommended reduction of this UF. Three reviewers explicitly stated that the application of an UF of 3 would be appropriate. Upon further consideration of the data and the external peer reviewers’ recommendations, the UF for subchronic to chronic extrapolation was changed from 10 to 3 in the Interagency Science Discussion draft Toxicological Review and has been retained in the completed assessment.

As discussed in Section 5.1.3, the 112 day Gorzinski et al (1985) study duration is minimally past the standard subchronic (90-day) study duration and falls well short of a standard lifetime study (i.e., two year chronic bioassay). As noted by the majority of external peer reviewers who supported a reduction in the UF, the (1) presence of renal effects at similar doses in the chronic NTP study, and (2) the higher BMDL from the chronic NTP study suggest that longer exposure is unlikely to exacerbate the atrophy and degeneration of renal tubules. However, there are insufficient data to exclude the possibility that chronic exposure could increase the severity of the observed kidney effects because the NTP (1989) study did not identify a NOAEL. The consistency in dose response relationships between chronic and subchronic studies and the remaining uncertainty about the effect of prolonged exposure at doses below the chronic LOAEL provide the rationale for the UF of 3. The text in Section 5.1.3 has been revised to clearly explain the available data and the rationale for the application of an UF of 3.

Topic #3: Weight of evidence supporting the cancer descriptor of “likely to be carcinogenic to humans” for hexachloroethane – *OMB requested additional consideration of the human relevance of the renal and adrenal gland tumors observed following hexachloroethane exposure. OMB also requested revisions to the weight of evidence section*

indicating that the peer reviewers commented that the available data fall on the “low end” of the spectrum for the “likely to be carcinogenic to humans” cancer descriptor.

EPA Response: Five of the six external peer review panelists agreed with EPA’s conclusion that HCE is “likely to be carcinogenic to humans.” Several of the panel members provided qualifying comments related to the mode of action and potential human relevance and these are summarized in Appendix A. One reviewer stated that while the data indicate that HCE is “likely to be carcinogenic to humans,” the weight of the evidence is on the low end of the spectrum for this descriptor.

EPA agrees with the majority of the reviewers that the cancer descriptor of “likely to be carcinogenic to humans” is an appropriate characterization of the weight of the evidence and is in accordance with the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a). This descriptor is appropriate when the weight of the evidence is adequate to demonstrate carcinogenic potential to humans but does not reach the weight of evidence for the descriptor “carcinogenic to humans.” An example provided in the U.S. EPA *Guidelines for Carcinogen Risk Assessment* ([U.S. EPA, 2005b](#)) is “an agent that has tested positive in animal experiments in more than one species, sex, strain, site, or exposure route, with or without evidence of carcinogenicity in humans.” As discussed in Section 4.2.1.2, the results from several rodent bioassays indicate that HCE exposure can cause tumors in two species, both sexes of animals, and multiple sites. On this basis, these data support the cancer descriptor “likely to be carcinogenic to humans.” However, EPA acknowledges that there are uncertainties associated with relating the observed tumors in animals following exposure to HCE to human carcinogenicity.

The rationale in Section 4.7.1 for the selection of the cancer descriptor has been further edited to clarify that additional mechanistic data, particularly related to the formation of the renal tumors in male rats, would inform the uncertainty associated with the assumption that these tumors are relevant to humans. In addition, a statement has been included to indicate that if the renal tumors were determined to not be relevant to humans, then the weight of evidence regarding human carcinogenic potential would be reduced.

Abbreviations and Acronyms

BMDL	Lower limit on the benchmark dose
CDC/ATSDR	Centers for Disease Control/Agency for Toxic Substances and Disease Registry
DoD	Department of Defense
EPA	U.S. Environmental Protection Agency
IRIS	Integrated Risk Information System
LOAEL	Lowest observed adverse effect level
NIEHS/NTP	National Institute of Environmental Health Sciences/National Toxicology Program
NOAEL	No observed adverse effect level
OMB	Office of Management and Budget
RfD	Reference dose
UF	Uncertainty factor

