OMB Staff Working Comments on EPA's Toxicological Review of Formaldehyde Inhalation Toxicity [dated March 17, 2010] and Draft Charge to External Reviewers

April 27, 2010

General Science Comments:

- Throughout section 4, the hazard characterization, EPA takes the approach, particularly in sections 4.1 and 4.2, of setting up each section, focused on a specific endpoint, with an overall summary followed by the details of each study evaluated. In many cases, EPA provides a concluding summary, similar to the overall summary in the beginning of the subsection. The overall summary appears to present the weight of evidence conclusions regarding the endpoints. It would be useful if EPA were to clarify for readers the parameters EPA used to reach their weight of evidence conclusions for each endpoint. Specifically, it would be helpful for EPA to:
    - Provide an overall perspective on how negative results were considered as well as how determinations of clinical and statistical significance were made.
    - Provide in the opening of Section 4 a discussion of the parameters and framework EPA used to reach their overall conclusions regarding formaldehyde's impact on individual endpoints.
    - Provide in the overall summaries the citations of the specific studies EPA relied on to reach the conclusion as well as information regarding the level at which EPA concludes that clinically significant effects and/or statistically significant effects have been documented. This information is provided in some subsections, but not all.
    - Provide for each of the endpoint discussions in section 4.1, a table that describes the studies discussed, presents information on exposure levels and levels at which effects of interest were seen, their statistical significance, and perhaps includes information on the key strengths and limitations of each study. Seeing the information presented this way may be helpful in understanding how EPA reached their overall conclusion regarding formaldehyde's impact on the endpoint. This would be particularly helpful for endpoints for which EPA developed candidate RfCs. Presenting such a table in section 4.4 would also be very helpful to readers as this is where EPA once again synthesizes the major conclusions regarding noncancer impacts.
    - Provide information regarding whether or not the critical effect is considered to be adverse or perhaps a precursor to an adverse effect. Whether or not the endpoint is reversible upon cessation of exposure should also be helpful information. EPA may also want to consider a charge question to expert reviewers asking them to comment on the specific non-cancer endpoints EPA has chosen and if reviewers agree with EPA's characterization of their health significance.

- We applaud EPA for making chapter 5.1 so easy to read. The flow, the writing, and the presentation of information made the section very accessible. We are very supportive of EPA's approach to so clearly present many alternative derivations and candidate RfC values. [minor point: we note that when a non-color printer is used, the text boxes showing the alternate RfC derivations are a bit hard to read. EPA may want to consider a background that does not have a pattern in it.]

- In the discussion of cancer slope factor derivations, EPA provides a 'reality check' type of discussion where a calculation of crude incidence rates that would be expected from the proposed risk values are compared to current incidence rates. This discussion is very informative and useful.

As we saw at the recent SAB review examining how EPA implemented the 2007 SAB Arsenic panel recommendations, this is exactly the type of evaluation expert reviewers were seeking. It would be very useful to have a similar type of 'reality check' discussion in section 5.1.4, or elsewhere, in regards to the RfC derivations. EPA is proposing candidate values in the range of 4-9ppb. From Section 2 of the draft toxicological review we know that levels in homes average from 17-33 ppb (see Salthammer study cited in Section 2) under normal living conditions indoors. Similarly, as per Figure 2-3 and Table 2-2, mean outdoor levels range from about 2.5 to 8ppb. As typical outdoor levels are about equal to the proposed RfC values and the typical indoor levels are about four times greater, one could ask whether or not we are seeing the effects described in the candidate RfC studies, in particular are we seeing the effects predicted in the Rumchev, Garrett and Krzyzanowksi studies? And are we seeing the eye irritation in indoor environments that is predicted by the three studies evaluating this endpoint. This type of reality check is worth exploring and it might help to inform the discussion to ask public commenters and expert reviewers to weigh in on this discussion. Discussion of other ambient or background exposures that may cause these same effects could also be part of the dialogue.

  - In addition we note that other federal, state and government agencies have also proposed or finalized non cancer exposure values for formaldehyde. For example, in addition to the ATSDR chronic MRL at 8ppb, Health Canada in 2005 proposed a guideline of 40ppb to protect against both noncancer and negligible cancer risk (http://www.hc-sc.gc.ca/ewh-semt/pubs/air/formaldehyde-eng.php), CalEPA suggested an acute value of 27ppb (http://www.arb.ca.gov/research/indoor/formaldGL08-04.pdf), WHO suggested a value of 83pppb (http://www.inchem.org/documents/ehc/ehc/ehc89.htm#PartNumber:10) and the state of Wisconsin set a value at 100ppb for irritant effects, although they noted that sensitive individuals may see effects at lower levels (http://www.dhfs.state.wi.us/eh/Air/pdf/Frmldhyde.pdf). It may be helpful, perhaps in an appendix, to provide a summary of these other values and discuss how the EPA proposed RfC's are similar and different to the approaches that other agencies have suggested. This type of discussion may be very informative for public commenters and peer reviewers who may be grappling with how to handle risk levels that are in the same range as background exposure levels.

