Formaldehyde Expert Panel Report

Part A – Peer Review of the Draft Background Document on Formaldehyde

The Report on Carcinogens (RoC) expert panel for formaldehyde exposures met at the Hilton Raleigh-Durham Airport Hotel at Research Triangle Park, North Carolina on November 2-4, 2009, to peer-review the draft background document on formaldehyde exposures and make a recommendation for listing status in the 12th Edition of the RoC.

Members of the expert panel are as follows:

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One of the charges to this panel was to determine whether the information in the draft background document on formaldehyde exposure is presented in a clear and objective manner, to identify any missing information from the body of knowledge presented in the document, and to determine the utility of the body of knowledge in the background document for drawing conclusions about the carcinogenicity of a candidate substance and for applying the RoC criteria for listing.

The expert panel discussed all of the sections of the draft background document on formaldehyde, including the adequacy and clarity of information, and offered specific proposed revisions to be made to the document. The panel voted 9 yes/0 no to accept the draft background document (with proposed changes) and that it is adequate for drawing conclusions about the carcinogenicity of formaldehyde exposure and for applying the RoC listing criteria. Following are the expert panel's proposed revisions for each section of the background document:

Section 1. Introduction

1. Section 1.2 Physical-chemical properties
   - Table 1-2 (Page 3) – Add to last row, "mg/m^3 = 1.23 ppm (assuming normal temperature)."
2. Section 1.3 Formaldehyde Polymers
   - Table 1-3 (Page 5) – Change vapor pressure of 1,3,5-trioxane from "NR" to "13.0 mm Hg at 77.0°F" and add reference in footnote NOAA 2009, [http://cameochemicals.noaa.gov/chemical/21192].

Section 2. Human Exposure

1. General comments
   - Add statement that some studies in Section 2 used personal monitoring and some used area monitoring, noting that personal exposure measurements are more relevant and, in general, would be expected to be higher than area measurements. (Use Lavoué *et al*. 2006 as a guide.)
   - The results from epidemiologic studies that presented exposure levels are in ppm making these two sections difficult to compare. Revise Section 2 to present exposure levels in ppm rather than mg/m^3 and revise the conversion factor provided at the end of Section 2.4 to reflect this (i.e., the inverse of 1.23). See revised tables in Appendix 1.
   - In some places the following statement is made: "Major sources of formaldehyde exposure for the general public have included combustion sources (both indoor and outdoor), automobile emissions, off-gassing from numerous construction and home furnishing products, off-gassing from numerous consumer goods, and cigarette smoke." Aren't automobile emissions and cigarette smoke combustion sources? Change to: "Major sources of formaldehyde exposure for the general public have included combustion sources (both indoor and outdoor)--including industrial and automobile emissions, home cooking and heating, and cigarette smoke--off-gassing from numerous construction and home furnishing products, and off-gassing from numerous consumer goods."

- There is no mention in the document of the methods used to measure formaldehyde, particularly in air. A variety of sampling and analytical techniques have been used. NIOSH notes six different analytical methods for monitoring formaldehyde air concentrations (http://www.cdc.gov/niosh/docs/2003-154/). Add a section citing the different methods used and a brief summary of how their results may compare with each other. The differences in monitoring methods influence the variability of reported formaldehyde concentrations.
  Recommended text: "It is important to note that a variety of sampling and analytical techniques have been used to estimate formaldehyde air levels, and these differences could impact the comparability of data across studies. Currently there are six methods provided for the measurement of formaldehyde in the NIOSH Manual of Analytical Methods alone: three methods for formaldehyde in air, one for aldehydes screening in air, one for organic and inorganic gases in air, and one for formaldehyde on dust. The use of different analytical methods results in differences in sensitivity and error in the measurement of formaldehyde across studies. For example, the limits of detection across the three NIOSH methods that are specific to formaldehyde in air range from 0.07 to 1.0 µg/sample. Also, due to advances in analytical methods, there are temporal differences in sensitivity and error. In some reports, the actual sampling and analytical methods have not been provided."

2. Section 2.1 Use
   - Page 13, lines 16-24 – Amend text to add information about formaldehyde releases from de Groot *et al.* 2009.
     Recommended revision for this paragraph: "Some products are not preserved with formaldehyde directly, but instead, with agents that break down and release formaldehyde under conditions of usage (de Groot *et al*. 2009, WHO 2002). The levels of decomposition and formaldehyde release depend mainly on temperature and pH (WHO 2002). de Groot *et al*. (2009) identified 42 substances that they determined, either unequivocally or with a high degree of certainty, were formaldehyde-releasers (note that this includes chemicals that release formaldehyde as a result of decomposition and chemicals synthesized from formaldehyde that may still contain residues of free formaldehyde, such as formaldehyde resins). Formaldehyde releasers that are used in cosmetics include quaternium-15, imidazolidinyl urea, diazolidinyl urea, DMDM hydantoin, and 2-bromo-2-nitropropane-1,3-diol (de Groot *et al*. 2009). Other products that often contain formaldehyde releasers are industrial and household cleaning agents, soaps, shampoos, paints, lacquers, and cutting fluids (WHO 2002). Examples of formaldehyde-releasing antimicrobial agents used in metalworking fluids are tris(*N*-hydroxyethyl) hexahydrotriazine, tris(hydroxymethyl)nitromethane and hexahydro-1,3,4, tris(2-hydroxyethyl)-*S*-triazine (de Groot, 2009, NIOSH 2001). No data were identified on formaldehyde levels resulting from formaldehyde releasers."

3. Section 2.3 Biological Indices of exposure
   - Page 16, line 26 – Add to this paragraph's description of the study by Shaham *et al.* "These findings have been questioned, however, because of the excessively high level of DPCs reported in the controls, which are an order of magnitude higher than those typically reported. Therefore, Shaham *et al.'s* findings need to be replicated in other molecular epidemiology studies (Zhang *et al*. 2010)."

4. Section 2.4 Occupational exposure
   - Page 19, lines 22-26 – Change the citation (from ATSDR to OSHA 1992, http://ehs.okstate.edu/training/OSHAFHYD.HTM) for the information that states: "OSHA (1992) estimated that about 1.9 million workers were exposed to formaldehyde at concentrations between 0.1 and 0.5 ppm [0.12 and 0.61 mg/m^3], about 123,000 at concentrations between 0.5 and 0.75 ppm [0.61 and 0.92 mg/m^3], about 84,000 at concentrations between 0.75 and 1 ppm [0.92 and 1.23 mg/m^3], and about 107,000 at concentrations greater than 1 ppm [1.23 mg/m^3]."
   - Page 20, line 10
     i. After the semi-colon, add information on dermal/ocular exposure from the IPCS, CCOHS, and ATSDR, and de Groot stating that (1) dermal exposure to solutions containing formaldehyde causes irritation, allergic contact dermatitis, and skin sensation, and (2) topically applied formaldehyde is absorbed and excreted in the urine and feces.
     ii. Finish the paragraph stating "…however, no data were found on occupational dermal exposures."
   - Page 20, lines 19-29 to page 21, lines 1-6 – Edits to study by Lavoué 2008:
     i. Page 20, line 22 – After "exposure levels," add "Due to the database design, only detected personal measurement results (n = 5,228) were analyzed with linear mixed-effect models, which explained 29% of the total variance." Delete N = 5,228 from line 20. Then add the following sentence: "This study did not include 28 measurements that were below the limit of detection."
     ii. Page 21, lines 5-6 – Delete sentence: "The authors… exposure levels." and add "Exposure levels in IMIS were marginally higher during non-programmed [non-scheduled] inspections compared with programmed [scheduled] inspections. An increasing exterior temperature tended to cause a decrease in exposure levels for cold temperatures (−5% per 5°C for T < 15°C) but caused an increase in exposure levels for warm temperatures (+15% per 5°C for T > 15°C)."
   - Tables 2-1 to 2-14. (Pages 24-57)
     i. Organize the tables so that the studies in the United States are separated from the studies from other countries (i.e., present U.S studies first in the tables). This may help readers to examine the data and find out whether a significant number of individuals in US are exposed to unacceptable levels of formaldehyde.
     ii. Explain that the number of digits in the air concentrations that are provided varies between studies. Recommended language: "knowing that there is inconsistency in the number of digits, we are reporting the exact values as given in the original articles."
5. Section 2.4.1 (Occupational exposure) Formaldehyde and formaldehyde-based resin production
   - Page 23, lines 1-4 – Make the underlined edits. "In Canada, formaldehyde production is done in a continuous closed circuit and is completely automated (IRSST 2006); however, no information was found on <u>whether</u> processes used in the United States for formaldehyde or formaldehyde-resin production <u>were open or enclosed circuit</u> or the potential for releases <u>of formaldehyde</u> to air."