Appendix

ATSDR comments p. A-2

NIEHS/NTP comments p. A-5

OMB comments p. A-6

DoD comments p. A-13

Agency for Toxic Substances and Disease Registry (ATSDR) Comments on the final Agency/Interagency Science Discussion Draft IRIS Toxicological Review of Hexachloroethane (dated April 2011)

Memo to: Environmental Protection Agency

From: NCEH/ATSDR, Centers for Disease Control and Prevention

Regarding: Interagency review of EPA's Draft Toxicological Review, IRIS Summary and Fact Sheet for Hexachloroethane

Date: May 17, 2011

General Comments

Submitted for ATSDR/DTEM review are EPA draft documents Toxicological Review of Hexachloroethane (HCE), IRIS Summary on HCE, and the HCE Fact Sheet. This information presents the scientific basis supporting the human health assessment of HCE that will appear on the EPA online database, the Integrated Risk Information System (IRIS). The draft health assessment being reviewed here includes a chronic reference dose (RfD), reference concentration (RfC), and a carcinogenicity assessment.

Overall, this toxicological review and assessment is well written. EPA has clearly synthesized the scientific evidence and presents a non cancer and cancer hazard assessment of HCE that is logical, transparent, and concise.

Non Cancer Toxicity of Hexachloroethane

A chronic RfD of 7×10^{-4} mg/kg/day has been proposed for HCE. This value is based on a 16-week oral (via diet), subchronic study in rats (Gorzinski et al., 1985). Atrophy and degeneration of renal tubules in male rats was selected as the critical effect for RfD derivation.

A major concern of this reviewer was the relevance of this male rat renal end point to human risk assessment. Chronic progressive nephropathy (CPN) in the aging male rat typically complicates the assessment of chemically induced renal changes in chronic rat studies. However, lesions of CPN in exposed male rats may be utilized as potential

endpoints for estimating non carcinogenic risk if exposed male and female rats have CPN lesions that exhibit a clearly defined dose response.

The question that had to be answered here by EPA is whether the exacerbation of CPN lesions in male rats was HCE- induced (with dose response), or was the exacerbation of these kidney lesions brought about by nephropathy associated with accumulation of α_{2u} -globulin.

If accumulation of α_{2u} - globulin played a role in the exacerbation of CPN lesions in male rats exposed to HCE—these end points would not be suitable or relevant for extrapolation to human risk assessment.

In the data and conclusions that are presented by EPA there is insufficient evidence to attribute the kidney effects of HCE- exposure to an α_{2u} - globulin mode of action. With this being the case, ATSDR concurs with the selection of “atrophy and degeneration of renal tubules in male rats” as an appropriate point of departure (POD) for RfD derivation.

The RfD of 7×10^{-4} mg/kg/day was derived by applying a total uncertainty factor (UF) of 1000 to a BMDL₁₀ of 0.728 mg/kg/day . The UF of 1000 was composed of the following components: UF of 10 for interspecies extrapolation; UF of 10 for intraspecies variation; UF of 3 for subchronic-to-chronic exposure duration extrapolation; and UF of 3 for database deficiencies.

This reviewer suggests that the total uncertainty factor should be 3000 (rather than 1000). The individual component UF that I disagree with, is the UF of 3 that was used to account for extrapolation from subchronic-to-chronic exposure duration. I recommend that the most appropriate UF here would be 10.

Part of the rationale that EPA gives for using the UF of 3 in this situation is that evidence suggests that an increase in duration of HCE exposure may not increase the incidence of nephropathy. Generally, in regards to chemical exposure one would expect that increased duration of exposure to a nephrotoxin would increase the incidence/severity of nephropathy. Furthermore, chronic progressive renal disease is a common senescent change that begins fairly early in the life of a male rat—and making an accurate judgment of how increased duration of exposure relates to increased incidence of nephropathy is difficult because of the “normal” baseline of nephropathy in male rats as they age. Nephropathy effects involving the male rat kidney is a far from optimal endpoint to use

as the basis for using an UF of 3 (rather than the typical default of 10) to account for subchronic-to-chronic duration extrapolation.

If the UF used for subchronic-to-chronic exposure duration was 10 (rather than the proposed 3) the resulting RfD would be 2×10^{-4} mg/kg/day.