- In section 5.2 EPA states that "the weight of evidence suggests that formaldehyde carcinogenicity can be attributed, at least in part, to a mutagenic MOA" and thus EPA uses only linear low dose extrapolation. EPA refers readers to the EPA cancer guidelines to support this approach. We note that the EPA cancer guidelines also state: "Nonlinear approaches generally should not be used in cases where the mode of action has not been ascertained. Where alternative approaches with significant biological support are available for the same tumor response and no scientific consensus favors a single approach, an assessment may present results based on more than one approach." As the mode of action section clearly describes an integrated mode of action where multiple key events may be acting (see 4-446, and page 6-21, lines 11-13), and Section 4.5.3 clearly and transparently lays out multiple plausible modes of action with significant biological support, it would be helpful for EPA to present alternative approaches to linear modeling for the tumor endpoints, informed by the alternate plausible modes of action discussed in Section 4.5.3. Even if presented only as a sensitivity analysis, by which to compare the results of the linear extrapolation, this information would be useful and informative. In addition, if the peer reviewers have concerns about EPA's MOA conclusion, or would like to be informed by evaluating the results of a non-linear modeling

approach, having the alternative cancer quantification derivations available for consideration will also speed the peer review process.

Specific Science Comments:

- Specific examples of where understanding how clinical significance, statistical significance, and negative findings were treated would improve public understanding of how the data were evaluated are listed below. For instance when evaluating an individual study if the confidence interval shows that the effect is not statistically significant, EPA may want to simply characterize the findings as suggestive of an association. In some cases, it may be helpful for EPA to present the confidence intervals surrounding the risk values.
    - Page 4-21/22, in discussing Fransman et al.
    - Page 4-24, line 3-6 and page 5-13, line 15-17 in discussing Tavernier et al 2006
    - Page 4-25, in discussing Rumchev 2002
    - Page 4-49, line 18-25
    - Page 4-56 line 18-20, in the context of Page 4-50, line 28-29
    - Page 5-7, line 20-22
    - Page 5-11, line 10-11
    - Page 5-61, lines 18-21
    - Page 4-76, line 26
    - Page 4-88, line 29-30
    - Page 4-92, line 3 and line 5
    - Page 4-92, line 21
    - Page 4-93, line 15
    - Page 4-421, line 13
    - Page 4-15, in discussing Herbert et al 1994
- Specific examples where EPA may want to characterize which studies in particular where relied upon to reach the conclusion:
    - Page 4-36, line 14
    - Page 4-42, line 12
    - Page 4-45, line 18-19
    - Page 4-68, line 27
    - Page 4-70, line 26
    - Page 4-83, line 14
    - Page 4-417, line 23-32
    - Page 4-419, line 16
    - Page 4-390, line 24
    - Page 4-393, line 17
    - Page 4-426, line 24-34
    - Page 5-70, line 7
- Page 2-3, lines 25-31, discusses how formaldehyde is formed naturally in the atmosphere. If data are available regarding the levels of formaldehyde produced, adding this information would be helpful.
- Section 2, perhaps addition to section 2.3, the National Cancer Institute (NCI) notes (http://www.cancer.gov/cancertopics/factsheet/Risk/formaldehyde) that formaldehyde is produced in small amounts by most living organisms as part of normal metabolic processes. EPA may want to provide further details regarding the levels normally produced in the human body on a daily basis in section 2. Understanding how these levels relate to the proposed RfC levels will be helpful information and could be added to sections which provide the "reality check" type discussion in section 6. Section 3.1.2.1 discusses this a bit and provides background levels for methanol, but not formaldehyde levels. In section 3.1.2.6, EPA does provide further helpful information from the Heck and Casanova studies. These

studies suggest levels around 2.5 ug/g in blood, giving an average of 2.5 ppm (2.5 mg/L). Using Hillman (1984) as discussed on page 3-8, EPA derives a value of 210-810 ug as an endogenous level in humans. Section 3.5.2 discusses levels in exhaled human breath (mean about 4.3ppb in Moser 2005) in subjects breathing ambient air. Are there data available that would allow EPA to put the proposed RfC exposure levels (4-9ppb in air) and proposed cancer risk levels in a context that could compare the internal dose to the endogenous levels in humans? It may also be helpful to ask the expert reviewers to comment on how the production of endogenous formaldehyde in the body should be considered as EPA proposes an RfC and cancer risk values.

- Page 2-4, line 1-3, in discussing atmospheric residence time, EPA provides a value which assumes no reaction with hydroperoxyl radicals. It may be helpful to describe how this assumption relates to typical atmospheric condition.

- Page 3-53, line35, it may be helpful to clarify EPA's conclusion here. The text seems to be saying that although the extent of mechanistic data available is more than most cases, EPA is still concerned that using rat and monkey data to inform allometric scaling to humans is still weak. Is this the correct interpretation? It may also be helpful to clarify what EPA means by "the empirical strength of a power law…".

- Page 4-1, line 27-35. (note: for most comments made on Section 4, any conforming changes should also be considered for Section 6)
  - Line 27, it may be helpful to provide the level at which direct sensory responses are seen. Citations to the particular critical studies EPA is relying upon may also be helpful.
  - Line 31, it may be helpful for EPA to provide the levels at which irritations are seen after acute and chronic exposures.
  - Line 33, please provide citation for this statement regarding lifelong health effects from short-term or transient exposures.
  - Page 4-2, line 1-10, discusses conclusions from Doty, 2004. However a more thorough description of this study, including doses evaluated, does not appear to be provided in the subsections of 4.1.1.1.

