



Centers for Disease Control
and Prevention (CDC)
Atlanta, GA 30333

December 17, 2010

David B. Fischer
Senior Director, Chemical Product and Technology Divisions
American Chemistry Council
700 2nd Street, NE
Washington DC, 20002

Dear Mr. Fischer:

The National Center for Environmental Health (NCEH), Centers for Disease Control and Prevention (CDC) received the September 3, 2009 Request for Correction (RFC) from the Formaldehyde Council Inc. (FCI) regarding the CDC report entitled "Final Report on Formaldehyde Levels in FEMA-Supplied Travel Trailers, Park Models, and Mobile Homes." CDC program and scientific staff have carefully reviewed the FCI request to change statements in the CDC Final Report.

The FCI request pertains to three statements in the first two paragraphs of the background section of the 56-page CDC Final Report. The information provided in the background section of this report provides the context for the applied research stated in the report. This background section was not intended to be a comprehensive review of formaldehyde toxicity and thus was not intended to present information on all scientific opinions and literature related to formaldehyde toxicity. Instead, references were specifically selected to support discussion of the impacts on the most vulnerable populations. However, we agree that a more robust listing of references may be helpful and we have amended the web disseminated version of the report to include updated citations.

First request: It pertains to the following statement (Statement 1):

Statement 1 (as stated in the FCI letter): "...upper respiratory tract irritation can exacerbate symptoms of asthma and other respiratory illnesses (Main et al., 1983; Bracken et al., 1985; Kilburn et al., 1985; Imbus 1985; Anderson et al., 1979)."

The FCI states that Statement 1 is inaccurate because it "is not supported by the citations provided or by reviews from other government bodies including CDC's ATSDR."

CDC Response: This sentence fragment is in the opening paragraph of the Health Effects background section of the CDC Final Report. The first two sentences of this paragraph are:

Part 1: "Symptoms from acute exposure to formaldehyde commonly manifest as irritation

of the throat, nose, eyes, skin, and upper respiratory tract.”

Part 2: “This upper respiratory tract irritation can exacerbate symptoms of asthma and other respiratory illnesses.”

The references cited (Main et al., 1983; Bracken et al., 1985; Kilburn et al., 1985; Imbus 1985; Anderson et al., 1979) and other references in the scientific literature directly support the scientific statement that formaldehyde is an irritant, as indicated in Part 1. In a clinical review of formaldehyde exposure, Imbus et al. highlight two examples of formaldehyde exposure resulting in asthma symptoms. Three nurses occupationally exposed to formalin present asthma symptoms (recurrent wheezing and coughing) when exposed to formaldehyde. These symptoms were reproduced with an inhalation challenge test (Hendrick et al. 1977; Imbus 1985). Main et al. state, when referring to a group of individuals exposed to formaldehyde, that: “Symptoms of eye and throat irritation and increased headache, fatigue were significantly more common among the exposed group than the comparison group. Irritation of the nose, chest tightness, and shortness of breath were also more common among the exposed” (1983, p 896). In Kilburn et al.’s study of occupational formaldehyde exposure among four different worker groups, the proportion of individuals reporting respiratory symptoms (chest tightness, pain and burning, and shortness of breath), cough, eye and throat irritation increased with higher formaldehyde exposure (Kilburn et al. 1985). In Braken et al.’s study, subjects residing in urea formaldehyde foam insulation (UFFI)-containing homes, subjects residing in homes without UFFI, and subjects working in laboratories with regular formaldehyde exposure were surveyed for respiratory symptoms and formaldehyde exposure; although the magnitude of exposure varied across groups, all three groups were indeed exposed to formaldehyde and subsequently reported cough, phlegm and wheezing (Bracken et al. 1985). Anderson et al., in their study of mice and urea and phenol formaldehyde, reported decreases in respiratory rate with increased exposure to formaldehyde; urea formaldehyde was more debilitating than the phenol formaldehyde (Anderson et al. 1979). Additional supporting evidence points to the relationship between chronic low-level formaldehyde exposure and the prevalence of asthma and asthma symptoms in children (Garrett et al. 1999; Rumchev et al. 2002; Jaakkola et al. 2004).

Imbus also references a study by Nordman et al., which supports Part 2 of the Statement 1. Nordman et al. found that of 230 asthmatics, twelve showed decreased lung function during bronchial provocation tests with formaldehyde (Nordman et al. 1985). Krzyzanowski et al. reported, from their study of 298 children, that children living in houses with 60-120ppb formaldehyde reported significantly higher prevalence of asthma and chronic bronchitis; a linear relationship was observed between a decrease in peak expiratory flow rates and increase in residential formaldehyde levels (Krzyzanowski et al. 1990). A molecular mechanism to explain how formaldehyde may exacerbate asthma is under study (Staab et al. 2008; Thompson et al. 2008).