A chronic RfC of 3×10^{-2} mg/m³ has been proposed for HCE. This value is based on a 6 week subchronic inhalation study in rats (Weeks et al., 1979). Neurobehavioral effects in male and female Sprague-Dawley rats were selected as the critical effect. Based upon this study EPA considered 465 mg/m³ the NOAEL and 2,517 mg/m³ the LOAEL. The NOAEL of 465 mg/m³ was selected as the POD and there was an UF of 3000.

In regards to the proposed RfC of 3×10^{-2} mg/m³ that is being proposed : ATSDR concurs with the appropriateness of the study from which it is derived, the end point selection, the use of NOAEL/LOAEL methodology and assumptions, and the uncertainty factors applied in the derivation of this RfC.

Carcinogenicity of Hexachloroethane

In reviewing these documents, critical evaluation of the RfD and RfC values, and detailed assessment of non cancer hazard has been the primary focus of the review. However, the sections pertaining to the carcinogenicity of HCE are well written and scientifically sound.

National Institute of Environmental Health Science (NIEHS)/National Toxicology Program (NTP) Comments on the final Agency/Interagency Science Discussion Draft IRIS Toxicological Review of Hexachloroethane (dated April 2011)

NIEHS/NTP Comments on Hexachloroethane (HCE) Draft Document

The authors have addressed most of the comments raised by the External Peer Review Panel while revising this document. The document is clearly written and flows logically. We have the following comments for consideration:

The selection of Gorzinski study for derivation of chronic oral RfD is preferable because it provided NOAEL while the NTP studies did not. The dose levels used in the Gorzinski studies were 0, 1.0, 15 or 62 mg/kg. The difference between low and mid dose is 15 fold. This very wide dose spacing is not common in toxicology studies. Based on these studies the NOAEL could lie somewhere between 1.0 and 15 mg/kg for male rats. The authors may consider bringing this point up in their discussion on selection of a principal study.

The derivation of RfC is based on a single six week inhalation toxicity study, the top dose had clinical signs of CNS toxicity, and there were no effects in the lower two dose groups. HCE is considered as a systemic acting gas but did not induce any other systemic toxicity. Kidney is the major and most sensitive target of HCE mediated toxicity as shown by a number of oral studies. One would expect some effects on kidney in inhalation studies based on the chemical properties of HCE. There are a number of uncertainties because of very limited data base and it can be argued not to derive RfC for TCE. But one can also argue for it to have some numbers for guidance since the chances of having additional inhalation studies are not very promising.

Submitted by:

Rajendra S. Chhabra, BVSc.,PhD.,DABT

NIEHS/NTP

Office of Management and Budget (OMB) Comments on the final Agency/Interagency Science Discussion Draft IRIS Toxicological Review of Hexachloroethane (dated April 2011)

May 19, 2011

OMB staff focused on EPA's response to the external peer review. Where EPA agrees with the comments, we suggest that appropriate conforming changes be made in the main text of the toxicological review and the IRIS summary.

General Science Comments:

- While we note that the peer review report is already final, it would be helpful if the peer review report provided short summaries of the background of the expert reviewers. It may also be helpful if the peer review reports were to include information discussing any monetary funding (perhaps through a grant, cooperative agreement, sole-source agreement, or competitive contract) that the expert reviewer may have received from EPA's ORD. This would be consistent with generally-accepted disclosure practices for peer reviewers, particularly for reviews with significant public policy implications.
- EPA received the peer review report November 12, 2010. Since then, it does not appear that EPA has addressed all of the peer reviewer concerns. We note that the IRIS process (May 20 2009) states that EPA will make revisions in 60 days before beginning internal EPA review (duration 45 days). Following are a few examples of comments for which we cannot see how they were addressed:
 - Reviewers stated that the document was "repetitious", "excessive", should provide a "table up front listing all the studies EPA considered relevant", "may benefit from a clearer and more comprehensive discussion of possible modes of action", "missed opportunities to integrate and synthesize information to help the reader integrate the data", and should include a "brief executive summary" (see peer review report page 5-9). We did not see any substantive changes to address these concerns.
 - Dr. Lock strongly urges (in emphasis he added on page 11 of the peer review report) that EPA go back to the NTP 90 day study to confirm or refute the increase in α 2u-globulin protein using immunochemistry. Having this information is critical to determining whether the mode of action is relevant to

humans and is critical for the relevance of tumors. EPA simply states that this is a noted data gap. Considering the time EPA has taken to revise the report, it is not clear why EPA has not made the effort to conduct this study to gather this critical information. Would this study take more than 4 months for EPA to complete? Couldn't it have been conducted once EPA knew peer reviewers found it to be relevant and important?

