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Via Messenger and E-Mail
Scientific Review Panel
c/o Jim Behrmann
California Air Resources Board
2020 "L" Street
Sacramento, California 95812

Re: Petition for Review of Formaldehyde Risk Assessment, CAS No. 50-00-0

Dear Panel Members:

I am writing on behalf of the Formaldehyde Council, Inc. (Council), the successor to the Formaldehyde Epidemiology, Toxicology and Environmental Group, Inc. (FETEG). This letter supplements the petition for review of the formaldehyde risk assessment that was submitted by FETEG, dated April 11, 2002.

This letter responds to the recommendation of the Office of Environmental Health Hazards Assessment (OEHHA) to California Air Resources Board (CARB) Chairman Alan C. Lloyd, Ph.D., that the Council's petition be denied. It also addresses recent studies evaluating whether formaldehyde exposure increases the risk of leukemia. Specifically, this letter (1) demonstrates how the new evidence, if accepted, would change the original risk assessment, (2) emphasizes the importance of the new biologically-based model that is used to develop a new quantitative estimate for the risk of developing cancer, (3) discusses the extent of peer review, and (4) addresses recent studies that evaluate whether formaldehyde exposure increases the risk of leukemia.

I. Response to the OEHHA Recommendation

On November 21, 2002, OEHHA submitted its recommendation to Chairman Lloyd recommending that he deny the FETEG petition. As explained below, the Council

submits that the OEHHA response incorrectly applied the Scientific Review Panel standards for evaluation and response to submittals of new scientific information as evidence for review of toxic air contaminant risk assessments, approved on December 12, 1989, and incorrectly reached the conclusion that the petition should be denied.

On December 16, 2002, Dr. Rory Conolly from the Chemical Industry Institute of Toxicology (CIIT) made a presentation to a dozen representatives of OEHHA and CARB in which he explained the CIIT model of formaldehyde dosimetry and mode of action and the manner in which the use of the mechanistic data reduces the uncertainty involved in risk assessment. It was hoped that OEHHA would reconsider its negative recommendation of the petition, in light of comments made by Dr. Stan Dawson and Dr. David Morry that the presentation had provided them with a better understanding of and appreciation for the CIIT risk assessment.

At the June 30, 2003 meeting of the Scientific Review Panel, Dr. Morry stated to the Panel that FETEG had not provided enough information to allow OEHHA to understand and reproduce the model, which he acknowledged to be extremely complex. To our knowledge, there is no pending request by OEHHA for additional information. The Council remains available to provide additional information about the CIIT model or any other issue to OEHHA or the Panel.

We attach a copy of the Power Point presentation made by Dr. Conolly on December 16, 2002, as Exhibit A, as a point of reference for some of the discussion that follows.

A. The new evidence would change the original risk assessment

The first step in the Scientific Review Panel's process for evaluation and response to submittals of new scientific information as evidence for review of toxic air contaminant risk assessments asks what in the original risk assessment would be qualitatively or quantitatively changed by the new evidence. The OEHHA response states that "OEHHA staff could find no statement in the petition specifying how the original findings (OEHHA, 1992) would be changed." As stated in the petition, the CIIT quantitative estimates of risk using the biologically-based model indicate that cancer risk to humans would not occur at environmental doses. (Petition, page 9.) The application of the CIIT biologically-based computational modeling would impact

the potency values found in the 1992 California risk assessment.

The first point to be addressed is whether the new evidence, *if accepted*, would change the determination of the health effects of the compound, and, if so, how. The OEHHA response acknowledges that the petition cites post-1992 evidence that conclude there is "little evidence" of a causal link between formaldehyde exposure and human cancer.

- "Turning first to the epidemiologic evidence, with respect to nasal and nasopharyngeal cavities have not been observed consistently in [human] cohort studies. Where there have been excesses, there has been little evidence of exposure-response; however, the total number of observed tumors in these investigations was small." (Petition, page 3.)