6. Section 2.4.2 (Occupational exposure) Wood based products and paper production
   - Page 30, lines 7-8 – The difference in exposure between urea-formaldehyde resins (UF) and phenol-formaldehyde resins (PF), which is mentioned in parentheses, is an important point and deserves more emphasis, perhaps with some information on the times period when the transition from UF to PF occurred, if possible. Recommended text: "The extent to which these measures have been implemented in the United States is not clear, but large-scale replacement of UF by PF does not appear to have occurred over the last 30 to 40 years. The relative use of UF has remained consistently higher than that of PF since 1970 when they represented 27% and 23%, respectively, of total 37% formaldehyde consumption in the United States compared with 22% and 18%, respectively, in 2006 (Bizzari 2007)."
   - Page 30, Table 2-3 – Remove the footnote on page 31 "Cited in IARC 2006 and ATSDR 1999; data presented are from the original article, because of discrepancies between data presented in the IARC and ATSDR papers."
7. Section 2.4.5 (Occupational exposure) Production of formaldehyde-based plastic products
   - Page 41, lines 6-7 – The statement "into particle-sized pieces" has little meaning. Particles come in a wide variety of sizes. Define the sizes of these particles, whether they are inches or micrometers. Recommended text to substitute: "...into small, granular-sized particles…"
8. Section 2.5. Environmental occurrence and fate
   Provide the metric conversion for data given in pounds; 1 metric ton = 2205 pounds.
   - Page 63, lines 19-24
     i. 9.2 million pounds (*4,172 metric tons*)
     ii. 1 million pounds (*454 metric tons)*
     iii. 8.2 million pounds *(3,719 metric ton)*
     iv. 13.2 million pounds *(6,122 metric tons)*
     v. 9 million pounds (*4,082 metric tons)*
   - Page 64, lines 6-7 – 610 million pounds *(276,644 metric tons)*
   - Page 71, line 18 – Change µg/s to "µg/sec" to be consistent with the paper.
   - Page 81, lines 8-13 & line 25
     i. 278,335 pounds (*126 metric tons*)
     ii. 904,547 pounds (*410 metric tons*)
     iii. 277,083 pounds (*126 metric tons*)
     iv. 373,000 pounds (*169 metric tons*)
   - Page 84, lines 6-14
     i. 373,000 pounds (*169 metric tons*)
     ii. 1.25 million pounds (*567 metric tons*)
     iii. 205,000 pounds (*93 metric tons*)
     iv. 11.9 million pounds (*5,397 metric tons*)
     v. 5 million pounds *(2,268 metric tons*)
     vi. 13.6 million pounds (*6,168 metric tons*)

9. Section 2.7 Regulations
    - Page 91, lines 11 and 28 – The OSHA PEL and NIOSH REL should both indicate TWA for emphasis and to differentiate them from short-term limits or ceilings; they should also be presented in the mg/m^3 equivalents. Suggested revisions:
        i. Occupational Safety and Health Administration (OSHA) – "Permissible exposure limit (PEL) = 0.75 ppm [0.92 mg/m^3] (8-h TWA)."
        ii. National Institute for Occupational Safety and Health (NIOSH) – "Recommended exposure limit (REL) = 0.016 ppm [0.02 mg/m^3] (10-h TWA)."

Section 3. Human Cancer Studies

1. General comments:
    - Organization
        i. Rename Section 3.2 to "Studies of occupational populations" and Section 3.3.2 "Studies of general population samples (not limited to any specific occupation)." Move Jensen and Anderson (1982) (physicians in Denmark, Section 3.3.4.1), and the studies on the Shanghai textile workers (Wong *et al.* 2006, Section 3.3.6.8; Li *et al.* 2006, new study; and Ray *et al.* 2007, new study) to the occupational section. Move the American Cancer Society Cancer Prevention Studies (Section 3.2.5.2) to the general population section.
        ii. Move cohort study of workers at leather tanneries in the United States (Stern *et al.* 1987) to Section 3.6.2.4
    - The use of square bracket comments are often uneven or inconsistent across studies. Describe the general limitations across the body of literature (such as misclassification of exposure, and low power), and delete comments on specific studies unless there is something unique about that study that warrants a special comment.
    - Identification and selection of literature
        i. Describe the exact criteria for study identification in the introduction. Also, it is important to search for studies related to the selected studies to identify more studies on formaldehyde, and presumably more negative findings for formaldehyde since these results were not highlighted as search terms.
        ii. Page 95 – States that a study was not reviewed if formaldehyde was not an *a priori* hypothesis. However, this is impossible to know for many studies. In many of the case-control studies, for example, the investigators evaluated a long list of chemical exposures using JEMs that were designed for other purposes, and it's not stated what the *a priori* hypotheses were. Delete this criterion.
        iii. Page 95 – It would be more informative to separate out the citations for the excluded studies to immediately follow each of the reasons for exclusion from the review (so the citations are separated according to the reason for exclusion) – See Table 1.
    - The study by Chen *et al.* 2008 (Section 3.3.4.5) of persons exposed to the smoke from mosquito coils, and the study by McDuffie *et al.* 2001 (Section 3.3.5.5) of persons exposed to formaldehyde-containing fungicides should not be included since there is no independent evaluation of formaldehyde and there are major potential confounders that are exactly correlated with the exposure of interest.

Add these studies to the exclusion list and list as the reason for exclusion: "exposure to complex mixture containing formaldehyde, and thus the effects specific for formaldehyde cannot be evaluated."

- Delete the study of Pesch *et al.* 2008 (Section 3.3.1.7) Add to excluded studies table. (The study design is inappropriate for making inferences for the effects of formaldehyde.)
- Meta-analyses: list studies that are included in the meta-analyses.
- Add a description of the following studies: Bertazz*i et al.* 1989, Blair *et al.* 1993, De Stefani *et al.* 2005, Li *et al.* 2006, Shangina *et al.* 2006, Ray *et al.* 2007, Richardson *et al.* 2008, Bachand *et al.* 2009, Hauptmann *et al.* 2009, and Elci and Akpinar-Elci 2009.