- On page A-4 EPA clearly notes four instances where reviewers requested further discussion of selections and rationale relating to the choice of the Gorzinski study. When we look at section 5.1.1 which discusses the choice of the study, we see no further elaboration (eg no redline changes from the external review draft) to address these reviewer comments.
- On Page 13 of the peer review report Dr. Haber suggested that the chronic study would have the advantage and stated that the “toxicological review should discuss these opposing considerations in choosing the principal study, rather than simply defaulting to the lowest POD.” Please address this comment in Appendix A and also add relevant discussion to the Tox review in section 5.1.4. It may be helpful for EPA to provide a table showing the positive and negative attribute of each study. From the discussion on page 111 of the tox review, EPA does talk about the limitations of the Gorzinski study, but then chooses it. If this is due to a policy choice to use the lowest POD, EPA should state this very clearly in section 5 and also in the IRIS summary. It is very important that risk managers and users of IRIS assessments understand where the science may take us and where policy comes into the determination. This seems like a policy decision.
- The EPA definition of chronic exposure (see http://www.epa.gov/iris/help_gloss.htm#c) is: “Repeated exposure by the oral, dermal, or inhalation route for more than approximately 10% of the life span in humans (more than approximately 90 days to 2 years in typically used laboratory animal species).” As the 1985 Gorzinski study is 112 days which falls into the definition of chronic as defined by EPA, it is still unclear why EPA is treating this as a subchronic study. This study clearly meets the EPA definition of ‘chronic’ rather than ‘subchronic’. Throughout the tox review this should be defined as a chronic study, not a subchronic study.
 - It is unfortunate that EPA did not explicitly point this out to peer reviewers. As per their comments, EPA revised the uncertainty factor (UF) for

subchronic to chronic from 10 to 3. Had EPA acknowledged that the study is 'chronic' as per EPA definitions, it is possible no UF at all would have been needed here. The three reviewers that recommended 2-4 or 3 instead of 10, may likely have suggested a value of 1, as did one reviewer.

- Regarding the database uncertainty factor for the RfC, five of the reviewers provided a quantitative comment. As noted on page A-10, two agreed with an UF=10 and three suggested an UF=3. It is not clear why EPA does not follow the advice of the majority of experts who provided comments. EPA's discussion on page A-11 provides a listing of missing studies, suggesting a default, checklist type of approach to the application of the database UF; while peer review comments suggest a more holistic weight of evidence approach to the UF. More discussion is needed as to why the reviewers expertise is discounted.
- On page A-12, EPA oversimplifies the reviewer responses to question C1. EPA states that five of the reviewers support the descriptor "likely to be carcinogenic". In looking at the peer review report, we note discrepancies. Dr. Costa, says this classification is "excessive" but "appears inevitable" and notes that it falls at the "low end of this group". Dr. Haber agrees that it is appropriate but caveats it by noting that "the weight of evidence is on the low end of the spectrum for this descriptor." Dr. Lash states: "although I think calling HCE a "likely carcinogen in humans" would seem to be overstated, consideration of the U.S. EPA cancer guidelines makes this the only plausible choice, although this reviewer is not entirely satisfied with such a choice." Page A-12 should be revised to better capture the reviewers concerns. More importantly, it is unclear why EPA has not revised the tox review to clarify throughout that the data fall at the low end of the spectrum for this descriptor. The 2005 Cancer Guidelines state: "Descriptors represent points along a continuum of evidence; consequently, there are gradations and borderline cases that are clarified by the full narrative. Descriptors, as well as an introductory paragraph, are a short summary of the complete narrative that preserves the complexity that is an essential part of the hazard characterization. **Users of these cancer guidelines and of the risk assessments that result from the use of these cancer guidelines should consider the entire range of information included in the narrative rather than focusing simply on the descriptor.**" (emphasis is provided in the cancer guidelines).
 - As per the expert reviewer comments and the Cancer Guidelines, the tox review and IRIS summary should clearly reflect the majority of reviewer

concerns that the weight of evidence is on the low end of the spectrum for this descriptor. This information should be provided whenever the descriptor is mentioned.

