DATE: April 13, 2010

SUBJECT: REVIEW OF US ENVIRONMENTAL PROTECTION AGENCY'S DRAFT FORMALDEHYDE ASSESSMENT

Submitted by : NCEH/ATSDR

The review of the literature seems adequate and completely covers the issues in the draft document. Specifically, Volume I of IV includes the critical studies relevant to the topic and the studies are presented with much detail. Volumes II and III of IV provide a very comprehensive review of the toxicological, genotoxic, carcinogenic effects, and risk assessment of formaldehyde.

Comments on Volume I

Specific comments are as follows:

- Page 2-1, line 29 – Please delete extra comma.
- Page 2-2, Table 2-1 – Please spell out CASRN to be consistent with rest of table.
- Page 2-3, line 3 and page 2-11, line 35 – The use of suntan lotion may be a bit confusing. Suggest changing to sunscreen to avoid confusion with tanning lotion.
- Page 2-3, line 2-6 – States that formaldehyde is used in a list of cosmetic products, however, pages 2-11 and 2-12 state that these cosmetic products contain formaldehyde releasing agents, but not actually formaldehyde. Suggest using consistent wording.
- Page 3-3: line 12 – Please delete a) line 14 - delete colon at end of sentence and replace with period; line 19-add comma after pool.

- Page 3-3, last paragraph – Choose another numbering format (such as "a" and "b") within this paragraph since i and ii are already used in the first numbering format of this section.

- Page 3-23, lines 5-6 – Specify which species this sentence is referring to.

- Page 3-28 line 22 and 27 – Insert 2005 after Moser et al.

- Page 3-33, line 12 – Delete the duplicate human respiratory tract.

- Page 3-33, lines 26-27 – Delete unnecessary parentheses.

Comments on Volume II

The volume was very lengthy and somewhat tedious to read, primarily because in Sections 4.1 through 4.3, each study was described in extreme detail regardless of the quality of the study or its relevance to risk assessment. The numerous summaries of the data given at the end of subsections were very helpful. Nevertheless, the volume didn't give any synthesis and evaluation of the data until Section 4.4, 370 pages into the text. It may be helpful to condense the information.

Specific comments are as follows:

- Inconsistent units are used i.e., parts per million (ppm); parts per billion (ppb); milligrams/cubic meter (mg/m^3); and micrograms/cubic meter ($\mu g/m^3$).

- Page 4-2, line 28**:** Pease change 392 to 397.

- Page 4-2, lines 34 and 35: Measurements of formaldehyde exposure were taken from two rooms of the home, usually the bedroom and living room, and the samples were kept…..

- Page 4-3, line 5: Change increase to increased.

- Page 4-3, line 29: Change geometric mean to median concentration

- Page 4-4, line 14: "(65% mobile homes, 27% conventional homes, 2% travel trailers, 2% office buildings, etc)."

- Page 4-5, line 29: A Swedish study conducted at a chemical plant found that nasal and eye discomfort were

- Page 4-8, line 12: The 0.25 mg/m^3 concentration is incorrectly converted to 308 ppb. It should be 0.203 ppm or 203 ppb.

- Page 4-18, line 15: change All four reports to All five reports

- Page 4-21, line 8: Do not offer information on the concentrations at which adverse effects would be expected in a…

- Page 4-23, line 11: Change "they did report at increased risk" to "they did report an increased risk."

- Page 4-23, line 16: A study performed by Tuthill (1984) measured formaldehyde in the homes of ~~exposure for~~ children

- Page 4-24, line 28: Change "gender to and odds ratio" to "gender to an odds ratio."
- Page 4-25, line 26: Change "were" to "of".

- Page 4-26, lines 28-34: The statement that starts on line 33 "This small study reported only incidence of lesions and did not score based on severity of lesions" is confusing because scores are provided in the previous text description (see lines 28 …) with such words as (with an average severity score of 2.3). Suggest deleting the highlighted sentence.

