Formaldehyde Council

Comments of the Formaldehyde Council, Inc. on Proposed Airborne Toxic Control Measure to Reduce Formaldehyde Emissions from Composite Wood Products; Comments on Staff Report: Initial Statement of Reasons for Proposed Rulemaking

April 16, 2007

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FORMALDEHYDE COUNCIL, INC.

The Formaldehyde Council, Inc. ("FCI") is a nonprofit trade association that represents the leading producers and users of formaldehyde in the United States that is dedicated to promoting the responsible use of formaldehyde. FCI members continue to invest considerable resources to advance the scientific understanding of formaldehyde.

Since its founding, FCI has become recognized as an expert resource in the science of formaldehyde toxicology and applicable risk assessment models. FCI members manufacture the majority of the U.S. production volume of formaldehyde. FCI's mission is to encourage accurate scientific evaluation of formaldehyde and formaldehyde-containing products and to communicate sound scientific information relating to the uses, benefits and sustainability of these products.

FCI is committed to advancing the state of scientific understanding on potential toxicology, epidemiology, and environmental effects related to formaldehyde, as well as providing accurate technical and scientific information relating to potential exposures, uses and effects of formaldehyde or formaldehyde-based products.

For more information about the FCI, including a list of members, visit www.formaldehyde.org.

Formaldehyde Council

April 16, 2007

Clerk of the Board
Air Resources Board
1001 I Street, Sacramento
California 95814

Submitted via: http://www.arb.ca.gov/lispub/comm/bclist.php

Re: Proposed Airborne Toxic Control Measure to Reduce Formaldehyde Emissions from Composite Wood Products; Comments on Staff Report: Initial Statement of Reasons for Proposed Rulemaking (Release date March 9, 2007)

Dear Clerk:

The Formaldehyde Council, Inc. (FCI) appreciates the opportunity to submit comments to the Air Resources Board on the Proposed Airborne Toxic Control Measure to Reduce Formaldehyde Emissions from Composite Wood Products. Formaldehyde is a key industrial chemical due to its versatility as an intermediate in the manufacture of numerous products including a variety of adhesives used in the production of particleboard, medium density fiberboard, and plywood. But, formaldehyde is also a ubiquitous chemical and is a natural constituent of all living systems which rely on formaldehyde as a one-carbon building block for the synthesis of more complex molecules. Formaldehyde is naturally occurring in the human body with concentrations of approximately 2 ppm in the blood.

Based on the vast differences between prevailing science on formaldehyde health effects and the positions presented in the ISOR, the Board should direct the ARB staff to make extensive revisions to the ISOR so that it is consistent with current science and current risk assessment practices. The heart of FCI's concern is that the risk assessment on which the proposal is based ignores or conflicts with a decade of internationally accepted science as reflected both in the scientific literature and by the consensus of expert agencies around the world. The Board has an obligation to ensure that the final agency decisions are based on evidence of requisite quality and quantity and that a reviewing court must enforce that duty. The differences between prevailing science and the ISOR are so severe that a rule based on such assumptions would be unscientific, arbitrary and capricious and an abuse of discretion.

I. EXECUTIVE SUMMARY

- Formaldehyde is a ubiquitous and natural constituent of all living systems, from bacteria and fish to rodents and humans. As such, formaldehyde is essential to basic metabolic processes and, as a consequence, is naturally present in the human body with blood concentrations of approximately 1-2 parts per million (ppm) and is a natural part of exhaled breath. Similar concentrations are found in monkeys and in rats. Exposure of humans, monkeys or rats to formaldehyde by inhalation has not been found to alter the

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concentration of formaldehyde in the blood. Solid wood inherently emits very low, but detectable, formaldehyde because of natural metabolic processes in trees.

- Ignoring the scientific reality of endogenous chemicals and determinations by the US Environmental Protection Agency (USEPA), the World Health Organization (WHO) and European governments, the staff report concludes that "there is no known safe threshold exposure level for formaldehyde." Report at page ES-2.
- In contrast, the World Health Organization (WHO) 2004 Guidelines for drinking-water quality sets a tolerable daily intake of 150 µg /kg of body weight, which would be 9,000 µg for a person weighing 60 kg (123 pounds).
- USEPA's Office of Air Quality Planning and Standards (OAQPS) tabulated the dose-response values used in the risk assessment of hazardous air pollutants. OAQPS' chronic inhalation cancer risk assessment of exposure to formaldehyde is 5.5 $\mu g/m^3 \times 10^{-9}$. Based on this unit risk factor, the benchmark ambient concentration for formaldehyde, a concentration representative of an additional lifetime cancer risk of 1 in 1,000,000 ($1 \times 10E^{-6}$) is 0.149 ppm (183 $\mu g/m^3$). EPA relied on a biologically based dose-response model (BBDR model) in its updated estimate of formaldehyde's chronic inhalation risk for in the development of two rules issued under the Maximum Achievable Control Technology (MACT) provisions of the federal Clean Air Act.
- The German Federal Institute for Risk Assessment (BfR) concluded in 2006: "Concerning the tumors in the upper respiratory tract, the steps in the induction of tumors are understood and include non-genotoxic mechanisms, which in the low concentration range are the most critical events. Hence, it seems well founded that a safe level can be derived despite the fact that genotoxicity also plays a role in tumor formation. Our analysis of the available human data suggests that a level of 0.1 ppm formaldehyde is "safe" for the general population."
- A July 2005 classification dossier prepared by France and lodged with the European Commission (EC Environment 2005) concludes: "In rats, tumour induction is associated with cytotoxicity and regenerative cell proliferation as a predominant feature with a clear threshold and it should therefore be noted that a threshold is also likely in humans."
- Both the USEPA and WHO positions are consistent with and based on the leading and internationally-accepted model for formaldehyde cancer risk assessment (BBDR model), which predicts no additional risk of cancer risk from exposures of about 1 ppm.
- In stark contrast to this global consensus, the staff report claims that reductions from 16 or 42 $\mu g/m^3$ to 9-25 $\mu g/m^3$ will reduce cancer.

- Regarding asthma and immune system effects, the ISOR (pages 134-135) continues to assume an association with low-level formaldehyde exposure. In doing so, it ignores conflicting comments submitted by OEHHA in 2004 on the draft indoor air report.

- The following end points and associated thresholds, which result from expert reviews, should be used.

  Sensory Irritation – The weight of the evidence supports a level of 0.75 to 1.0 parts per million (ppm).

  Skin Sensitization Threshold – As ATSDR (1999) concluded, exposure-response relationships for skin irritation and dermal allergic responses from acute exposure are well characterized (under patch testing conditions) in both normal and sensitized individuals, indicating that 1% solutions are not expected to be

> irritating to most people, and it is likely that dose-response relationships for dermal irritation from acute exposure may not be widely different from relationships for intermediate and chronic-duration exposures.
> *Odor Threshold* – The US Environmental Protection Agency and the Agency for Toxic Substances and Disease Registry concluded that the odor threshold for formaldehyde is approximately 1 ppm.

Based on an estimated population of 35 million people in California and OEHHA's estimate of a reduction of 35 cancer cases per million people over a 70-year lifetime, OEHHA's estimated number of cancer cases prevented per year in California is 18.[1] In contrast, using the cancer potency factors of the Other Agencies, the estimated number of cancer cases prevented per year in California ranges from 0.0005 to 0.008 (Table 1). In other words, the estimated time required to prevent *one* case of cancer in the entire population of California after implementing Phase 2 ranges from *125 to 2000 years*.

OEHHA's estimated cancer potency for formaldehyde is 2250-36,000 times greater than that of the Other Agencies. Either OEHHA has greatly overestimated the risk or US EPA, Health Canada, WHO, and Australia all have greatly underestimated the risk.

FCI recognizes that there may be social values or preferences that support the reduction of formaldehyde emissions. For the purposes of these comments, FCI has not undertaken a comprehensive review of California law and precedent to determine whether the staff proposal could be justified in some other fashion under state law. We are certain, however, that the reasons articulated as the health bases for the current proposal arise from a skewed presentation of the scientific literature that cannot be reconciled with an objective review or accepted science. This, in turn, leads to an inaccurate, if not misleading, characterization of formaldehyde health risks. FCI does not expect any health effects, including cancer avoidance, pre-phase 1 or after phase 1 or 2. From a health-basis there are no differences in the proposed changes.

FCI promotes good product stewardship and is aware of the large body of scientific literature indicating that formaldehyde exposure at sufficiently high levels can cause serious or severe acute and chronic effects. But, based on the vast differences between prevailing science on formaldehyde health effects and the positions presented in the ISOR, the Board should direct the ARB staff to make extensive revisions to the ISOR so that it is consistent with current science and current risk assessment practices.

The Board has an obligation to ensure that final agency decisions are based on a sound and objective evaluation of requisite quality and quantity. While reviewing courts do not second-guess the expert science judgments of agencies such as CARB, the courts must review the record to ensure that it reflects a sound and objective evaluation. Part of that review is an assessment of differing scientific interpretations and whether the agency's decision rests on rational basis for the positions that it espouses.[2]

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[1] [(35 cancer cases/million people)/70-year lifetime] x 35 million people/70 years = 18 cancer cases prevented per year

[2] See generally, Paul S. Miller & Bert W. Rein, "Gatekeeping" Agency Reliance on Scientific and Technical Materials after Daubert: Ensuring Relevance and Reliability in the Administrative Process, 17 Touro L. Rev. 297 (2000).

The only seeming consistency in the ISOR is that CARB staff appears to have actively sought to reach findings of adverse effects at any level. This is reflected, for example, in the ISOR's reliance on an outdated OEHHA assessment of carcinogenicity, while simultaneously rejecting OEHHA's comments that formaldehyde is not associated with asthma and immune effects at anticipated exposure levels. The differences between the prevailing science and the ISOR science rationale are so great that a rule based on such assumptions would be unscientific, arbitrary, capricious and an abuse of discretion.

CARB should carefully evaluate the proposal to reduce exposure to formaldehyde in light of the tenuous public health benefits represented by the estimated reduction in cancer cases in California. If reducing exposure to formaldehyde will not result in any meaningful reduction in cancer risk in California, the proposed action must be questioned. Given the fact that over 100,000 Californians are expected to die from cancer annually, it is especially important to focus the State's resources on strategies that will result in real reduction in cancer and improvement in public health.

II. GENERAL COMMENTS

A. Formaldehyde in Nature

Formaldehyde is one of the simplest biological forms of carbon. Even the most primitive organisms rely on formaldehyde as a one-carbon building block for the synthesis of more complex molecules. As a result of its importance in various metabolic processes, formaldehyde is naturally present in the human body with concentrations of approximately 1-2 parts per million (ppm) in the blood. Formaldehyde is exhaled in the breath, with studies suggesting that breath levels may range from the low parts per billion (1.2-72.7 ppb) to 0.3–1.2 ppm (Moser et al. 2005; Ebeler et al. 1997).

Due to the highly efficient activity of a variety of aldehyde dehydrogenase (ADH) enzyme systems, formaldehyde is rapidly metabolized. For example, blood was collected immediately following exposure of F-344 rats to 14.4 parts per million (ppm) of formaldehyde for 2 hours. Blood from eight unexposed rats served as controls. Analysis showed formaldehyde concentrations of 2.24 and 2.25 µg/g blood in exposed and controls, respectively (Heck et al. 1985). Formaldehyde concentrations in human venous blood from four males and two females were determined by analyzing blood samples collected before and after exposure to 1.9 ppm of formaldehyde for 40 minutes. Average formaldehyde concentrations before and after exposure were 2.61 and 2.77 µg/g blood, respectively. In neither rats nor humans was there a statistically significant effect of formaldehyde exposure on the average concentrations in the blood. In a similar study, three rhesus monkeys were exposed to formaldehyde at 6 ppm (6 hours/day, 5 days/week for 4 weeks) and the formaldehyde concentration in the blood measured by gas chromatography - mass spectrometry (GC-MS). The formaldehyde concentrations immediately after the final exposure in the three exposed and three unexposed animals were 1.84 and 2.42 µg/g blood, respectively. These results demonstrate that subchronic inhalation exposure of non-human primates to formaldehyde has no significant effect on the concentration in the blood, and that the average concentration of formaldehyde in the blood of monkeys is similar to that observed in human studies (Casanova et al. 1988). California risk assessments should recognize and account for the status of substances that the body naturally generates and for which there are highly efficient detoxification pathways, in contrast to substances for which metabolic detoxification pathways are absent or limited.

In the context of this rule making, it is worth noting that solid, untreated wood emits very low, but detectable, levels of formaldehyde because formaldehyde is a metabolism product that is naturally present. Meyer & Boehm (1997). Thus, a value of "zero" cannot be attained for formaldehyde emissions from wood products.