Specific Comments on Appendix A:

- Page A-1, while EPA mentions the concern by the reviewers that the document was repetitious and needed more synthesis, EPA does not provide a response to these comments.
- Page A-2, EPA notes that one reviewer stated that the data on renal cancer is consistent with a mode of action (MOA) that is a combination of α 2u-globulin nephropathy and exacerbation of chronic progressive nephropathy (CPN). EPA states that this is addressed in section 4.7.3.1. However, upon review it is not clear that EPA has made any changes to this section to reflect the reviewers comment. It would be helpful for EPA, here and throughout Appendix A, to clearly articulate changes that were made in response to reviewer comments, and where EPA believes no change was necessary. If EPA is rejecting the reviewer comment that the MOA is a combination of α 2u-globulin accumulation and CPN, EPA should state this more clearly.
- Page A-3, once again EPA discusses what they have concluded, but EPA does not address why they seem to disagree with the peer reviewer conclusion that the MOA is due to a combination of CPN and α 2u-globulin accumulation. More clarity regarding why EPA disagrees with the peer reviewer would be useful.
- Page A-4, as per comments above, in the response, EPA states where the topic areas of concern are discussed in the tox review. However when we look at the tox review (sections 5.1.1 and 5.1.2, we see no substantive edits to address the reviewers comments which all asked that EPA provide further discussion and rationale for the choices made.
- Page A-9, in response to the comments from Dr. Haber, “EPA states that a literature search did not identify any structure-activity relationships relevant to the neurobehavioral effects of

- HCE exposure.” Despite this negative finding, it would be helpful for EPA to include in the tox review, as suggested by Dr. Haber, a discussion of the striking difference in the target between the oral and inhalation studies and what the causes may be. Can EPA also please provide details of the literature search that was conducted and yielded no relevant information? It would be helpful to make this supporting information (describing the search) available in an appendix of the tox review.
- Page A-9, in response to question B3, EPA should not state that all reviewers thought the NOAEL approach was justified. As per the peer review report (see page 29), Dr. Kodell did not think EPA's reasons were valid without qualifications. He stated: “I do not believe it has been clearly described why BMD modeling could not be done in this case.”
- Page A-13, once again EPA discusses what they have concluded and where this information is discussed, but it is not clear what, if any, changes EPA has made in response to the peer reviewer concerns and comments. Despite significant reviewer comments in response to this question, we see very little redline in the relevant sections of the toxicological review.
- Page A-14, EPA's statement that five reviewers “agreed with the selection” of the NTP (1989) study is an oversimplification. It does not capture comments such as those from Dr. Haber noting that “The male rat kidney tumors are a reasonable basis for the quantitation, recognizing the uncertainties regarding human relevance.” Please revise the framing to capture the nuances of the reviewers comments.
- Page 14, EPA accurately notes that one reviewer questioned the use of linear low-dose extrapolation. Please provide a response to this concern.
- Page A-14, EPA states that a reviewer recommended deriving the oral slope factor from the hepatocellular carcinomas in male mice. A response to this comment should be provided. We note that according to the peer review report, at page 39, at least two reviewers thought these were the best data for oral cancer modeling. On page 108 of the draft tox review, EPA presents the values for these tumors (table 5-6) but it is not clear why EPA does not use these data. Considering the repeatedly noted uncertainties regarding the relevance of the rat kidney data by the peer reviewers with the most expertise in this area, it is not clear why EPA did not use the male mouse data instead. Does EPA think the rat kidney data are relevant or is it a case that EPA does not have sufficient data to show that they are not relevant. This is an important

distinction which should be made. It seems as though the peer reviewers do not think they are relevant, but also acknowledge that data gaps do not allow for proving this. However, this does not make them scientifically relevant, this makes it uncertain. If it was a policy decision to use the lowest POD, regardless of confidence in the relevance, EPA should state this clearly.