- "The Report concluded that there 'is little convincing evidence of increased risks of nasopharyngeal cancer in cohort studies of populations of professionals or industrial workers occupationally exposed to formaldehyde.'" (Petition, pages 3-4.)

- "The most recent evaluation of formaldehyde by IARC – post-dating the OEHHA review – considered the relationship between formaldehyde and nasal cancer to be limited, finding that the association observed in some studies resulted from bias, chance, or confounding with other studies." (Petition, page 4.)

- "Collins et al. conducted an updated meta-analysis of formaldehyde exposure and upper respiratory tract cancers and concluded that available studies do not support a causal relation between formaldehyde exposure and human nasopharyngeal cancer." (Petition, page 4.)

- "As for lung cancer, CIIT found 'there is little evidence for a causal relationship between exposure to formaldehyde and lung cancer in case control and cohort studies conducted to date. Increased in mortality or incidence have not been observed consistently, and where examined, there has been consistently no evidence of an exposure-response relationship.'" (Petition, page 4.)

- "A published review by Joseph McLaughlin, former Deputy Chief of the Biostatistics Branch at the National Cancer Institute, concluded: 'When the epidemiologic data on formaldehyde and human cancer are examined in light of the widely accepted causal criteria of strength of the association, consistency and specificity of results, dose-response effects, and biologic coherence and plausibility, the studies published so far fail to provide credible causal evidence.'" (Petition, page 4.)

OEHHA recommends that the ARB dismiss the new evidence as "premature on a change of determination of carcinogenicity because the studies cited that show 'little evidence' of a causal link between formaldehyde exposure and human cancer are only a small portion of the entire evidence for formaldehyde carcinogenicity, and review by an authoritative body, U.S. Environmental Protection Agency (EPA) or IARC, would be a more appropriate first step."

Neither of these considerations is an appropriate basis upon which to deny the petition. The new evidence, if accepted, would change the determination of the health effects of the compound; whether these studies represent a minority or majority portion of the evidence is not a part of the test. Likewise, the test does not require that a petitioner obtain an opinion from "an authoritative body" before bringing a successful petition to the Scientific Review Panel.

However, in fact, U.S. EPA has taken the first step in issuing a rule that proposes National Emission Standards for Hazardous Air Pollutants (NESHAP) for Stationary Combustion Turbines that uses CIIT modeling, which the agency explains "represents the best available application of the available mechanistic and dosimetric science on the dose-response for portal of entry cancers due to formaldehyde exposure." (69 Fed. Reg. 18333 (Apr. 7, 2004).) In choosing to use the CIIT data, U.S. EPA did not use the dose-response value reported in IRIS, noting that "[t]he dose-response value in IRIS is based on a 1987 study, and no longer represents the best available science in the peer-reviewed literature." (*Id.*)

The second point to be addressed is whether the new evidence, if accepted, would change the threshold determination adopted by the board and contained in the regulation, and if so, how. The OEHHA response states that "[t]he petition appears to

be silent on the issue of carcinogenic threshold." (OEHHA Response, page 2.) This is not correct. Again, the petition relies on the CIIT quantitative estimates of risk, which indicate that cancer risk to humans would not occur at environmental doses. (Petition, page 9.) The petition also refers to the draft of the World Health Organization's Concise International Chemical Assessment Document (CICAD), which reaches the conclusion that formaldehyde exposure poses a carcinogenic hazard only under conditions that both induce toxicity and cause sustained regenerative proliferation. (Petition, page 6.) The CICAD is now in final form and contains the same conclusion.[1] Finally, the petition refers to an unofficial English language translation of a document released by the German MAK Commission, which in its now available official translation concludes that the contribution of genotoxicity of formaldehyde "plays no or at most a minor part" in its carcinogenic potential so that "no significant contribution to human cancer risk is expected."[2]

Applying the Scientific Review Panel's test, this new evidence, *if accepted*, would change the determination adopted by the board that there should be no carcinogenic threshold for formaldehyde.