2. Introduction
   - Page 95, line 2 – Delete "body of."
   - Page 95, line 3 – Delete "and other descriptive studies are less informative for evaluating causality and therefore." Revised sentence reads "Case reports are excluded from this review."
   - Page 95, lines 7-8 – Revise "because the evaluation of formaldehyde exposure was not designed to be an *a priori* study hypothesis." Evaluation of an exposure is not a hypothesis.
   - Page 95, line 18 – "Other miscellaneous occupations" is not an industry.
   - Page 95, line 27 – Revise "numerous reviews with conflicting reviews…"
3. Section 3.1 Description of head and neck cancers
   - Expand the section to include all sites of primary concern such as respiratory cancers and lymphohematopoetic cancers in addition to head and neck. The heading should be "Cancer sites reviewed in 3.2 and 3.3."
4. Section 3.2 Cohort and PMR studies
   - Page 98, lines 8-9 – "Information on known confounding factors (e.g., smoking) is noted in each study summary…" Many of the studies that investigated potential confounding by smoking concluded that smoking was not a confounder. Revise to read "Information on *suspected* confounding factors (e.g., smoking)…."
   - Table 3-1 – Need to clarify that Hansen and Olsen is not a traditional cohort study. Note in the table that it is a record linkage study.
5. Section 3.2.1 NCI cohort
   - Page 104, line 7 – Replace "measured" with "assessed" or "estimated"
   - Page 106, lines 10-11 – Delete. This sentence is about analysis not "Exposure assessment."
   - Page 106, lines 25-27 – Change to: "Smoking was not considered to be a source of confounding <u>in internal analyses</u>, however, since..."
   - Page 107, lines 19-30, page 110, lines 23-30 and page 111, lines 1-5, Table 3.2, columns 5 to 7 – Note that the analyses of lymphohematopoietic cancers are derived from follow-up through 2004. Delete summary of earlier results from Hauptmann *et al.* on these pages.
   - Page 107, lines 1-3 – Change to: "…between exposure to formaldehyde and cancer mortality, <u>internal comparisons</u> were conducted using log-linear Poisson regression, stratified by calendar year."

- Page 108, lines 5-12 – Change to: "In external analyses, the SMRs for all lymphohematopoietic cancers indicated that the rates of lymphohematopoietic cancer death in the cohort were similar to the national rate in both the exposed and nonexposed groups."
- Table 3-2 – The title of the table does not exactly describe what is shown, and the footnote should be changed from > 0 to 1.9 ppm to > 0 to 2.00 ppm.
- Page 108, lines 10-12 – Change to: "An increased risk for Hodgkin's lymphoma was observed, but SMRs for other subtypes of lymphohematopoietic cancer among the exposed workers did not indicate increased mortality rates compared to the U.S. population."
- Page 109, line 2 – Change to: "…peak exposures in the highest exposure category were associated with a significant..."
- Page 109, line 11 – Change to: "…the highest category of peak exposure was associated..."
- Page 110, line 13 – Indicate that the RR is for the highest vs. lowest exposure category of peak exposure.
- Page 111, line 20 – Delete "also."
- Page 111, lines 6-10 – It is noted that adjustment for the 11 co-exposures did not alter results for lymphatic or myeloid leukemia. Also include the statement that adjustment for the 11 co-exposures did not meaningfully change the results for all subtypes of lymphohematopoetic cancers.
- Page 111, lines 11-19 – There are two different ideas mixed together here – cohort effects (by calendar year) and latency of exposure (time since exposure began). Of these two, the latency effects are of most interest here. Expand on this for each of the different types of lymphohematopoietic (LH) cancers. Also note that these different LH cancers may have different etiologies, and the relevant time period of formaldehyde exposure relative to diagnosis could differ by the specific LH cancer. Show the results by latency for the different types of LH cancers. Suggested text (replace lines 11- 14 up to "Beane Freeman…"):

  "Analyses considered calendar time periods and the effects of time since first exposure (Figure 1 of Beane Freeman *et al*., 2009). When time period analyses for trends in relative risk were examined, statistically significant excesses of risk were observed for myeloid leukemia in relation to peak exposures > 4.0 ppm (compared with peaks of > 0 to < 2.0 ppm) up to 1994 (RR = 2.79, 95% CI = 1.08 to 7.21, P_{trend} = 0.02). From 1995 through 2004, the risks for myeloid leukemia declined (RR = 0.71, 95% CI not reported, P_{trend} = > 0.50).According to the authors, the cumulative risks for myeloid leukemia (calculated by extending the calendar year of follow-up by one year) were elevated over the entire period of follow-up. Similarly, cumulative risks among medium and high peak exposure categories were elevated over most of the study follow-up period for Hodgkin's lymphoma and all lymphohematopoietic cancers combined. Risks for average exposure showed a similar pattern but at generally lower levels of risk. With respect to time since first exposure, among those exposed to peaks > 4 ppm vs. > 0 to < 2.0 ppm, the risk for myeloid leukemia was highest for less than 25 years since first exposure, and the RR for 15 to 25 years since first exposure was 2.44 (95% CI = 0.45 to 13.25) compared with < 15

years since first exposure. No data were presented for other lymphohematopoietic cancers and peak or average exposure, but the authors state that similar patterns were observed for all lymphohematopoietic cancers combined, leukemia, and Hodgkin's lymphoma, i.e., risks were highest 15 to 25 years since first exposure."

- Page 112, lines 3-5 – Suggested replacement text: "In an internal analysis of exposure-response relationships between average, peak, cumulative, and duration of exposure to formaldehyde and solid cancers, lagged by 15 years, the following results were reported."
- Page 112, lines 6-22 – Indicate the exact comparison being presented with each risk estimate. Report only the relative risks and not the trends and *P* values.
- Page 112 lines 6-7 – Delete "; the trend among exposed workers was P_{trend} …" Same comments hold for lines 12-13, and line 15.
- Page 112, lines 29-30 and Page 113, lines 1-5 – Delete summary of findings on lung cancer.
- Page 113, lines 10-25 – Delete summary of reanalysis by Marsh and Youk (2004) since this is on data that has been subsequently updated by Beane Freeman.
- Nasopharyngeal cancer:
  i. Page 111, line 20 – Note that the analysis of solid cancers span follow-up through 1994.
  ii. Delete text on page 113, lines 26-29 to page 114, line 1. Start the section "Marsh and Youk (2005) conducted a reanalysis of nasopharyngeal cancer data from the Hauptmann *et al.* (2004) study. They noted that the Wallingford, CT plant contributed five of the nine nasopharyngeal cancer deaths in the NCI study."
- Related studies (Marsh *et al.* 1994a,b, 1996), Page 114 (line 21) to 116 (line 2) – Delete the first 3 paragraphs because they recap studies that are outdated and are superseded by more recent publications. Report the findings from Marsh *et al.* 2007.

6. Section 3.2.2 NIOSH Cohort
   - Page 118, lines 20-27 – Delete text describing early, outdated results (proportionate mortality study).
   - Page 119, line 2 – It should also be noted in the square brackets that one would expect the SMRs to be lower than the PCMRs because of healthy worker bias.
7. Section 3.2.3. British chemical workers study
   - Page 120, line 19 to page 121, line 4 – Add results for leukemia and nasopharyngeal cancer to the study of Coggon *et al.* 2003.
   - Page 121, line 1 – Replace with "...observed for stomach or lung cancer."
8. Section 3.2.4. Studies of fiberglass workers
   - Section 3.2.4.1 (nested case-control study), page 123, line 10 – Separate "Statistical methods" and "Results" sections.
   - Section 3.2.4.1 (nested case-control study), page 123, line 25-26 – Delete "No clear trends …" This contradicts the reported results for the 5 year lag analysis reported in this paragraph (and does not seem supported by Figure 7 panel A of the paper).

- Section 3.2.4.2 (SC nested case-control study), page 125, line 17 – Separate "Statistical methods" and "Results" sections.