- Page 4-3, line 4-17, EPA states that a clear dose response was seen in residential occupants, in the Ritchie and Lehnen (1987) study, however it seems that smokers also reported similar effects. EPA states that confounding cannot be an alternative explanation, since the authors reported that formaldehyde was the most important explanatory variable. Can further information on the importance of smoking be provided? We note that section 5 provides a NOAEL of 50 ppb for this study. As exposures here are cited as ranging from 100-300 ppb, it is unclear how the NOAEL was determined. Perhaps more information on doses examined could be provided.

- Page 4-6, in discussing Kriebel et al 1993, can EPA say anything about whether or not the nose and throat irritation differences were statistically significant? It is not clear that they were, but considering the exposure level (730ppb), it is surprising that they would not be. Similarly this study saw no differences in asthmatics irritation levels.

- Section 4.1.1.2, discusses many endpoints including FEV, PEF, PEFR, FVC. As many studies are negative for some of these endpoints and some studies are positive for others, it may be useful to have a discussion regarding the physiological differences behind what each

of these endpoints measures and why we may expect formaldehyde to impact some of these measures of pulmonary function but not others. A table arraying the results of all the studies discussed in this section might be helpful as this endpoint (pulmonary function) is used for candidate RfC determinations.

- Page 4-45, line 22, it may be helpful to clarify which studies suggest a 'convincing relationship' as the sentence which follows clarifies that not all studies reported significant associations and line 29 refers to 'mixed results' in studies looking at congenital malformations.

- Page 4-56 lines 23-27 refer to support from studies by Gray and Wu, 2005, Hakim et al 1995, and Correa et al 1996. We could not find any discussion of these supporting studies in this section. Is it correct that the only statistically significant study in this section on developmental and reproductive is the Taskinen et al 1999 study? More discussion on how EPA derived their overall weight of evidence conclusion regarding this endpoint may be helpful.

- Page 4-56/ 4-57, section 4.1.1.9, for a summary section, this write-up could be more detailed. For each of the summary sentences it would be helpful to cite the specific studies that lead EPA to their overall summary regarding the specific non-cancer endpoints evaluated. Similarly, for each sentence where it appears that EPA's support is coming from specific studies, it would be most helpful to clarify for readers and reviewers which studies these are. Perhaps a summary table for the non-cancer effects would be most helpful, this way EPA could also array the exposure levels associated with each of the associations.

- Page 4-57, section 4.1.2.1.1, in discussing NPC (nasopharyngeal cancer), EPA mentions that it is rare and may be associated with EBV and other risk factors. When we look at http://www.cancer.gov/cancertopics/pdq/treatment/nasopharyngeal/Patient, there seems to be a focus on two risk factors only: "ethnic background and exposure to the Epstein-Barr virus can affect the risk of developing nasopharyngeal cancer." The cite then refers to Chinese or Asian ancestry. It may be helpful to have some summary discussion regarding how the critical studies considered these two main risk factors. If this is not addressed in any of the studies, it may be helpful to discuss the implications of this and how it relates to (or perhaps has no impact on) findings from the epidemiological literature.

- Page 4-59, table 4-1, this table is extremely helpful, in particular because it shows the confidence intervals around the risk values. Would there be a way to easily add the exposure levels at which the effects were seen? In many cases, the 95% confidence interval includes a range of 1.0 and thus the findings are not technically statistical significant, though we understand that multiple findings that are close to statistically significant may still carry some weight-of-evidence value. In other cases, EPA simply says NS, instead of providing the 95% confidence interval. It is not clear why the confidence range is provided sometimes but not all the time. We would suggest providing the detailed information whenever it is available, regardless of whether or not the result was statistically significant. (similar comment for table 4-4 where some of the confidence interval ranges are not provided)

- Page 4-67, EPA has a good discussion around Marsh 2007a and the impact of silversmithing as an artifactual confounder. It may be helpful to have a specific charge question asking the expert panel to comment on this as it appears to be a controversial aspect of the analysis and likely plays a role in the weight of evidence determination regarding NPC and formaldehyde.

It may also be helpful to add this study and its revised OR's to table 4-1. Similarly, it may be helpful to add and discuss Marsh and Youk 2005 as well as the other Marsh analyses. It is not clear why all the studies are not presented in table 4-1.

- Page 4-68, line 32-35, EPA refers to the theoretical possibility of coexposures at the plant as confounders, however the study itself seems to refer to other non-occupational exposures. What evaluation is EPA referring to regarding coexposures at the plant?

- Page 4-69, line16-23, refers to Hayes 1990 and other supporting evidence. The Hayes study is presented in the table but is not discussed elsewhere. Does EPA have data regarding the confidence intervals around the PMR estimate? Further discussion may help readers to understand how this study and the Hansen and Olsen, 1995 study provide modest support. An expanded discussion regarding which statistics EPA is relying upon and what parameters were used to inform the weight of evidence conclusion regarding the associations may be helpful.