- Page 4-27, lines 3-4: Holmström et al. (1989) collected nasal biopsy samples from workers not exposed to formaldehyde and 70 workers exposed ~~air or~~ to formaldehyde at a median concentration of 240 ~~ppm~~ ppb. (See p 4-17 line 19, concentration is correctly reported as 0.240 ppm (240 ppb).

- Page 4-28, line 29: What is SI-induced? This term is not defined or mentioned elsewhere in the volume.

- Page 4-29 line 4: Change "median" to "mean".

- Page 4-30, line 35: Change "value" to "values".

- Page 4-31, line 1: of formaldehyde in the application of carbamide-formaldehyde glue was found to be 0.71 ppm TWA…

- Page 4-38, line 32-34: Blood serum albumin (HSA) samples were collected and assayed for IgE and IgG activity against formaldehyde. None of the workers had IgG activity against formaldehyde. Five workers had comparable IgE activity against both formaldehyde HSA and HSA that was more than twice the normal control serum levels. No IgE antibodies were detected in the other 32 workers. (See write-up on p 4-40.)

- Page 4-57, line 29: Change "**4.1.2.1.1. *NPC" to "4.1.2.1.1. Nasopharyngeal Cancer (NCP)"***

- Page 4-59, Table 4-1: Please make the tabular entry clear that Hauptmann et al. (2004) study is the NCI cohort.

- Page 4-72, Table 4-2: For the Luce et al., 1993 entry, it is not clear what the average levels of ≤2 and ≥2 represent– are they concentrations? Or are they low (1-3) as defined by Luce et al.?

- Page 4-73, Table 4-2: For the Hayes et al. entry exposure levels in the Exposure Assessment column are expressed as low (<0.0 ppm) [what does this mean?], medium (0.1-1 ppm); and high (>1 ppm), but in the Results… column, the levels are given as ≤2 and ≥2. Why the discrepancies.

- Page 4-76, 4.1.2.1.3: The paragraph is very confusing. On line 35, it says (see Table 4-3), but the studies to which this refers are not entered in Table 4-3. Nor are the subsequently cited industrial worker cohorts where buccal-pharynx cancer was examined in Table 4-3. The studies that appear in Table 4-3 are discussed starting in the last of page 4-77.

- Page 4-84, line 16: Change **"4.1.2.2.1. *LHP cancers"*** to **"4.1.2.2.1 *Lymphohematopoietic (LHP) cancers"***

- Page 4-85, line 5: Delete "and laboratory technicians".

- Page 4-88, line 3: The PMR for myeloid leukemia is given as 1.61 [95% CI: 1.02-2.41] on p 4-88 but as 1.57 [95% CI: 1.01-2.34] on Table 4-4, p 4-105. The data for other leukemia is also missing from Table 4-4.

- Page 4-93, lines 14-22: It is not clear whether these data refer to the Stayner study or to the update by Pinkerton.

- Page 4-95, line 14: Says that formaldehyde levels ranged from 0.1 to 1.0 mg/m^3, but the entry in Table 4-4 on p 4-104 reports 1-5 $\mu g/m^3$.

- Page 4-95, line 16 and 17: The text says there were 2 (1.0 expected) lymphomas, and 2 (0.5 expected) multiple myelomas, yet the tabular entry reports these as SMRs of 1 and 4. This entry in Table 4-4 is misleading.

- Page 4-95, lines 21-35: Why is the Dell and Teta (1995) study even discussed? It seems to be more about benzene and toluene. Nowhere in the description of the study does it say there was formaldehyde exposure.

- Page 4-96. Section 4.1.2.2.1.3 is titled Summary of non-respiratory tract

cancers and then is followed by Sections 4.1.2.2.2 and 4.1.2.2.3, which are discussions of brain and CNS cancer and pancreatic and other cancer. Aren't these also non-respiratory tract cancers? Perhaps the summary should follow these subsections on p 4-107.

- Page 4-98, Table 4-4: For the Harrington and Shannon entry, the study design column should indicate that there are 12,944 laboratory technicians. The 2,079 number is just for the pathologist and is not inclusive of laboratory technicians.