9. Section 3.2.5. Studies of woodworkers and related industries
   - Section 3.2.5.1 (Finland, Partanen *et al.* cohort), pages 126-128 – State the number of cancers by sites (e.g. 118 lung cancers, 1 SNC…).
   - Section 3.2.5.1 (Finland), page 127 – Separate out the "Statistical methods" and "Results" sections for respiratory cancers and lymphohematopoietic cancers.
   - Section 3.2.5.1 (Finland), page 127, lines 16-30 – It is not clear whether the results for formaldehyde listed here are for 'formaldehyde fumes' or 'formaldehyde attached to wood dust', since both of these exposures were considered. The results should be presented separately, if they are separate in the paper.
   - Section 3.2.5.2 (ACS study) (Stellman *et al.* 1998 and Boffetta *et al.* 1989*),* pages 128-130.
     i. Indicate that this is from CPS-II (CPS-I was a separate study with a different population).
     ii. Page 129, lines 20 to 21 – Revise square bracket comment to state that results for formaldehyde were not presented for SNC and NPC. Only 2 cases of SNC and one of NPC were observed in the entire study population.
     iii. Page 129, lines 29 to 31 to page 130, lines 1 and 2 – Delete square bracket comment about misclassification.

10. Section 3.2.6 Miscellaneous studies.
    - Page 130, line 8 – Replace "miscellaneous" with "other."

11. Section 3.2.8 Studies of health professionals, embalmers, and funeral directors
    - Section 3.2.8.1 (Health professional, pathologists), page139, lines 12-30, to page 140, lines 1-11 – The summary of the UK pathologists' studies gives excessive attention to outdated studies. The findings of Harrington and Shannon (1975) and Harrington and Oakes (1984) should be reduced or deleted entirely since they are superseded by Hall *et al.* (1991).
    - Section 3.2.8.2 (Embalmers and funeral directors, United States), Page 144, lines 20-21. Results for whites and non-whites are noted to be different, but they are almost exactly the same (PMR = 1.07 vs. 1.08).
    - Walrath and Fraumeni (1983, 1984) and Hayes *et al.* 1990 could be shortened, since parts of these studies have now been superseded by Hauptmann *et al.* (2009).

12. Section 3.2.8.3 Stern *et al.* 1987
    - Page 146, lines 8-9 – The sentence should be rephrased: "….No statistically significant …."

13. Section 3.3.1. (Case-control studies of paranasal sinus and nasal cavity).
    - Page 147, line 10 –The square bracket makes the point that wood dust (a known carcinogen) is a potential confounder or effect modifier. This point does not have to be repeated for each of the studies.
    - Section 3.3.1.1 (Denmark, Olsen and colleagues), page 148 – Delete sentence from line 22: "The authors noted…"
    - Section 3.3.1.1 (Denmark, Olsen and colleagues), page 149, lines 10-12 – Delete the square bracket comment.

- Section 3.3.1.2 (Netherlands, Hayes *et al.* 1986), page 150, line 11 – What is called 'low' exposure to wood dust (scores 0-2) was called 'unlikely' exposure on line 6.
- Section 3.3.1.5 (Sweden, Edling *et al.* 1987a, 1988), page 153 – Move these two cross sectional studies to Section 5 because the endpoint is nasal mucosa changes and not cancer; delete "and some "cross-sectional studies" (which refers to these studies) in the introduction to the case-control subsection (page 146, line 25).
- Section 3.3.1.6 (France, Luce *et al.* 1993), page 155, lines 26 – Delete "cancers of."

14. Section 3.3.2 Nasopharyngeal case-control studies.
    - Section 3.3.2.1 (Denmark, Olsen and colleagues), Page 157 – This study appears to use much of the same data used in the "cohort" described in section 3.2.6.3 (see comment above for Hansen and Olsen): Add a square bracket comment to state that presumably many of these cases were included in Hansen and Olsen (1995, 1996). A similar comment should be made for the sinonasal findings reported in Section 3.3.1.
15. Section 3.3.3 Other head and neck case-control studies.
    - Section 3.3.3.6 (Europe, Berrino *et al.* 2003), page 171, lines 29-30 – The potential for exposure misclassification noted in the bracket comment here is not any more than for the other studies. Delete bracket comment.
    - Section 3.3.3.8 (Turkey, Elci *et al.* 2003*),* page 173 – Note that a limitation was use of other-cancer controls. Also, more results should be presented for this study, such as results for different levels of probability or intensity.
16. Section 3.5 Lymphohematopoietic malignancies case-control studies.
    - Section 3.3.5.2 (U.S., Boffetta *et al.* 1989*),* page 180, lines 7-8 – The fact that subjects assigned to the high-exposure group had lower OR than those in the low-exposure group is a fact, not an opinion and should not have square bracket comments.
    - Section 3.3.5.6 (U.S., Wang *et al.* 2009), Page 183, line 4 – delete "and solvent exposure." Line 10: add solvent "and formaldehyde" exposure. Line 19: delete "solvent," and add "ever exposure to "formaldehyde." Remove other references to solvent exposure and clarify that analyses reported in this section are for formaldehyde. Line 26: the *P* values for trend should be replaced by point estimates for medium and high categories of exposure.
17. Section 3.3.6 Cancer at other sites
    - Section 3.3.6.6 (Canada, Dumas *et al.* 2000), page 190, lines 20-26 – Delete the square bracket comments (lines 20-26) regarding case reports since case reports were not comprehensively reviewed.
18. Section 3.4 Summary by tumor site, introduction
    - Page 192, line 11: before "Few", state "All studies of occupational groups are potentially subject to biases introduced by selection of healthy persons into the working population." Line 19: change to " Four studies of occupational populations." Line 22: delete "and;" Line 23: insert "(4) The latest NCI study of workers in the funeral industry (Hauptmann *et al.* 2009)" after "(Pinkerton *et al.* 2004). Line 23: replace sentence with: "Detailed exposure-response relationships, according to peak, average, duration, and cumulative exposure,

were only examined in the NCI studies (Hauptmann *et al.* 2004, 2009; Beane Freeman *et al.* 2009)."

19. Section 3.4.1 Summary by tumor sites, paranasal sinus and nasal cavity.
    - Section 3.4.1.3, page 196 – Move Luce *et al.* 2002 to section 3.4.1.2 (case-controls studies). Add a square bracket comment to note that this pooled analysis includes several of the studies described in the case-control section (i.e., Luce *et al.* 1993, Hayes *et a*l. 1986, Vaughan *et al.* 1986), and thus there is some overlap. List the 12 papers in the Luce *et al.* pooled analysis.
    - Section 3.4.1.3, page 196, line 26 – The study by Bosetti *et al.* 2008 (repeated later for other sites) is *not* a pooled study (although the authors use this term), but is only a meta-analysis of results (the term pooled study is used to describe studies use pooled raw data and the authors did not do this). Change the descriptions in the text and the headings to reflect that it is a meta-analysis.