- Page 4-83, line 26-28, EPA refers to the Hildesheim study. It may be helpful to provide further detail on the exposure response relationship that was seen. The only finding of statistical significance was when people were classified as 'ever exposed' but when the groups were broken into duration of exposure, the results were not statistically significant.

- Page 4-366, for the human studies discussed in 4.3.4.2.2, it may be helpful for EPA to clarify which studies took into account differences in smoking habits between the control and exposed cohorts.

- Page 4-378, line 13, in discussing Ritchie and Lehnen 1987, EPA refers to a LOAEL of 200 ppb. Should this also mention the NOAEL (50ppb) EPA presents in table 5-6?

- Page 4-378, EPA is proposing a possible MOA related to stimulation of the trigeminal nerve. As sensory irritation is used to derive the candidate RfCs, EPA may want to consider a charge question for the expert reviewers regarding plausible modes of action.

- Page 4-381, line 27-29, as EPA discusses how many of the studies examining pulmonary function show only slight deficits or are transient and did not show statistical significance, it is unclear why EPA finds pulmonary function alterations to be an "important symptom often associated with formaldehyde exposure". More discussion of this finding might be useful. In the MOA discussion which follows, EPA may want to provide some citations and may want to consider a charge question as this endpoint is also used for candidate RfC development.

- Page 4-391, in discussing behavioral effects and human data EPA seems to suggest that the human data provide support for the animal data. It may be helpful to clarify what studies EPA is basing this on.

- Page 4-393, line 28-30, EPA seems to be implying that because the co-exposures in each occupational study were different, these should not negate the findings linking the associations to formaldehyde exposure. Is this what is intended? If so, it is not clear that this conclusion necessarily follows. Plausibly confounding co-exposures would be an issue of concern even if the specific substances were different in different studies, wouldn't they?

- Page 4-401, as the discussion of MOA for developmental and reproductive effects ranges from possible endocrine effects to genotoxicity of the gametes, EPA may want to consider a

specific charge question taking comment on the MOA determinations for this endpoint and other endpoints which are used for RfC and cancer slope determinations.

- Page 402, section 4.4.9.8, as part of the data gaps discussion, EPA may want to include discussion of the data gap related to the lack of information to inform the MOA.

- Page 4-430, lines 2-7, in discussing MOA can EPA provide more information regarding the dose levels at which regenerative cell proliferation and clastogenic effects are seen?

- Page 5-2, line 7, EPA lists the identified effect categories. It may be helpful for EPA to explain how these categories were chosen from all the non-cancer endpoints identified in Section 4. It may also be helpful to have a discussion regarding how strong the weight of evidence is for effects in each category and the general level at which formaldehyde exposure is statistically related to each of these effects. A summary table might be very helpful here. This weight of evidence determination could include discussion of the mode of action and how the available information increases or decreases the likelihood of these effects being related to formaldehyde exposure.

- Page 5-5, line 6-18, it appears that for sensory irritation the effect is eye irritation (as per line 13). It would be helpful for EPA to replace "sensory irritation" with "eye irritation" moving forward in the rest of the document and in summaries as this is a more specific descriptor.

- Page 5-6, line 7, refers readers to table 5-1 to see the candidate RfC studies for the URT pathology endpoint. This table appears to be missing as table 5-1 shows POD's for nervous system toxicity only. It would be helpful for EPA to add this table to help readers understand the weight of evidence, including an array of studies considered for quantifying an RfC for this endpoint. Similarly, it would be very useful to have a table describing the studies considered for the endpoint of pulmonary function effects. It would also be helpful if these tables included information on whether or not the effects found were statistically significant.

- Page 5-9, line 17-35, in discussing the choice of the Kryzanowski et al study, it may be helpful to have some discussion regarding the lack of linearity in the adult results and what this may mean for mode of action. Some discussion of this, and discussion of whether or not PEFR measurements are related to adverse effects or are measurements of a precursor to an adverse effect would be helpful. It may also be helpful to discuss whether or not changes to this measurement are expected to be reversible upon cessation of exposure. It may be helpful to ensure that there are some clinical pulmonologists on the expert panel to help comment on the use of this endpoint as a candidate RfC.

- Page 5-10, line 30-33, refers to NOAEL and LOAEL values from the Rumchev and Garrett studies. However in Section 4, how EPA determined these values was never described, the values are simply stated in summary sentences. It may be helpful to add this information to both sections. For the Rumchev study, page 4-25 states that effects in asthmatics were statistically significant at exposures > 48 ppb. Was 30ppb the next lower exposure group? Was it the average of a range of exposures? When discussing the Garrett study, page 4-24, it is not clear whether or not the effects seen were statistically significant as the text states that the odds ratios did not remain statistically significant after controlling for parental allergy and asthma. More clarity on the details of these candidate RfC studies would be helpful to readers and reviewers.

- Page 5-22, line 1, in discussing Bach, EPA discusses the inability to perform BMD modeling. This discussion is very informative, and in discussing the other candidate RfC values, it would be helpful to have a similar discussion.

- Page 5-30, line 3-8, in discussing the FDR for the candidate RfC, EPA indicates that the findings in the highest exposure group were not statistically significant. It is not clear how this was considered in determining if this exposure group should be treated as a LOAEL or NOAEL. More clarity regarding this discussion would be helpful.