As evidenced by these enumerated references and others, science does support both Part 1 (“Symptoms from acute exposure to formaldehyde commonly manifest as irritation of the

throat, nose, eyes, skin, and upper respiratory tract.”) and Part 2 (“This upper respiratory tract irritation can exacerbate symptoms of asthma and other respiratory illnesses.”). Furthermore, we specifically chose the word “can” in Part 2 to indicate possibility and cited studies in support of the goal of protecting the most vulnerable population against the prospect of any harm from exposures. While there may not be complete agreement in the scientific literature as to whether formaldehyde does or does not exacerbate asthma, there is sufficient evidence to support our original statement.

FCI also judges that Statement 1 is not supported by reviews from other government bodies including CDC’s ATSDR Toxicological Profile on Formaldehyde. FCI ends the quote from page 236 of the ATSDR Toxicological Profile with the following sentence: “Formaldehyde exposures at the concentrations tested (usually >3ppm) did not exacerbate existing asthmatic conditions, either at rest or after exercise.” However, the following two sentences in the Toxicological Profile state: “However, Nordman et al. (1985), in a human population of 230 persons suffering asthmatic symptoms and exposed to formaldehyde, found that when exposed to 2.04 ppm formaldehyde for 30 minutes, eight subjects demonstrated an immediate bronchial reaction, four subjects demonstrated a delayed reaction, and two subjects demonstrated both immediate and delayed reaction. Peak expiratory flow rates dropped 19-49% in the immediate-reaction group and 21-47% in the delayed reaction group” (Agency for Toxic Substances and Disease Registry 1999). Therefore, a more complete reading of the ATSDR Toxicological Profile on Formaldehyde shows that Statement 1 to be supported by the ATSDR Toxicological Profile.

Statement 1 is also supported by three expert review panels:

- In 2007, the National Heart and National Asthma Education and Prevention Program Expert Panel updated its 1997 report with a statement on formaldehyde on page 166: “Formaldehyde and volatile organic compounds have been implicated as potential risk factors for asthma and wheezing.” (National Heart and National Asthma Education and Prevention Program Expert Panel 2007)
- The National Academy of Science summarized on page 223 of the Spacecraft Maximum Allowable Concentrations for Select Airborne Contaminants: “Exposures to formaldehyde in air can result in immunologically-induced sensitization of the respiratory tract” (McCoy 2008).
- Institute of Medicine’s expert review panel concluded on page 246 of Clearing the Air: Asthma and Indoor Air Exposure that there is: “limited or suggestive evidence of an association between formaldehyde exposure and wheezing and other respiratory symptoms” (Institute of Medicine 2000).

Finally, the FCI suggests that studies in the CDC Final Report were “cherry-picked” because studies that do not support Statement 1 were not included. It is important to note the context of the report which focused on the potential long-term formaldehyde exposure of extremely vulnerable populations, including elderly, children, and the chronically ill, in a residential setting. The literature cited was relevant for a conservative public health evaluation to ensure protection of this entire vulnerable population and was not intended to serve as a complete toxicological profile. In addition, Statement 1 expresses that “upper

respiratory track irritation *can* exacerbate symptoms of asthma and other respiratory illnesses” (emphasis added). It is not necessary for all studies to find evidence for exacerbation of asthma and other respiratory illnesses for Statement 1 to be accurate and supported by the reference provided. Studies have different designs, different statistical powers and examine different exposure levels and durations. Since there is evidence that exacerbation of asthma and other respiratory illnesses can occur (and this is supported by the references given), Statement 1 is accurate even if exacerbation was not detected in all studies. However, CDC/NCEH recognizes that a more robust listing of references may be helpful and we have amended the web disseminated versions of the report to reflect the citations discussed above. Please see Appendix A for the list of references added to the report.

Second request: The FCI’s second request pertains to the following statement (Statement 2):

Statement 2: "At 800 ppb, nearly everyone develops some acute irritative symptoms; however, formaldehyde-sensitive persons have reported symptoms at levels around 100 ppb (Main et al., 1983; Bender et al., 1983). Additional studies have found health effects at 100 ppb in sensitive persons chronically exposed to formaldehyde (Ritchie et al., 1987)."