- Page 4-99 Table 4-4: For the Luce et al. entry the cohort consisted of 5,485 pathologists, not 4,485.

- Page 4-102, Table 4-4: The Pinkerton et al. entry should make it clear that it is an update of the Stayner et al study.

- Page 4-103, Table 4-4: The Coggon et al. entry should make it clear that it is an update of the Gardner et al. study.

- Page 4-103, Table 4-4, For the Bertazzi et al entry, indicate the exposure levels were 0.16 to 3.1 ppm.

- Pagev 4-110, 4.2.1 Noncancer Health Effects: This title is misleading because cancer effects appear here also (see also page II-v – Contents – misleading). It should be renamed Non cancer and Cancer effects.

- Page 4-131, lines 22-27: Inconsistent referencing to exposure levels 145 ppm vs.145.6 ppm. There are other instances in the document where this occurs; suggest global checking.

- Page 4-144, Table 4-15: Fill in the empty boxes in the column for extra-pulmonary effects.

- Page 4-148, Table 4-17: Indicate in the title that there were 10 male and 10 female rats examined, otherwise the number of animals with the effects is unclear.

- Page 4-169, lines 22 and onward: Suggest presenting the data for formaldehyde alone rather than formaldehyde and HCl.

- Page 4-205, line 20 and 21: Johannsen et al. (1986) performed a subchronic study by using rats ~~and dogs~~ exposed to paraformaldehyde dissolved in drinking water and dogs exposed to formaldehyde in the diet.

- Page 4-206, line 17: This says that the study suggest a NOAEL of 150 mg/kg/day. There was decreased weight gain.

- Page 4-217, lines12 and 13: Sub chronic exposures at 61 and 99 ppm formaldehyde would be expected to result in frank toxic effects in mice (see Section 4.2.1). The study (Leach et al 1983) was conducted in rats, not mice. Would frank effects at 61 and 99 ppm be expected to in rats?

- Page 4-225, line 26: Change "systematic" to "systemic".

- Page 4-227, line 8: One form of sensitivity directly affects sensory nerve… Is there a word missing between the two commas?

- Page 4-288, lines 4: The Kilburn and Moro (1985) study was available only in abstract and was not found as a subsequent published article. Why include it? If the abstract appeared 25 years ago and was never published, maybe it was rejected or the authors withdrew it.

- Page 4-288, line 14 to p 4-290, line 16: Why include these studies by Gofmekler and Bonachevskaya, 1969, Gofmekler 1968, and Pushkina et al 1968 if they are so flawed. The extensive detail descriptions, including the tabular data is somewhat distracting and adds to the length and tedium; suggest condensing the discussion. They are even included in Table 4-69, where levels of 0.01 and 0.08 ppm are identified as LOAELs for developmental effects. This is somewhat misleading in that a LOAEL of 5 ppm is identified on p 4-309, line 17 from the Martin study (See below).

- Page 4-290, line 32: Sanotskii et al 1976 is cited parenthetically. Is it cited anywhere else in the document?

- Page 4-295, line 19: Another abstract is cited.

- Page 4-309, line 17: The LOAEL for developmental effects in rats is 5 ppm. ATSDR's Toxicological Profile did not give much credence to the 5 ppm level as LOAEL in the Martin 1990 study. Neither did Martin. It is further misleading, because much lower LOAELs are identified in Table 4-69. For example, 0.01 and 0.08 are identified as LOAELs in Table 4-69 for the Gofmekler studies and 0.41 ppm in the Senichenkova studies. As noted in General Comments, this is kind of reporting that each study was described in extreme detail regardless of the quality of the study or its relevance to risk assessment.

- Page 4-317, Table 4-70: Suggest reporting the Hurni and Ohder (1973) ppm dietary concentrations as mg/kg/day as was done in the text. The concentrations of formaldehyde in the chow were 0, 125, or 375 ppm, equivalent to doses of 0, 3.1, or 6 9.4 mg/kg-day, respectively.

- Page 4-324, line 2: Change “chronicle” to “report” Chronicle means to record in chronological order or to make a historical record.