Specific Comments on the toxicological review:

(In addition to comments below, please see comments above regarding general comments and Appendix A and make appropriate conforming changes in the tox review and IRIS summary)

- Page xiii, please clarify that the document was provided for interagency science discussion. The IRIS process document does not call this a review and language in the tox review should be consistent.
- Page 66 (and elsewhere) as per reviewer comments please clarify that the while HCE is classified as “likely to be carcinogenic”, the data fall at the low end of the spectrum for this category.
- Page 66, considering reviewer comments regarding the relevance of pheochromocytomas in male rats (see peer review report at page 36 where Dr. Lash states: “Additionally, the relevance of pheochromocytomas is subject to considerable uncertainty as well, and this seems to be minimized by the current document.”), it is not clear why EPA is including them as supporting the cancer justification.

Specific Comments on the IRIS summary:

- The IRIS summary should provide a link to the interagency comments associated with this final document. It is not clear how EPA is making interagency comments publicly available if no link from the final IRIS summary or tox review is provided. If an outsider were to go to IRIS to find an IRIS summary, they would have no way of knowing there were interagency comments available.
- It is not clear why the IRIS summary does not include the BMD modeling results for the male mice. Even though EPA has not chosen this endpoint, due to concerns about relevance and the role of α 2u-globulin, this endpoint should be carried forward and presented, perhaps in the supporting information section, for risk managers that may choose to use it. The discussion in the IRIS summary should also include clear

discussion regarding the question of the relevance of the rat kidney tumors to humans. It is not clear that EPA has articulated the state of the science regarding the data gaps that do not allow EPA to either prove or disprove relevance. EPA needs to be clear that due to the data gaps, EPA is invoking a policy choice to consider them relevant and to use them for the point of departure.

**Department of Defense Comments on
HCE Tox Review**

Comments submitted by: Chemical Material Risk Management Directorate	Organization: Department of Defense	Date Submitted: 5/18/2011
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*Comment categories: Science or methods (S); Editorial, grammar/spelling, clarifications needed (E); or Other (O). Also please indicate if Major i.e. affects the outcome, conclusions or implementation of the assessment.

Comment No.	Section	Pages	Comment	Suggested Action, Revision and References (if necessary)	*Category
1	5.4.3	109	The last two statements of section 5.4.2 are unclear, and potentially incorrect. "It is recognized that an alpha 2u-globulin-associated mode of action may, in fact, be responsible for the tumors observed in male rats and that more than one mode of action may be operating to induce the nephropathy observed across species and sexes. In that case, the renal tumors would be utilized for quantitation of cancer risk as they would be characterized as not relevant to humans."	Recommend that the last two sentences be edited for accuracy and clarity.	S
2	5.1.5 Previous RFD Assessment	93	The added statement " <i>in accordance with current risk assessment practices</i> " requires a reference. In particular, we believe this is in accordance with IRIS practices, not necessarily EPA practice.	Please provide the relevant reference, with page number if it is a document. Risk assessors may disagree as to what is "current practice", and regulatory risk assessments may differ from state-of-the-art risk assessments due to legislative or other constraints.	S
3	5.3	104	This page states that " <i>There are no available human occupational or epidemiological studies of inhalation exposure to HCE.</i> " However, the studies presented in section "4.1. STUDIES IN HUMANS—	We recommend that EPA's IRIS program provide some of the criteria used to determine when	S