The FCI judges Statement 2 to be inaccurate for two reasons: (1) “it is incorrect to state that this is what everyone will experience” and (2) “the statements about reported effects at 100 ppb are demonstrably incorrect.”

CDC response: Statement 2 is in the second paragraph of the Health Effects background section in the CDC Final Report. Statement 2 has two parts:

Part 1: Nearly everyone develops some acute symptoms of irritation when exposed to 800 parts per billion [800 ppb] of formaldehyde.

Part 2: Some people report symptoms when exposed to 100 parts per billion [100 ppb] of formaldehyde.

In Part 1 of Statement 2, the CDC Final Report does not say that “everyone” will develop symptoms. The CDC Final Report says that “*nearly* everyone” exposed to 800 ppb of formaldehyde will develop acute symptoms of irritation. Bender et al. (1983) support this statement with a reference to a study reporting “15 of 16 subjects exposed to 0.8 ppm [which is equivalent to 800 ppb]” of formaldehyde presented eye, nose, and throat irritation (Bender et al. 1983). Bender et al.’s study of eye irritation and formaldehyde response demonstrated statistically significant irritation at concentrations of 1,000 ppb (sample size 27), and the authors suggested that a larger sample size might have generated similar results at concentrations of 700 and 900 ppb (study sample sizes 7 and 6, respectively) (Bender et al. 1983). Main et al. demonstrate that varying levels of formaldehyde exist in mobile home trailers and the presence of formaldehyde was associated with increased eye irritation, throat irritation, fatigue and headache (Main et al. 1983).

Further support that nearly everyone exposed to 800 ppb of formaldehyde will develop acute symptoms of irritation is found in the manuscript by Hanrahan et al. (1984). Hanrahan et al. describe an association between exposure to formaldehyde at 800 ppb and eye irritation based on a cross-sectional survey using a random sample of mobile homes and sixty-one participants (Hanrahan et al. 1984). Observations from these participants, who were exposed to formaldehyde concentrations ranging from 100 ppb to 800 ppb, were used in a logistic regression model which predicted an 80% prevalence of eye irritation at 800 ppb.

The FCI also judges Statement 2 to be inaccurate stating that “statements about reported effects at 100 ppb are demonstrably incorrect.” However, a reference with reported effects at 100 ppb is provided in the CDC Final Report. The cited article by Ritchie et al. (1987) describes a Minnesota Department of Health (MDOH) cross-sectional study of 2,000 individuals living in 397 mobile and 494 conventional homes in Minnesota who were concerned about exposure to formaldehyde. Ritchie et al. states, when referring to the results of their analysis of MDOH data, that: “The Minnesota data indicate excessive occurrence of skin rash, eye, nose and throat irritation, and headache at HCHO [formaldehyde] concentrations of 0.1 ppm and above and corroborate conclusions of the WHO Work Group that concentrations greater than 0.1 ppm may be sufficient to call for corrective action” (Ritchie et al. 1987).

In addition, Statement 2 is supported by the ATSDR-established minimal risk level (MRL) of 0.008 ppm (the equivalent of 8 ppb) for respiratory health outcomes associated with chronic inhalation exposure to formaldehyde. The MRL is established from numerous toxicology studies as “an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects” (Agency for Toxic Substances and Disease Registry 2010). In the case of formaldehyde, this indicates that some risk of adverse health effects exists for individuals exposed to more than 8 ppb. It follows that formaldehyde-sensitive individuals may experience negative health effects at concentrations of 100 ppb.

The FCI provides, as supporting information, studies that did not find effects at 100 ppb. However, the CDC Final Report does not state that all individuals have these effects rather that “formaldehyde-sensitive persons have reported symptoms at levels around 100 ppb.” In addition, it does not state that *all* studies have found effects instead that “*additional* studies have found health effects at 100 ppb in sensitive persons chronically exposed to formaldehyde” (emphasis added). These statements are accurate and are supported by the references as well as the scientifically-established MRL. However, CDC/NCEH recognizes that a more robust listing of references may be helpful and we have amended the web-disseminated version of the report to reflect the citations discussed above. Please see Appendix A for the list of references added to the report.

Third request: The FCI third request pertains to the following statement (Statement 3):

Statement 3: "Sensitive and sensitized persons can experience symptoms without detecting odor and thus receive little or no warning of exposure (Kulle et al. 1987; Weisel et al. 2005)."

The FCI judges Statement 3 to be inaccurate stating "there is no evidence that inhaled formaldehyde is capable of sensitizing the respiratory tract."