Section 4. Cancer Studies in Experimental Animals

1. Section 4.1 Inhalation studies
    - Page 281-282. The unusual nature of the nasal tumor type and site with regard to occurrence in untreated animals should be discussed. Also state that the majority of the tumors occurred at the end of the nose where formaldehyde levels are expected to be highest (Morgan *et al*.). Also add that more than half (57%) of the tumors were found on the anterior portion of the lateral aspect of the nasoturbinate and adjacent lateral wall (Levels I and II, see Figure 4-1), and 26% were found on the midventral nasal septum (Levels II and III)."
    - The study author's conclusions about which tumors were likely to be treatment-related are reported, as are levels of statistical significance, but considerations of biological significance are not independently addressed in the report. The biological significance of the tumor findings, and observations of the same types of uncommon nasal tumors (even at low rates) in other studies in formaldehyde-treated animals should be discussed.
    - In Section 5, an unusual situation regarding experimental animal study reporting arises. In discussing Pyatt *et al.* (2008), the draft Background document [footnote 3 on page 451] notes that an U.S. EPA analysis reported that a significant increase (and dose-response) in lymphomas in female mice and leukemia in female rats was observed in the formaldehyde inhalation studies conducted by Battelle, and published as Kerns *et al.* (1983a,b). Kerns *et al.* (1983a,b) did not present incidence data for lymphomas or leukemias, nor was there any mention made of observations of hematopoetic neoplasms, or of bone marrow findings in these studies. The Background document also notes that Pyatt *et al.* (2008) disputes the U.S. EPA report that the incidences of lymphomas and leukemias were increased in the Battelle studies. Unfortunately, the incidence data are not provided in Pyatt *et al*. The data are available in the unpublished Battelle study report. At the very least, the report of increased tumor incidences contained in Pyatt *et al*. (2008), and Pyatt *et al.*'s dispute of these reports, should be noted in Section 4, as part of the study descriptions for the rat and mouse inhalation studies referred to as Kerns *et al.* (1983a), but the document should note that it

can not be evaluated because the data are not publically available or peer-reviewed.

- Page 281, lines 14-15 – After the sentence: “Lesions were confined to the nasal cavity and proximal trachea.” add: “However, in a later review article, Nelson *et al.* (1986) reported bone marrow hyperplasia in the rats exposed to formaldehyde. This was not considered a primary effect of the formaldehyde exposure by the authors. [No specific details were provided.]”
- Page 283, Paragraph beginning on line 12 – Include the body weights in the study by Appleman *et al.* 1988, which is given in the tables in the paper.
- Page 277, Table 4-1 and page 292 Table 4-8 (first row) – Check the conversion from mg/L to ppm.

2. Table 4-8 and Section 4.1.5 Summary of inhalation studies
   - In the column headed ‘tumor incidence,’ the table reports incidence for malignant tumors only (e.g., squamous-cell carcinoma), and the incidence data are presented for only one type of malignant tumor per study. In some studies other rare types of nasal tumors were observed, however, including benign tumors. In order to give a more complete picture of treatment related tumor incidence data, the incidence data for these tumors should also be presented here. The combined incidence of benign and malignant tumors (for cases where the benign tumor type is capable of progressing to the malignant form, e.g., squamous papilloma in Sellakumar *et al.* 1985 and Kamata *et al.* 1997 and nasal polypoid adenomas can progress to carcinomas of the respiratory epithelium in male rats for Kerns *et al.* 1983a,b) should be presented in the column reporting tumor incidence. (See revised Table 4-8 below.)
   - The entry for the Feron *et al.* (1988) rat studies presents incidence data for squamous-cell carcinoma, but not polypoid adenoma, and only for the treatment groups exposed for 13 weeks. Tumors were also seen in treatment groups exposed for 4 or 8 weeks (See Table 4-2) and should be included in Table 4-8. (See revised Table 4-8 below.)
   - Increases in treatment-related adenoma should be reported in the column headed “results and comments.” (See revised Table 4-8 below.)
   - A statement regarding the uncommon occurrence of these tumors (and other nasal tumors) should also be added.
   - Comments on small group size should also be included in this column: Appelman *et al.* 1988, n = 10; Rusch *et al.* 1983, n = 20 for rats, n = 10 for hamsters, n = 6-9 for monkeys; Woutersen *et al*. 1987, n = 10; Wilmer *et al.* 1989, n = 25, Kamata *et al.* 1997, n = 32. (See revised Table 4-8 below.)
   - The discussion of study findings (Section 4.1.5) should go beyond numbers of positive and negative studies to include discussion of the adequacy of study design to detect increases in tumors, based on factors such as exposure duration, study duration, group size, etc. The summary should also note, as appropriate, that the nasal tumors observed are rare/uncommon in the test species/strain. The report of controversy of the increased incidence of lymphomas in female mice and leukemia in female rats seen in the studies of Battelle in Kerns *et al.* 1983a, as cited by Pyatt *et al*. 2008 should also be included in this section. Section 4.4 (Summary) should be similarly revised.
3. Section 4.2 Oral and dermal administration (general comments)

- In reporting the gastrointestinal tumor findings observed, the unusual nature of the tumor type and site with regard to occurrence in untreated animals should be discussed.
- Biological significance, as well as statistical significance of the tumors observed should be discussed, as should the observations of similar tumors in other studies.

4. Section 4.2.1 Drinking-water studies
   - Page 297, line 15 – Add as last sentence in paragraph: "This is in contrast to Til *et al.* (1989) study where lesions were found in the stomach."
   - Data to be added on page 300, Second line after …significant. "The numbers in the final 2002 report by Soffritti *et al.* had increased by 71 animals with hemolymphoreticular tumors from the preliminary report on the same study (Soffritti *et al.* 1989) with no explanation provided by the authors; the tumors were pooled and designated as hemolymphoreticular tumors which was questioned by an IARC review (IARC 2006). [Although the facilities are not specific pathogen free, survival was approximately 50% at weeks 104-112 across all groups of males and approximately 50% at weeks 112-120 across all groups of females, suggesting adequate survival.]"
   - Page 300, line 2 – remove "also", to read: "IARC 2006 noted Soffritti *et al.* 2002 reported a significant increase…"
5. Table 4.13 and Section 4.2.3 Summary of oral and dermal studies
   - Some of the comments on Table 4-8 are applicable to Table 4-13. It is noted that Table 4-13 appropriately presents combined incidence data for benign and malignant gastrointestinal tumors.
   - Section 4.2.3 should go beyond numbers of positive and negative studies, to include discussion of the adequacy of study design to detect increases in tumors, based on factors such as exposure duration, study duration, group size, etc. The summary should also note, as appropriate, that the tumors observed are rare/uncommon in the test species/strain.

Table 4-8 Summary of nasal tumor incidence in inhalation studies of formaldehyde in experimental animals

Strain	Exposure		Conc. (ppm)	squamous-cell carcinoma		non-squamous tumors				Results and Comments	Reference
						Malignant		Total [a]			
	h/d (d/wk)	# wk		M	F	M	F	M	F		
Mice (subchronic and chronic)											
C3H	1 (3)	35	[0] [41] [82] [163]	0/26 0/23 0/34 0/35		0/26 0/23 0/34 0/35		0/26 0/23 0/34 0/35		[Sex and age not reported, examined lung tissue and did not examine nasal tissue, short duration, short exposure time], high mortality in high-exposure group	Horton *et al.* 1963
$B6C3F_1$	6 (5)	104	0 2.0 5.6 14.3	0/120 0/120 0/120 2/120	0/120 0/120 0/120 0/120	0/120 0/120 0/120 0/120	0/120 0/120 0/120 0/120	0/120 0/120 0/120 0/120	0/120 0/120 0/120 0/120	All groups initially contained 119 to 121 animals [number of mice in each group not specifically reported]. Interim sacrifices at 6, 12, 18, 24, and 30 mo. The only tumors occurred in 17 males sacrificed at 24 mo [number of animals evaluated unclear]	Kerns *et al.* 1983a,b
Rats (subacute and subchronic)											
F344	22 (7)	26	0 0.19 0.98 2.95	0/20 0/20 0/20 0/20	0/20 0/20 0/20 0/20	0/20 0/20 0/20 0/20	0/20 0/20 0/20 0/20	0/20 0/20 0/20 0/20	0/20 0/20 0/20 0/20	[Short duration, small number of animals/group], increase in squamous metaplasia/hyperplasia and basal-cell hyperplasia in high-exposure groups	Rusch *et al.* 1983
Wistar	6 (5)	13	0 1 10 20	0/10 0/10 0/10 0/10	0/10 0/10 0/10 0/10	0/10 0/10 0/10 0/10	0/10 0/10 0/10 0/10	0/10 0/10 0/10 0/10	0/10 0/10 0/10 0/10	[Short duration, small number of animals/group], exposure-related increase in proliferative lesions of the nasal respiratory and	Woutersen *et al.* 1987