The final point to be addressed is whether the new evidence, if accepted, would change the potency which was the basis of the original risk assessment, and if so, how. The OEHHA response acknowledges that the petition quotes results of a CIIT report which derives potency values that "are far below those obtained by OEHHA." OEHHA then dismisses the CIIT results as needing further validation and acceptance of the model as well as peer review, again failing to apply the applicable test. The test is whether the new evidence, *if accepted*, would change the potency which was the basis of the original risk assessment. As the OEHHA response acknowledges, the CIIT model derives specific potency values that are "far below" those that formed the basis of the original risk assessment.

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[1] International Programme on Chemical Safety, *Concise International Chemical Assessment Document 40: Formaldehyde*, §11, ¶ 11.1.1.2.1 (2002) (Exhibit B). The petition referenced a draft Concise International Chemical Assessment Document (CICAD) for formaldehyde. (*See* petition, footnote 15.)

[2] German MAK Commission, *Formaldehyde*, §6, ¶1 (undated) (Exhibit C).

B. The Importance of the New Evidence as it Relates to the Science Used to Establish the Original Risk Assessment

The Scientific Review Panel process also requires a description of the importance of the new evidence as it relates to the science (*e.g.*, evidence, data, calculations, assumptions, and procedures) used to establish the original risk assessment. This is really the heart of the petition, as it proposes to introduce and use a new biologically-based model to develop a new quantitative estimate for the risk of developing cancer. (Petition, pages 7-10.)

The OEHHA response criticizes the petition for failing to "provide any description of the relationship of the CIIT calculations to those in the original risk assessment." (Response, page 3.) But much of the petition is devoted to detailing the CIIT model, and to explaining how it differs from the linear calculation used by the U.S. EPA in 1987. (Petition, page 7-10.) The model is also explained in detail in Dr. Conolly's Power Point presentation (Exhibit A).

The OEHHA response also concludes that the model is "just a re-interpretation of the same basic evidence reviewed by OEHHA." (Response, page 3.) The OEHHA response overlooks the statement in the petition that the CIIT model "incorporates vastly more data into a biologically based model than used by the U.S. EPA in 1987 with a linear default calculation." (Petition, page 7.) The new model is more than just a "re-interpretation of the same basic evidence …." While the new model uses the same data that the OEHHA model used, it also uses additional data and offers risk assessments that are validated against epidemiological data on formaldehyde workers. (Petition, page 10.) The petition also seeks reopening because the new approach follows the U.S. EPA's proposed revised cancer guidelines, is biologically-based, and uses principles of mode-of-action modelings. Moreover, the Council submits that it is appropriate for CARB to reopen a risk assessment to consider application of a new model to evidence that formed the basis for the original risk assessment if the new model will offer new insight and a more accurate interpretation of the evidence.

At a Toxicology Forum held in February 2004, Dr. Annie Jarabeck of the Office of Research and Development at the U.S. EPA noted that the development of the DNA-protein cross-links as a dosimeter has improved under the auspices of a steering committee formed between U.S. EPA, CIIT, FETEG, and Health Canada in what Dr. Jarabeck described as "a collaborative private partnership effort to essentially

support the development of the biologically-based model."[3] Dr. Jarabeck indicated that the U.S. EPA has an interdisciplinary team engaged in the process of reanalyzing its health risk assessments. (Transcript, pages 153-54.)

When the U.S. EPA Science Advisory Board published its request for nominations for additional expertise for the Formaldehyde/Acetaldehyde/Vinyl Acetate Toxicological Review (FAVATR) Panel, it noted "the precedent setting nature of the assessments using mode of action and biologically based models." The FAVATR Panel is charged with reviewing the new evidence "for consistency in application of the proposed revised cancer guidelines and principles of mode-of-action modeling, with special emphasis on: (a) Weight-of-the-evidence issues to identify key events; (b) the use of pharmacokinetic and pharmacodynamic date; (c) motivation for dose surrogate and effect measures; (d) model structures for interspecies dosimetric adjustment; (e) model structures for dose-response analysis; (f) data-derived uncertainty factors for interspecies and intrahuman variability; and (g) leveraging of data on critical health effects and model structure sharing between routes and across chemically-related compounds to help inform alignment of the estimates."[4]

The U.S. EPA has determined that there have been sufficient advancements to warrant a reassessment of its risk assessment for formaldehyde, based, at least in part, on the insights offered by the CIIT model. The Council submits that it is likewise appropriate for CARB to do the same through the granting of the petition.