Once formaldehyde enters the environment, it begins to break down through natural processes and does not persist or bioaccumulate. Chenier (2003). From a regulatory and public policy perspective, it always is necessary to differentiate and recognize the relative importance of substances that are naturally occurring, biogenic chemical components, especially those that have multiple and highly efficient pathways existing for their conversion into a usable source. Such is the case with formaldehyde and its conversion to a carbon source, formate. Formaldehyde's role in our environment is vastly different from substances that have no roles in normal metabolism and physiology.

B. Extensive Scientific Literature and Risk Assessment Development

Formaldehyde is one of the most studied chemicals, with literally hundreds of studies on metabolism, toxicity and effects in animals and humans. Formaldehyde is a well-known sensory irritant to the eyes, nose, and throat. Controlled studies demonstrate that the general irritation threshold in a normal population is around 1.0 ppm. With the discovery in 1979 that formaldehyde caused nasal cancer in rats following lifetime exposure to very high levels,[3] an extensive effort was undertaken, and continues today, to understand better the potential for similar effects in humans.

After decades of serious study, the state of the science is robust. Highly regarded experts in the field of toxicology have concluded that formaldehyde is not likely to be carcinogenic to humans under low exposure conditions, specifically, those exposures that do not cause cytotoxic effects. Lacking sufficient evidence showing cancer in humans exposed to formaldehyde, assessors have historically made predictions of hypothetical cancer risk posed by low-dose formaldehyde exposure using the highly conservative linear multistage model and numerous default assumptions to extrapolate potential risks to humans from laboratory animal data. However, estimates of the risk of developing cancer as the result of exposure to formaldehyde have been lowered over time as new experimental data replaces default assumptions and mathematical models for extrapolating from animals to humans and high doses to low doses have become more sophisticated.

Risk estimates associated with exposure to formaldehyde have continually decreased as scientific knowledge increased and newer, more complete scientific studies have become available. For example, for lifetime exposure to 0.1 ppm the 1987 and 1991 USEPA risk value declined from 1.6 in 1,000 to 3.3 in 100,000. In 1999, the BBDR risk assessment model estimated the risk from the same exposure to be 3.3 in 10,000,000. In other words, as the mode of action became better understood, the risk levels were adjusted to be consistent with this evolving body of knowledge.

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[3] Studies revealed that long-term inhalation exposures to formaldehyde at concentrations of 6 ppm or more led to nasal cancers in rodents. (Monticello et al. 1991, Kerns et al. 1983). These concentrations are over 1,000 times higher than typical environmental levels, which are in the parts per billion (ppb) range, and eight times higher than the U.S. occupational exposure limit. USEPA classified formaldehyde as a "probable human carcinogen" in 1987 on the basis of these rodent studies.

C. Evaluating Chronic Health Effects

In promulgating the National Emissions Standard for Hazardous Air Pollutants for Plywood and Composite Wood Products, the USEPA stated:

> We believe that the CIIT modeling effort represents the best available application of the available mechanistic and dosimetric science on the dose-response for portal of entry cancers due to formaldehyde exposures . . . The CIIT model incorporates state-of-the-art analysis for species-specific dosimetry, and encompasses more of the available biological data than any other currently available model."[4]

FCI supports this scientific decision by USEPA, which is also consistent with the USEPA position in the gas turbine MACT rulemaking.[5]

The BBDR model has been accepted and used by several international and national standards-setting bodies and is widely respected. These widely respected organizations, listed below, draw heavily on the BBDR approach and several characterizations state that formaldehyde is likely to be carcinogenic in humans only at doses that cause cell proliferation, not at low doses.

- The National Academy of Sciences (2004) endorsed the BBDR risk assessment, over USEPA's 1987 Integrated Risk Information System (IRIS) number, in its review of indoor air contaminants on submarines. A subcommittee of the National Research Council (NRC) developed exposure guidance levels for formaldehyde (assuming exposure 24 hours per day for several weeks at a time). The report contains a thorough discussion of the literature discussing the relevant epidemiologic and toxicologic studies on formaldehyde, and, with regard to cancer endpoints, states, "The more recent CIIT assessment results in a theoretical cancer risk well below the U.S. Department of Defense "acceptable" risk level of 1 in 10,000, even for a lifetime exposure at the 0.3 ppm 90-day continuous exposure guidance level (CEGL). The subcommittee concluded that the CIIT assessment more *accurately reflects the scientific weight of the evidence for formaldehyde than does EPA's approach*." (Emphasis added.)

- In its review of formaldehyde under its Existing Chemicals program, the Organization for Economic Cooperation and Development (OECD 2002) issued a Screening Information Data Set (SIDS) Initial Assessment Report, which stated, "The increasing severity of damage in higher concentrations is a function of the concentration. Another way of expressing this result is that formaldehyde toxicity is independent of the total dose (c x t) but that it depends on the dose rate [(c x t)/t = c] or concentration. This can be explained

[4] 69 Fed. Reg. 18333-34 (Apr. 7, 2004). "For formaldehyde, we do not use the dose-response value reported in IRIS. The dose-response value in IRIS is based on a 1987 study, and *no longer represents the best available science* in the peer-reviewed literature. Since that time, significant new data and analysis have become available" (emphasis added).

[5] 69 Fed. Reg. 18333-34 (Apr. 7, 2004)(Stationary combustion turbines); 69 Fed. Reg. 45944 (July 30, 2004); 70 Fed. Reg. 44012 (July 29, 2005); 71 Fed. Reg. 8342 (Feb. 16, 2006) (Plywood MACT). As has been common for EPA MACT rules, EPA's plywood MACT rule is the subject of a judicial petition for review. *NRDC and Sierra Club v. U.S. EPA*, Case No. 04-1323 (D.C. Cir.). NRDC also filed a petition for reconsideration directly with EPA. In its final decision on the petition for reconsideration EPA confirmed that it will use the cancer potency derived from the BBDR model and not the current EPA IRIS value. 71 Fed. Reg. 8342, 8348-8349 (Feb. 16, 2007).

by saturation of detoxification pathways for formaldehyde at high concentrations. Strong non-linearity in the induction of cell proliferation, DNA-protein-crosslinks, cytotoxic effects and carcinogenicity are observed (CIIT 1999). The observed non-linearity is likely attributable to a large extent to mechanisms present in biological systems to deal with low levels of formaldehyde." (OECD 2002 at 17-18.) In sum, the report found that "[t]aking into account the extensive information on its mode of action, formaldehyde is not likely to be a potent carcinogen to humans under low exposure conditions." (OECD 2002 at 2.) OECD found no further research on human health was needed.

- In an updated assessment of formaldehyde, Environment Canada and Health Canada stated that it considered the BBDR dose-response model "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." (Environment Canada and Health Canada 2002 at 68.)

- In finalizing the Concise International Chemical Assessment Document on Formaldehyde, (CICAD), the World Health Organization (2002) relied on the BBDR cancer risk assessment for formaldehyde and concluded that formaldehyde exposure poses a carcinogenic hazard only under conditions that both induce toxicity and cause sustained regenerative proliferation.

- The German MAK Commission, which sets occupational exposure values, reviewed formaldehyde and concluded: "In the low dose range, which does not lead to an increase in cell proliferation, the Commission therefore considers that the 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." (German MAK Commission , 2001, at 193.) This conclusion is supported by the results of a risk assessment which, for persons exposed to concentrations of 0.3 ml/m^3 (0.37 mg/m^3) at the workplace for 40 years, yielded a very low additional cancer risk for non-smokers of 1.3 x 10^{-8} and for smokers of 3.8 x 10^{-7} (CIIT 1999) (German MAK Commission, 2001, at 193).

- In November 2006, the Australian National Industrial Chemicals Notification and Assessment Scheme (NICNAS) issued a final Priority Existing Chemical (PEC) Assessment Report on Formaldehyde.[6] NICNAS was formed in 1990 to "provide a national notification and assessment scheme to protect the health of the public, workers and the environment from the harmful effect of industrial chemicals; and assesses all chemicals new to Australia and assesses those chemicals already used (existing chemicals) on a priority basis, in response to concerns about their safety on health and environmental grounds." The formaldehyde PEC provides a summary of the BBDR model, on which the report relies.[7]

Collectively, these applications of the BBDR risk assessment model reflect its broad, international acceptance among expert agencies. The results of the BBDR model and the human implications indicate that: (1) cancer risks associated with inhaled formaldehyde are *de*

[6] Report No. 28. See pages vii, 88- Available at: http://www.nicnas.gov.au/publications/car/pec/PEC28/PEC_28_Full_Report_PDF.pdf (last visited April 5, 2007).

[7] Id. at Appendix 9 (pp. 259-266) and pages vii-viii.

minimis (i.e., one in a million or less) at relevant human exposure levels, and (2) protection from the non-cancer irritant effects of formaldehyde also should be sufficient to protect for any potential carcinogenic effects. There is widespread agreement in the scientific community that the BBDR model represents the future of biologically-based cancer risk assessment. Like any new methodology, particularly one with this degree of complexity, there are opportunities for improving the certainty of the modeled predictions. This is already underway with research to elucidate additional details concerning the mode of action of formaldehyde-induced tumors and developing better data for use in the model. The results of these studies, the most recent of which we discuss below, should result in even greater confidence that the BBDR model provides the best and most scientifically defensible methodology for determining whether formaldehyde poses an increased risk of cancer to humans at levels that are protective for its well-characterized irritant effects.

1. The BBDR risk assessment model is the most advanced model for evaluating potential cancer risk

With input from USEPA, Health Canada, and peer reviewers, a team of researchers at the CIIT Centers for Health Research (CIIT) published a thorough evaluation of potential cancer risk from formaldehyde in 1999, incorporating over 20 years of research and integrating various toxicological, mechanistic, and dosimetric data (CIIT 1999).[8] That evaluation was refined and restated in 2004. A list of references supporting or comprising the body of knowledge underlying the CIIT work appears at the end of these comments.

CIIT used the detailed understanding about how formaldehyde causes cancer in animals to construct a biologically-based model to describe these effects. Combined with the data on the similarities and differences between animals and humans, findings in animals can be extrapolated to humans with increased confidence. Biologically-based modeling greatly minimizes the need for the unfounded assumptions and uncertainties inherent in currently used regulatory approaches for carcinogens, i.e., the so-called no threshold model, which assumes (based on no data whatsoever) that cancer risk is linear to zero. The model developed by CIIT for formaldehyde-induced upper respiratory tract tumors is the best model to predict the doses of formaldehyde required to produce tumors in animals and in humans.

The most recent application of the BBDR model combines animal data with human respiratory tract cancer to smokers, nonsmokers, and a mixed population of nonsmokers and smokers to predict the likelihood of cancer occurring in humans at various levels of formaldehyde exposure. When the animal data were used in one way, the model predicted no additional risks of respiratory tract cancer up to about 1 ppm formaldehyde for all three cases. When the animal data were used in an even more conservative way, the estimate of additional cancer risk was up to 1,000 times less than estimates based on presently used methods for extrapolating animal data to humans. Even when elevated breathing rates due to different levels of physical activity were put into the model (which could lead to increased uptake of formaldehyde), this did not make large differences in predicted additional risks. As shown below in Figure 1, the evolution of predicted cancer risks associated with exposure to 0.1 ppm formaldehyde for 6 hr./day, 5 days/week has dramatically decreased as the scientific basis for using the animal data to predict

[8] The BBDR risk assessment represents the collective work of numerous experts as reflected in dozens of peer-reviewed papers. A sampling of the papers underlying this work is presented after the list of references at the end of these comments. A more comprehensive bibliography can be generated through the publications section of the CIIT website: http://www.ciit.org.

potential risks to humans has improved. The BBDR model shows that cancer risk is negligible until formaldehyde exposures reach levels associated with cytotoxicity and resulting cellular proliferation. Assuming 80 years of continuous exposure to formaldehyde at 100 ppb, the BBDR model predicts an increased risk of developing cancer at 3.3×10^{-7} (i.e., 3.3 in 10,000,000) for non-smokers, well below the one in a million risk level typically used by regulators to establish an acceptable level of exposure. The same model predicts a risk of 5.3×10^{-6} in smokers.