Strain	Exposure h/d (d/wk)	Exposure # wk	Conc. (ppm)	squamous-cell carcinoma M	squamous-cell carcinoma F	non-squamous tumors: Malignant M	non-squamous tumors: Malignant F	non-squamous tumors: Total [a] M	non-squamous tumors: Total [a] F	Results and Comments	Reference
										olfactory epithelia, including severe squamous metaplasia and moderate keratinization in both sexes in 10 & 20 ppm dose groups	
Wistar	6 (5)	13	0 10 20	0/45 1/44 3/44	NT	0/45 0/44 1/44	NT	0/45 0/44 3/44	NT	[Short duration], 1 carcinoma *in situ* & 2 polypoid adenomas also detected in high-exposure group and thought to be exposure-related	Feron *et al.* 1988
Wistar	6 (5)	8	0 10 20	2/45 1/44 1/43	NT	0/45 0/44 0/43	NT	0/45 0/44 1/43	NT	[Short duration], One polypoid adenoma detected in high dose group and thought to be exposure related	Feron *et al.* 1988
Wistar	6 (5)	4	0 10 20	0/44 0/44 1/45	NT	0/44 0/44 0/45	NT	0/44 0/44 1/45	NT	[Short duration], One polypoid adenoma detected in high dose group and thought to be exposure related	Feron *et al.* 1988
Wistar	8 (5) 8 (5) 8 (5) 4[b] (5) 4[b] (5)	13 13 13 13 13	0 1 2 2 4	0/25 0/25 0/25 0/25 0/25	NT	0/25 0/25 0/25 0/25 0/25	NT	0/25 0/25 0/25 0/25 0/25	NT	[Short duration, small number of animals/group], exposure-related effects observed only in high-exposure group and included hyperplasia and squamous metaplasia of the respiratory epithelium	Wilmer *et al.* 1989

Strain	Exposure h/d (d/wk)	Exposure # wk	Conc. (ppm)	squamous-cell carcinoma M	squamous-cell carcinoma F	non-squamous tumors: Malignant M	non-squamous tumors: Malignant F	non-squamous tumors: Total [a] M	non-squamous tumors: Total [a] F	Results and Comments	Reference
Rats (chronic)											
F344	6 (5)	104	0 2.0 5.6 14.3	0/118 0/118 1/119 51/117	0/114 0/118 1/116 52/115	0/118 0/118 0/119 4/117	0/114 0/118 0/116 1/115	1/118 4/118 6/119 8/117	0/114 4/118 0/116 2/115	Nasal carcinoma observed in 1 rat of each sex in the high-exposure groups; polypoid adenoma observed in all groups except female control and medium-exposure groups; undifferentiated carcinoma or sarcoma and carcinosarcoma observed in high-exposure males	Kerns *et al.* 1983a,b
Wistar	6 (5)	52	0 0.1 1.0 10	0/10 0/10 0/10 0/10	NT	0/10 0/10 0/10 0/10	NT	0/10 0/10 0/10 0/10	NT	[Low number of animals/group] Reported that rats with damaged nasal mucosa were more susceptible to the cytotoxic action of formaldehyde; squamous metaplasia/basal cell hyperplasia in high dose groups for damaged and undamaged noses; neither group had neoplasias	Appelman *et al.* 1988
Wistar	6 (5)	120	0 0.1 1.0 10	1/54 1/58 0/56 15/58	NT	0/54 0/58 0/56 2/58	NT	0/54 0/58 0/56 2/58	NT	Reported results are for groups with damaged noses; 1 or 2 nasal tumors also occurred in groups with undamaged noses or in groups exposed for only 3 months ; for undamaged nose group, 1 SCC detected in every exposed group	Woutersen *et al.* 1989

Strain	Exposure		Conc. (ppm)	squamous-cell carcinoma		non-squamous tumors				Results and Comments	Reference
						Malignant		Total [a]			
	h/d (d/wk)	# wk		M	F	M	F	M	F		
Sprague -Dawley	6 (5)	life	0 15	0/99 38/100	NT	0/99 2/100	NT	0/99 2/100	NT	Squamous papillomas observed in 10 rats- total squamous cell tumors 48/100; mixed carcinoma and fibrosarcoma observed in 1 rat each	Sellakumar *et al.* 1985
Sprague -Dawley	6 (5)	104	0 12.4	NT	0/15 1/16	NT	0/15 0/16	NT	0/15 0/16	[Small number of animals.] Pronounced squamous-cell metaplasia or dysplasia reported in 10 of the exposed rats and none of the controls	Holmström *et al.* 1989a
F344	6 (5)	104	0 0.7 2 6 10 15	0/90 0/90 0/96 1/90 20/90 69/147	NT	0/90 0/90 0/96 0/90 2/90 2/147	NT	0/90 0/90 0/96 0/90 7/90 16/147	NT	Polypoid adenoma; one rhabdomyosarcoma, and one adenocarcinoma also observed in the two highest exposure groups. The population-weighted unit length labeling index was correlated with regional tumor incidence.	Monticello *et al.* 1996
F344	6 (5)	120	0 0.3 2 15	0/32 0/32 0/32 13/32	NT	0/32 0/32 0/32 0/32	NT	0/32 0/32 0/32 0/32	NT	[Small number of animals/group] Squamous-cell papilloma also observed in 3 rats in the high-exposure group; total squamous cell tumors 16/32 in high dose group.	Kamata *et al.* 1997

Strain	Exposure h/d (d/wk)	Exposure # wk	Conc. (ppm)	squamous-cell carcinoma M	squamous-cell carcinoma F	non-squamous tumors: Malignant M	non-squamous tumors: Malignant F	non-squamous tumors: Total [a] M	non-squamous tumors: Total [a] F	Results and Comments	Reference
Hamsters (subchronic and chronic)											
Syrian golden	22 (7)	26	0 0.19 0.98 2.95	0/10 0/10 0/10 0/10	0/10 0/10 0/10 0/10	0/10 0/10 0/10 0/10	0/10 0/10 0/10 0/10	0/10 0/10 0/10 0/10	0/10 0/10 0/10 0/10	[Short exposure duration and small number of animals], no significant responses reported	Rusch *et al.* 1983
Syrian golden	5 (5) 5 (1)	life life	0 10 30	0/132 0/88 0/50	NT	0/132 0/88 0/50	NT	0/132 0/89 0/50	NT	Minimal increase in hyperplastic and metaplastic areas in the nasal epithelium of 5% of the exposed animals.	Dalbey 1982
Monkeys (subacute and subchronic)											
Cynomolgus	22 (7)	26	0 0.19 0.98 2.95	0/6 0/6 0/6 0/6	NT	0/6 0/6 0/6 0/6	NT	0/6 0/6 0/6 0/6	NT	[Short exposure duration, small number of animals], squamous metaplasia/hyperplasia in the nasal turbinates in the high-dose group	Rusch *et al.* 1983
Rhesus	6 (5)	6	0 6	0/3 0/3	NT	0/3 0/3	NT	0/3 0/3	NT	[Short exposure duration and small number of animals], increased cell-proliferation rates and squamous metaplasia of the transitional and respiratory epithelia of the nasal passages and respiratory epithelia of the trachea and major bronchi	Monticello *et al.* 1989

NT = not tested.
[a]Total non-squamous tumors are other carcinomas plus polypoid adenomas.
[b]Exposed for 30-minute intervals, 8 times/day, separated by 30-minute non-exposure periods.