C. Extent of Peer Review

In Dr. Conolly's presentation to the CARB and OEHHA representatives in December 2002, he reviewed in more detail the peer review processes that were conducted in Ottawa in March 1998 and in Geneva in January 2001. The 12 members of the

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[3] Transcript of Toxicology Forum: Formaldehyde Session, Washington, D.C., pages 253-60 (Feb. 2, 2004) (Exhibit D).

[4] Environmental Protection Agency Science Advisory Board, Environmental Health Subcommittee, Request for Nominations for Additional Expertise for the Formaldehyde/Acetaldehyde/Vinyl Acetate Toxicological Reviews (FAVATR) Panel, Federal Register, Vol. 68, No. 42 (March 4, 2003) (Exhibit E).

Ottawa panel and several members of the 20-member ad hoc CICAD panel and 19-member final CICAD panel are identified in the presentation. (*See* Exhibit A.)

Since the time the petition was submitted, Health Canada has issued its final Priority Substances List Assessment Report on Formaldehyde. Like the draft, which was included with the petition, the final report notes that "the biologically motivated case-specific model … is considered to provide the most defensible estimates of cancer risk, on the basis that it encompasses more of the available biological data, thereby offering considerable improvement over default …."[5]

II. Formaldehyde and Leukemia

Since the Scientific Review Panel discussed the FETEG petition and the OEHHA response at its June 30, 2003 meeting, the results of updates of three major studies of industrial workers exposed to formaldehyde have been made public. The studies were conducted by the University of Southampton in the United Kingdom (the Coggin study), the National Institute of Occupational Safety and Health (the NIOSH study), and the National Cancer Institute (the NCI study). At its June 30, 2003 meeting, the SRP expressed an interest in reviewing these studies in connection with its consideration of the FETEG petition. For this reason, the Council submits the following information addressing formaldehyde and leukemia.

The three studies were presented by the authors and discussed at a recent Toxicology Forum held on February 2, 2004, in Washington, D.C.[6]

The NCI study involved a cohort of about 25,000 workers in ten U.S. plants that produced or used formaldehyde, and the subjects were employed prior to and were alive in 1966. The recent NCI study summarized the findings from the 1980 to 1995 follow-up. Exposure data was estimated based on information collected on work histories through 1980. (Transcript, pages 43-44.) The authors noted there was "no evidence at all for an association" between formaldehyde exposure and lung cancer. (Transcript, page 62.) The authors concluded that there was some biologic

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[5] Environment Canada and Health Canada, *Priority Substances List Assessment Report: Formaldehyde* at 65-66 (Feb. 2001) (Exhibit F).

[6] *See* footnote 3 and Exhibit D.

plausibility for nasopharyngeal cancer, and that there was clear exposure response for some of the metrics for leukemia. However, the authors acknowledge that they cannot explain the lack of response for cumulated exposure, and that it is difficult to interpret the origination of the leukemia at sites far from the site of initial contact. (Transcript, pages 63-64.)

The NIOSH study involved a cohort of over 11,000 garment workers exposed to formaldehyde in three plants in the mid-to-late 1950's. The follow-up study updated vital status through December 31, 1998. The authors observed no nasal cancers or nasopharyngeal cancers, but their power to detect a twofold increase in those cancers was less than 20 percent. (Transcript, page 81.) They also did not find any evidence of an association between formaldehyde and mortality from respiratory cancers, including lung cancer. (Transcript, page 83.) The authors acknowledged that they were limited in their ability to evaluate exposure response relationships due to a lack of data on individual estimates of exposure. Nevertheless, they concluded that the findings support a "possible relationship" between formaldehyde exposure and myeloid leukemia mortality. (Transcript, page 82.)