- Page 5-35, lines 3-17, for sensory irritation (eye irritation), EPA selects three studies as candidate studies. As EPA was able to conduct BMD modeling on only the Hanrahan et al study, and EPA has always stated that BMD modeling is preferred to a NOAEL/LOAEL approach, it is not clear why EPA isn't showing a preference for the Hanrahan et al study. We suggest that EPA propose using this study alone, based on the robustness of the available data in that it allows for BMD modeling, as a candidate RfD in addition to approaches which average or present a range of findings. Similarly, for the studies which look at the respiratory effects endpoint (as per table 5-6), only the Krzyankowski study used a BMD approach. It would be helpful for EPA to specifically ask reviewers to comment on the proposed approaches.

- Page 5-36, in table 5-4, it is unclear how EPA determined that the NOAEL for the Ritchie and Lehnen study was 50 ppb. Similarly, for other studies that present a NOAEL, it is difficult to determine from previous text how these values were derived. More clarity on this, as well as a clear presentation of BMD modeling results for endpoints which rely on the BMD approach would be helpful.

- Page 5-39, lines 25-30, in discussing the narrowed list of best studies evaluated, it would be useful for EPA to include discussion of whether or not these effects are considered adverse and also irreversible.

- Page 5-40, in discussing the ATS statements regarding pulmonary function tests, it may be helpful to note whether or not ATS specifically mentions PEFR measurements.

- Page 5-41, in discussing Krzyzanowki, the details of the BMD modeling (including discussion of model fit) should be provided as is typically done in these sections of the toxicological reviews. EPA may also want to consider a charge question which takes comment on the details of the BMD modeling approach for the cases where it is used.

- Page 5-44, in determining the Rumchev NOAEL, from figure 5-5, it appears that the 50-59 ug/m^3 exposure group was the NOAEL. EPA describes this in text as being 30-49 ug/m^3. Please clarify which is correct as this impacts the NOAEL value. From the figure, it appears that the value should be 55 ug/m^3 (46 ppb rather than 33 ppb). In addition, on page 5-45, as EPA states that it is unclear whether a study of children under 3 yrs of age is adequate and thus is unclear as to whether or not the subchronic to chronic 3x uncertainty factor (UF) is needed, EPA may want to present a derivation without the UF as another alternate derivation. This could results in a candidate RfC equal to the NOAEL (46 or 33 ppb). EPA may want to also ask the expert panel to comment specifically on the appropriateness of such a derivation.

- Page 5-50, in describing Garrett, EPA states it is unknown whether the findings in the low-exposure group are comparable to the responses that would be observed in an unexposed population. It would seem that this argument is relevant to whether or not an UF for human

variability is needed. It would also be helpful for EPA to explain why this group is treated as a LOAEL rather than NOAEL, given that it did not show statistically significant effects. In addition, EPA may want to present the derivation using the low exposure group as a NOAEL, thus not applying an UF for LOAEL to NOAEL extrapolation, as an alternate derivation and take comment on it.

- Page 5-56, for the eye irritation studies, EPA may want to explicitly take comment on their determination of the POD for each of these studies as some decisions appear to be based on professional judgment, rather than explicit data. In addition, this section should provide the modeling details for the Hanrahan BMCL calculation.

- Page 5-62, line 21, states "It is preferable that the critical effect be the most sensitive of the effects which is well supported by the given study." We assume this means that once the critical (most sensitive) effect is identified, a weight of evidence evaluation of the entire database regarding exposure levels at which the effect is seen should be considered, not just the study with the lowest value. It would be helpful for EPA to clarify this point. Page 5-65, line 5, more clarity on why the mid-exposure level was considered the NOAEL in the Taskinen study would be helpful. Perhaps EPA can provide a table describing dose levels and effects, including statistical significance.

- Page 5-74, in discussing the POD determination, EPA may want to include discussion of how BMD modeling is typically preferred by the agency.

- Page 5-82, line 23-24, EPA refers to the "preferred estimated" as being $1.1x\ 10^{-2}$ for NPC. It is unclear what is meant by "preferred". Isn't this the plausible upper bound value? As EPA is using human data, it may be helpful to also clearly provide central or 'best estimates' for the cancer risk values as well, particularly since these are often needed for regulatory impact assessments associated with regulatory determinations. Similar presentation would be helpful for all tumor types and for the combined cancer incidence and risk estimate values.

- Page 5-83, EPA provides a very helpful discussion which compares the unit risk estimate to actual case numbers. In one case, EPA assumes 20ppb exposure (a value within the range of human indoor exposures, but not a necessarily a high-end exposure value) and estimates 880 cases of NPC per year. Is this plausible, since it represents just over 40% of estimated NPC cases? It would be useful to see how the levels would compare if EPA used the best estimate cancer risk value, rather than the upper bound risk value. A similar discussion would be useful on page 5-95, where EPA calculates that a 20 ppb exposure results in about 16% of all Hodgkin lymphomas per year. EPA may want to specifically ask the expert reviewers to comment on the comparative analyses provided and their implications for derived risk values.