			<p>EPIDEMIOLOGY, CASE REPORTS, CLINICAL CONTROLS”, reviews such studies. Although these exposures include chemicals other than HCE, EPA has used such studies as the critical one for quantitative analysis for other chemicals.</p>	<p>epidemiological studies, which always have exposure to more than one chemical, are deemed relevant for quantitative analysis. In this case, they appear to have been sufficiently relevant to be included in the review, but summarily dismissed in the quantitative analysis.</p>	
6	5.1.3	93, third bullet	<p>We agree with the reduction of the uncertainty factor for subchronic to chronic, but are unclear why this UF was not reduced to 1. The presence of chronic studies, plus EPA’s statements that the severity of these effects does not appear to increase with increased exposure, suggest that this UF should be 1. In the peer review comments Dr. Kodell agrees (page 22 post-meeting comments), “<i>I recommend not applying a UFD, or equivalently, setting UFD=1.</i>” Also, as Dr. Costa stated (post-meeting comments, page 19), “<i>a 300 UF applied to the BMDL10 derived from the Gorzinski et al. (1985) study would suffice, for a resulting RfD of 0.002 mg/kg/day.</i>”</p>	<p>Recommend further consideration of adopting UF of 1 for subchronic to chronic.</p>	S/M
7	4 and 5	N/A	<p>While the revisions made to the Toxicological Review for Hexachloroethane further improve the clarity of the document and the rationale for the various decision/approaches taken in the risk assessment, there is room for additional improvements regarding redundancy of information and overall length of the document.</p>	<p>We understand the necessity of repeating some of the information throughout various sections of the document, the lengthy information can be synthesized in a more concise and brief manner. Recommend reducing the repetitive and lengthy information in the different sections of the document (e.g., Sections 4.6, 4.7 and specifically, Section 5). Further, recommend synthesizing the information in sections 4.5.1, 4.5.2,</p>	S

				and 4.5.3 rather than present the information study-by-study.	
8	5.1.1 and Appendix A	86 and Pgs. A-2, A-3 and A-4	<p>From our reading of the external peer reviewers' comments, it appears that EPA stressed the need for a NOAEL in order to perform a quantitative analysis. Preference for a NOAEL was justified prior to the use of BMD modeling. However, since EPA uses the (non-statistically significant) response at the NOAEL for its benchmark dose (BMD) modeling, the rationale for requiring a NOAEL is problematic. ?If the available data do not allow BMD modeling to estimate a point of departrue, then the presence of a NOAEL matters.</p>	<p><u>As the BMD approach does not use the NOAEL explicitly, we recommend that EPA not include this criterion when evaluating the data for quantitative analysis.</u></p> <p>If EPA wishes to continue this practice in future chemical risk assessments, they should either justify it or should use the NOAEL as a zero response. The current practice does not seem logical.</p>	S
9		Global	<p>We concur with Dr. Bishop's and Dr. Lash's comments (pages 5 and 7) that the document would benefit from inclusion of an upfront summary of these key points: 1) the relative paucity of literature on HCE and particularly the very limited data in humans; 2) the choices of principal studies and toxicity endpoints for calculation of the RfD/Cs, with the confidence in the final draft proposed values; 3) the principal studies and toxicity endpoints used to derive the cancer potency and why they differ from the previous values; and 4) a table listing all the "key" studies (with type/species/sex/strain) that EPA considered relevant to this review.</p> <p>We also recommend a brief mention upfront of the main areas of scientific differences of opinions voiced by the external peer reviewers to increase transparency and balance.</p>	<p><u>We recommend that EPA strongly consider all of the reviewers' comments that relate to increased clarity or transparency.</u> If reviewers who have been selected for their expertise in this area are having difficulty understanding the document, others can be expected to have even more difficulty.</p>	S
10	5.1.3. RfD	93	We agree with Dr. Lock who questioned the selection of the critical study	Consider further justifying the selection	S