- Page 4-324, line 34: 10 ppm should be 15 ppm.

- Page 4-330, line 13: 10 ppm should be 15 ppm.

- Page 4-330, line 22: Swenberg et al (1983) should be Swenberg et al (1980).

- Page 4-345, lines 14 and 15: “…Speit et al. (2000) ~~it has been~~ have shown that formaldehyde causes DNA repair inhibition at a concentration range of 0.125 mM to 10 mM~~)~~.

- Page 4-345, line 17: Change “followed” to “followed”.

- Page 4-353, line 20: **4.3.3.2. Mutagenicity in Other Non-Mammalian Cell Systems.**

- Page 4-404, line 10: The use of mosquito coils in the Philippines (West et al. 1993). This has not been discussed anywhere else in Volume II.

- Page 4-411, line 8: Bosetti et al., (2008) has not been discussed previously in Volume II.

- Page 4-429, line 14: Change “calstogenicity” to “clastogenicity”.

- Page 4-432, line 24: Altered ciliary beat has been noted in as little as 15…

Comments on Volume III

1. **Rumchev et al., (2002)**

    - Under Alternative A page 5-69 of US EPA’s Draft Assessment of Formaldehyde, EPA proposed to use an uncertainty factor (UF) of 3 for human variability, and also to use an UF of 3 for extrapolation from sub-chronic to chronic exposure, and apply these UFs to a No Observed Adverse Effect Level (NOAEL) of 33 parts per billion (ppb), which was based on results from Rumchev, et al., (2002) to derive at a chronic Reference Concentration (RfC) of 3.3 ppb for chronic inhalation exposure to formaldehyde.
    - In the Rumchev et al., (2002) study, the formaldehyde/asthma hypothesis was investigated in young children whose ages ranged from 6 months to 3 years old.

- Children of those ages have developing immune and enzymes systems, and developing central nervous systems.
- Nitrogen dioxide, volatile organics, dust mite, and PM 10 particles were also detected in air samples from the homes investigated in the Rumchev et al., (2002) study.
- The investigators in Rumchev et al., (2002) indicated that their equation model showed that children in the study exposed to formaldehyde air levels exceeding 49 ppb were at increased risk of an incidence of asthma.
- However, there was no indication of any adjustments made for co-exposure to formaldehyde, and the other contaminants reported in that study i.e., nitrogen dioxide, volatile organics, dust mite or PM 10 particles.
- Therefore, the effects observed in the young children in that study may have been as a result of exposure to formaldehyde, or from co-exposure to formaldehyde and other indoor air contaminants.
- Moreover, difficulties in differentiating wheezing , because the children in the investigation were so young, may have provided confounding variables in the study; and the questionnaires employed in the study were filled out by the parents of those children months after the occurrences of the asthmatic symptoms.
- Therefore, because of undeveloped enzyme and immune systems in the young children examined in the Rumchev et al., (2002) study, the children may have been especially vulnerable to toxic insults of indoor air contaminants or to co-exposure to indoor air contaminants, and could be considered a sensitive population.

- Why use an UF of 3 for human variability if a sensitive population was present?