- Page 5-95, footnote 12, EPA presents values using the ADAF calculations and estimates that if EPA were to assume lifetime exposure, a 20ppb exposure would account for about 27% of incident Hodgkin lymphomas per year. We suggest EPA have a charge question regarding whether or not the ADAF should be applied to formaldehyde, and if this application, based on the MOA discussions, should perhaps be dependent on exposure levels. In addition, EPA should ask reviewers to comment on whether it would be appropriate to apply this factor to all tumors or perhaps just specific cancer endpoints.

- Section 5.4.4, as the ADAF guidance recommends that information specific to the exposure scenarios of concern be used in the evaluations, we recommend that EPA refer readers to the guidance for examples on how to apply the factors, rather than creating a full life time exposure value in this assessment. If the life-time exposure value is retained, EPA should remind risk managers to apply case specific exposure values that are appropriate to the particular risk management scenario under consideration.

- Page 5-137, line18, it is unclear why EPA considers the impacts of the partial risk to be negligible. As there seem to be questions about whether or not the factors should be applied to Hodgkin lymphoma and leukemia values, EPA may want to consider a specific charge question asking the expert reviewers to comment on this as well as EPA's determination that the ADAF's should be applied to all cancer endpoints.

Editorial Comments (with Scientific Impacts):

- In addition to the list of abbreviations and acronyms it may be helpful to define each acronym and abbreviation in the text of the document the first time it is used. We also note that some acronyms are not defined in the preface list (eg FA, SI).

- Page1-2, line 20-21, EPA states that relevant literature was reviewed through April 2009, but some critical literature after this date has been considered. As some 2010 literature, and late 2009 literature is cited, it may be helpful to explain the process EPA used to determine which studies were considered "critical literature" for inclusion.

- Page 2-3, line 3-6, EPA lists consumer products that formaldehyde is used in. It may be helpful to clarify whether it may be in some brands of some of these products or whether it is known to be in all of these products, regardless of brand/source. Currently the language says " is present in", which leads readers to assume it is in all of these products regardless of brand/source. Clarification on page 2-11 will also be helpful.

- Page 2-7, cites NLM 2001. We could not find this citation in the references

- Page 2-10, EPA discusses mobile homes and trailers. EPA may want to clarify for readers if these are the same types of units or are different. Are all trailers considered mobile homes? It is our understanding that HUD regulates mobile homes but not trailers, so the distinction may be important.

- Page 3-29, table 3-5, please clarify units in the table.

- Page 3-26, line 22, was the omission truly 'explicit'?

- Page 3-51, line 4-6, in discussing Conolly 2000, EPA mentions possible errors in the paper. As Connolly now works within EPA, perhaps he could be asked directly about the issue and it can be clarified in the document.

- Page 4-12, line 1-2, please provide citation for this statement.

- Page 4-12, in describing ATS 2000 (cited in references as ATC 2000) it may be helpful to put the ATS statement in quotations. Also, while this is an important part of a discussion regarding what constitutes an adverse effect, perhaps it belongs elsewhere in the document where there is a broader discussion of this topic. It is unclear why this discussion is in the

section describing eye, nose, and throat irritation as the specific example given discusses lung function.

- Page 4-15, in discussing, Holness & Nethercott, 1989, and Horvath et al 1988, it may be helpful to provide information on exposure levels.

- Page 4-20, line 3, EPA describes the Stenton and Hendrick study as reporting on formaldehyde and asthma. However Figure 4-1 from the same study states that the exposure was to formalin.

- Page 4-25, line 33-35, please provide citations for this statement. Similarly on page 4-26, line 1-2, it may be helpful to specifically cite the studies EPA found to be limited.

- Page 4-26, in section 4.1.1.4, EPA begins to apply NOAEL and LOAEL values, where possible, to specific studies described. This is very helpful. EPA may want to consider doing this in the earlier sections of 4.1.1 (4.1.1.1, 4.1.1.2, and 4.1.1.3).

- Page 4-26, line 5-7, please provide citations for this statement. On line 13 in describing protective and defensive mechanisms, it may be useful to provide information on the levels of exposure that are expected to cause these responses.

- Page 4-28, line 23 and 25 (and elsewhere throughout the section), it may be helpful to clarify that the LOAEL is for increased eosinophils (rather than simply stating 'nasal histopathology'). Line 29- please define SI.

- Page 4-28, section 4.1.1.4.2, EPA refers to this section as mucociliary clearance, however many of the studies did not examine clearance, but instead examined mucociliary activity. (eg Holmstrom and Wilhelmsson). EPA may want to discuss the relationship between activity and clearance or perhaps clarify exactly what was examined throughout the document.

- Page 4-29, line 17, the sentence begins 'thus' however it is not clear what previously discussed studies reported epithelial lesions. Do you mean to refer to mild nasal swelling? On line 27, it may be helpful to clarify why the Holmstrom and Wilhelmsson study is the most robust. Describing how total exposure was carefully calculated and averaged may be helpful (line 31).

- Page 4-30, line 16, EPA refers to studies in section 4.1.1.2 which showed exacerbation of asthma. It may be helpful to specifically cite the studies EPA is referring to.

- Page 4-30, line 31, suggest replacing "diverse studies" with "three studies"

- Page 4-31, line 29, please clarify that the studies reported on the incidence of self reported chronic bronchitis.