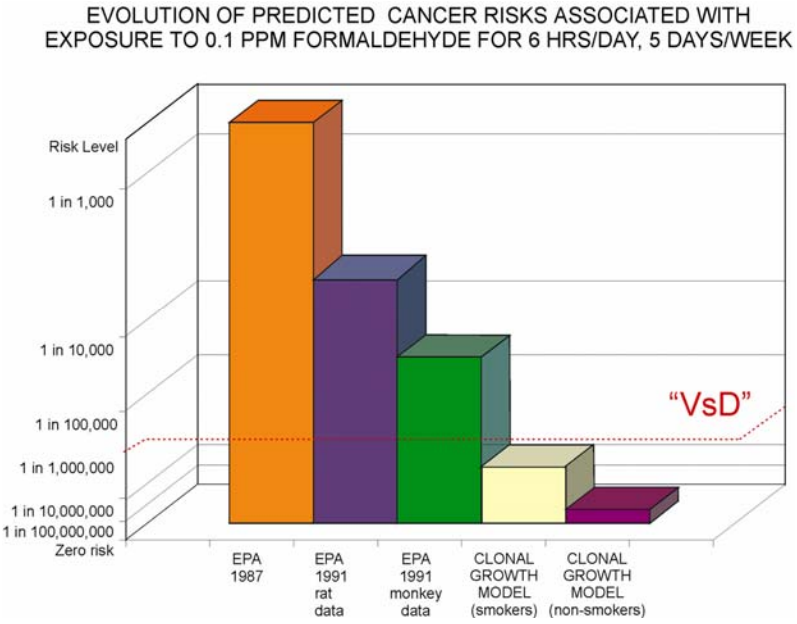

FIGURE 1

2. Genomics

In a state-of-the-art, three-week inhalation study at CIIT that was sponsored by FCI, F344 rats were exposed to provide information on the time-course and concentration dependence of genomic changes produced by formaldehyde in tissues of the upper respiratory tract of the rat. Exposures were conducted at three concentrations plus controls. The concentrations mirrored the lower concentrations in the Monticello study (0.7, 2.0, and 6.0 ppm) to provide further biological information concerning the pathology changes that begin at the upper end of this dose regime. Genomic evaluations (4 animals per concentration/time point) were conducted at four time-points: 6 hours, 24 hours (6 hrs plus 18 hrs recovery), 5 days, and 19 days. The initial genomic evaluation focused on respiratory and transitional epithelium from the anterior nose, the region of the highest tumor frequency.

The CIIT study was intended to provide initial information on dose-response trends for genes or gene families and to associate these changes with toxicity, metaplasia, and proliferation in these nasal tissues. The following points summarize the preliminary findings of the CIIT study. A longer-term study (subchronic, 90-day) is expected to be conducted in 2007 at CIIT to link this short-term work with the results from the 2-year Monticello results.

- Gene changes were noted for a variety of genes at the 6 hr, 5 day and 19 day sampling times for some, but not all dose levels.

- The pattern of gene transcription changes and the groups of genes significantly affected by exposure differed markedly for the four sampling times. Immediately after the first exposure, up-regulation (i.e., increased activity) and down-regulation (decreased activity) was noted for many genes at 6 ppm, while only a few genes showed changes at 2 ppm, and there were no gene changes observed at 0.7 ppm. At 6 ppm, up-regulation was observed for a gene associated with oxidative stress signaling and a gene associated with inflammatory signaling, while down-regulation was noted with several kinase and phosphatase genes.

- At the 24 hour sampling time, representing an 18 hour recovery after a single 6 hour exposure, no evidence of any gene change was noted at any concentration.

- Immediately after the exposure on day 5, there were more changes in genes at the 2 ppm exposure level than at 6 ppm. Again, no changes were observed at 0.7 ppm. A preliminary gene ontology analysis showed significant enrichment in genes associated with cell adhesion (i.e., the ability for cells to stay together). Positive trends were also seen for several genes involved in the degradation of the extracellular matrix and the inflammatory response. The changes in cell adhesion and inflammatory signaling genes are likely reflections of cellular alterations associated with adaptive responses and tissue toxicity.

- Immediately after the exposure on day 19, response trends were consistent with those observed after the first exposure. No statistically significant gene changes were observed at either 0.7 ppm or 2 ppm while significant gene changes were again observed at 6 ppm.

This research represents a first attempt to evaluate the genomic alterations occurring upon single and repeated exposures to formaldehyde in the rat. While a more robust analysis (i.e., 90-day subchronic) is being planned to better understand these changes in relation to toxicity, proliferation, and metaplasia, this initial study shows a pattern of changes in a variety of genes and gene families. In this preliminary evaluation, pathological changes were restricted to the 2 ppm and 6 ppm concentrations and primarily consisted of inflammation and hyperplasia, with some squamous metaplasia observed at the highest concentration. The three types of endpoints show relatively consistent dose-response gene expression patterns for the 3 week exposure period evaluated, with no changes noted at 0.7 ppm, primarily transient changes at 2 ppm, and more notable changes at 6 ppm.

In summary, the results of this study of genomic changes indicate a highly concentration and time dependent response. An immediate response in a number of genes was observed at 6 ppm, and a similar response was still observed after 3 weeks suggesting that cells had adapted to this exposure concentration. In contrast, the response at 2 ppm was highest after one week of exposure, but was no longer observed at 3 weeks. No consistent genomic responses were observed at 0.7 ppm at any time point suggesting a clear biological threshold for formaldehyde-related effects.[9]

[9] FCI understands that the results from this CIIT study will be published by the researchers.

3. Implications for Chronic Risk Assessment

The German Federal Institute for Risk Assessment (BfR) prepared a Toxicological Assessment of Formaldehyde in 2006.[10] While FCI does not endorse the entire analysis, the conclusions in BfR 2006 are noteworthy.

> Concerning the tumors in the upper respiratory tract, the steps in the induction of tumors are understood and include non-genotoxic mechanisms, which in the low concentration range are the most critical events. Hence, it seems well founded that a safe level can be derived despite the fact that genotoxicity also plays a role in tumor formation. Our analysis of the available human data suggests that a level of 0.1 ppm formaldehyde is "safe" for the general population. The proposed level of 0.1 ppm is 2 fold lower than the level derived from animal data by applying appropriate safety factors. In the literature, a physiologically based model has been reported which has been applied to the animal data. From the reported calculations and their extrapolation to the human situation a level of 1 ppm, 10 times the level proposed by us, was considered to be safe. Therefore, the recommended level of 0.1 ppm seems to be a conservative estimate.

A classification dossier prepared by the Toxicology Unit of INRS (France) for the Commission of the European Communities Environment (DG XI)[Classification and Labelling of Dangerous Substances (ECBI/38/05)(July 2005)](EC Environment 2005) also conflicts with the conclusion of the ISOR with regard to the question of whether a threshold exists for toxicological effects from formaldehyde exposure. With regard to animal data, the dossier states (italics added):

> Experimental results and mechanistic data therefore *support a threshold type dose-response* for induction of nasal tumours with regenerative cell proliferation being the predominant feature in the carcinogenic process.
> The mechanism of tumour induction through chronic persistent irritation, cytotoxicity and regenerative proliferation is clearly identified. Finally, there is no convincing evidence of a carcinogenic effect at distant sites or via other routes of exposure.

With regard to human and animal data, the dossier concludes that:

- tumors are only found at the site of direct contact, i.e. in the nasal tissue of rats
- nasal tumors were only significantly increased in rats, in mice there was no significant response and in hamsters no tumors were observed at all
- tumor formation after inhalation exposure to formaldehyde only occurs at doses with massive cytotoxicity leading to a clear increase in regenerative cell proliferation.

With regard to the mode of action and its relevance for humans, such as mutagenicity, cytotoxicity with growth stimulation, tumors are only to be expected at dose levels with massive cytotoxicity in conjunction with growth stimulation (regenerative cell proliferation) and mitogenesis. Such high doses cannot be tolerated by humans under any realistic conditions because such irritation will not be tolerated. This threshold identified in animals and by mechanistic experiments is also likely to be operative in humans. "In rats, tumour induction is associated with cytotoxicity and regenerative cell proliferation as a predominant feature *with a*

[10] Federal Institute for Risk Assessment (BfR) is the scientific body of the Federal Republic of Germany that prepares expert reports and opinions on questions of food safety and consumer health protection on the basis of internationally recognized scientific assessment criteria.

clear threshold and it should therefore be noted that a threshold is also likely in humans" (p. 43, italics added).

Non-genotoxic chemicals such as chloroform have had mode of action (MOA) risk assessments completed (Golden et al, 1997; Lipscomb & Kedderis, 2006). A challenge in the risk assessment of formaldehyde has been to understand how best to perform a dose-response assessment of a chemical that has both inflammatory or cytotoxic and mutagenic or clastogenic properties. Traditional approaches to risk assessment separate these endpoints for non-cancer versus cancer evaluation. However, for formaldehyde, the MOA is likely dependent on, and secondary to the cytotoxicity of the chemical. For chemicals such as formaldehyde, an appropriate assessment is based on systems biology and a detailed understanding of the biochemical events leading to toxicity, which describes and relies on a common MOA to integrate the various observed endpoints of toxicity. The MOA approach can serve as a platform to harmonize approaches to non-cancer and cancer toxicity at the point of contact (i.e., no significant entry into the body). The harmonized risk characterization is based on an evaluation of the dose-response continuum and relies on epithelial changes that have recognized prognostic value for more overt toxicity and that should be recognized as sentinel information, applicable to both cancer and non-cancer effects. These observations are necessary to conclude that a sufficiently robust understanding of the mode of action exists, based upon the explicit criteria spelled out in USEPA's most recent guidelines for Carcinogen Risk Assessment (USEPA, 2005).

Additionally, formaldehyde is naturally produced and an important component of various metabolic processes. As a result, it is a constituent of living systems, from bacteria and fish to rodents and humans. Because there are naturally evolved, highly efficient detoxification pathways to manage formaldehyde, it should be assessed differently than an agent that has no role in normal metabolism and physiology. Standard risk assessment methodology does not account for this important distinction. In contrast, the BBDR risk assessment model, used by USEPA in the plywood MACT, overcomes this limitation. This biologically-based model has garnered broad recognition from national and international expert agencies as the best available science for evaluating the chronic health effects of formaldehyde. Risk assessments should recognize the biochemical and physiological implications of substances that are naturally generated in the body and for which highly efficient metabolic pathways have evolved.

D. Evaluating Acute Health Effects

1. Sensory Irritation and Formaldehyde

There is a robust database on the dose-response characteristics of formaldehyde induced sensory irritation. Reviews of the formaldehyde literature have noted that the most sensitive endpoints reported are for eye and upper respiratory tract irritation (USEPA/NAC, 2003; Arts et. al., 2006). A concentration of 1 ppm appears to be the approximate threshold for complaints of symptoms ranging from none to mild to moderate with no clear concentration-response relationship or increase in complaints among exposed subjects compared with controls. For example, a study in asthmatics (Harving et al., 1990) found no association between subjective ratings of sensory irritation and increasing formaldehyde exposures at concentrations of 0, 0.01, 0.1, and 0.69 ppm. USEPA/NAC (2003) identified 0.9 ppm as the highest exposure concentration at which the responses of subjects whose eyes were sensitive to formaldehyde were not significantly different from controls. Even at 3 ppm, however, the majority of subjects reported only mild (typically defined as present but not annoying) to moderate (annoying)

irritation. In only one study, again in asthmatics at 3 ppm, did any subject rate the eye irritation as severe (1 of 180 subjects) (Sauder et al, 1987).

This same study (Sauder et al, 1987) illuminates why well conducted studies are necessary in order to properly understand and quantify the irritant properties of formaldehyde. In this study, 22% of subjects exposed to air containing no formaldehyde reported eye irritation, and 33% reported nose or throat irritation. Such a large incidence of false positive reporting would likely have an influence on any study for which it was not accounted.

Many of the controlled inhalation studies included potentially sensitive individuals. These studies either excluded less sensitive individuals (e.g., those without complaints of eye irritation at 1.3-2.2 ppm or smokers) or focused on potentially sensitive individuals (e.g., asthmatic individuals and those with formaldehyde-related contact dermatitis or previous formaldehyde sensitivity). As summarized by USEPA/NAC (2003), Bender (2002), and Paustenbach et al. (1997), the results of these studies indicate that sensitive individuals might experience eye irritation at 1 ppm. Below 3 ppm, the chemical appears to be rapidly eliminated in the upper airways, because asthmatics (who normally react to mid-and lower-respiratory airway irritants) engaging in moderate exercise showed no decrements in several pulmonary function parameters when exposed at concentrations up to 3 ppm. Thus, asthmatics exposed to airborne formaldehyde at exposure concentrations at or below 3 ppm do not appear to be at greater risk of suffering airway dysfunction than non-asthmatics. In addition, the short-term chamber studies indicate that adaptation or accommodation to irritation can develop over time (NRC 2004). These studies support that formaldehyde irritancy does not follow Haber's law (concentration x exposure time = response) for extrapolating between short-term and long-term time periods. Generally, concentrations that do not produce short-term sensory irritation also do not produce sensory irritation after repeated exposure. Consequently, conventional safety factors applied to a non-cancer risk assessment for formaldehyde are unnecessary.