CDC response: Statement 3 is in the second paragraph of the background section. The last two sentences of the paragraph are: "Typically, olfactory recognition occurs around 500 ppb, leaving the average exposure from a home below this level. Sensitive and sensitized persons can experience symptoms without detecting odor and thus receive little or no warning of exposure (Kulle et al. 1987; Weisel et al. 2005)."

The CDC Final Report did not specifically state, as suggested in the FCI request, that inhaled formaldehyde is capable of sensitizing the respiratory tract. Instead, the CDC Final Report stated that some people who are exposed to formaldehyde can experience symptoms without detecting the odor of formaldehyde. This statement is supported by the cited manuscript by Kulle et al. (1987) which states that "at 3 ppm, all nine subjects experienced eye irritation" but formaldehyde odor was detected by only six of nine participants. Furthermore, at lower concentrations of 2.0 ppm, "six subjects reported mild eye irritation and four reported moderate eye irritation," but only eleven of the nineteen participants detected odor. In addition, this statement is supported by the aforementioned ATSDR-established MRL of 8 ppb for respiratory health outcomes associated with chronic inhalation exposure to formaldehyde. As previously stated, olfactory recognition may not occur until exposure levels reach 500 ppb. However, the MRL suggests some risk of adverse noncancer health effects at levels as low as 8 ppb. Therefore, persons sensitive to effects of formaldehyde may experience adverse health effects prior to odor detection.

In response to FCI's statement, two separate studies in children have reported allergic sensitization, as measured by increased formaldehyde-specific IgE antibody formation, following inhalation exposure to environmental levels of formaldehyde (0.012-0.075 ppm) (Wantke et al. 1996; Garrett et al. 1999). Additionally, we refer to The National Academy of Science summary on page 223 of the *Spacecraft Maximum Allowable Concentrations for Select Airborne Contaminants*: "Exposures to formaldehyde in air can result in immunologically induced sensitization of the respiratory tract" (McCoy 2008). There is also literature showing that formaldehyde can induce allergic skin sensitization in both humans and animals (Maibach 1983; Lee et al. 1984; Fischer et al. 1995; Kiec-Swierczynska 1996; Marks et al. 1998). However, CDC/NCEH recognizes that a more robust listing of references may be helpful and we have amended the web-disseminated version of the report to reflect the citations discussed above. Please see Appendix A for the list of references added to the report.

Conclusion: In summary, after careful review of FCI's request we find that the statements in the CDC "Final Report on Formaldehyde Levels in FEMA-Supplied Travel Trailers, Park Models, and Mobile Homes" are supported by scientific literature. To ensure that this is clear, CDC/NCEH **has amended** the web disseminated version of the CDC Final report to include the 20 additional references referred to in this response. Please see Appendix A for the list of references added to the report.

A written appeal or electronic request for reconsideration may be submitted within 30 days of receipt of the agency's decision. The appeal must state the reasons why the agency response is insufficient or inadequate. The appeal must attach a copy of the original request and the agency's response to it. Also, clearly mark the appeal with the words "Information Quality Appeal." Appeals may be sent to:

By Mail:

Centers for Disease Control and Prevention
Management Analysis and Services Office
1600 Clifton Road, N.E., Mailstop E-11
Atlanta, Georgia 30333 **or**

By Fax:

Facsimile: (404) 929-2781 **or**

By Electronic Mail:

E-mail: InfoQuality@cdc.gov **or**

By Website Submission:

Submission: <http://www2.cdc.gov/PublicInquiry/PIAppealForm.asp?theID=35>

Sincerely,



Vikas Kapil, DO, MPH, FACOEM
Chief Medical Officer and Associate
Director for Science, National Center
for Environmental Health, and
Agency for Toxic Substances and
Disease Registry
Centers for Disease Control and Prevention

Appendix A

This list of references will be added to the web version of the CDC Report “Final report on Formaldehyde Levels in FEMA-supplied travel trailers, park models, and mobile homes” in support of the three following statements (page 4, paragraphs 1 & 2).