- Page 4-31, line34, is the citation to Ohtani 2004 correct? We note that this was an *in vitro* experiment using human cells. Thus it is not clear that systemic effects were examined.

- Page 4-32, line 1, please clarify that the associations with formaldehyde exposure in Erdei et al, were likely due to a mix of air pollutants, including formaldehyde (as per line 26-27). It

may also be helpful to clarify in this summary sentence, on line 1, that the children were immunologically compromised (as per line 11).

- Page 4-34, line16, it may be helpful to clarify how EPA, or study authors, defined "formaldehyde-sensitive subjects." Similarly, on page 4-37, line 20, it may be helpful to define what is meant by "formaldehyde specific IgE."

- Page 4-35, line 34, it may be helpful to explain the implications of having elevations in the "binucleated micronucleated cell rate"

- Page 4-42, line 7-9, please provide citation. For lines 26-28, please provide citation or clarify if this is a hypothesis.

- Page 4-46, line 1-2, can EPA provide the confidence intervals surrounding the relative risk values? Line 5-15, in describing Axelsson et al 1984, is there any information available regarding other exposures in the laboratories (including non-solvent exposures that may be associated with spontaneous abortions)?

- Page 4-48, line 33, EPA refers to the John et al 1994 study as also supporting an association. It may be helpful for EPA to clarify which previously discussed studies did show a relationship. Many of the previously discussed studies had confounding exposures or were not statistically significant.

- Page 4-52, line 15-18, in EPA's discussion that this negative report does not "temper the conclusion" that formaldehyde exposure has been shown to increase the risk of spontaneous abortion, it may be helpful for EPA to clarify the dose levels at which the increased risk is seen and also which studies specifically support the overall conclusion. Similar comment for line 31-34, where EPA refers to the results of this second study as not appearing to be "exculpatory of a true casual relationship." This is a section where a table arraying all the studies and their outcomes (including statistical significance) may be particularly helpful to readers.

- Page 4-54, line 12-14, it would be helpful to clarify which studies EPA is referring to as providing the collective evidence. Similarly on line 19-20, EPA may want to clarify which studies specifically looked at diminished fertility (it is unclear how EPA is defining this).

- Page 4-56, line 6-8, it may be helpful to clarify, or perhaps show in a table, those studies that cannot be dismissed in regards to showing a positive relationship with formaldehyde exposure.

- Page 4-68, line 8-10. It is unclear why EPA is citing IARC 1995. As they updated their findings in 2006, shouldn't EPA be citing the most recent review?

- Page 4-69, line 2, please provide a citation for the analysis regarding particulates.

- Page 4-69, line 4-8, EPA may want to soften these sentences or provide citations to support the arguments. Does the medical literature provide no basis for the supposition or is the medical literature silent on any possible association? Similarly, if there are data regarding how common the activity is in Wallingford, please cite these data. A charge question on this may be helpful.

- Page 4-83, line 15, EPA may want to replace "in some studies" with "in one study". Additionally, when EPA states that some studies have "suggested a dose-response" it would be helpful to clarify what "suggested" means in this context.

- Page 4-84, line 26, it may be helpful to specifically cite the studies from table 4-4 that EPA finds to show support for an increased risk.

- Page 4-89, line 35, it may be helpful to show the confidence intervals surrounding these SMR values. We could not find all this information in Table 4-4. Similar comment for page 4-90, line 22-23.

- Page 4-91, line 11, suggest deleting "representing the formaldehyde industry", unless this is relevant to the discussion and EPA provides similar information for all commenters. On line 14, EPA may want to provide a specific cite to the discussions that are referred to. In addition, as the assignment of peak exposures in the Hauptmann 2003 study appears to be an area of disagreement, perhaps a charge question specifically addressing this would be helpful.

- Page 4-97, line 1-35, please provide citations for the discussion here regarding mode of action. EPA may also want to consider moving this discussion to the section of the toxicological review which discusses mode of action and biological plausibility. Please also provide citations on page 4-109, lines 19-24.

- Page 4-368, line 7-11, it may be helpful to provide information on the formaldehyde exposure levels in these studies.

- Page 4-386, line 1, please clarify the 2009 citation

- Page 4-386, line 5-14, EPA's policy guidance suggests a case by case consideration of genomics data in the weight of evidence determinations. Is it true that genomic data may only be applied to discussion of MOA.

- Page 4-387, line 15-17, EPA may want to clarify the exposure.

- Page 4-388, line 1, it may be helpful for EPA to clarify exactly what changes they consider to be adverse effects

- Page 4-388, line 14, suggest replacing "these data indicate" with "these data suggest".

- Page 4-388, line 23, EPA may want to clarify exactly which "omics" changes are being referred to here.

- Page 4-390, line 32, instead of saying "exquisitely sensitive", it would be helpful to provide the specific exposure level at which effects are seen.

- Page 4-393, section 4.4.8.5 provides a very brief discussion of data gaps. Is this intended to be the full discussion of data gaps for all non-cancer effects? We don't recall seeing this discussion in other sections of the non-cancer discussion. A broader discussion of non-cancer endpoint data gaps would be helpful.