2. Confounding Factors in Sensory Irritation Testing

There are several explanations for reported eye irritation levels by formaldehyde below 1.0 ppm, the primary one, however, is associated with the substance's odor. Formaldehyde has a pungent odor and the odor of formaldehyde is detected and/or recognized by most human beings at concentrations below 1.2 mg/m^3 (1 ppm) (IPCS 1989). In general, odor detection is not regarded as a toxicologically relevant endpoint -- annoyance does not represent a sensory or psychological effect, but rather a psychological discomfort from the presence and increasing concentration of an odor. (Arts et al. 2006b).

Foul odors are detected by both olfactory and trigeminal stimulation. The olfactory stimulation relays messages to the brain using the first cranial nerve for odor perception while trigeminal stimulation is responsible for sensing the ocular and nasal irritation of a chemical using the fifth cranial nerve. (Paustenbach and Gaffney 2006) In other words, olfactory receptors detect odor threshold while trigeminal nerve endings in the cornea and nasal mucosa signal sensory irritation thresholds in the eyes and upper respiratory tract, respectively. Olfactory receptors respond to chemical stimuli usually at lower concentrations and with greater selectivity than do the trigeminal endings and are responsible for the discrimination of different odorous substances. (Arts et al. 2006b). Although anatomically distinct, both pathways help people to distinguish and characterize inhaled air.

Studies have shown that even a pure odorous substance, lacking any trigeminal stimulation, elicited reports of sensory irritation. (van Thriel 2006). For the majority of chemicals, odor has a zero correlation with actual exposure risk, but odor may have a substantial correlation with perceived exposure risk. However, as Paustenbach and Gaffney (2006) note, "detection of odors by workers may tap into the person's aversions to unpleasant odors, in general." Because the vast majority of volatile chemicals stimulate the olfactory system at concentrations well below that at which they will elicit trigeminal activation, the evaluation of irritation from volatiles is often confounded by the perception of odor. (Arts et al. 2006b) Formaldehyde is not an irritant at its odor threshold; however, much of the public immediately perceives the substance and its odor as harmful, which strongly influences individuals to indicate irritation where only odor exists. Thus, the results of measurements of sensory irritation can strongly be biased by subjective feelings and interpretations, in many instances caused by the odor of the compound. Therefore, the perception of odor intensity is an important factor that must be considered when evaluating a substance for an occupational exposure limit, especially substances that like formaldehyde have odors perceived as unpleasant.

3. Previous Expert Evaluations of Formaldehyde and Sensory Irritation

Several expert reviews have been conducted of the formaldehyde literature relating to sensory irritation. Based on the reviews by the National Academy of Sciences' National Research Council (NRC 2004), Arts et al. (2006), Bender (2002) and Paustenbach et al. (1997), the weight of the scientific evidence demonstrates that the threshold for formaldehyde sensory irritation of the most sensitive endpoint (i.e., eye and respiratory tract irritation) is in the range of 0.75 to 1 ppm.

a) NRC (2004)

In reviewing the exposure of U.S. Navy personnel in submarines to several different contaminants, a subcommittee of the NRC developed exposure guidance levels for formaldehyde (assuming exposure 24 hours per day for several weeks at a time). The report contains a thorough discussion of the literature on the relevant epidemiologic and toxicologic studies on formaldehyde, and concludes:

> A concentration of 1 ppm appears to be the approximate threshold between complaints of symptoms ranging from none to mild to moderate with no clear concentration-response relationship or increase in complaints among exposed subjects compared with controls (subjects exposed to clean air) and definite symptoms of discomfort in a number of exposed subjects.[11]

b) Arts et al. (2006a)

Arts et al. (2006a) evaluated literature related to critical health effects of formaldehyde exposure including sensory irritation and the potential to induce tumors in the upper respiratory tract. The authors reviewed the subjectively measured sensory irritation threshold levels in humans and compared this with findings obtained in animal experiments. In addition, a benchmark dose

[11] National Research Council (2004) Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants, Subcommittee on Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants, Committee on Toxicology, at 89.

(BMD) analysis of sensory irritation was used to estimate response incidences at different formaldehyde concentrations. The BMD method used by the authors takes all individual data into account by means of a curve based on all the data points.[12] Arts et al. concluded that:

- when minimal/mild/slight irritation, which is still not annoying, is taken as a cut off level, eye and nasal irritation were found at formaldehyde levels of ≥1 and ≥2 ppm,

- the minimal/mild/slight irritation level would be ≥3 ppm formaldehyde for throat irritation, whereas levels of up to 3 ppm did not result in dyspnoea (chest tightness/discomfort) or cough.[13]

The authors were sensitive to the challenge of setting appropriate exposure levels based on sensory irritation. Because human perception of sensory irritation can be influenced strongly by subjective feelings and interpretations, the authors contend that it would be better to base the sensory irritation threshold on objective measurements. In the authors' view, the only study that reported objectively measured eye irritation (but not nasal irritation), viz. an increase in eye blinking frequency at a concentration of 1.7 ppm formaldehyde (Weber-Tschopp et al., 1977), is in line with minimal/mild/slight eye irritation reported at levels of 1 ppm and higher. It was noted that the increase in eye blinking frequency was not doubled yet at 3.2 ppm (Weber-Tschopp et al., 1977).

Collectively, Arts et al.'s review leads to the conclusion that: "Sensory irritation is first observed at levels of 1 ppm and higher. From both human and animal studies it was concluded that at airborne levels for which the prevalence of sensory irritation is minimal both in incidence and degree (i.e. < 1 ppm), risks of respiratory tract cancer are considered to be negligibly low."[14]

c) Bender (2002)

Bender (2002) reviewed whether human sensory irritation data found in controlled/chamber studies and workplace studies are sufficiently robust for use in establishing a Reference Concentration for formaldehyde. Bender (2002) determined that chamber studies provided the highest quality data for determining the presence of eye, nose or throat irritation at a known level of formaldehyde. Chamber studies show that individuals began to sense eye irritation at about 0.5 ppm formaldehyde; 5 to 20 percent reported eye irritation at about 0.5 to 1 ppm, and greater certainty for sensory irritation appeared at 1 ppm or greater.[15]

Bender, et al., also evaluated reports of eye irritation among controlled studies, and found that it is not unusual to have a 20 to 30 percent response rate for eye, nose, or throat irritation

[12] Arts et al. (2006a) at 15.
[13] *Id*. at 18-19 (references omitted).
[14] *Id.* at 2. The Arts et al. analysis also confirms that anticipated exposure levels will not create the biological conditions or events triggering chronic risk concerns. "Overall, an exposure level of 1 ppm did not induce respiratory epithelial hyper/metaplasia, whereas levels of 2-3 ppm induced slight respiratory epithelial hyper/metaplasia, and levels of about 6 ppm and higher induced extensive hyper/metaplasia, necrosis, and severe rhinitis. An increased incidence of nasal cell carcinomas was seen from about 10 ppm, concomitant with clear cytotoxic effects. IARC (2004) concluded that there is sufficient evidence in experimental animals for the carcinogenicity of formaldehyde." Manuscript at 14.
[15] Bender (2002) at 13.

associated with controls. Bender, et al., concluded that sensory irritation at levels below 1 ppm is often difficult to distinguish from effects that occurred in controls.[16]

d) Paustenbach et al. (1997)

Paustenbach et al. (1997) represents the results of deliberations of this panel of experts convened to review the literature on sensory irritation. The expert panel reviewed approximately 150 published scientific articles and concluded that the most sensitive adverse effect of formaldehyde is eye irritation. Eye irritation "does not become significant until a concentration of at least 1.0 ppm is reached, and, based on most studies, for most people this level of irritation rapidly subsides."[17] Moderate to severe eye, nose, and throat irritation does not occur until airborne concentrations exceed 2.0 to 3.0 ppm.[18]

According to the expert panel, the weight of the evidence showed that reports of irritation below 0.3 to 0.5 ppm formaldehyde were too unreliable to attribute the findings solely to formaldehyde. Specifically, response rates below 20 percent were assumed to be too near the background level of irritation among the general population to be able to attribute that level of response to exposure to a specific contaminant.[19] In response to studies that showed irritation response at concentrations below 0.1 ppm, the panel explained: "it is likely that this level of response was attributable to other environmental factors, the background incidence of eye irritation, self-selection bias, or the effects of interviewer interaction."[20]

e) IRSST (2006)

The Québec Institute of Research Robert-Sauvé en santé et en sécurité du travail (IRSST) recently completed a thorough evaluation on the *Impacts of a Lowering of the Permissible Exposure Value to Formaldehyde: Impacts of Formaldehyde Exposure on Health.*[21] IRSST is a private, non-profit scientific research organization known for the quality of its work and the expertise of its personnel. The Board of Directors is composed of an equal number of trade union and employers' representatives.

With respect to the issue of sensory irritation, this evaluation critically considered all available studies with the notable inclusion of a rigorous dose-response analysis of the available data. Unlike other evaluations, based on pre-established criteria, this analysis considered sensory irritation effects (e.g., eye irritation, moderate and severe, and moderate nose and throat irritation), the percentage of workers who might experience such effects, and most importantly, the associated dose-response relationships.

> The relationship between acute formaldehyde exposure and the appearance of effects was established based on the collection of all rough data from each of the studies considered to have a degree of confidence moderately high to high. Hence, these studies are all led in a controlled setting. Moreover, the effects selected for the establishment of a dose-response relationship are the irritating effects to the eyes and

[16] *Id.*
[17] Paustenbach et al. (1997) at 252.
[18] *Id.* at 218.
[19] *Id.* at 251.
[20] *Id.* at 250-51.
[21] The report is available on the IRSST website at http://www.irsst.qc.ca.

> airway mucosa (nose and throat) as well as perception of odor. These effects are most frequently reported following an acute exposure to formaldehyde suggesting that they are the critical effects (those that appear with the lowest concentrations).
>
> For each of the controlled studies, the number of subjects presenting irritating effects, according to the class of exposure and the severity of the effect, was listed. The degree of exposure was fractioned into six distinct classes: from 0 to <0.3 ppm, from 0.3 to <0.75 ppm, from 0.75 to <1.0 ppm, from 1.0 to <2.0 ppm, from 2.0 to <3.0 ppm, and >3.0 ppm (which in fact combined the exposures between 3.0 and 4.0 ppm).[22]
>
> By combining the data from the different controlled studies, a global dose-response relationship was established. More specifically, the total number and the proportion of subjects presenting irritating effects by type of effects, severity of effects and class of exposure were compiled in the form of a table by adding the numbers of the different studies. This data allowed the creation of dose-response curves where the background noise value, that is to say the frequency of irritations in the absence of exposure, was subtracted.[23]

The conclusions of the IRSST review are noteworthy.

> Our analysis indicates that, for concentrations less than 0.75 ppm, the frequency of irritation in workers exposed to formaldehyde was about the same as the one observed in individuals without occupational exposure. This means that appearance of irritation at such concentrations can hardly be associated with occupational exposure to formaldehyde. For concentrations between 0.75 and 3 ppm, the estimated proportion of workers who may experience moderate irritating effects to the eyes, nose, and throat, attributed to formaldehyde is between 1.6 and 14.9%.[24]

Many of the controlled inhalation studies included potentially sensitive individuals. These studies either excluded less sensitive individuals (e.g., those without complaints of eye irritation at 1.3-2.2 ppm or smokers) or focused on potentially sensitive individuals (e.g., asthmatic individuals and those with formaldehyde-related contact dermatitis or previous formaldehyde sensitivity). As summarized by USEPA/NAC (2003), Bender (2002), and Paustenbach et al. (1997), the results of these studies indicate that sensitive individuals might experience eye irritation at 1 ppm. Below 3 ppm, the chemical appears to be rapidly eliminated in the upper airways, because asthmatics (who normally react to mid-and lower-respiratory airway irritants) engaging in moderate exercise showed no decrements in several pulmonary function parameters when exposed at concentrations up to 3 ppm. Thus, asthmatics exposed to airborne formaldehyde at

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[22] *Id*. section 4.1.1.2.
[23] *Id.* section 4.1.1.3.
[24] *Id.* section 7.1. IRSST (2006)(section 6.1.4) also compared its review to the analysis in Paustenbach (1997): "In addition, not only were controlled studies considered in the determination of the dose-response relationship, but studies showing a lower confidence level were also considered, that is, studies performed in the workplace. The background noise in the general population was not subtracted, and the irritation classification was not based on the degree of severity of the effect (mild, moderate, or severe irritation). In spite of a methodology, which was different from the one used in this study, it was concluded that a ceiling value of 1 ppm for 15 minutes was appropriate to prevent moderate, although transitory, eye irritation. The authors [Paustenbach (1997)] also stated that at such concentrations, formaldehyde should not cause eye irritation in at least 75% of workers and possibly up to 95%."

exposure concentrations at or below 3 ppm do not appear to be at greater risk of suffering airway dysfunction than non-asthmatics. In addition, the short-term chamber studies indicate that adaptation or accommodation to irritation can develop over time (NAS, 2004). These studies support that formaldehyde irritancy does not follow Haber's law (concentration x exposure time = response) for extrapolating between short-term and long-term time periods. Generally, concentrations that do not produce short-term sensory irritation also do not produce sensory irritation after repeated exposure. Consequently, conventional safety factors applied to a non-cancer risk assessment for formaldehyde are unnecessary.