2. **Garrett et al., (1999)**

- Under Alternative A page 5-51 of US EPA'S Draft Assessment of Formaldehyde, EPA proposed to calculate an RfC of 2.8 ppb for chronic inhalation exposure to formaldehyde by applying an UF of 3 for extrapolation of a Lowest Observable Adverse Effect Level (LOAEL) to a NOAEL, and applying another UF of 3 for human variability to a LOAEL of 28 ppb, which was derived from the results of the Garrett et al., (1999) study.
- EPA's justification for using the UF of 3 for human variability is that "since the study findings controlled for both parental asthma and family history it was unclear whether the effects observed in the children were from a sensitive population."
- Garrett et al., (1999) indicated that an apparent association between asthma in children and formaldehyde exposure existed, but the "association did not remain after adjustments were made for parental allergy and parental asthma i.e., the odds ratio for asthma in children was not significantly different from 1."
- The LOAEL probably should have been considered a NOAEL based upon the lack of statistical significance of an adverse effect when an adjustment was made for parental allergy and parental asthma.
- If it was an actual LOAEL (28 ppb), then the population on which the LOAEL is based is the most sensitive population and any adjustment for sensitivity may be inappropriate.
- The effects were based on recall over a year period. It is possible that the reported symptoms did not actually occur within the one-year study period. In addition, positive responses may have been reported merely because a child had an allergy or asthmatic problems in the past, and the parents wanted this recognized.
- The presence of airborne chemicals other than formaldehyde and NOx were not tested. Oven cleaners, bleach, ammonia, and other household chemicals such as paints or solvents can cause asthma-like symptoms. Furthermore, asthmatics are often sensitive to other odors, such as perfume and deodorants. Moreover, emotional stress (with or without the presence of airborne chemicals) can sometimes elicit an asthmatic event.
- Although 33% of the children were reported to be exposed to passive smoking, there were no adjustments for passive smoking indicated.

- Heavy smoking (especially in cars) can elicit asthma attacks or other symptoms of respiratory distress.
- Since samples were collected only four times, additional uncertainty may have been created.
- The actual exposure level was not known at the time the reported asthma or asthma-like events were experienced (*i.e.* proximity to the 4 monitoring sessions is unknown).
- Although tests for environmental particles such as pollen and mold were conducted, it is unclear what the precise cause of any reported asthma-like symptoms was.
- This may be a possible cause of the onset of symptoms in the study population, although it was apparently not considered or even known to the researchers.
- The study population may have been biased, since there was a larger number of respondents to the study solicitation by parents with asthmatic children.
- To the best of our knowledge, the hypothesis that exposure to indoor air levels of formaldehyde enhances asthmatic episodes to allergens has not been reported by results from a controlled environment, until recently.
- For example, Ezratty et al., (2006) exposed 12 subjects between 18 and 44 years of age to 400 ppb of formaldehyde, or to pure air, in a controlled study for 60 minutes on 2 different days at 0700 hr.
- The formaldehyde exposures were on the same day of the week, and separated by 2 weeks between.
- The objective of the Ezratty et al., (2006) study was to ascertain whether a 1 hour exposure to 400 ppb of formaldehyde enhances the asthmatic responses to inhaled pollen allergen in volunteers who were reported to have pre-existing intermittent asthma.
- The investigators in Ezratty et al., (2006) concluded that inhalation exposure to 400 ppb of formaldehyde did not enhance the asthmatic response to allergen, and that an underlying protective effect was observed.
- These investigators also indicated that “additional studies with repeated exposures to formaldehyde are necessary to clarify the interactions of formaldehyde and allergens in the airways of subjects with pre-existing asthma” (Ezratty et al., 2006).
- However, a recently published meta-analysis study has provided support for the formaldehyde inhalation exposure/asthma hypothesis (McGwin et al., 2010).

- Under Alternative B on page 5-52 of US EPA'S Draft Assessment of Formaldehyde, EPA indicated that Figure 5-8 refers to formaldehyde levels related to increased incidences of asthma from the Garrett et al., (1999) study, but Figure 5-8 depicts prevalence of eye irritation from the Ritchie and Lehnen (1987) study (See figure 5-8).
- Please make units consistent in Tables with those in the Text, e.g. make all units parts per billion, or micrograms/cubic meter for clarity (See pages 5-48; 5-51; 5-53 and 5-54).