- Page 4-394, line 9, is it appropriate to imply that FDR (fecundability density ratio) is a measure of "risk of pregnancy loss"? Is it possible that FDR also measures inability to conceive? Page 4-395, line 3, refers to the study as a finding of reduced fertility and increased risk of spontaneous abortion. It may be helpful to clarify exactly what the FDR is a surrogate for.

- Page 4-410, line 1-3, can a citation be provided?

- Page 4-412, table 4-90. It is unclear why some risk values are bolded and others are not.

- Page 4-424, table 4-94, EPA may want to provide information on statistical significance in the results column.

- Page 4-434, line 7, it may be helpful for EPA to define what is meant by "level 3"and "level 2"

- Page 5-8, line 5, "chrinic" should be "chronic"

- Page 5-25, line 30 (and elsewhere in section 5), EPA states "where adversity is characterized as per EPA risk assessment guidelines". Although a citation is provided, it would be helpful for EPA to provide a footnote describing how these guidelines define adversity. Page 5-31, table 5-3, it may be helpful to provide information in the table regarding whether or not the effects seen in each study were statistically significant.

- Page 5-36, table 5-4, it may be helpful to provide information in the table regarding whether or not the effects seen in each candidate study were statistically significant.

- Page 5-39, section 5.1.1.2.2, thus far the document has had a consistent flow in the order by which non-cancer effects are discussed. It may be helpful to simply reorganize this so that the studies are presented consistent with the order provided in the summary on page 5-39, line 26-29.

- Page 5-70, for the general discussion of other endpoints not considered, it may be most helpful to have a summary table comparing the PODs from some of the studies EPA considers to be key studies for the candidate PODs and RfC values.

- Page 5-101, line 11 and 24, please clarify what is meant by a "reasonable estimate". Aren't these upper bound estimates?

- Page 5-138, line 1-19, as per comments above, suggest deletion of this text. Similar deletion is suggested for page 6-42, line 19-21 and in section 6.2.2.8 (page 6-45 and 6-46).

- Chapter 6 as per discussion on Page I-xxxii, in 6.2.1.5 EPA should include a clear discussion of EPA's confidence in the candidate RfC values, and a confidence descriptor (eg high, low, medium) as EPA typically does for RfC and RfD values. Taking into account typical background exposures, expert reviewers could be asked to comment on EPA's determination of their confidence in the overall values.

Comments on the Draft Charge:

(Note: some suggestions for charge questions are provided in comments in the above sections and have not been reiterated here but should be considered as equally important .)

General Comments:

- EPA's charge asks the panel to consider, among other things, "theory and experience". It may be helpful to also emphasize the value of having the committee provide, when possible, peer reviewed citations to support their findings.

- It may be helpful to broaden the charge to also take comment on EPA's conclusion regarding the following topics:
  - findings regarding metabolism
  - conclusions regarding the potential modes of action for each non-cancer and cancer endpoint discussed
  - conclusions regarding the weight of evidence supporting the findings related to formaldehyde exposures and each non-cancer endpoint.
  - conclusions regarding susceptible populations and the ALDH2 and ALDH3 polymorphism and how EPA might use this information
  - conclusions regarding animal data which support the cancer MOA (in particular the Soffriti studies)
  - EPA's evaluation of the rodent modeling relating to toxicokinetics, dosimetry modeling and the evaluation of dose response models of DPX, cell replication and genomics data, and BBDR models for risk estimations using animal models
  - EPA's decision to rely upon the re-implemented Subramanian 2007 model
  - EPA's characterization and presentation of the information related to the uncertainty in the non-cancer and cancer estimates
  - EPA's characterization of data gaps

- In addition, EPA may also want to ask the peer reviewers to comment on the significant of risk values that are at or below background. This may have impacts for how EPA may recommend the values be used and considered by risk managers.

- Since the development of Agency Information Quality (IQ) guidelines required by statute, many agencies have been using charge language that tracks with the standards of their own IQ guidelines. For example, such language often focuses on whether or not the information in question is accurate, clear, complete, transparently and objectively described, and scientifically justified. We believe it may be useful for EPA to follow a similar approach and incorporate some of the language from your IQ guidelines into the formulation of the charge questions. It will also be helpful for EPA to ask reviewers to comment on both the objectivity of the presentation and the objectivity of the substantive results and underlying assumptions.

Section A:

- EPA may want to consider asking the expert reviewers to specifically comment on which alternate values are most scientifically supported. The panel should be explicitly asked to comment on EPA's final recommendations, including the application of uncertainty factors for each alternate derivation.

Section B:

- EPA may want to consider charge questions which ask the NAS to comment on the conclusions related to each specific cancer endpoint.

- EPA may want to consider a charge question asking about EPA's choice to use the NCI cohort over other studies. In addition, this could include taking comment on the choice of exposure metric (peak vs cumulative), as well as the derivation of the extra risk level (EPA used 0.05% for determination of the POD for NPC and LHP).
- EPA may want to consider a question to reviewers regarding the uncertainties in the cancer derivations (for NPC, EPA states that the major uncertainty is "the appropriate model/exposure metric for extrapolation to environmental exposures") and how these uncertainties may affect the interpretation of the results and use of the results.
- EPA may want to consider a specific question regarding how EPA grouped and treated leukemia subtypes.
- EPA may want to consider a charge question regarding EPA's approach to combining cancer risks for all sites.