4. Odor Threshold

While odor is not a toxicological effect, we mention odor because it is sometimes confused with sensory irritation, particularly in self-reporting studies or evaluations. The odor threshold for formaldehyde is approximately 1 ppm.

In its toxicological profile for formaldehyde, the Agency for Toxic Substances and Disease Registry (ATSDR 1999) states that the odor threshold for formaldehyde in humans has been reported to be 1 ppm, but others have noted that it may range as low as 0.05 ppm. ATSDR then describes the odor threshold aw 0.5 to 1.0 ppm.

USEPA 1988 concluded that the odor threshold for formaldehyde is 0.83 ppm.[25]

[25] USEPA cited Amoore, J.E. and Hautala, E. Odor as an aid to chemical safety: Odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. Journal of Applied Toxicology, 3(6):272-290 (1983).

III. SPECIFIC COMMENTS ON CHAPTER VII HEALTH IMPACTS

For ease of comparison and cross-referencing, the section headings and sequence in this portion of the FCI comments follow Chapter VII of the ISOR. The page numbers following the headings refer to the corresponding pages in the ISOR.

Total Daily Formaldehyde Exposure as the Basis for Risk Assessment (Page 132)

Average and Elevated Formaldehyde Concentrations (Page 132)

While exposure assessments appear in the ISOR, FCI does not address the validity of exposure assessments in these comments. We note, however, that in Table VII-1, the 46.7 ppb figure for the high end is doubtful. Additionally, the 17.2 ppb under conventional homes only accounts for newly built homes, which artificially inflates the exposure amounts. There is no discussion of concentrations in an average home. More important, however, is the use of significant number assumptions in the table that give the illusion that these concentrations represent precise measurements when they do not.

Health Effects Values for Formaldehyde (Page 133)

The reference to potential immune function effects is accompanied by few references and should be rewritten with a broader review of the literature. This section has semi-quantitative language, "very low doses" that are simply not useful. The concentrations should be supplied. Are these case reports? The information in this section is scant.

Health Effects in Humans (Page 133)

In this section, the references stop at 1994. As mention in the first section of these comments, there are several good papers since that time that are available. This section should be updated. The problems with this section are common throughout. Without controlled studies, the cited outcomes have little probative value and lack the scientific rigor necessary for regulation.

Respiratory Effects and Irritation – Acute Exposure (Page 134)

Regarding asthma and immune system effects, the ISOR fails to address comments by OEHHA in its 2004 comments to CARB on the draft indoor air report. OEHHA commented that "our understanding of the data is that formaldehyde is not associated with non-occupational asthma. Although the literature is inconsistent, most occupational health scientists would say that high occupational exposures are needed to see formaldehyde-specific asthma." In another section of comments, OEHHA goes on to say: "There is little evidence that allergic sensitization occurs at typical indoor exposures. Any statement on sensitization should be qualified by indicating that sensitization has been described following relatively high occupational exposures." OEHHA also states that "we do not support the statement that concentrations above 27 ppb might result in initiation of an immune response in a sensitive individual. The scientific evidence for initiation of immune response at levels below workplace exposures is not strong." The ISOR should be revised to reflect the OEHHA position or provide a well-articulated basis for a differing conclusion.

The presentation on eye irritation and uncertainty development is not used by the rest of the world or by the National Research Council (2004). The ISOR basically says that irritation occurs at ambient levels in the home based on calculations. This calculated "finding" is not supported by empirical data.

Average exposures are not very useful unless average and peak exposures are basically identical. In some of the referenced studies, the average concentrations are around 0.2 ppm while peaks can go higher than 20 ppm. The existing knowledge regarding the mode of action for these end points makes the discussion of averages useless.

This section has semi-quantitative language, such as "very low doses" (page 135) that is not useful. The concentrations should be supplied. Are these case reports? The information in this section is scant.

Green et al. (1987) is used to claim that there are lung function deficits at 3 ppm; however, there are other papers that show no change in normal or asthmatics at 2 ppm. There are better conducted studies then Green et al. (1987) and the ISOR needs to review the literature with less bias.

Occupational Exposures (Pages 137-138)

This section on irritancy studies in workers has the same problems as the preceding home studies. On what basis does one isolate an irritant response for formaldehyde in pulp mill workers? There is an unstated assumption that formaldehyde is the only potential occupational irritant at these locations, which is obviously untrue.

The report references Srivastava et al. (1992), which reported worker complaints of a variety of problems that the workers attributed to occupational exposure to formaldehyde concentrations estimated to be 0.03 mg formaldehyde/m^3 air as an 8-hour time-weighted average (TWA) and described as 0.025 ppm in the ISOR. First, we note that the reported exposure levels are near those associated with ambient air rather then occupational settings. The exposure levels raise a question as to whether this study really assesses responses to occupational exposure to formaldehyde. Second, the type of self-reporting involved in this study may be helpful in preparing for objective research, but these subjective evaluations are unreliable. ARB must consider biological consistency and probability in reviewing papers reporting on subjective self-evaluations. The reported symptoms include respiratory, gastrointestinal, musculoskeletal, and cardiovascular problems, suggesting some other agent then formaldehyde, assuming that the self-evaluations are accurate. The references to this study should be deleted from the ISOR.

The draft report referenced Gorski and Karkowiak (1991) and summarized that study as "showing no significant association between formaldehyde exposure, pulmonary function (FVC, FEV_1 and PEF) in normal or asthmatic workers, and occurrence of specific IgE antibodies to formaldehyde." Draft ISOR at 136. Rather then comparing and contrasting to other studies that show health effects at doses where none should be expected, the ISOR deletes the reference to this study altogether in an apparent decline from scientific review to simple advocacy.

Immunological Effects in Humans (Page 138-139)

The discussion on the immune system is flawed and fails to address recent studies using controlled chamber concentrations that contradict most of the historical literature that is referenced. The ISOR does not consider whether these data are the result of formaldehyde exposure or some other chemical/substance/protocol issue. For example, there is no discussion of any potential confounders, such as mold, in the entire document. On page 139, the report states: "while the human studies are not entirely consistent with each other, and there is a potential for confounding in each, nevertheless, taken together, they suggest that children are more sensitive to formaldehyde toxicity than adults." The ISOR does not mention the confounding factors, how or why the studies may disagree, or how the staff developed an outcome "taken together."

The section on immune functions contains few references and should be rewritten with a broader review of the literature. Similarly, this section has semi-quantitative language, "very low doses" that is simply not useful. The concentrations should be supplied. Are these case reports? The information in this section is scant.

Reproductive and Developmental Effects in Humans (Page 139)

The weight of the evidence demonstrates that formaldehyde does not result in reproductive and developmental effects. Both the ATSDR and WHO reviews concluded that formaldehyde is not associated with adverse reproductive and related outcomes. Although some animal and human studies have reported non-specific reproductive or developmental effects (Taskinen et al. 1999; Zeljenkova and Szabova 2004), the weight of available scientific data presents insufficient evidence to conclude that formaldehyde causes reproductive or developmental effects.

A comprehensive review of all the available data, including the meta-analysis data evaluating the relationship between spontaneous abortions and occupational exposure to formaldehyde, was conducted by Collins et al. (2001). For studies that showed an increased RR, some important limitations in study design were highlighted, such as the use of self-reported data or judgement on the level of exposure with no attempt to validate the exposure estimates with measurements. Collins, et al. (2001) examined the potential for reproductive and developmental effects from formaldehyde exposure. The authors note that formaldehyde is unlikely to reach the reproductive system in humans in concentrations sufficient to cause damage since it is rapidly metabolized and detoxified upon contact with the respiratory tract. While there are effects seen in *in vitro* studies or after injection, there is little evidence of reproductive or developmental toxicity in animal studies under exposure levels and routes relevant to humans. Most of the epidemiology studies examined spontaneous abortion and showed some evidence of increased risk (meta-relative risk=1.4, 95% CI 0.9-2.1).

> We found evidence of reporting biases and publication biases among the epidemiology studies and when these biases were taken into account, we found no evidence of increased risk of spontaneous abortion among workers exposed to formaldehyde (meta-relative risk=0.7, 95% CI 0.5-1.0). The small number of studies on birth defects, low birth weight, and infertility among formaldehyde workers; the limitations in the design of these studies; and the inconsistent findings across these studies make it difficult to draw conclusions from the epidemiology data alone. However, information from experimental studies and studies of metabolism indicate reproductive impacts are unlikely at formaldehyde exposures levels observed in the epidemiology studies.

Infants and Children (Pages 139-142)

These studies of infants and children can have many confounding variables, such as environmental tobacco smoke (ETS), mold, etc. The ISOR does not mention any of these potential issues when reviewing the data.

In discussing Garrett et al. (1999), the ISOR states that "no evidence of an association between asthma in the children and formaldehyde levels." Without any substantive explanation, the ISOR jumps to the conclusion that "these data do suggest that formaldehyde levels commonly found in homes can enhance sensitization of children to common aeroallergens." There is no explanation for this assumption. The staff apparently suggests that formaldehyde exposure is required prior to an allergic event, an untested and unsupported theory that cannot serve as a basis for regulation.

Garrett et al. (1999) is a study of asthmatic and non-asthmatic children in two small towns in Victoria, Australia. This paper does not address differences in adult and children's responses, since relevant data for adults were not collected. It does characterize the Wantke *et al.* (1996) study relevance as "unclear" because the sensitization was not associated with symptoms. Several factors compel caution in relying on this study:

- The paper likely was based on a graduate student thesis (the acknowledgements note a postgraduate publication award), and the paper presents *extensive* multi-variate analysis. Of all the analyses performed, the study notes:
    1) a crude odds ratio for atopy of about 1.4 with an increase in bedroom levels of formaldehyde of 10 μg/m^3 (adjusted for parental asthma and sex); however, the confidence interval for this finding is 0.99 - 2.00; and
    2) an adjusted odds ratio of 1.42 for atopy with an increase in the highest recorded formaldehyde level by 20 μg/m^3 (confidence interval 0.99-2.04). (As the majority of scientists and researchers recognize, odds ratios of 1.4 are generally not considered to be strong evidence of a causal connection.)

- The study took place in two small towns "surrounded by open-cut brown coal mines and power stations, which provide considerable employment." The authors had difficulty locating nonasthmatic children to participate in the study. Outdoor measurements were taken but not reported.
- The authors note there was no significant association between formaldehyde levels and house age. This is surprising, since any off gassing of formaldehyde from wood products or other formaldehyde-containing materials would be expected to decline over time. Thus, the accuracy of formaldehyde measurements could be open to question.
- In discussing the implications of their findings, Garrett *et al.* note the increased prevalence of allergic diseases in many Western countries, and suggest that materials emitting formaldehyde have become increasingly popular at the same time. The authors apparently do not appreciate that formaldehyde resin technologies have been improved substantially over the last two decades, and that releases of formaldehyde have been greatly reduced.
- It is difficult to rule out systematic recall or selection bias in this case-control study.

- With respect to exposure issues, no personal monitors were used, and there were no associations or trends for levels reported for the bedrooms, which are the one place in the house where some form of continuous exposure is likely to occur.
- The distribution of results claimed by the investigators hardly seems to be persuasive evidence of a systematic health risk. There was no significant increase in the adjusted risk for either asthma or respiratory symptoms with increasing formaldehyde exposure.

Wantke et al. (1996) studied 62 students in Austria and reported finding IgE specific to formaldehyde. However, among the 24 of the 62 children who had elevated IgE specific to formaldehyde, only 3 had RAST scores over 2.0. There was no dose-response relationship between formaldehyde levels and RAST scores. The three classrooms studied had 43, 69 and 75 ppb of formaldehyde measured, respectively. RAST scores were not elevated at 69 ppb compared to the 43 ppb classroom, as shown below.