Section 5. Other Relevant Data

1. General Comments
   - Change all ppb doses to ppm throughout the entire RoC document (for all inhalation exposures) to be consistent among all studies.
   - Add descriptions of the following recent references: Kuper *et al.* 2009, Li *et al.* 2007, Georgieva *et al.* 2003, Schlosser *et al.* 1999, and Lapidot *et al.* 1992.
2. Section 5.1 Absorption, distribution, and excretion
   - Page 319, line 9 – Replace sentence starting "Metabolically it is …," with "Formaldehyde can also be produced from metabolism of serine, glycine, methionine, and choline, as well as from a variety of xenobiotics, such as drugs, food additives, and other environmental chemicals (IARC 2006)."
   - Page 319, line 11 – Change "The endogenous concentrations of formaldehyde in human blood are about 2 to 3 μg/g of blood" to "The endogenous concentration of formaldehyde measured in the blood of 6 human subjects was 2.66 ± 0.14 μg/g (mean ± SE), equivalent to about 0.1 mM."
   - Page 319, line 20 – At the end of the paragraph add the following: "Although formaldehyde is a gas at room temperature, in aqueous solution formaldehyde is rapidly hydrated and is in equilibrium with its hydrated form, methanediol. The relative concentrations of formaldehyde and methanediol are dependent on temperature, with the chemical equilibrium constant for hydration $K_h = e^{3769/T - 5.494}$, where T is temperature in degrees Kelvin (Winkleman *et al*. 2002 *Chemical Engineering Science*. 57: 4067-4076). At both room temperature (298 degrees Kelvin) and body temperature (310 degrees Kelvin), the dominant form is methanediol because the equilibrium is far to the right, *i.e.*, towards methanediol (K_h = 1279 at room temperature and K_h = 784 at body temperature). This propensity of reactive formaldehyde to hydrate (forming methanediol) and thereafter to slowly be regenerated (from methanediol) to free formaldehyde explains how such a reactive molecule can be distributed and undergo metabolism throughout the body."
   - Page 321, line 2 – Change "deposit" to "be absorbed."
   - Page 323, lines 4-5 – Change "free formaldehyde" to "formaldehyde-methanediol" Point out the half-life includes the half-life of both formaldehyde and its hydrated form (methanediol), because they are in equilibrium.
   - Page 324, lines 4-5, 11-13, and Table 5-2 – Indicate that the ± values refer to SEs.
   - Page 326, line 29 – Nishi *et al.* 1988, could not confirm that the victim had ingested formaldehyde, although it is likely that he did so. After "suicide" add "apparently."
   - Page 327, Table 5-3 – Add "apparent" after "following" in the title.
   - Page 327, line 3 – change "formic acid" to "methanol."
3. Section 5.2 Airway deposition models
   - Page 332, line 4 – Change the word "examine" to "simulate."
   - Page 332, lines 18-21 – Remove sentence starting "The models were calibrated …" Replace with "None of the cited papers (Kimbell *et al.* 1993, 1997, Kepler *et al.* 1998, Subramaniam *et al.* 1998) mention calibration of the models; however, according to Kimbell and Subramaniam 2001, the proportionality constant between the nasal wall absorption rate and the air-phase concentration adjacent to the nasal wall was estimated so that the overall formaldehyde uptake

predicted in the rat CFD model was consistent with measured uptake data (as reported in a meeting abstract by Patterson *et al.* 1986, *i.e.*, > 93% was retained by the nose). The proportionality constant was assumed by the authors to be associated with solubility and was used in all uptake simulations for the rat, monkey, and human."

4. Section 5.3 Metabolism
   - Page. 333, line 12 – Remove reference to (Franks 2005) and substitute (IARC 2006). Delete lines 12-19. Replace with: "This reactive conjugate is detoxified in a reaction catalyzed by formaldehyde dehydrogenase (also known as alcohol dehydrogenase 3 [ADH3]) which results in the formation of *S*-formylglutathione. This latter metabolite is converted to formic acid and glutathione by *S*-formylglutathione hydrolase (Figure 5-1)."
   - Footnote: "ADH3 is the same enzyme as glutathione-dependent formaldehyde dehydrogenase, which is officially designated 'ADH5 alcohol dehydrogenase 5 (class III), chi polypeptide.' Other names include ADHX, S-nitrosoglutathione reductase (GSNO), and formaldehyde dehydrogenase (FDH). The ADH5 gene is ubiquitously expressed in human tissues, albeit with tissue-specific variation in levels of expression; it has been measured in all human tissues from embryos through adults. (Thompson *et al.* 2009). ADH5 is polymorphic, and several studies have identified polymorphisms that may be functional including (1) a SNP in the promoter region, which was associated with decreased transcriptional activity (Hedberg *et al.* 2001), and (2) a common haplotype (frequency 41.8%) and two SNPs that were associated with increased risk of childhood asthma in a study of Mexican children (Wu *et al.* 2007). The health impact of these polymorphisms has not been evaluated."
5. Section 5.4.2.1 Toxic effects in humans, Inhalation exposure
   - Page 339, lines 10-12 – Delete the text related to the Ballenger (1984) reference because there appears to be an error in the Ballenger review about these data.
   - Page 345, line 2 – Change the word "occasional" to "potential."
6. Section 5.4.2.3, Toxic effects in humans, Oral exposure
   - Page 349, line 17 – change "11" to "13."
   - Page 351, line 5 – Insert "and employees" after "students."
7. Section 5.4.2.4 Toxic effects in humans, Hematological and immunological effects
   - Page 351, line 23 – Insert a sentence at the end of the paragraph (Kuo *et al.* 1997 study). "No differences in other hematologic indices were noted in this study." Add text describing the Zhang *et al.* (2010) study which described human exposures to formaldehyde that result in hematological changes and effects on progenitor cells.
   - Page 354, lines 17-22 – Regarding the Erdei *et al.* 2003 study: Add a bracketed comment of the limitations of this study, which include selection bias (chose only the most polluted houses and did not control for other socioeconomic variables), the effects are also correlated with NO_2 levels (so can not differentiate HCHO from NO_2 effects) and the subjects were also exposed to dust mites (which would complicate any assessment of immunologic effects).
   - Page 354, line 23 to page 355, line 2 – Ye *et al.* 2005 study. Add a bracketed comment that the control group (students) was a poor control for a worker population.