	Derivation		<p>for the non-cancer effects. Although EPA states (page A-4) that <i>“All of the reviewers agreed with the selection of Gorzinski et al. (1985) as the principal study;”</i> Dr. Lock, in his post meeting comments states (page 9) <i>“...for the noncancer endpoint, the administration of hexachloroethane in the diet leads to loss due to sublimation and in the Gorzinski paper, although they attempt to take this into account, the actual dose the rats receive is still not very precise ... So I wondered why the more recent NTP (1989) 90-day study, where the dose was by gavage and hence the exposure somewhat more precise, was not used?”</i> Lack of accuracy on exposure has often been a reason that studies have been rejected by IRIS for quantitative (and sometime qualitative) analysis. Yet in this case, a study with an imprecise exposure is selected over one with a precise exposure, and no explanation is provided.</p>	<p>of the Gorzinski study in light of Dr. Lash's comment.</p> <p>We would further appreciate some standard information on the criteria used by IRIS for evaluating the quality of the exposure data, as we have observed apparent inconsistencies across IRIS evaluations. While we understand that there may be justifications for these discrepancies, absent any criteria, the choices may appear to be <i>ad hoc</i>, subjective, and potentially biased toward those studies that agree with the chemical manager's hypotheses.</p>	
11	5.2.1	98 - 99	<p>During the peer review Dr. Haber commented on the adequacy of the Weeks et al., data stating that (pg. 24) <i>“it appears to barely meet the guidelines for study adequacy, and more details need to be provided to document that it was sufficient as a principal study. The previous EPA evaluation was based on essentially the same database, and apparently did not consider the data adequate, in light of the absence of a current RfC.”</i> We believe her comment should have been addressed in the text of the HCE Toxicological Review.</p>	<p>EPA should explain more clearly why a study that was deemed insufficient for quantitative analysis is now deemed sufficient. Furthermore, if there is such limited data available, we recommend that EPA consider not performing a quantitative analysis for this endpoint, as it has chosen to do for other chemicals. If a quantitative analysis is retained, EPA should explain why these limited data are sufficient when other, apparently similar data were not. Alternatively, EPA could provide an integrative analysis of all of the data from all routes of exposure, as we and</p>	S

				the peer reviewers have suggested. In this case, however, the UF for database insufficiency should be reconsidered as well.	
12	5.4.3	108 and B-58	<p>The male mouse hepatocellular carcinoma model results alone did not meet EPA's criteria for dose-response modelling, at least for the model presented. The chi square value is 0.9 and it our understanding that 1 is required for the model to be considered an adequate fit.</p> <p>The cancer potency that EPA might use for HCE if someone were to publish the one (of six) missing assays from the list of criteria in its document for alpha-2μ -globulin-related, aged male rat kidney tumors should be accurately presented.</p>	Recommend reevaluating the male mouse liver tumor benchmark dose modelling and insure that it is accurate and that the model presentation and selection is appropriate.	S
13	General		<p>Though EPA clearly discusses their rationale for using studies of male rat kidney cancer for determining the oral SF, we still believe that is alpha 2μ-globulin related. We agree with those external peer reviewers (top of page A-2 and A-14) that stated that the kidney cancer observed in male rats is alpha 2μ-globulin-related and therefore not relevant to human carcinogenicity. In 1991, EPA's alpha-2u-globulin analysis marked the first time that EPA deemed tumors in animals not relevant for carcinogenicity in humans. In 1997 after EPA's decision, ATSDR concluded (in its <i>Toxicological Profile for Hexachloroethane</i>), "These tumors are considered to be unique to male rats and are not-indicative of tumorigenic potential in other species because they were associated with hyaline droplet nephropathy." This conclusion is found on a fact sheet on EPA's Superfund web site (http://www.epa.gov/osw/hazard/wastemin/minimize/factshts/hexchlet.pdf)</p> <p>On page 10 of the post-meeting comments, Dr. Lock states (bold text is original) "<i>I strongly recommend that somebody goes back to the rat</i></p>	Reconsider and revise.	S

			<p><i>NTP 90 day study and confirms or refutes an increase in this protein using immuno-cytochemistry in the kidneys of male rats. ...I attach a recent review I wrote in collaboration with Dr Gordon Hard on this issue; current thinking supported by studies confirms that chemicals can exacerbate the progression of chronic progressive nephropathy in both male and female rat kidneys.</i> His review confirms the general acceptability of our position.</p>		
14	Table 4-19. Oral toxicity studies for HCE	58	<p>It is unfortunate that again the data for the key study needed to be corrected after the external peer review. Given the time taken for the preparation of these documents and the number of internal authors and reviewers listed, we recommend that each document have at least one person who has the responsibility of quality control on the data presented in the document. To quote Dr. Kodell, <i>“There are quite a few annoying errors in the text and tables in the discussion and summarization of the toxicology data that make it difficult at times to follow the presentation.”</i> See also the DoD comment on the male mouse liver tumor benchmark dose modelling.</p>	<p>EPA should perform <u>a quality review of the document before it is presented for interagency review</u>. While we and other reviewers have found some of the mathematical errors or inconsistencies between text and tables, our short review time does not allow us to perform a complete quality review on the entire document.</p>	E