Number of Students with
Specific IgE to Formaldehyde in Wantke, Table 2

	75 ppb (n=22)	69 ppb (n=22)	43 ppb (n=18)
RAST over 2.0	2	0	1
RAST 1.3-1.9	10	6	5
RAST 1.0-1.2	10	16	12

Thus, there does not appear to be dose-response relationship between formaldehyde and IgE. Moreover, the IgE levels in the study did not correlate with either number or severity of reported symptoms. The authors acknowledge that “IgE-mediated sensitization to formaldehyde is rare and a matter of controversy.” They further state: “Our data as well as the literature [ref. omitted] do not conclusively explain the clinical relevance of specific IgE against formaldehyde.” The Wantke *et al.* study did not compare children and adults, and thus also does not speak to any differential sensitivity.

Franklin et al. (2000) measured exhaled nitric oxide as an indicator of subclinical inflammatory response in 224 Australian children. The authors report increased nitric oxide in the breath of children in homes with over 50 ppb versus under 50 ppb formaldehyde. The range and mean exposure values are not provided. There were no measurements of the outdoors or school exposures to these children. The nitric oxide results were independent of atopy, and thus their significance is unclear. The study showed formaldehyde concentrations in the home had no effect on FVC or FEV_1 measures of pulmonary function in the children. The study does not compare children and adults, since relevant data for adults were not collected.

The same section references Krzyzanowski et al. (1990) for the absence of a "threshold for formaldehyde effects on ventilatory function in children" and adverse health effects "as low as at 30 ppb in nonasthmatic children" (pages 140-141). In Krzyzanowski et al. (1990), researchers questioned a group of 298 children (ages 6 to 15) and 613 adults using a self-administered respiratory questionnaire. Using regression analysis, the investigators found *no* significant association between exposures in children and self-reported chronic respiratory symptoms. Prevalence rates of chronic bronchitis or asthma reportedly diagnosed by a physician were significantly higher when residential concentrations of formaldehyde exceeded 60 ppb, especially in the presence of tobacco smoke. However, the study itself fails to point out an obvious difficulty from the data displayed in Tables 3 and 4 of the study.

There was no dose-response relationship with formaldehyde:

Prevalence Per 100 Subjects
Reported by Krzyzanowski in Tables 3 and 4

	≤ 40 ppb	40-60	>60
Chronic Bronchitis			
No Environmental Tobacco Smoke (ETS)	4.3 (n=141)	0 (n=12)	10.0 (n=10)
ETS	1.9 (n=106)	0 (n=10)	45.5 (n=11)
Asthma			
No ETS	8.5 (n=142)	8.3 (n=12)	0 (n=10)
ETS	15.1 (n=106)	0 (n=12)	45.5 (n=11)

More than 83 percent of the subjects in the study lived in homes in which the two-week average formaldehyde concentrations were less than 4 ppb. The average concentration measured was 26 ppb, with only a few homes exceeding 9 ppb. Thus, average concentrations appear to be driven by a few outliers. Findings of this study are questionable in view of these levels of formaldehyde found in the home environment. In addition, there were no measurements of allergens, or other agents present in the home.

The authors did report greater changes in peak expiratory flow rate in children than in adults. The use of peak expiratory flow rates does not confirm the presence or absence of asthma or bronchitis. This finding is the only data in any of the studies cited in the Public Review Draft document to suggest differential effects in children versus adults -- hardly a convincing basis for concluding that children are more sensitive to formaldehyde. In sum, it appears that this study is at odds with the weight of the literature, and should not be relied upon absent some further verification.

In Rumchev, et al. (2002), household formaldehyde levels were determined by passive sampling in the homes of 88 children aged 6 months to 3 years who were diagnosed at a hospital with asthma, and compared with 104 community controls. Cases had a statistically significant higher mean formaldehyde exposure compared to controls, 32 ppb (38 $\mu g/m^3$) and 20 ppb (24 $\mu g/m^3$), respectively. After adjustment for confounding factors, such as indoor air pollutants, relative humidity, indoor temperature, atopy, family history of asthma, age, sex socioeconomic status, pets and environmental tobacco smoke, Rumchev et al. (2002) reported that children exposed to formaldehyde levels of 60 $\mu g/m^3$ had a 39% increase in odds of having asthma compared to children exposed to less than 10 $\mu g/m^3$ (or estimated to be approximately 1.4 95% CI 1.1-1.7 from data presented in a graph). However, considering the marginally increased risk observed, together with the number of potential sources of bias, such as selection bias and validity of diagnosis in the young, this study should not be considered sufficiently robust evidence of an association between formaldehyde exposure and increased risk of asthma in children or an appropriate basis for regulation or governmental guidance.

In addition, as noted previously, formaldehyde is exhaled in the breath, with studies suggesting that breath levels may range from 1.2 - 72.7 ppb to 300 – 1,200 ppb (Moser et al. 2005; Ebeler et al. 1997). Based on the existing literature, the exposure levels reported in Rumchev et al.

(2002) are in the range of formaldehyde expected to be found in exhaled breath. This raises the questions of causation, association, and how one might reasonably differentiate self-exposure from an exogenous source of exposure at approximately the same concentration.

Those limitations and weaknesses are validated by a second report by Rumchev, et al. (2004), which was not referenced in the ISOR and which raises questions regarding whether Rumchev (2002) is an adequate basis for the derivation of a reference concentration specifically for formaldehyde. Rumchev, et al. (2004) used the same cohort of children and evaluated the same asthma endpoint as Rumchev, et al. (2002), but focused on the association with the other chemicals and particulates rather than formaldehyde. As for formaldehyde, Rumchev, et al. (2004), found that asthmatic cases were exposed to higher levels of VOCs.

An editorial was published concurrently (Brunekreef, B. 2004) with Rumchev et al. (2004), which focused on NO_2, VOCs, and particulates. The editorial indicates that (1) diagnosis of asthma in children is "notoriously difficult," and (2) case-control studies, as used by Rumchev, inherently are rife with potential and actual sources of confounding and bias. An example given is that Rumchev et al. (2004) did not attempt to evaluate the impact of recent indoor painting. These issues raise serious questions regarding the adequacy of the study as a sole source for deriving a reference exposure.

As Brunekreef (2004) noted in his comments on Rumchev et al. (2004) and other studies:

> The issue of whether indoor VOCs are a risk factor for asthma in children therefore seems still to be largely undecided. In view of the methodological difficulties outlined above, prospective studies are more likely to produce progress in deciding whether we need to worry about indoor VOCs as determinants of asthma at the relatively low concentrations typically encountered in the home environment.

In view of the issues raised by Rumchev (2004) showing that a number of VOCs were associated with asthma as well as the inherent and broader limitations associated with Rumchev, et al. (2002), Rumchev, et al. (2002) does not provide a reasonable basis for adopting a new level. A careful reading of the studies cited as the basis for concluding that children are differentially sensitive to formaldehyde shows essentially no support for that proposition. [26]

The ISOR never provides a substantive discussion that shows how the staff collectively interprets or resolves apparently conflicting data through an analysis of the strengths and weaknesses of the studies, such as the Garrett et al. (1999) and Krzyzanowski et al. (1990). These inconsistencies in the data should be explained.

Human Carcinogenicity (Page 147)

With regard to carcinogenicity, the weight of evidence points to a threshold mode of action, with cytotoxicity/cell replication as the driving force. Formaldehyde is a low potency carcinogen in light of the: (1) relationship of the concentrations leading to tumor formation and pre-tumorigenic

[26]Sufficient evidence of a causal relationship or an association with asthma only exists for cats, cockroaches, house dust mites, ETS (preschoolers), dogs, fungi or molds (Rhinovirus) and high-level exposures to nitrogen oxides, not formaldehyde or other VOCs. See the National Research Council (2004) *Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants,* p. 87.

changes and (2) steep sub-linear dose-response curve for various effects associated with the carcinogenic response.

Genotoxicity (Page 147)

The cited studies by Shaham have been further discredited with new published data beyond prior work by Heck. Neither Schmid and Speit nor Heck's work is addressed in this regard, nor is there any discussion relating the human and animal genotoxicity sections of the report. Schmid and Speit (2007) concludes that the data gathered from human biomonitoring of blood from workers exposed to formaldehyde and relating this information to systemic genotoxic effects of formaldehyde is not plausible. Schmid and Speit (2007) demonstrate that the DNA-protein crosslinks, associated with formaldehyde exposure which is integral to further DNA damage, is quickly reversed in the blood cells. It is only at higher formaldehyde concentrations (≥200μM) that enough DNA-protein crosslinks were formed resulting in DNA damage and cytotoxicity. Since such high levels of formaldehyde are not seen in human blood of exposed workers and any DNA-protein crosslinks created as a result of lower formaldehyde exposure are quickly reversed, the reported effects seen in the sister chromatid exchange tests, in Shaham et al. (1997, 2002), Yager et al. (1986), He et al. (1998) and Ye et al. (2005), are highly unlikely to be related to formaldehyde exposure.

Nasopharyngeal Cancer (Pages 147-149)

A comparison of the ISOR discussion of nasopharyngeal cancer with the summary presented in the general comments section above reflects a pattern of ignoring newer work, such as that of Marsh et al. (2002, 2004, 2005). The "recent occupational studies" mentioned in this section are 17 years old and are stretched to find "some indication of possible histological change due to formaldehyde exposure." Marsh et al. (2006) concludes that the NCI analysis was misleading because an important interaction term between the plant group and exposure variable was not taken into account and, due to the low numbers of tumors, there were considerable uncertainties in the risk estimates. Adami and Chang (2006) reviewed the literature on the occurrence of NPC and concluded that, for this specific tumor type, there are several risk factors that may lead to an appreciable increase, e.g. specific diets or familial history. For formaldehyde, the authors stated that “epidemiologic evidence” is limited.

Cohort studies

In an update of a mortality study of approximately 14,000 British industrial workers from 1941 (Acheson et al., 1984) up to 2000 (Coggon et al., 2003), only one case of nasopharyngeal cancer was identified in the cohort versus two expected, although estimated formaldehyde exposures were highest compared to the other two studies listed below. Coggon et al. (2003) concluded that: ”The evidence for human carcinogenicity of formaldehyde remains unconvincing.”

In an update of a mortality study involving a cohort of approximately 11,000 garment workers in the US from 1955 to 1982 (Stayner et al., 1985; 1988) and then to 1998 (Pinkerton et al., 2004), no cases of nasopharyngeal cancer were identified (0.96 expected). Pinkerton et al. (2004) states: ”We found no evidence of an association between formaldehyde exposure and mortality from respiratory cancers.”

An update of the largest mortality study of over 25,000 workers in formaldehyde industries in 10 different plants in the US initially followed up through 1980 (Blair et al., 1986) and now up to 1994 (Hauptmann et al. 2004) is frequently referenced as the "NCI study." In this study, 8 cases

of nasopharyngeal cancer compared to 4 expected were observed in the exposed workforce. Six of these were located in one single plant (Plant 1) out of the ten plants examined. Later, 1 of these 8 cases turned out to be an oropharyngeal cancer; in addition, there have been two additional nasopharyngeal cancer cases among the workers employed in these plants but not exposed to formaldehyde. Even if the misclassified case remains included, nasopharyngeal cancer rates are not significantly increased compared with those of the general US population (SMR 2.1; exact 95% CI 0.91, 4.14). If this misclassified case would be excluded, the association would be even weaker.

Taking all cohort studies with a total of approximately 50,000 exposed workers together, 9 cases (only 8 being true nasopharyngeal cancers) have been observed versus 7 expected; not a relevant difference. These three studies are the most relevant, but there is no reason to give particular preference to the NCI study.

As early as 1996, Marsh et al. (1996) identified a specific feature of the former NCI-study comprising workers of 10 different plants. There was no even distribution of the observed nasopharyngeal cancer cases between the different plants; they were concentrated in one plant. Specifically, 4 of the total of 5 exposed cases observed arose in one of the 10 plants. A detailed analysis of the “suspected clustering in this one plant” showed that “only one case had any appreciable exposure to formaldehyde”.

In a second follow-up (up to 1998) by Marsh et al. (2002), the clustering of nasopharyngeal cancer was confirmed as three additional cases were found, leading now to 7 exposed cases in a single plant. In addition, inconsistencies in the exposure effect relationship were identified pointing against a causal connection with formaldehyde:

- The majority of the seven nasopharyngeal cancer cases in the single plant was found in short-term workers with an exposure duration of less than one year. Only 3 of 7 were exposed to formaldehyde longer than one year and each had low average intensities of exposure (ranging from 0.02-0.60 ppm).
- 6 of the 7 nasopharyngeal cancer cases were hired between 1947 and 1956, again an indication of a cluster.
- SMRs (Standardized Mortality Ratios) for nasopharyngeal cancer were greater among short-term (<1 year) than among long-term workers.