The Coggin study involved a cohort of over 14,000 workers employed at six chemical factories in the United Kingdom between 1938 and 1982. Again, exposure data was not available from the early years and the classification of exposure was largely based on subjective reports of managers and workers. (Transcript, page 88.) The Coggin study found an exposure-response relationship between formaldehyde and lung cancer, which became less clear when adjusted for local differences in mortality. (Transcript, page 94.) The authors found the possibility of a small increase in the risk of sino-nasal and nasopharyngeal cancer. (Transcript, pages 95, 102.) The study found no excess in brain cancer and no excess of leukemia. (Transcript, page 96.)

The discussion of the studies by the authors at the Toxicology Forum was followed by a meta-analysis presented by Dr. Jim Collins. (Transcript, pages 109-145.)[7] He reviewed the three epidemiology studies, as well as 15 other studies on leukemia and formaldehyde exposure. Dr. Collins obtained the raw data from the NCI study and calculated standardized mortality ratios using an external comparison group. He found that the relative risk estimates for leukemia were lower and in fact frequently

[7] Power Point presentation by Collins et al., *Evaluating Formaldehyde and Leukemia Risk* (undated) (Exhibit G).

less than expected when an external comparison group was used. (Transcript, pages 134-135.) He concluded that the biological evidence does not support an association between formaldehyde exposure and leukemia. (Transcript, page 138.)

The Toxicology Forum also included a discussion by a six-member panel consisting of Dr Henry Heck, Dr. Annie Jarabek, Dr. Aaron Blair, Dr. Leslie Stayner, Dr. Gary Marsh, and Dr. Bob Tarone. (Transcript, pages 144-94.)

Dr. Heck summarized the biological data. (Transcript, pages 145-53.) He characterized as undisputed a finding that blood concentration does not change in humans, rats or monkeys with formaldehyde exposure. He also cited seven inhalation bioassays of formaldehyde in rats, mice and hamsters at very high concentrations, and noted that leukemia was not induced in any of those inhalation bioassays. He also reported studies in which he and fellow researchers used tritium C-14 labeled formaldehyde to examine the possibility of covalent binding to DNA proteins in rats and monkeys, and in none of those species was there evidence of binding to the proteins or the DNA of bone marrow. Dr. Heck concluded that the experimental data in animals do not support leukemia as a toxic response to inhaled formaldehyde. (Transcript, page 152.)

Dr. Blair was the senior author of the earlier NCI report. He noted that the latency found in the recent NCI study "seems a little out of whack for leukemia." (Transcript, pages 162-63.) Dr. Stayner, the senior author of the earlier NIOSH report, questioned the biological plausibility of leukemia caused by formaldehyde exposure. (Transcript, pages 172-73.)

The recent reports discussed below have reviewed the three studies with a focus on the findings relating to formaldehyde exposure and leukemia. These studies have also concluded that it is implausible or improbable that formaldehyde induces leukemia.

A panel of reviewers was asked by two of the plants participating in the NCI study to comment on a draft manuscript of the study.[8] The reviewers found that the study had

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[8] Casanova et al., *Comments on a Draft Manuscript entitled "Mortality from lymphohematopoeietic malignancies among workers employed in formaldehyde industries* (March 21, 2003) (Exhibit H).

a number of strengths, including large size, long follow-up, and development and consideration of several indices of formaldehyde exposure. However, the panel concluded that the draft manuscript's conclusions are not well justified. The panel identified a number of major concerns. For example, the panel noted that the leukemia found in the study had a longer time since exposure period than one would expect of an induced leukemia. The panel expressed concern that the authors used a two-year lag on formaldehyde exposures without offering any basis for this choice. The panel also noted that the conclusions relied heavily on the findings reported in the exposure-response analysis for peak formaldehyde exposure, and that no satisfactory explanation was offered for the failure to find an association using the two most conventional measures of lifetime exposure – cumulative exposure and duration. The panel believed there were insufficient external comparisons for the exposure-response analysis, and the use of internal comparisons alone were insufficient to support the conclusions. The panel also concluded that the biological evidence does not support the hypothesis that formaldehyde can induce distant site toxicity.