3. **Ritchie and Lehnen, (1987)**

- Under Alternative A page 5-59 of US EPA's Draft Assessment of Formaldehyde, EPA proposed to apply an UF of 3 (human variability) to a NOAEL of 50 ppb to derive at an RfC of 17 ppb for chronic inhalation exposure to formaldehyde.
- EPA indicated that the basis for using the UF of 3 for human variability was because of "prevalence rates decreasing the likelihood that effects on sensitive individuals would be lost due to response averaging."
- The subjects in the Ritchie and Lehnen (1987) study were less than 7 years of age and up to 54 years of age in both sexes.
- According to Ritchie and Lehnen (1987), "subjects exposed to formaldehyde in the Hanrahan (1984) study showed a dose response relationship for burning eyes and eye irritation, and age had an inverse relationship with burning eyes and eye irritation in that study."
- However, negative effects of age for the eye irritation response were not reported by data from the Ritchie and Lehnen (1987) study.
- Nose and throat irritation data for respondents under the age of 7 were not used in the Ritchie and Lehnen (1987) study.
- Furthermore, there was no indication in the Ritchie and Lehnen study that respondents under age 7 eye irritation data were used;
- Therefore, the study does not appear to have made adjustment for age in the model.
- The effects observed may have been driven by children under 7 years of age, and if so, an UF should not be used.
- By contrast, if it can be determined that the adverse effects observed in the Ritchie and Lehnen (1987) study were driven by a group that is over 7 years of age, then it would be prudent public practice to act conservatively and apply an UF of 3 for human variability.

- Alternative A page 5-59 of US EPA'S Draft Assessment of Formaldehyde, EPA stated that the prevalence rate in the less than 100 ppb exposure to the formaldehyde group from the Ritchie and Lehnen (1987) study was 1 to 4%.
- However, on page 324 of Ritchie and Lehnen (1987) study under the eye irritation section it depicts that at less than 100 ppb of formaldehyde exposure there was approximately 1 to 2% of the subjects reported eye irritation.
- Although there was no information provided to indicate what age group was mostly responsible for the adverse irritation effects in the Ritchie and Lehnen study, it seems as though a sensitive sub-population may have been incorporated, since the subjects in the study ranged from less than 7 years of age with developing enzyme, immune and central nervous systems, to 54 years of age of both sexes.
- Why use an UF of 3 for human variability since a sensitive sub-population in the Ritchie and Lehnen (1987) study may have been present?

4. **Taskinen et al., (1999)**

- The final group of women in the Taskinen et al., (1999) study as shown in Table I consisted of 602 women. From this group there were drawn unexposed and exposed individuals. Whereas for the Formaldehyde and Phenols variables the total number of exposed and unexposed was 602.
- The sum of the unexposed and exposed for Organic Solvents, Dusts and Wood dusts variables was 630.
- Where did these 28 individuals come from?
- Are they the 28 cases where the time-to-pregnancy (TTP) period had started before entering the branch (page 211 lines 19-20) of the Taskinen et al. study?
- Were these 28 cases included in the analysis of TTP and Organic Solvents, or Dust or Wood dust?
- If this is a typographic error, in which categories where the number over represented?

- **Exposure Assessment.** From Table II there were 114 out of 235 women, roughly 49% of the exposed women, where no data of formaldehyde measurements were available.
- However, for exposure assessment, "measurement from workplaces of the same industrial activity were used as the basis of estimation" (page 208).

- Are there studies that show a good correlation on exposure measurements between workplaces with same industrial activities?
- Could it be that the measurements used may have overestimated as well as underestimated the exposure measurements, and thus weakened the conclusion of the study?
- Has the data been analyzed using only women from workplaces where the measurements were done?
- If this the case, have the results been different in term of statistical significance?

- **Recall Bias**. In the calculation of the Daily Index, the proportion of the exposed work time during a work-data depends on the detailed work task description from the questionnaires.
- In this case, might the recall bias have been a problem?