Marsh and Youk (2005) reevaluated the NPC cases of the new NCI study (Hauptmann et al., 2004). Six of the 8 exposed cases came from a single plant, leading to a regional-rate based SMR of 10.32 (95% Confidence Interval 3.79 -22.47). The other two exposed and the two non-exposed cases each came from different plants of the remaining 9 plants of the NCI study. For these other 9 plants, the SMR was calculated to be 0.65 (0.08-2.33). In addition, the exposure association reported by Hauptmann et al. (2004) with peak and average intensity was driven entirely by the data from this single plant.

Marsh and Youk (2005) concluded that

- there was little evidence for a causal association between NPC and formaldehyde
- the NCI conclusion of a possible association was mainly driven by the Wallingford plant
- the large NPC mortality at the Wallingford plant may reflect non-occupational or occupational risk factors associated with employment outside of this specific plant.

Overall, the detailed analysis of the NCI findings, especially in relation to the single plant, casts doubt on a causal association indicated by the NCI study between formaldehyde and NPC development.

Case-control studies

The case-control studies on nasopharyngeal cancer and formaldehyde are hampered by weak exposure assessments, in particular for the probably more relevant periods several decades ago. The potential impact of selection and information bias seems to be even higher than for the cohort studies. Thus, their results in general are not very reliable and far from conclusive:

- The relative risk in the Olsen et al. (1984) study was non-significantly decreased in men, and non-significantly increased in the much smaller group of women (negative study).
- Vaughan et al. (1986) found a slightly but not significantly increased risk for occupational formaldehyde exposure. Besides very weak exposure information there are several limitations of this study, e.g. lack of adjustment even for age, the strongest predictor of cancer. Thus, this study cannot be considered as one supporting an association (non-informative study).
- Roush et al. (1987) did not find an elevated risk for workers probably exposed for most of their working lives, but a non-significantly elevated risk for the highest exposure category. However, potential selection and information biases as well as very weak exposure information based on resident directories are major shortcomings of this study (non-informative study).
- West (1993) reported partly significant increases only for selected exposure categories in a study performed in the Philippines. He found even stronger associations for other exposures such as dust and/or exhaust, anti-mosquito coils or herbal medicines. The IARC Working Group 1995 noted with regard to this study that the authors did not control for the presence of Epstein-Barr virus antibodies, which showed a strong association with nasopharyngeal cancer in another study in the same region (non-informative study).
- The study of Armstrong et al. (2000) is definitely negative.
- Hildesheim et al. (2001) report a modest and not significantly increased risk (relative risk =1.4; 95% CI 0.93-2.2). However, no dose response was observed with increasing duration or cumulative use (slightly positive).
- Vaughan et al. (2000) detected a slightly, but not significantly elevated odds ratio of 1.3 (95% CI: 0.8-2.1). They observed a significant trend with cumulative exposure, but in contrast to the NCI study not for the maximum exposure concentration. In contrast to other authors, an increased risk for wood dust exposure could not be observed in this study (slightly positive study).

Thus, if a positive study is considered as one in which a clear and significant association is demonstrated, none of the case-control studies can be regarded as positive. In summary, the results of these case-control studies should be regarded as equivocal, two of them being clearly negative, three not contributing much information and two showing some slightly elevated risk.

Meta-analyses

The most recent meta-analysis by Collins et al. (1997) is quoted inappropriately as if it would demonstrate a significantly elevated risk. Collins et al. point out the relevance of correcting for

underreporting of expected numbers of death when dealing with a rare and frequently underreported cancer such as nasopharyngeal cancer. After correcting, they calculated a meta relative risk of 1.0 (95% CI 0.5, 1.8) for the cohort studies and 1.3 (0.9, 2.1) for the case-control studies. The authors emphasize that it is unlikely that the few cases in the case-control studies had meaningful formaldehyde exposures because only a minority of the jobs classified as having it actually entailed such exposure. In their paper Collins et al. emphasize the weaknesses of the previous meta-analyses leading to conflicting results (see page 648).

It is instructive to contrast the short and inaccurate treatment of Collins et al. (1997) in the ISOR with that presented in the November 2006 Priority Existing Chemical Assessment on formaldehyde prepared by the Australian Department of Health and Aging, National Industrial Chemicals Notification Assessment Scheme (NICNAS), which was previously referenced with regard to NICNAS' use of the BBDR model.

> In a more recent and comprehensive meta-analysis, Collins et al. (1997) initially considered 47 epidemiology studies. Several of these studies were not included in the analysis, because workers who had formaldehyde exposure were not evaluated separately or the study only reported relative risks, the study population was included in a more recent study, or the methodology and results were insufficiently described. In total the meta-analysis was based on the results from 11 cohort, 3 proportionate mortality and 18 case-control studies, and included new data published since Partanen (1993). Furthermore, the authors of studies were contacted to obtain data not included in their publications. The exposure potential of jobs that were classified as having formaldehyde exposure in the community-based case-control studies was also reviewed, as exposure assessment was much more uncertain in these studies than in cohort studies.
>
> When all studies were included, no increased risk of lung cancer was seen with exposure to formaldehyde (mRR = 1.0, 95% CI 0.9 - 1.0). In cohort studies, a very small borderline, though significant, increased risk was seen for industrial workers (mRR = 1.1, 95% CI 1.0-1.2), while no increased risk was seen for pathologists (mRR = 0.5, 95% CI 0.4 - 0.6) or embalmers (mRR = 1.0, 95% CI 0.9 - 1.1). Similarly, no increased risk was seen in the case-control studies (mRR = 0.8, 95% CI 0.7 - 0.9).
>
> No increased risk of sinonasal cancers was seen with exposure to formaldehyde (mRR = 1.0, 95% CI 1.0 - 1.1). Evaluating by study design revealed no increased risk for cohort studies (mRR = 0.3, 95% CI 0.1 - 0.9) but a significantly increased risk for case-control studies (mRR = 1.8, 95% CI 1.4 - 2.3). This increased risk was attributable to a significantly increased risk for the combined 6 European case-control studies (mRR = 2.9, 95% CI 2.2 – 4.0), whereas no increased risk was seen for the combined 5 US case-control studies (mRR = 1.0 95% CI 0.7 - 1.5). Collins et al. (1997) report that it is difficult to reconcile European findings with other findings unless it is assumed that confounding factors, or bias, were affecting the results.
>
> A significantly increased risk of nasopharyngeal cancers was seen with exposure to formaldehyde (mRR = 1.3, 95% CI 1.2 - 1.5). However, evaluation of nasopharyngeal cancers was hampered in some industrial cohort studies, as expected numbers were not reported when there were no observed deaths. To

> overcome this, the expected number of deaths was estimated based on the ratio of expected lung cancers to nasopharyngeal cancers in the study by Blair et al. (1986) that reported nasopharyngeal deaths. Expected numbers were also not reported in the cohort studies of embalmers and medical specialists. Using a similar approach, based on the ratio of expected lung cancers to nasopharyngeal cancers in the study by Hayes et al. (1990), a non-significant increased risk was found for nasopharyngeal cancers and exposure to formaldehyde when all industrial cohort studies were combined (mRR = 1.2, 95% CI 0.4 - 2.5). While no increased risk of nasopharyngeal cancers was seen for all cohort studies combined (mRR = 1.0, 95% CI 0.4 – 2.5), a non-significant increased risk of such cancers was seen for all case-control studies combined (mRR = 1.3, 95% CI 0.9 - 2.1).[27]
>
> Collins et al. (1997) concluded that the data did not provide convincing evidence of a casual relationship between formaldehyde exposure and nasopharyngeal cancers. The authors attributed the differences in their results to the two earlier meta-analysis to be mainly due to the inclusion of a number of recently published negative cohort studies

FCI includes this excerpt not because we agree with all of the evaluations in the NICNAS PEC on formaldehyde. Rather, we reference this passage as an example of the type of summary that allows everyone with an interest to understand how one agency read the study and what elements the agency viewed as notable. This type of summary also serves to distinguish clearly the author's conclusions from those of the reviewing agency.

Summary on epidemiology study evaluation

Recapitulating, the available epidemiological studies on formaldehyde consistently show no or a minimally increased risk for nasopharyngeal cancer with one clear exception of the remarkably elevated risk in plant 1 of the NCI study. A serious critique to the Hauptmann (2004) study is the fact that the author disregards the peculiar results at this specific plant. Instead of focusing only on formaldehyde, it would have been important to try to identify other risk factors, which may have played a relevant role in particular in those three cases exposed to low levels of formaldehyde for much less than one year.

Local genotoxicity in humans

With regard to possible NPC formation in humans, local genotoxicity observed in workers has to be taken assessed. There are several investigations on micronuclei formation in nasal and buccal cells in exposed humans with both positive and negative results. These data have to be interpreted with caution since the methods used are still quite investigative and have several methodological problems as noted by Fenech et al. (1999):

- high variability of the results when the same subjects are tested repeatedly
- large differences between healthy subjects
- protocols are not yet standardized
- problems to differentiate between epithelial cells and leucocytes

[27] NICNAS (2006) pp. 89-90 (footnote omitted).

- possibility for misinterpretation of degenerative epithelial cells

Therefore such study results cannot be interpreted with confidence presently.

The recent IARC evaluation for nasopharyngeal cancer basically relies on the outcome of the study of Hauptmann et al. (2004), which has only been carried through up to 1994 whereas Pinkerton et al. (2004) and Coggon et al. (2003) performed updates up to 1998 and 2000, respectively. Therefore the NCI has decided to carry out a mortality analysis in this cohort up to the most recent years. The results of this latest update are to be expected in 2007. The update will comprise approximately an additional 10 years of mortality experience and lead to a much clearer picture because the significance of mortality data will sharply increase in mortality studies with the aging of the workforce.

In conclusion, the three large industrial worker cohort studies are most relevant for a decision as regards classification for carcinogenicity in humans. There was no significant increase for NPC in association with formaldehyde exposure in general. The association seen with two of four exposure metrics in the NCI study only is driven by just 1 of 10 plants (SMR 10.3). For this specific plant there may well be other factors relevant for NPC development apart from formaldehyde exposure. Even the authors of the NCI study argue cautiously: “In this cohort of formaldehyde workers, some evidence was found of an exposure-response relation with mortality from nasopharyngeal cancer (based on small numbers)…”

In Siemiatycki et al. (2004), three of the co-authors being affiliated with IARC, the strength of evidence regarding nasopharynx and formaldehyde has also only been considered as suggestive only but not as strong.

Leukemia (Pages 149-150)

The report characterizes Collins and Lineker (2004) as being supportive of an increase risk of leukemia. As discussed above, this is an incorrect reading of the paper.

Golden et al. (2005) report that chemically-induced leukemia is a well-studied phenomenon with benzene and a number of cancer chemotherapeutic drugs recognized as capable of causing this effect. Abundant *in vitro* and *in vivo* data in animals and humans demonstrate that exposure to sufficient doses of these recognized leukemogens can initiate a cascade of events leading to hematopoietic toxicity and the subsequent development of leukemia. Golden et al. (2005) addresses the biological plausibility that formaldehyde might be capable of causing any type of leukemia by providing a broad overview of the scientific data that must be considered in order to support or refute a conclusion that a particular substance might be leukemogenic. Data on benzene and selected chemotherapeutic cancer drugs are used as examples and are briefly summarized to demonstrate the similar biological events thought to result in leukemogenesis. These data are compared and contrasted with the available data on formaldehyde in order to judge whether they fulfill the criteria of biological plausibility that formaldehyde would be capable of inducing leukemia as suggested by the epidemiological data. Based on the epidemiological data, it is reasonable to expect that if formaldehyde was capable of inducing leukemia *in vivo* and *in vitro* data would offer supporting evidence for biological plausibility. In particular, the authors conclude that there is (1) no evidence to suggest that formaldehyde reaches any target organ beyond the site of administration including the bone marrow, (2) no indication that formaldehyde is toxic to the bone marrow/hematopoietic system in *in vivo* or *in vitro* studies, and (3) no credible evidence that formaldehyde induces leukemia in experimental animals. As discussed in the review, based on the key biological events that occur in the process of

chemically-induced leukemia, there is inadequate biological evidence currently available to corroborate existing weak epidemiological associations. This provides an insufficient database to conclude that there is a causal relationship for formaldehyde and leukemia risk.