8. Section 5.4.2.5 Toxic effects in humans, Neurophysiological effects
   - Page 358, lines 17-23 – Kuo *et al.* 1997. Delete the last sentence of the paragraph (study authors' conclusions).
9. Section 5.4.3.1 Toxic effects in experimental animals, Irritation, sensitization, and respiratory effects
   - Page 362, line 16 – Insert "to ovalbumin" after "response."
10. Section 5.4.3.2 Toxic effects in experimental animals, cytotoxicity
   - Page 363, line 16 – Delete "three times as high" and replace with "slightly higher."
11. Section 5.4.3.3 Toxic effects in experimental animals, Neurotoxicity
   - Page 364, line 8 – Change "2003" to "2003a." Add discussion of Malek *et al*. 2003b which reported that formaldehyde exposure (0.1, 0.5, 5 ppm for 2 h) caused significant locomotor behavior of adult male and female rats after single exposure.
12. Section 5.4.3.4 Toxic effects in experimental animals, Immunologic and other effects
   - Page 365, line 25 – After "function" add "[including routine hematology, bone marrow cellularity, and CFU progenitor cell enumeration (Dean *et al.* 1984)]."
   - Page 367, line 7 – Insert "and nerve growth factor" after "IL1β."
   - Page 367, line 9 – Delete the sentence starting "nerve growth factor."
   - Page 367, line 19 – Insert "in the OVA-immunized mice" after "factor."
   - Page 368, lines 11-12 – Insert "slightly" before increased on line 11; HCHO increased the liver enzymes statistically but only to a small degree (Woutersen *et al.* 1987).
13. Section 5.4.3.5 Toxic effects in experimental animals, Reproductive and developmental effects
   - Page 369, line 18 – Delete "and liver": HCHO concentrations were higher in fetal brain, but not higher in fetal liver, compared to those in maternal brain and liver. Radiolabel may have been eliminated more slowly in the fetal liver compared to maternal liver, but the concentrations were always higher in the maternal liver (Thrasher and Kilburn 2001).
14. Section 5.6.1 Genetic and related effects, prokaryotes
   - Page 375, line 10 – regarding "differential toxicity". Add two references to Table 5-15 (Nakano *et al.* 2007, Salem *et al.* 2009) and briefly describe the findings.
   - Page 376, Table 5-15 – Change the results for differential toxicity in *E. coli* (without S9) from "+ (2/2)" to "+(4/4)."
15. Section 5.6.3.1 Genetic and related effects, mammalian systems, DNA adducts, DNA-crosslinks, and DNA damage
   - Page 379, line 4 – Insert "In a recent report, more than 100 proteins involved in formaldehyde induced DPC were identified through the employment of mass spectrometric methods (Qiu and Wang 2009). HL-60 human acute promyelocytic leukemia cells were treated for 10 min with 45 mM formaldehyde. DPC were purified from the nuclei and the crosslinking was reversed. The subsequent proteins were resolved by SDS-PAGE and identified via mass spectrometric identification of the in-gel tryptic digests. Many of the identified proteins are involved in transcription, gene regulation, DNA replication, and DNA repair. While the formaldehyde concentrations employed in this study are high, similar proteins

are likely to be involved in DPC at concentrations employed in the studies outlined in Table 5-17."

16. Section 5.6.3.2 Mammalian systems, cytogenetic effects, *in vivo* studies
    - Page 392, Table 5-20 – In the micronuclei portion of the table, missing data from Speit 2009 (15 ppm, negative) as well as from Morita *et al.* 1997 in which micronuclei effects from formaldehyde exposure were negative (po: 200 mg/kg, negative), (iv: 30 mg/kg, negative). For both papers, add species/strain.
17. Section 5.6.4.1 Human *in vivo* studies, DNA-protein crosslinks and strand breaks
    - Page 395, end of paragraph, line 19 – Add to the description of the study by Shaham *et al.* 2003, "These findings have been questioned, however, because of the excessively high level of DPCs reported in the controls (Zhang *et al.* 2010)." (This comment was made by the section 2 subgroup)
    - Page 396, Table 5-23 – Change the last two rows (Shaham *et al.* 2003) from "low and high exposure" to "low and high DNA-protein crosslinks."
    - Page 397, line 1 – Change to "Costa *et al.* (2008) compared DNA damage as measured by the comet assay in 30…."
    - Page 397, end of section – Add a description of Pala *et al.* 2008, which found that formaldehyde-albumin adducts were significantly increased among workers with high exposure to formaldehyde compared to workers with low exposure. This study did not have unexposed controls (N =27 low exposed workers and N = 9 high exposed workers).
    - Page 397, end of section – Insert the following statement summarizing the findings of Wang *et al*. 2009: "Formaldehyde-based DNA adducts (similar to those observed in experimental animals treated with *N*-nitrosomethyl carcinogens) were observed in leukocytes of smokers of greater than 10 cigarettes per day and some nonsmokers (Wang *et al.* 2009). The levels of these adducts were roughly ten times higher in smokers. The formaldehyde source could be tobacco smoke, metabolism of a tobacco-specific compound or as secondary metabolite formed as a result of lipid peroxidation or inflammation."
18. Section 5.6.4.2 Human *in vivo* studies, DNA repair and mutations
    - Page 399, line 13 – Insert "In addition," before "chromosomal damage."
19. Section 5.6.4.3 Human *in vivo* studies, cytogenetic effects
    - Add the findings from Pala *et al.* 2008 (discussed in Section 2 and above) to the text and tables on chromosomal aberrations, micronuclei, and sister chromatid exchange which did not find increased levels of these three endpoints in workers with high exposure to formaldehyde compared to workers with low exposure (indicate measured exposure levels). This study did not have an unexposed control group, and the numbers of workers (with data) in the high exposed groups were small (N = 5 for CA, 2 for SCE, and 7 for MN).
    - Add results from Zhang *et al.* (2010) on chromosomal aberrations.
20. Section 5.6.5 Gene expression
    - Add additional study by Lee *et al.* 2008, which identified formaldehyde inducible genes that are associated with cell proliferation and differentiation, immunity and inflammation, and detoxification.

21. Section 5.7.1 Mechanistic considerations, Genotoxicity
    - Page 428, line 30 to page 429, line 2 – Change to "Merk and Speit (1998) reported that formaldehyde-induced DNA-protein crosslinks are related to chromosomal effects (SCE and micronuclei) but not directly to gene mutations in the *hprt* gene in V79 cells." Delete the citation for Speit *et al*. 2000 because it does not have any information regarding gene mutations, and only reports on SCEs and micronuclei.
    - Page 429, line 17 – After "same" insert "for HCHO exposures at or below 2 ppm only."
    - Add information that formaldehyde inhibited O^6-alkylguanine DNA alkyltransferase and increased the mutagenicity of *N*-methylnitrosourea (MNU) in normal human pulmonary fibroblasts. These studies indicate that formaldehyde could modulate the mutagenic activity of alkylating agents (Grafström *et al.* 1985).
    - Add the de Graaf *et al.* (2009) findings that different DNA repair pathways are important for different types of dosing (low chronic exposure vs. high acute exposure). This may be relevant to human cancer studies evaluating risks associated with different exposure metrics (such as cumulative exposure and peak exposure).
    - Regarding inhibition of DNA repair, add (Emri *et al.* 2004) who reported that low concentrations of formaldehyde exposure delayed DNA repair (as measured by SSB from nucleotide excision repair) after UV irradiation in human skin cells. Formaldehyde exposure (low concentrations) also caused an increase in UVC-induced chromosomal damage.
22. Section 5.7.2 Mechanistic considerations, glutathione depletion and oxidative stress
    - Page 436, line 9 – Insert "but not at 13 weeks (Gülec *et al.* 2006)" after "weeks."
23. Section 5.8.5 Summary, Mechanistic considerations
    - Page 456, lines 22-25 – The recent reports of formaldehyde adducts in leukocytes of smokers (Wang *et al.* 2009), albumin adducts (Pala *et al*. 2008), DPC measured in the Shaham *et al.* (2003) study, and the hematologic changes measured by Zhang *et al.* (2010) study, suggest that formaldehyde may enter the systemic circulation of humans exposed to formaldehyde.

Report Approved: [redacted]
Kenneth E. McMartin, Ph.D., Chair

1-21-2010
Date

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