- **Regarding the Fecundability Density Ratio (FDR).** The odds ratios for formaldehyde were, as for Table VI page 209, adjusted for the following potential confounding factors: employment (yes/no); smoking; alcohol consumption, irregular menstrual cycles and, number of children.
- The aOR was significant for the high formaldehyde-exposed group (aOR 0.64; 95%CI=0.43-0.93).
- At page 210, first paragraph, it seems also that when phenols were entered in the model the aOR strengthened (aOR=0.57; 95%CI=0.37-0.85) and we are assuming that it refers to the formaldehyde-exposed group versus non-exposed group, since it did not mention that the categorical variable formaldehyde was used as four groups (high/medium/low/unexposed).
- In this case, the number of observations that were calculated in the model should have been lower than the previous one, since "all women exposed to phenols (n=68 from Table VIII and in the text) were also exposed to formaldehyde, but not vice versa."
- In the introduction section of the Taskinen (1999) paper, page 207, it is stated and given references that occupational exposures to organic solvents have been related to several reproductive effects, among them reduced fertility and spontaneous abortions that are health outcome variables in the investigation.
- In the Taskinen (1999) study, exposure to organic solvents was not associated with Fecundability Density Ratio and we note that in the model was also included formaldehyde.
- In this case the categorical variable formaldehyde entered as two groups (exposed/unexposed) or four groups (high/medium/low/ unexposed).
- In the latter case, what were the aOR for the different formaldehyde-exposed groups?

- That is, when in the model were included formaldehyde and organic solvents was the aOR for formaldehyde still statistical significant, and what was the magnitude of any change?
- Since the rational to adjust the OR for organic solvents with the inclusion of formaldehyde would have been the fact that formaldehyde have been reported to be somewhat associate with prolonged time to pregnancy, this is also true for the organic solvents and therefore should have been a confounding variable in the model for FDR and formaldehyde exposure.

- **Regarding the Previous Spontaneous Abortion Outcome**. It is not clear whether the previous spontaneous abortion reported by women has been previously diagnosed by a doctor or self-diagnosed.
- However, there were 96 women reporting spontaneous abortions, and of this, 52 women had the same work place during the year of spontaneous abortions as they had during the beginning of the time-to-pregnancy.
- The analysis restricted only to these 52 women reported a significant OR to have had a spontaneous abortion.
- Although it is not specified on page 210 of the Taskinen (1999) paper what type exposure, except that there were three groups (high/medium/and low).
- We may assume that it was formaldehyde since the abstract stated that "Additionally, an association was observed between exposure to formaldehyde and an increased risk of spontaneous abortion.."
- In the last sentence of the method section is stated that: "The odds ratios (OR) for other outcomes were calculated by unconditional logistic regression: adjustments were done for age, employment, smoking and alcohol consumption."
- So, is it correct to assume that the OR for spontaneous abortion was adjusted only by these confounding factors?
- Among these 52 women, there were women with endometriosis, since their endometriosis has been associated with spontaneous abortions?
- Among these 52 women, there was also reported exposure to organic solvents (a variable that has been previously associated with spontaneous abortions, as stated in the introduction, and therefore could have been a risk factor)?
- If there were organic solvent exposures, would the inclusion of this variable in the model have altered the statistical significance of the formaldehyde exposure?
- There was also no mention of this important finding in the discussion section, or in the conclusion section, whereas several paragraphs are spent discussing the endometriosis and salpingo-oophoritis results.
- Yet these finding found relevance in the abstract. One wonders whether the authors were unsure about the spontaneous abortion finding.

- **Regarding the Endometriosis Outcome**.
- Is the OR for organic solvents adjusted also for formaldehyde?
- If so, what would have been the OR for each formaldehyde-exposed group?

5. **ATSDR's Toxicological Profile on Formaldehyde**
    - ATSDR is currently re-evaluating the chronic inhalation exposure Minimal Risk Level of 8 ppb for formaldehyde through the development of a Toxicological Profile for Formaldehyde.
    - The agency will soon release an updated literature review for formaldehyde.
    - Finally, ATSDR does not refute or cast doubt upon the Hauptman et al. (2004) epidemiological study, which provided results of increased risks of formaldehyde induced nasopharnyxgeal cancer in former workers from 10 US formaldehyde related plants. Reportedly, the National Cancer Institute derivation of its carcinogenic classification of formaldehyde was based on the results of the Hauptman et al. (2004) epidemiological study. ATSDR suggests to approach and to evaluate the results of the Hauptman et al., (2004) study with caution. This is based upon our knowledge of independent reviews of the epidemiological data by other authors who previously have casted doubt on the Hauptman et al. (2004) study i.e., Marsh et al., (2007) and Bosetti et al., (2006).

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