Golden et al. (2005) is consistent with Heck and Casanova (2004), in which the authors report the following:

> The possibility that inhaled formaldehyde might induce various forms of distant-site toxicity has been proposed, but no convincing evidence for such toxicity has been obtained in experimental studies. This review summarizes the biological evidence that pertains to the issue of leukemia induction by formaldehyde, which includes:
>
> (1) the failure of inhaled formaldehyde to increase the formaldehyde concentration in the blood of rats, monkeys, or humans exposed to concentrations of 14.4, 6, or 1.9 ppm, respectively;
> (2) the lack of detectable protein adducts or DNA-protein cross-links (DPX) in the bone marrow of normal rats exposed to [3H]- and [14C]formaldehyde at concentrations as high as 15 ppm;
> (3) the lack of detectable protein adducts or DPX in the bone marrow of glutathione-depleted (metabolically inhibited) rats exposed to [3H]- and [14C]formaldehyde at concentrations as high as 10 ppm;
> (4) the lack of detectable DPX in the bone marrow of Rhesus monkeys exposed to [14C]formaldehyde at concentrations as high as 6 ppm;
> (5) the failure of formaldehyde to induce leukemia in any of seven long-term inhalation bioassays in rats, mice, or hamsters; and
> (6) the failure of formaldehyde to induce chromosomal aberrations in the bone marrow of rats exposed to airborne concentrations as high as 15 ppm or of mice injected intraperitoneally with formaldehyde at doses as high as 25 mg/kg.
>
> Biological evidence that might be regarded as supporting the possibility of leukemia induction by formaldehyde includes: (1) the detection of cytogenetic abnormalities in circulating lymphocytes in seven studies of human subjects exposed to ambient concentrations in the workplace (but not in seven other studies of human subjects or in rats exposed to 15 ppm); (2) the induction of leukemia in rats in a single questionable drinking water study with formaldehyde concentrations as high as 1.5 g/L (but not in three other drinking water studies with concentrations as high as 1.9 or 5 g/L); (3) the detection of chromosomal aberrations in the bone marrow of rats exposed to very low concentrations of formaldehyde (0.4 or 1.2 ppm) (but not in another study at concentrations as high as 15 ppm); and (4) an apparent increase in the fraction of protein-associated DNA (assumed to be due to DPX) in circulating lymphocytes of humans exposed to ambient concentrations in the workplace (1-3 ppm). This evidence is regarded as inconsequential for several reasons, including lack of reproducibility, inadequate reporting of experimental methods, inconsistency with other data, or insufficient analytical sensitivity, and therefore, it provides little justification for or against the possibility that inhaled formaldehyde may be a leukemogen. In contrast to these inconclusive findings, the abundance of negative evidence mentioned above is undisputed and strongly suggests that there is no delivery of inhaled formaldehyde to distant sites. Combined with the fact that formaldehyde naturally occurs throughout the body, and that multiple inhalation bioassays have not induced leukemia in animals, the negative findings provide convincing evidence that formaldehyde is not leukemogenic.

Lung Cancer (Pages 150-151)

The report cites Blair et al. (1986), but seems to have forgotten that there are several updates to this study. Relying on only one of a series of updated studies on the same cohort disregards good practice in evaluating epidemiological studies.

Animal Carcinogenicity (Page 152)

During the 1980s, studies demonstrated that formaldehyde leads to nasal tumors in rats after exposure to concentrations associated with severe irritation and compensatory cell replication in the respiratory epithelium of rats. In mice there was a slight, non significant nasal tumor response of about 1% at 15 ppm (a concentration that led to approximately 50 % nasal tumor bearing rats) (Kerns et al.,1983) while no tumors were found in hamsters at 10 (5d/w) or 36 ppm (1d/w) (Dalbey, 1982). Thus, there is a clear difference in sensitivity for the three species investigated.

In vitro, formaldehyde is genotoxic/mutagenic in various test systems exhibiting high cytotoxicity. In vivo DNA-protein cross-links occur at the site of direct contact (predominantly nasal mucosa), but no genotoxic effects were found at distant sites, i.e. no systemic effects were demonstrated.

Over the last 20 years, the large number of scientific studies has not changed the picture for nasal carcinogenicity in rodents. The new data strengthened the evidence that the decisive factor for formaldehyde carcinogenicity is cytotoxic irritation and compensatory cell proliferation besides genotoxicity as manifested by DNA protein binding. See prior discussion and CIIT report Sept. 28, 1999; Conolly et al. (2002; 2003; 2004).

IV. FORMALDEHYDE AND REGULATORY RISK MANAGEMENT

The Board is considering a proposal to limit formaldehyde emissions from composite wood products. This action is driven by a cancer risk assessment of formaldehyde performed by the OEHHA. This cancer risk assessment of formaldehyde was conducted in 1992 and reissued essentially unchanged by OEHHA in 2005 as part of the Air Toxics Hot Spots Program.[28] However, more sophisticated and biologically-based risk assessments of formaldehyde by other respected regulatory agencies, including US EPA and Health Canada, conflict with the conclusions of OEHHA's risk assessment. More importantly, these assessments indicate that the proposed reductions in formaldehyde emissions would not produce the reductions in cancer cases in California predicted by OEHHA's risk assessment.

OEHHA performed a conservative cancer risk assessment, designed to estimate the cancer risk to humans at low exposure levels of formaldehyde by extrapolating the results of cancer in laboratory rats at higher levels of exposure. Based on the OEHHA risk assessment using the 95% upper-bound confidence limit, the estimated cancer risk over a 70-year lifetime from the current average exposure to formaldehyde in California is 35 cancer cases per million people (Table 1). CARB also estimated that the benefit of implementing Phases 1 and 2 of the proposal would result in a net reduction of cancer cases of 12 and 35 per million people, respectively, over a 70 year lifetime. Assuming a steady population of 35 million in California, this would

[28] OEHHA (1992) Cancer Risk Assessment for Airborne Formaldehyde. January, 1992. OEHHA (2005) Air Toxics Hot Spots Program Risk Assessment Guidelines. Part II. Technical Support Document for Describing Available Cancer Potency Factors. May, 2005. pp. B-287-295.

amount to reduction in cancer cases of 18 per year in California. If OEHHA's estimates were accurate, the proposed reductions in formaldehyde emissions would have a small (but not insignificant) benefit. By comparison, over 100,000 Californians are expected to die from cancer annually.

Notably, OEHHA's estimates are at odds with more realistic risk assessments by other respected agencies. Since OEHHA conducted its risk assessment in 1992, new and relevant scientific data on formaldehyde has been published, which has not been incorporated in OEHHA's risk assessment despite requests to re-open the risk assessment process. Using this information, a robust, biologically-based approach to estimating the potential cancer risk of formaldehyde to humans was developed and published. Importantly, this approach to assessing the potential cancer risk of formaldehyde has been embraced and adopted by regulatory agencies in the US and internationally, including US EPA (2006)[29], Health Canada (2001)[30], the World Health Organization (WHO, 2002)[31], and the Australian Government (2006)[32].

Table 1 compares the estimated cancer risks of formaldehyde exposure in California using the cancer potency estimates (i.e., the inhalation unit risk per $\mu g/m^3$) for formaldehyde adopted by OEHHA and the other agencies. The cancer potency estimates in Table 1 are all based on the same study of formaldehyde in rats. With the exception of the choice of the cancer potency factor, all assumptions and calculations were exactly the same as those used by OEHHA. So, the only reason for the difference in the results in Table 1 is the different estimates of the cancer potency of formaldehyde.

[29] US EPA (2006) National Emission Standards for Hazardous Air Pollutants: Plywood and Composite Wood Products; List of Hazardous Air Pollutants, Lesser Quantity Designations, Source Category List. Fed Reg Vol. 71, No. 32, 8348-49. February 16, 2006.

[30] Health Canada (2001) Priority Substances List Assessment Report: Formaldehyde. February, 2001.

[31] WHO (2002) Concise International Chemical Assessment Document 40: Formaldehyde. Geneva.

[32] Australian Government Department of Health and Ageing (2006) Priority Existing Chemical Assessment Report No. 28. Formaldehyde. National Industrial Chemicals Notification and Assessment Scheme. November, 2006.

Table 1. Comparison of Estimated Cancer Risk of Formaldehyde in California using OEHHA Methodology and the Cancer Potency Factors of Various Organizations

Organization	Inhalation unit risk per □g/m^3	Cancer Risk per Million for Adult (current average exposure)	Cancer Cases Reduced per Million post Phase 2	California Cancers Prevented per Year post Phase 2
US EPA (1988)	13 x 10^{-6}	186	76	39
OEHHA (1992)	**6 x 10^{-6}**	**86**	**35**	**18**
US EPA (1992) proposed according to OEHHA (1992)	2 x 10^{-6} 0.2 x 10^{-6}	28 3	12 1.2	6 0.6
Health Canada (2001)	0.00017 x 10^{-6}	0.002	0.001	0.0005
WHO (2002)	0.00019 x 10^{-6}	0.002	0.001	0.0005
Australia (2006)	0.0024 x 10^{-6}	0.03	0.014	0.007
US EPA (2006)	0.0027 x 10^{-6}	0.04	0.016	0.008

As noted above, based on OEHHA's estimates of formaldehyde's cancer potency and the average exposure to formaldehyde in California, the implementation of Phase 2 is estimated by OEHHA to prevent 35 cancer cases per million people. In contrast, the other agencies' cancer potency factors, combined with OEHHA's estimates of average exposure to formaldehyde in California, produce an estimated reduction of cancer cases much smaller than one in a million. For example, only 0.001 cancer cases per million people (or one cancer case per *billion* people) would be prevented using the cancer potency factors adopted by Health Canada and WHO (Table 1). Similarly, US EPA's (2006) cancer potency factor predicts a reduction of only 0.016 cancer cases per million people.

Based on an estimated population of 35 million people in California and OEHHA's estimate of a reduction of 35 cancer cases per million people over a 70-year lifetime, OEHHA's estimated number of cancer cases prevented per year in California is 18.[33] In contrast, using the cancer potency factors of the Other Agencies, the estimated number of cancer cases prevented per year in California ranges from 0.0005 to 0.008 (Table 1). In other words, the estimated time required to prevent *one* case of cancer in the entire population of California after implementing Phase 2 ranges from *125 to 2000 years*.

OEHHA's estimated cancer potency for formaldehyde is 2,250 to 36,000 times greater than that of the other agencies. Either OEHHA has greatly overestimated the risk or US EPA, Health Canada, WHO, and Australia all have greatly underestimated the risk. These other agencies have expressed a strong preference for using the risk assessment methodology of Conolly et al. (1999), such as USEPA's decision to use this risk assessment model for formaldehyde when it established emission standards for plywood and composite wood products.

[33] 35 cancer cases prevented per million people over a 70-year lifetime x 35 million people divided by 70 years = 18 cancer cases prevented per year

> In the case of formaldehyde, we have determined that the cancer potency derived using the approach developed by [Conolly et al., 1999] and peer-reviewed by an independent expert peer review panel sponsored by EPA and the Canadian government represents an appropriate alternative to EPA's current IRIS URE for formaldehyde, and is therefore the best available peer-reviewed science at this time."[34]

The cancer risk assessment of formaldehyde by OEHHA does not rely on what US EPA calls "the best available peer-reviewed science at this time." In fact, the OEHHA risk assessment of formaldehyde does not even mention the work upon which USEPA, Health Canada, WHO and Australia rely for their risk assessments of formaldehyde.

CARB should carefully evaluate the proposal to reduce exposure to formaldehyde in light of the tenuous public health benefits represented by the estimated reduction in cancer cases in California. If reducing exposure to formaldehyde will not result in any meaningful reduction in cancer risk in California, the proposed action must be questioned. Given the fact that over 100,000 Californians are expected to die from cancer annually, it is especially important to focus the State's resources on strategies that will result in real reduction in cancer and improvement in public health.

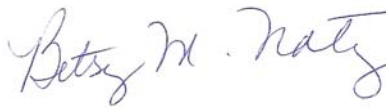
V. CONCLUSION

In these comments, FCI has endeavored to address the proper scientific framework for the health risk assessment for formaldehyde in this rulemaking. FCI and its members have continued to invest heavily in toxicological research to support the scientific community's efforts to better understand the toxicological properties of formaldehyde and refine risk assessment methodologies to continue to protect human health and the environment with increasing levels of certainty.

The Board has an obligation to ensure that the final agency decisions are based on evidence of requisite quality and quantity and that a reviewing court must enforce that duty. The differences between prevailing science and the ISOR are so severe that a rule based on such assumptions would be arbitrary and capricious and an abuse of discretion.

The Formaldehyde Council and its members would be happy to discuss this matter or provide additional analysis if it would assist the Air Resources Board.

Sincerely,



Betsy M. Natz
Executive Director

[34] National Emission Standards for Hazardous Air Pollutants: Plywood and Composite Wood Products; List of Hazardous Air Pollutants, Lesser Quantity Designations, Source Category List. 71 Fed Reg 8348-49 (Feb. 16, 2006).

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