The report can be found here:

<http://www.cdc.gov/nceh/ehhe/trailerstudy/assessment.htm#final>

Statement 1: Symptoms from acute exposure to formaldehyde commonly manifest as irritation of the throat, nose, eyes, skin, and upper respiratory tract. This upper respiratory tract irritation can exacerbate symptoms of asthma and other respiratory illnesses. (Main et al., 1983; Bracken et al., 1985; Kilburn et al., 1985; Imbus 1985; Anderson et al., 1979)

1. Garrett, M., M. Hooper, et al. (1999). "Increased Risk of Allergy in Children Due to Formaldehyde Exposure in Homes." *Allergy* 54: 330-337
2. Hendrick, D. and D. Lane (1977). "Occupational Formalin Asthma." *British Journal of Industrial Medicine* 34: 11-18.
3. Institute of Medicine (2000). *Clearing the Air: Asthma and Indoor Exposures*. Washington DC, National Academy of Sciences.
4. Jaakkola, J. J., H. Parise, et al. (2004). "Asthma, Wheezing, and Allergies in Russian Schoolchildren in Relation to New Surface Materials in the Home." *American Journal of Public Health* 94(4): 560-562.
5. Krzyzanowski, M., J. J. Quackenboss, et al. (1990). "Chronic respiratory effects of indoor formaldehyde exposure." *Environmental Research* 52(2): 117-125.
6. McCoy, J. T. (2008). *Formaldehyde. Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants*. C. o. T. Committee on Spacecraft Exposure Guidelines, National Research Council, National Academies Press. 5: 206-249.
7. [NHLBI et al.,] National Heart, Lung, and Blood Institute, and National Asthma Education and Prevention Program Expert Panel (2007). *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*. Bethesda, MD, US Department of Health and Human Services, National Institutes of Health.
8. Nordman, H., H. Keskinen, et al. (1985). "Formaldehyde asthma -- Rare or overlooked?" *J Allergy Clin Immunol* 75: 91-99.
9. Rumchev, K., J. Spickett, et al. (2002). "Domestic Exposure to Formaldehyde Significantly Increases the Risk of Asthma in Young Children." *European Respiratory Journal* 20(403-408).
10. Staab, C., M. Hellgren, et al. (2008). "Dual Functions of Alcohol dehydrogenase 3: implications with focus on formaldehyde and S-nitrosolglutathione reductase activities." *Cellular and Molecular Life Sciences* 65: 3950-3960.
11. Thompson, C. M. and R. C. Grafstrom (2008). "Mechanistic Considerations for Formaldehyde-Induced Bronchoconstriction Involving S-Nitroglutathione Reductase." *Journal of Toxicology and Environmental Health Part A* 71: 244-248.

Statement 2: At 800 ppb, nearly everyone develops some acute irritative symptoms; however, formaldehyde-sensitive persons have reported symptoms at levels around 100 ppb (Main et al., 1983; Bender et al., 1983). Additional studies have found health effects at 100 ppb in sensitive persons chronically exposed to formaldehyde (Ritchie et al., 1987).

1. [ATSDR] Agency for Toxic Substances and Disease Registry. (1999). "Formaldehyde." Toxic Substances Portal Retrieved June 29, 2010, from www.atsdr.cdc.gov/substances/toxsubstance.asp?toxid=39.
2. Hanrahan, L., M. Kay, et al. (1984). "Formaldehyde Vapor in Mobile Homes: A Cross Sectional Survey of Concentrations and Irritant Effects." American Journal of Public Health 74: 1026-1027.

Statement 3: Sensitive and sensitized persons can experience symptoms without detecting odor and thus receive little or no warning of exposure (Kulle et al. 1987; Weisel et al. 2005).

1. Fischer, T., K. Andersen, et al. (1995). "Clinical standardization of the TRUE Test formaldehyde patch." Current Problems in Dermatology 22: 24-30.
2. Garrett, M., M. Hooper, et al. (1999). "Increased Risk of Allergy in Children Due to Formaldehyde Exposure in Homes." Allergy 54: 330-337.
3. Kiec-Swierzynska, M. (1996). "Occupational allergic contact dermatitis in Lodz:1990-1994." Occup Med 48: 205-208.
4. Lee, H. K., Y. Alarie, et al. (1984). "Induction of formaldehyde sensitivity in guinea pigs." Toxicology and Applied Pharmacology 75(1): 147-155.
5. Maibach, H. (1983). Formaldehyde: effects on animal and human skin. Formaldehyde Toxicity. J. Gibson. Washington DC, Hemisphere Publishing Corporation: 166-174.
6. Marks, J., D. Belsito, et al. (1998). "North American Contact Dermatitis Group patch test results for the detection of delayed-type hypersensitivity of topical allergens." J Am Acad Dermatol 38: 911-918.
7. Wantke, F. and Wantke (1996). "Exposure to gaseous formaldehyde induces IgE-mediated sensitization to formaldehyde in school-children." Clinical and experimental allergy 26(3): 276.