A study by Henry Heck and Mercedes Casanova looked closely at the biological evidence that pertains most directly to the question of whether formaldehyde can induce leukemia and concluded that "[t]he abundant evidence on this question renders unlikely the possibility that inhaled formaldehyde can induce toxicity at distant sites."[9] The authors' conclusions are summarized in the enclosed power point presentation.[10]

Philip Cole and Charles Axten evaluated the three recent epidemiological studies based on Cole's guidelines for causation in the general case. They concluded that the formaldehyde-leukemia hypothesis fails each of the four guidelines of general causation – replicability, strength of association, coherence, and response to manipulation.[11]

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[9] Heck et al., *The Implausibility of Leukemia Induction by Formaldehyde: A Critical Review of the Biological Evidence on Distant-Site Toxicity* (undated) (Exhibit I).

[10] Power Point presentation by Casaheck Consulting, *Formaldehyde and Leukemia Risk* (April 7, 2004) (Exhibit J).

[11] Cole et al., *Formaldehyde and Leukemia: An Improbable Causal Relationship* (March 7, 2004) (Exhibit K).

Likewise, a meta-analysis of formaldehyde exposure and leukemia risk concluded that the epidemiology data do not show consistent findings across studies of leukemia risk, and that the inconsistent findings and the lack of biological plausibility argue against formaldehyde as the cause of increased risk.[12]

The studies evaluating the three new epidemiological studies are consistent with the studies cited in the petition suggesting little evidence of a causal relation between formaldehyde exposure and human cancer, and further support the granting of the petition.

III. Conclusion

The Council submits that the information contained in and with its petition and this supplemental letter warrant the granting of its petition and reconsideration of the risk assessment on formaldehyde. The Council requests that the Scientific Review Panel recommend to the Chairman Lloyd that the petition be granted.

Sincerely,

GENE LIVINGSTON

GL/sma

Enclosures

cc: Betsy Natz, Formaldehyde Council, Inc. (w/o encls.)

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[12] Collins et al., *A Review and Meta-analysis for Formaldehyde Exposure and Leukemia Risk* (March 10, 2004) (Exhibit L).

List of Exhibits

A. Power Point presentation by Conolly, *Biologically motivated computational modeling of formaldehyde dosimetry and mode of action: Using mechanistic data to reduce risk assessment uncertainty* (Dec. 16, 2002).

B. International Programme on Chemical Safety, *Concise International Chemical Assessment Document 40: Formaldehyde* (2002).

C. German MAK Commission, *Formaldehyde* (undated).

D. Transcript of Toxicology Forum: Formaldehyde Session, Washington, D.C., pages 253-60 (February 2, 2004).

E. Environmental Protection Agency Science Advisory Board, Environmental Health Subcommittee, Request for Nominations for Additional Expertise for the Formaldehyde/Acetaldehyde/Vinyl Acetate Toxicological Reviews (FAVATR) Panel, Federal Register, Vol. 68, No. 42 (March 4, 2003)

F. Environment Canada and Health Canada, *Priority Substances List Assessment Report: Formaldehyde* at 65-66 (Feb. 2001).

G. Power Point presentation by Collins et al., *Evaluating Formaldehyde and Leukemia Risk* (undated).

H. Casanova et al., *Comments on a Draft Manuscript entitled "Mortality from lymphohematopoeietic malignancies among workers employed in formaldehyde industries* (March 21, 2003).

I. Heck et al., *The Implausibility of Leukemia Induction by Formaldehyde: A Critical Review of the Biological Evidence on Distant-Site Toxicity* (undated).

J. Power Point presentation by Casaheck Consulting, *Formaldehyde and Leukemia Risk* (April 7, 2004).

K. Cole et al., *Formaldehyde and Leukemia: An Improbable Causal Relationship* (March 7, 2004).

L. Collins et al., *A Review and Meta-analysis for Formaldehyde Exposure and Leukemia Risk* (March 10, 2004).